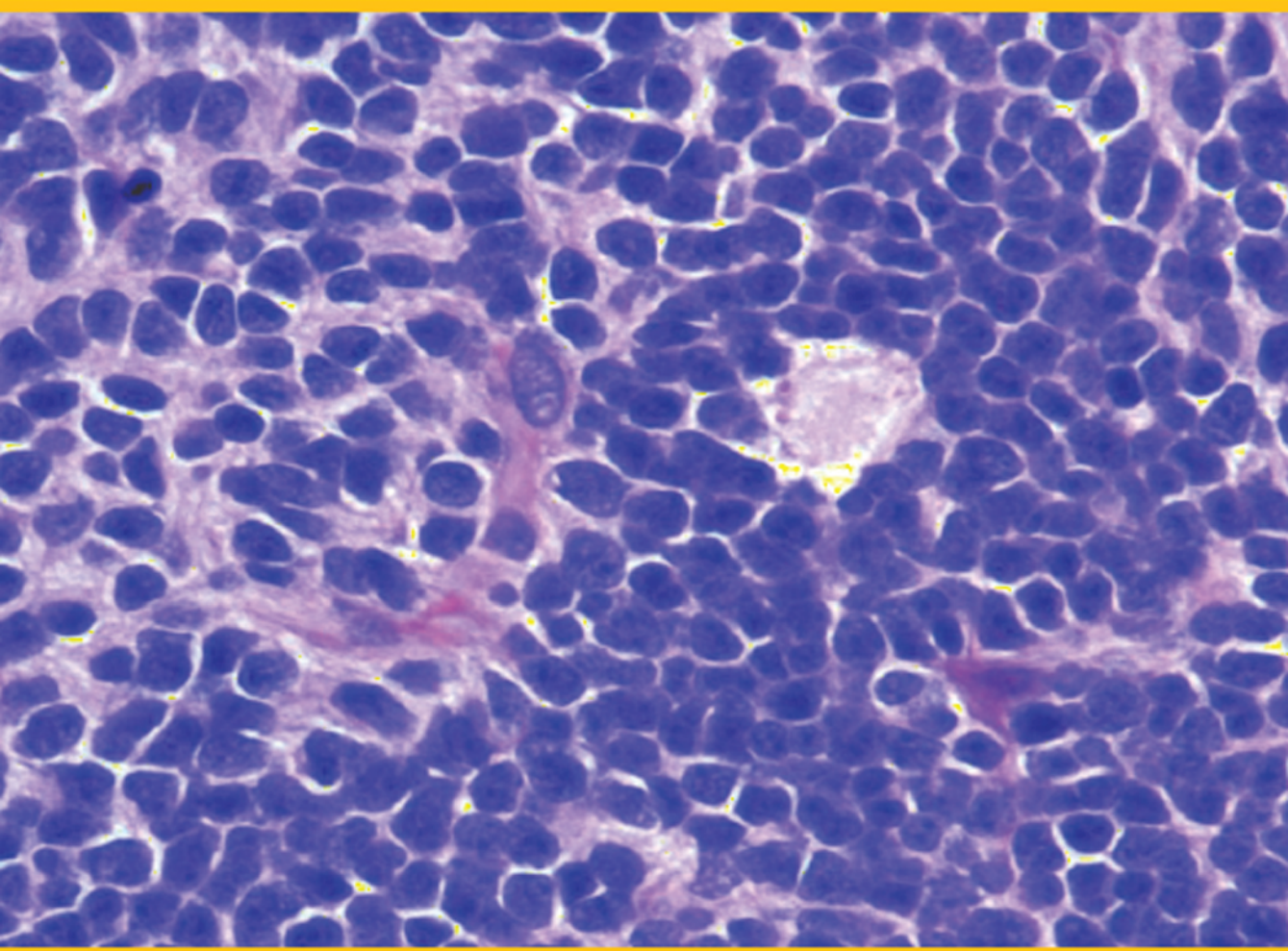
PEDIATRIC PATHOLOGY

A Course Review



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Pediatric Pathology
A Course Review

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To my husband, Ashok, who is the *Wind Beneath My Wings*

Contents

Preface

This course review book is an assimilation of the comprehensive, yet concise notes that I made for myself as a study guide for board exam preparation (during the year of my fellowship in pediatric pathology). Later, I supplemented those notes with the experience I gained during my 5 years of practice as a pediatric pathologist. The pages that follow cover most of the major topics in pediatric pathology including the embryo, fetal, perinatal, infant and child developmental organ system, and pediatric hematopathology. A chapter on selected topics of pediatric blood transfusion and coagulation is enclosed. Readers will find two separate glossaries embodied in the book (one each for developmental and organ system pathology), which provides alphabetically arranged important terminology with explanations. In addition, I have included a self-assessment section with a quiz containing 115 select cases in anatomic and hematopathology with photomicrographs for each. The correct diagnosis appears at the end of each question. These are mostly spot diagnoses and will help in preparation for the glass slides and the practical part of the examination.

This book is in an outline format, and while by no means can it replace any of the existing excellent pathology textbooks, it is a good resource for pathologists in training, especially pediatric pathology fellows and residents in anatomic and hematopathology, who are preparing for their board examinations. It may also serve as a quick reference guide for pathologists in practice as well as for medical students who are interested in making pathology their career choice.

I have learned from my own personal experience that after you have studied the excellent textbooks in pediatric pathology over the year of your fellowship training, this review course can serve as an outstanding study guide during the last few weeks, days, and hours before the board exams. The handy size and the outline format help keep all the important facts and details fresh in the minds of young pathologists in training, especially during the long airplane journey, sometimes tedious airport delays, and the hotel stay, in the days preceding the board exams.

Any feedback from readers is most welcome. Every effort has been made to keep the book as accurate and precise as possible; however, I would love to hear of important omissions or errors that have slipped into the text, so that together we can improve the quality of this material.

Glossary: Developmental and Fetal Pathology

Acute intrapartum twin-to-twin transfusion: Larger recipient twin is anemic and the smaller donor twin is plethoric

Alagille syndrome: Mutation of *JAG1* gene, del(20p). Intrahepatic bile duct paucity, neonatal jaundice

Algor mortis: Postmortem cooling of the body. Infants/children cool more quickly. Internal organs reach ambient temperature within 18–24 hours

Alkaptonuria: Accumulation of homogentisic acid, pigmented cartilage

Alpha-mannosidosis: Vacuolated lymphocytes in peripheral blood

Amnion nodosum: Fetal surface nodules, pinpoint in size, composed of fetal squames, vellus hair, fibrin, and fibroblasts. Related to oligohydramnios

Amniotic rupture sequence (ARS): Sporadic condition and does not recur. Distinguished from malformations in syndromic setting; clefts do not follow anatomic lines of closure, asymmetrical lesions, abnormal amnion attachments, strands, entanglements. Amniotic surface of placenta may be necrotic/absent, reactive granulation tissue in chorion. Anomalies include encephalocele, body and facial clefts, constrictor ring (Streetor band)

Amoebiasis: Multiple flask-shaped ulcers in colon with extensive necrosis, minimal inflammatory reaction, phagocytosed erythrocytes. Hepatic abscess has anchovy paste appearance. Phase contrast microscopy of a wet stool sample to detect organisms with ingested erythrocytes

Anencephaly: Open neural tube in cephalic region, absent cranial vault, bulging of eyes, exposed degenerating neural tissue in skull floor

Angelman syndromes: del(15), developmental delays, neurological problems, seizures, happy puppet, frequent/unexpected laughter

Apert syndrome: Craniosynostosis, midline hypoplasia, symmetric syndactyly of hands and feet, hearing loss

Atavism: Rudimentary development of an anatomic structure known to have been present in the phylogenetic ancestor, anatomic structure/trait reappearing that had disappeared generations back, e.g., vestigeal tail

Autosomal recessive polycystic kidney disease: Bilateral kidney enlargement and retention of fetal lobulation, elongated cysts of collecting ducts, associated congenital hepatic fibrosis

BAPP: β-amyloid precursor protein stain confirms the hypoxic/traumatic axonal injury pattern

Battledore placenta: Marginal cord insertion in the placenta—associated with hypercoiling and stillbirth

Beckwith-Weidemann syndrome: Large body size, hemihypertrophy, large organs, umbilical hernia, macroglossia, grooves on ear lobule, cytomegaly of adrenal cortex, Wilms tumor

Bone in rickets: Growth plate shows abundant osteoid that may extend into the metaphysis, fragmentation and fraying of epiphysis on x-ray. Skull has ping-pong ball sensation on touching away from the suture lines (craniotabes)

Brain in Down syndrome: Neurofibrillary tangles similar to Alzheimer brain

Branchial arch syndromes: Hemifacial microsomia, Goldenhar syndrome, and Treacher Collins syndrome

***C-Kit* gene:** Encodes tyrosine kinase that is required for melanoblast migration

Campomelic syndrome: Bent femurs

***Candida albicans* infection:** Rounded white spots (1–2 mm) on the umbilical cord

Cat eye syndrome: Trisomy 22p, downslanting palpebral fissures, hypertelorism, ocular coloboma, preauricular skin tags/pits

Cebocephaly: Most extreme variant, single median eye with varying duplication of intrinsic ocular structures, arrhinia, and proboscis (protrusion from forehead) formation; noted with alobar holoprosencephaly

Cephalhematoma: Accumulation of blood between skull and external periosteum. Confined by the sutures of skull bones

Cephalocele: Herniation of brain or meninges through a defect in the skull

Chagas disease: *Trypanosoma cruzi* in fetal vessels in the villi of placenta, giant cell transformation

Chain of custody: Procedure established to verify the possession of an object from the time it is collected until it is offered into evidence in court

CHARGE association: Coloboma, heart defects, choanal atresia, mental retardation, genital hypoplasia, ear anomalies

Chignon: Circumscribed area of edema and hemorrhage in the vertex of skull—due to suction facilitated delivery

Child abuse prevention and treatment act (P.L 93-247): Abuse and neglect are defined as, "the physical or mental injury, sexual abuse, negligent treatment, or maltreatment of a child under the age of 18 by a person responsible for the child's health or welfare under circumstances which indicate that the child's health or welfare is harmed or threatened thereby."

Confined placental mosaicism: Survival advantage to the trisomic zygote

Congenital gigantism of toes: Neurofibromatosis

Congenital syphilis: Hydrops fetalis, pneumonia alba with gummatous necrosis, osteochondritis, enchondritis, morbilliform rash on skin

Conradi-Hunermann syndrome: Chondrodysplasia punctata of patella

Craniosynostosis: Premature fusion of one or more sutures of skull. Most mutations for major craniosynostosis syndromes are on *FGFR2*

Crouzon syndrome: Craniosynostosis, maxillary hypoplasia, shallow orbits, and ocular proptosis

Currarino syndrome: AD disorder. The triad includes partial sacral agenesis, presacral tumor (anterior meningocele, enteric cyst, or teratoma) and anorectal malformation. S1 and half of remaining sacrum is spared giving rise to "scimitar sign" on imaging. Mutations in *HLXB9* gene

Cystinosis: Cystine crystals, kidney shows glomerular sclerosis, hyalinization and fibrosis

Cytogenetics of complete mole: Diploid XX or XY; all paternal

Cytogenetics of partial mole: Triploid XXY, XXX, XYY; paternal and maternal

Death cases that need to be reported to the medical examiner/coroner: All sudden/unexpected deaths, all child deaths outside hospital, deaths in emergency room, and all unnatural deaths

Death due to drowning: Hemorrhage of petrous bone

Deformation and disruption: Extrinsic interruption of normal development

Diffuse chorioamnionic hemosiderosis: Complication of circumvallate membrane insertion—due to persistent marginal bleeding

DiGeorge syndrome: Velocardiofacial syndrome, del(22q11.2). Parathyroid hypoplasia/aplasia, hypocalcemia, thymic hypoplasia, outflow tract anomalies of heart and anomalies of lower face

Dysplasia and malformation: Intrinsic abnormalities of primordium

Elfin facies: Williams syndrome, idiopathic hypercalcemia

Epiglottitis: Secondary to *Haemophilus influenzae* infection

Erb palsy: Injury to the fifth and sixth cervical roots of brachial plexus. Traumatic delivery related

Exstrophy of bladder: Risk of development of neoplasia of bladder several decades after birth

Farber disease: Multiple skin nodules

Fetal alcohol syndrome: Telecanthus, absent philtrum and thin vermillion border of upper lip

Flow cytometry: Useful in perinatal pathology in two scenarios: diagnosis/typing of congenital leukemias and in the classification of suspected triploidy/tetraploidy. Performed on the dissociated cells of fetus or placenta

Fragile X syndrome: *FMR-1* gene, CGG nucleotide repeat. Large floppy ears, macroorchidism, mental retardation

Friderichson-Waterhouse syndrome: Fulminant infection with *Haemophilus influenzae* and *Neisseria meningitides*, hemorrhagic infarction of bilateral adrenal glands

Gastroschisis: Premature ablation or disruption of omphalomesenteric artery

Gaucher cells: Histiocytes in bone marrow have "crinkled tissue" appearance due to cytoplasmic striations

Goldenhar syndrome: Malformed ear, micrognathia, bilateral cleft lip/palate, agenesis of thumb

Group B streptococcal (GBS) pneumonia: Mimics hyaline membrane disease in preterm infants. Gram-positive bacterial colonies in the membranes

GSD type II: EM; dense lysosomes filled with glycogen

GSD type IV: Storage material in the cells is diastase resistant, pectinase labile

Hanhart complex: Oral involvement, micrognathia and limb defects

Hemifacial microsomia: Abnormal ear, asymmetric jaw

Hemosiderosis of liver: Iron overload. Iron staining confined to Kupffer cells and there is no tissue damage

Holoprosencephaly: Developmental defect with impaired midline cleavage of embryonic forebrain. Graded into alobar, semilobar, and lobar types

Homicidal suffocation: Pulmonary siderophages may be seen

Hurler syndrome: MPS type I, coarse facial features, prominent supraorbital ridges and depressed nasal bridge

Hyperthermia: Core body temperature greater than 40°C

Hypothermia: Core body temperature lesser than 35°C

Immediate cause of death: Complication of the initial disease or injury that ultimately leads to death

Infants born to diabetic mothers: Macrosomic, pancreatic islets are enlarged with large hyperchromatic beta cells, calcified thrombi in renal veins

Intervillous space: Preservation of intervillous space in massive perivillous fibrin deposition while in placental infarction the perivillous space is collapsed

Jeune thoracic dystrophy: Asphyxiating thoracic dystrophy, very small thorax, and extreme pulmonary hypoplasia. Lethal in infancy

Klinefelter syndrome: 47, XXY, tall males with gynecomastia and arachnodactyly. Testes have atrophic tubules and hyperplastic clusters of Leydig cells

Klumpke paralysis: Injury to the seventh and eighth cervical roots and the first thoracic nerve root. Traumatic delivery related

Krabbe disease: Globoid cells in white matter leukodystrophy, demyelination of nerve cells

Lesch-Nyhan syndrome: Hyperuricemia, gouty arthritis, choreoathetosis, spasticity and self-mutilation

Limb body wall complex: Vascular disruption believed to be the cause. Marked deformation of fetus including thoracoschisis, abdominoschisis, facial cleft, severe scoliosis, pseudoencephalocele, internal structural anomalies, short umbilical cord with placenta adherent to viscera

Lisch nodules of iris of eye: Neurofibromatosis

Livor mortis: Postmortem purple discoloration of skin and internal organs that develops in the dependent portions of the body. It is deep-purple red in asphyxia deaths and bright cherry-red in deaths due to carbon monoxide/cyanide poisoning/snow

LSD-induced embryopathy: Skeletal defects and microcephaly

Maceration: Retained dead fetus in utero; skin slippage, heme staining of skin, relaxation of autolyzed muscles

Malformation syndromes: Mandelian or chromosomal in origin

Manner of death: The circumstance under which death occurred. Five types: natural, accidental, homicide, suicide, and undetermined

Marfan syndrome: Dislocation of lens of eye, cystic medionecrosis, dissection of aortic wall

Mechanism of death: Physiological derangement or biochemical disturbance (produced by the cause of death) that is incompatible with life

Meckel-Gruber syndrome: Abdominal distension due to renal multi-cystic dysplasia, encephalocele, polydactyly of hands and feet

Menkes syndrome: *ATP7A* gene involved. X-linked recessive trait. Defect in intestinal copper absorption with low serum levels of copper and ceruloplasmin. Child has coarse kinky hair (pili torti)

Mesenchymal dysplasia: Anomalous villous stromal development. Hydropic chorionic villi, villous cisterns, stromal hypercellularity, generalized villous hypovascularity. Beckwith-Wiedemann syndrome may be associated

Metachromatic leukodystrophy: Accumulation of cerebroside sulfate, EM of white matter neuron; prismatic/tuffstone inclusions

Minor abnormalities of Down syndrome: Epicanthal folds, anteverted nares, single palmer crease, clinodactyly (absent middle crease) of fifth finger

Molar triploidy: Diandry, paternal origin, symmetrical IUGR, partial hydatidiform molar placenta

Monoamniotic twins: Cord complications include cord knots, entanglements, cord braiding, leading to asphyxia of fetuses

Monozygotic twins: Display discordance for major malformations

Neonatal hemochromatosis: AR, advanced congenital cirrhosis, iron overload in hepatocytes. Less involvement of biliary epithelium and Kupffer cells

Neurenteric cysts: Congenital cysts intraspinal and extramedullary found in contact with CNS. Lined by GI mucosa

Neurogenic arthrogryposis: Due to exposure to hyperthermia in early gestation

Neuronal ceroid lipofuscinosis: EM; granular osmiophilic deposits, curvilinear bodies, fingerprint profiles

Niemann-Pick disease: Histiocytes in bone marrow have "soap bubble" appearance of cytoplasm

Non-molar triploidy: Digyny, maternal origin, severe asymmetrical IUGR, syndactyly of fingers and toes, non-molar hypoplastic placenta

Non-disjunction: Failure of homologous chromosomes or sister chromatids to segregate properly during cell division

Oculocerebrorenal syndrome of Lowe: Hydroureters and hydronephrosis. Congenital cataract, metabolic acidosis, and mental retardation

Otocephaly: Extreme mandibular hypoplasia, microstomia, and synotia

Parvovirus B19 inclusions: Found in fetal erythroid precursors. Amphophilic inclusions displace chromatin to the nuclear margin and cells are enlarged

Pentalogy of Cantrell: Due to abnormal development of septum transversum during fourth week of development. Clefting/agenesis of distal sternum, diaphragmatic hernia, midline ventral abdominal defect/omphalocele, defective apical pericardium and its communication with peritoneal cavity, ectopia cordis

Persistent cloaca: Any type of persistent connection between bladder, rectum, and/or vagina. May be found in both sexes

Phenytoin embryopathy: Hypertelorism, micrognathia, microcepahy, depressed nasal bridge

Placental changes after intrauterine death of fetus: Karyorrhectic debris in blood vessels, vascular septation, villi with collapse of blood vessels, hyalinization, collapse of maternal vascular space

Placental infarcts: Pregnancy-induced hypertension, maternal thrombotic disorders

Placental malaria: Parasitized maternal red cells can be seen

Plagiocephaly: Asymmetric skull

Polysplenia: Associated with laterality defects and complex congenital heart defects

Polysplenia field defect: Asplenia, dextropulmonary isomerism, bowel malrotation

Potter facies: Posteriorly rotated low set ears, small receding chin, beaked nose

Potter sequence: Renal agenesis deformations, decreased fetal urine and oligohydramnios, exaggerated facial creases, cutis laxa, beaked nose, bowing of legs

Prader-Willi syndrome: del (15), marked obesity, hypogenitalism, small penis, and cryptorchidism

Proximate cause of death: Initiating disease or injury leading to events that terminate in death

Prune belly syndrome: Absent/hypoplastic abdominal wall muscles, bladder outlet obstruction, hypoplasia of kidneys

Rigor mortis: Postmortem rigidity and stiffness of muscles due to muscle contraction. Loss of ATP from muscle cells with increase in lactic acid

Roberts syndrome: Phocomelia of upper limb, cleft lip/cleft palate

Robin sequence: Cleft palate, micrognathia and glossoptosis

Rubella-induced congenital changes: Congenital defects of eyes, heart, pulmonary branch stenosis, hepatic cirrhosis, PDA, chronic encephalitis, amyloidosis of pancreatic islets, fetal death

Rubeola (measles): Associated with malnutrition and vitamin A deficiency. Morbilliform confluent skin rash, Warthin-Finkeldey giant cells (multinucleated giant cells with intranuclear inclusions) in the lymphoid tissue of body, subacute sclerosing panencephalitis

Schisis association: Anencephaly and omphalocele

Scurvy: Bony changes; failure of deposition of intercellular ground mesenchymal tissue by fibroblasts, osteoid tissue by osteoblasts, thin cortex, and trabeculae

Sequences, isolated defects and field defects: Multifactorial in origin

SIDS: Intrathoracic and multiple pinpoint thymus petechiae may be seen. Liver may show increased extramedullary hematopoiesis

Sirenomelia: Fusion and varying degrees of hypoplasia of lower extremities

Smith-Lemli-Opitz syndrome: Cystic kidney and pancreatic giant cells

Staphylococcal scalded skin syndrome: Mimics severe burns on the body and there is extensive fluid and electrolyte imbalance

Stickler syndrome: Severe myopia, mutation in *COL2A1* gene

Sturge-Weber dysplasia: Unilateral vascular malformation of face (trigeminal nerve distribution) and the body

Subgaleal hemorrhage: Delivery-related hemorrhage between the fibrous aponeurosis of scalp and periosteum of skull. Hemorrhage extends over suture lines and overlies multiple skull bones

Syndactyly: Syndactyly of the third and fourth fingers is suggestive of triploidy

Tay-Sachs disease: EM; membranous concentric bodies

Tessier classification: Classification system in which various unusual types of bony and soft tissue facial clefts are described

Thanatophoric dysplasia: Prominent forehead, shallow nasal bridge and rhizomelic limbs

Thanatophoric dysplasia, type I: Curved femurs and flat vertebrae

Thanatophoric dysplasia, type II: Straight femurs, not so flat vertebrae, craniosynostosis and cloverleaf skull

Thymus in Down syndrome: Hassall corpuscles are large, cystic, and calcified

Translocation: Transfer of genetic material between non-homologous parts of two chromosomes. May be balanced (no net gain or loss of diploid chromosomal content), unbalanced (net gain or loss of translocated portions of chromosomes), or Robertsonian (centric or pericentric translocation of an acrocentric chromosome)

Transverse digital reduction defects: Complication of chorionic villous sampling (performed before 10 weeks' gestation)

Trisomy 13: Midline facial defects (cleft lip, premaxillary aplasia), hypotelorism and polydactyly, micromulticystic kidneys, increased fetal lobulation, heterotopic pancreas in duodenum, defects over vertex of scalp, arrhinencephaly, alobar holoprosencephaly, absent corpus callosum bilateral cleft lip/palate, postaxial polydactyly of hands, penile chordee

Trisomy 16: Common in embryos and fetuses that abort early in pregnancy

Trisomy 18: Micrognathia, low-set ears, omphalocele, marked intrauterine growth retardation (IUGR), overlapping fingers, rocker bottom feet, multivalvular heart defects, camptodactyly (fixed flexion deformity of one or more fingers)

Tuberous sclerosis: Multiple angiomyolipomas in kidney, cerebrocortical tubers with pachygyria, glial nodules in ventricles, angiofibromas of face

Turner syndrome: 45, X karyotype. Pterygium colli, edema on dorsum of hands and feet. Skin shows increased thickness of subcutaneous connective tissue without increase in lymphatic channels

Twin zygosity: Monozygotic twins can be monochorionic or dichorionic. Dizygotic twins are always dichoronic

Twin-to-twin transfusion (prenatal): Donor twin is small, anemic, and flexed due to oligohydramnios. Recipient twin is large and plethoric

Type II Pfeiffer syndrome: Cloverleaf skull, broad thumbs, and great toes

Tyrosinemia: Micronodular cirrhosis and hepatocellular carcinoma

Umbilical artery catheterization: May be complicated by occlusive thrombus of abdominal aorta and iliac arteries with infarcts of kidney/bowel/gangrene of lower limbs

Untrained CPR: On a young infant can cause injuries such as rib fractures, facial bruises

VATER/VACTERL association: Vertebral, anal, trachea-esophageal, renal, and limb anomalies that occur frequently together. Cardiac defects occur in VACTERL. Fanconi anemia should be excluded by chromosome breakage studies

Velamentous cord insertion: Cord insertion in the placental membranes—associated with chorionic plate fetal vascular thrombosis and stillbirth

Vital reaction: Tissue response to injury (histologic/histochemical change) that may not be visible to the naked eye

Vitamin A deficiency: Conjunctival xerosis and perifollicular keratosis

WAGR syndrome: del(11p), Wilms tumor, aniridia, ambiguous genitalia, and mental retardation

Warfarin embryopathy: Nasal hypoplasia

Wilson disease: *ATP7B* gene involved. Levels of hepatic copper elevated and liver and serum ceruloplasmin diminished. Kayser-Fleischer ring in eye, liver cirrhosis, lenticular degeneration with lesions in basal ganglion

Wolf-Hirschhorn syndrome: Terminal deletion of chromosome 4p, prominent forehead and glabella, heart, and renal anomalies

Wolman disease: Gastrointestinal mucosa contains a large population of lipid-laden histiocytes on oil red O stain

Glossary of Organ System Pathology

Abnormalities of systemic venous connections: Large azygous or hemiazygous vein indicates interruption of IVC; also known as azygous continuation of IVC. An absent innominate vein may predict persistent left superior vena cava which mostly drains into the coronary sinus

Acanthosis nigricans: Cutaneous manifestations of large number of diseases, patchy dark thick velvety skin

Achondroplasia: AD mutation in *FGFR3*. Homozygous and heterozygous patients display normal trunk length, narrow chest, large head, and severe rhizomelic shortening of extremities. Disorganization and retardation of physeal growth plate

Acute rheumatic heart disease: Acute fibrinous pericarditis

Agenesis of corpus callosum: Complete ACC or partial (the posterior part composed by body and splenium is absent). Overlying cingulate gyrus may also be absent. ACC associated with other CNS anomalies

Agyria/lissencephaly (type I): Total absence of convolutions (smooth brain), associated craniofacial anomalies and neurologic impairment, widely open sylvian fissure. Abnormal lamination of cortex with four layers instead of six

Aicardi syndrome: Genetic malformation syndrome of brain characterized by partial or complete absence of corpus callosum, retinal abnormalities, and infantile spasms

Alagille syndrome: AD disorder, mutation in *JAG1* gene. Multisystem disorder with syndromic paucity of intrahepatic bile ducts

Alkaptonuria: Aortic valve cusps and endocardium are heavily pigmented

Alport syndrome: Hematuria and high-frequency deafness among affected families. X-linked inheritance

Alveolar capillary dysplasia with misalignment of pulmonary veins: In the alveolar septa, capillaries are deficient in number and are separated from alveolar space. Pulmonary veins accompany bronchovascular bundle and share the same connective tissue sheath in centroacinar space. Complicated by pulmonary hypertension

Amniotic fluid and meconium aspiration syndrome: Sign of intrauterine fetal distress. More likely seen in term or post-term fetuses

Anaplastic large cell lymphoma: Mature T-cell phenotype, t(2; 5) *ALK* gene involvement, CD30+. Tumor cells are anaplastic in appearance

Anencephalic infants: Extremely small hypoplastic adrenal glands

Annular pancreas: Ring of pancreatic tissue completely encircling the duodenum. Association with Down syndrome

Anti-oncogenes: Suppress the formation of tumors. *Retinoblastoma (RB)* gene is an oncogene and if lost, increased susceptibility to retinoblastoma

Aphakia: Congenital absence of the lens

Area cerbrovasculosa: Angiomatous mass containing numerous CSF-filled cavities, replacing normal brain in anencephaly.

Arnold-Chiari malformation: Type II is the most frequent. Hydrocephalus with increase in head size at birth. Cerebellar vermis displaced in the upper cervical canal, hypoplasia of cerebellum, elongated pons and medulla with cavitation, Z-shaped deformity of lower medulla due to overriding the upper spinal cord

Arrhythmogenic right ventricular dysplasia: Fatty infiltration of the right ventricular myocardium on biopsy. Clinically, ventricular tachycardia, left bundle branch block, and RV dilation

Askin tumor: Ewing/PNET family, tumor of the chest wall, t(11;22), mutation of gene *EWS*

Asplenia bilateral right sidedness (right atrial isomerism): Absent spleen (Ivemark syndrome), nucleated RBCs in peripheral smear, bilateral trilobed lungs and bilateral eparterial bronchi, atria are isomeric with appendages of morphologic right type in both. High mortality rate and difficult surgical correction

Ataxia-telangiectasia: Progressive cerebellar ataxia, conjunctival and facial telangiectasia, sensitivity to ionizing radiation, and predisposition to malignancies. Elevated serum AFP. Chromosomal breakage and instability

Autoimmune hepatitis: Positive ANA, anti-smooth muscle autoantibodies. Interface and intralobular lymphoplasmacytic infiltrates

Autosomal dominant polycystic kidney disease (ADPKD): Manifest in adulthood but rarely in childhood. Gene involved is *PKD2* encoding polycystin-2. Kidneys may be normal in size to enlarged, rounded cysts (up to 3 cm in size), derived from any part of nephron or collecting ducts, scattered throughout cortex and medulla

Autosomal recessive polycystic kidney disease (ARPKD): Infantile polycystic kidney disease, protein product of involved gene is fibrocystin. Bilateral symmetrically enlarged reniform kidneys with radially oriented 1–2 mm cortical and medullary fusiform to rounded cysts (dilated collecting ducts). Associated with pulmonary hypoplasia, oligohydramnios, Potter sequence, and congenital hepatic fibrosis

Basophil counts: Fairly constant during life (children and adults) unless there is hemorrhagic disturbance or infection

Beckwith-Wiedemann syndrome: AD transmission. Chromosome 11p15. Cytomegaly of adrenocortical cells and increased risk of developing adrenocortical carcinoma, Wilms tumor, and hepatoblastoma. Creased ear lobe with posterior helical pit, macroglossia, and omphalocele

Bernard-Soulier syndrome: Hereditary qualitative platelet disorder with mild to moderate thrombocytopenia and presence of mucocutaneous bleeding. Defect in BSS is defect/decrease of GPIb complex. Platelets are enlarged with abnormal clustering of granules, abnormal platelet function tests, and prolonged bleeding time. Platelets show an abnormal aggregation response to ristocetin

Biliary atresia: Loss of patency of the lumen of extrahepatic biliary tree. It is a necroinflammatory progressive process leading to obstruction of the lumen and loss of biliary flow. Surgical treatment with portoenterostomy (Kasai procedure) = better if performed within 60 days of birth

Blue rubber bleb nevus syndrome: Vascular malformations on skin, GI tract, and other organs leading to intestinal bleeding and chronic anemia

Bone tumors: Conditions predisposing to bone tumors are previous radiation, bone infarction, Paget disease, chronic osteomyelitis, metallic implants

Branchial cleft cyst: Remnants of branchial clefts, appear later in childhood/adolescence. Lateral side of face/neck, preauricular cysts, sinuses, tags. Lined by stratified squamous/respiratory epithelium. Wall contains cartilage, lymphoid tissue, or mucinous glands

Bronchopulmonary dysplasia (BPD): Complication of treatment of RDS. Predisposing factors; premature infant with surfactant deficiency, barotrauma, oxygen toxicity, inflammation, and pulmonary edema. Surfactant therapy has decreased the incidence of BPD

Buphthalmos: Enlarged eye due to raised intraocular pressure. May be associated with infantile glaucoma

Burkitt lymphoma: Endemic (African) or sporadic. Endemic involves bones of face while sporadic involves GI tract. Common in immunocompromised children. Mature B-cell phenotype expressing cell surface CD19, CD20, CD22, CD10, BCL-6, and cell surface IG. Translocation involves *C-MYC* gene t(8;14). Tumor cells are mature appearing with uniform size and shape, coarse cytoplasmic vacuolization, starry-sky appearance (infiltrating macrophages with apoptotic debris), high Ki-67 staining (99%)

Campomelic dysplasia: Chondro-osseous dysplasia, 46, XY gonadal dysgenesis, female phenotype

Carney syndrome: AD inheritance. Myxomas of heart, skin, and other organs, lentiginous skin pigmentation, endocrine overactivity. Mutations of *PRKAR1A* gene

Caroli disease: Congenital dilatation of intrahepatic bile ducts

Cat scratch disease: Caused by an organism *Bartonella henselae* (causative agent of bacillary angiomatosis in HIV patients). Lymph nodes display necrotizing granulomatous lymphadenitis with follicular hyperplasia, stellate microabscesses. Caused by bite or scratch of a cat

CDA type 2: Also known as hereditary erythroblastic multinuclearity with a positive acidified serum lysis test or HEMPAS. It is the most common type of congenital dyserythropoietic anemia

Chediak-Higashi syndrome: Primary immunodeficiency with susceptibility to bacterial and viral infections, partial oculocutaneous albinism. Peripheral blood neutrophils show presence of large cytoplasmic granules. Cytotoxic activity of NK cells is reduced

Choledochal cyst: Congenital segmental dilatation of bile ducts, hyperbilirubinemia

Cholesteatoma: Mass/lesion in middle ear/mastoid area. Arises from squamous rests (congenital form) or from ingrowth of squamous epithelium in middle ear after multiple episodes of otitis media and perforation of tympanic membrane. Lined by epidermis and contains cholesterol crystals

Chordee: Ventral midline fibrous band causing curvature of the penis

Choristomas: Tissue histologically normal for a part or organ, other than the one in which it is located. For example, brain tissue in lungs of anencephalic infants

Chronic granulomatous disease: Linked to problems of phagocytic intracellular respiration due to defective or reduced NADPH oxidase. Increased risk of infection by catalase positive microorganisms, recurrent bacterial and fungal infections involving skin, bones, LNs, and viscera. Catalase inhibits the activity of peroxidase and H_2O_2. Tissue shows infiltration by histiocytes that may be multinucleated and laden with yellow-brown pigment. X-linked inheritance, boys affected by disease

Cicatrices: On forearm, legs, and digits. Caused due to amniotic bands

CNS tumors linked to heritable disorders: NF1 (neurofibromas, MPNST, optic nerve gliomas, astrocytomas), NF2 (schwannomas, meningiomas, spinal ependymoma), Von Hippel-Lindau (hemangioblastoma of cerebellum), tuberous sclerosis (subependymal giant cell astrocytoma), Cowden (Lhermitte-Duclos), Gorlin (medulloblastoma), Turcot (medulloblastoma and GBM)

Coagulation system: Divided into five elements: vascular endothelium, circulating platelets, coagulation factors, coagulation inhibitors, and fibrinolysis

Coats disease: Retinal telangiectasia with leakage of vessels causing an exudative retinal detachment

Cochlear damage: Damage to cochlea/vestibular ganglia may be caused by massive intraventricular and intracerebral hemorrhage in newborn

Cockayne syndrome: Progeria-like syndrome with postnatal growth failure, premature senescence, and multiorgan failure. Mutations in *CSA* and *CSB* genes

Coloboma: Sporadic/trisomy 13/CHARGE syndrome/ intrauterine exposure to LSD.

Arise from failure of closure of optic (embryonic) fissure at fifth embryonic week. Typical colobomas located inferonasally and may involve the iris, ciliary body, chorioid, and optic disc

Congenital adrenal cortical hyperplasia (adrenogenital syndrome): Ambiguous genitalia in the newborn. Most frequent cause is 21-hydroxylase deficiency (most common and salt-losing form. Diagnosed by elevated serum levels of 17-hydroxyprogesterone). Other enzymes involved are 11-hydroxylase and 17-hydroxylase deficiency. Elevated serum ACTH, androgens, and aldosterone

Congenital cholesteatoma: Superior portion of middle ear, medial to intact tympanic membrane. Conductive hearing loss. Cystic epithelial remnant of embryonic origin

Congenital heart block: Manifestation of neonatal lupus erythematosus. Transplacental transfer of anti-RO/LA antibody (anti-SSA, anti-SSB, and anti-RNP)

Congenital hepatic fibrosis: Usually associated with autosomal recessive polycystic kidney disease. Bridging portal fibrosis containing numerous dilated biliary structures (ductal plate malformation). Infant dies in early life due to pulmonary hypoplasia secondary to intrauterine oliguria and oligohydramnios

Congenital nephrotic syndrome of Finnish type (CNF): Occurs worldwide, AR inheritance trait. *NPHS1* gene mutations. Mesangial hypercellularity, tubular microcysts and late glomerular sclerosis. *EM*: Thin GBM with focal splitting. Develops in fetus, elevated AFP in amniotic fluid, enlarged placenta. Steroid nonresponsive proteinuria

Congenital pulmonary airway malformation (CPAM): Proliferative lesion presenting in newborn or stillborn infants. Type I show mucogenic cell clusters along walls of larger cysts. Type 2 lesion may show rhabdomyomatous dysplasia and may be seen in extralobar lung sequestration

Congenital pulmonary lymphangiectasis: Dilated lymphatics surrounded by loose connective tissue expand the interlobular septa and subpleural space. Complicated by chylous pleural effusion

Cornea: Five layers of cornea from outer to inner include epithelium, Bowman layer, stroma, Descemet membrane, and endothelium

Cronkhite-Canada syndrome: Multiple juvenile polyps throughout the GI tract, alopecia, hyperpigmentation

Cryptophthalmos: Also known as ablepharon. Embryonic lid folds fail to develop. Conjunctiva, cornea, and lid folds are replaced by skin

Cryptorchidism: Failure of testicular descent to the scrotum

Cryptosporidium: Protozoan that causes watery diarrhea. On mucosal biopsy of small or large intestine; small oocysts, 2–5 μ, attached to the microvillous border of intact enterocytes

Dandy-Walker malformation: Dilatation of the fourth ventricle and hypoplastic/absent vermis. Associated with other CNS or extra-CNS defects

Denys-Drash syndrome: 46, XY phenotypic males. Testicular and renal dysgenesis, Wilms tumor, dysfunction of WT-1 during late stage of development

Diffuse large B-cell lymphoma: Associated with immunodeficiency states, mature B-cell phenotype, expression of cell-surface immunoglobulins as well as CD19, CD20, CD22, and CD79a

Diffuse mesangial sclerosis: Congenital nephrotic syndrome with postnatal clinical onset. *WT-1* gene mutations. May be associated with Denys-Drash syndrome. Prominent mesangial sclerosis with tubular microcysts. *EM*: Irregularly thickened GBM with thin lamina densa and mesangial sclerosis. AFP not elevated and placenta not enlarged (except in Drash syndrome). Steroid non-responsive proteinuria

Duodenal atresia: Associated with Down syndrome

Dysgenetic gonads with tumors: Most common tumor is gonadoblastoma, histologically benign but has a potential to become malignant. The second-most common tumor is germinoma. Patients have a 46, XY, 46, XY/45, X mosaic karyotype. They are phenotypically female with/without masculinization

Dysostoses: Malformation of individual bones either singly or in combination

Ear pits: Lobular crease and posterior pits of ear are seen in BW syndrome

Ebstein malformation: Large dilated right atrium secondary to marked tricuspid regurgitation. Displacement of the tricuspid valve into the right ventricle

Ectopia lentis: Dislocation of eye lens due to zonular rupture. May be seen in Marfan syndrome, homocystinuria, and trauma

Ectrodactyly: Congenital absence of all or part of fingers and toes; split hand/lobster claw hand

Embryonal rhabdomyosarcoma botryoides: Cervix and upper vagina, grape-like appearance, primitive rhabdomyoblasts, cambium cell layer

Epulis: Also known as gingival granular cell tumor of the newborn. Located in alveolar ridge of newborn. Unlike other granular cell tumors it is S100-ve

Erythema toxicum neonatorum: Erythematous macules and pustules in skin of newborn, disappears in 4 to 5 days. Intense eosinophilic infiltration

***ETV6-NTRK3* fusion gene:** t(12;15) identified in secretory carcinoma of breast, congenital fibrosarcoma, and cellular mesoblastic nephroma

Exencephaly: Absence of skull/calvarium and the malformed brain is protected by thick duramater like membrane

Familial adenomatous polyposis (FAP): AD, numerous colorectal adenomatous polyps. Mutations in *APC* gene. Prophylactic colectomy to prevent malignancy

Fanconi anemia: Congenital anemia with marrow red cell aplasia and pancytopenia. AR trait associated with abnormal chromosome breakage. Multiple other associated non-hematopoietic anomalies in the body

Fetal circulation: Three shunts that permit most of the blood to bypass liver and lungs; ductus venosus, foramen ovale, and ductus arteriosus

Fibrolipomatous hamartoma of nerve: Macrodactyly and involves median nerve

Focal nodular hyperplasia: Well-demarcated liver tumor with central stellate scar

Follicular cysts of ovary: Found commonly in fetus and newborn. Thin-walled cysts may be several centimeters in size, lined by luteinized theca and granulosa cells. Cause unknown

Frasier syndrome: Chronic renal failure. Dysfunction of WT-1 in early stage of development. 46, XY gonadal dysgenesis in phenotypic female

Gardner syndrome: FAP associated with soft tissue tumors such as osteomas of face, skull, fibromas, and desmoids

Gartner duct cysts: Found in cervix, uterus, lateral walls of vagina, broad ligament. Lined by columnar epithelium and represent remnants of mesonephric ducts

Giardia: Watery diarrhea, malabsorption, transmitted from person to person. Small curved trophozoites attach above the surface of small bowel epithelial cells

Glanzmann thrombasthenia: Hereditary qualitative platelet disorder with defect in GPIIB/IIIA integrin fibrinogen receptor. Normal platelet counts and morphology but prolonged bleeding time and poor adhesion of platelets. Clinically manifested by mucocutaneous bleeding, GI tract bleed, and epistaxis

Gonadal dysgenesis with Y chromosome: Susceptible to develop gonadoblastoma and germinoma

Goodpasture syndrome: Pulmonary hemorrhages and rapidly progressive glomerulonephritis, anti GBM antibodies in capillaries

Gorlin syndrome: Also known as nevoid basal cell carcinoma syndrome. AD inheritance. Prone to develop keratocysts

of the jaw, multiple basal cell carcinomas of skin, and medulloblastoma

Graft versus host disease: Common complication of allogenic bone marrow transplant. More common in HLA nonidentical recipients. Caused by donor T-cytotoxic lymphocytes (CD8+). Skin, GI tract, and liver involved. May be fatal in one third of bone marrow transplant cases. Differential diagnosis is with drug therapy, infection, chemotherapy effect

Hamartomas: Excessive localized overgrowth of mature cells (same level of maturity as other cells in that organ/tissue) with disorganized/altered growth pattern. For example, rhabdomyoma of heart

Hematogones: Found in bone marrow of infants/young children. Immature lymphoid cells with scant blue cytoplasm, round nucleus with fine chromatin and small nucleoli. Immature B-cell phenotype expressing TdT, CD10, CD19, and variable CD20 and cell surface immunoglobulin expression. Increased in bone marrow with solid tumors, ITP, and following chemotherapy

Hemophagocytic lymphohistiocytosis (HLH): Primary (familial), AR disorder with mutations of perforin gene. Bone marrow, LNs, and viscera show histiocytic proliferation with hemophagocytosis. Histiocytes express S100 and CD68. Other clinical features should also be present: fever, thrombocytopenic anemia, abnormal LFTs, increased ferritin levels, and hyperlipidemia. Prognosis is bad with a rapid downward course. Secondary HLH may be associated with a wide variety of infections

Henoch-Schonlein purpura: Follows streptococcal or viral respiratory infection. Palpable purpura, arthritis, and abdominal pain. Vasculitis with deposition of IgA in affected dermal and glomerular vessels

Hereditary sideroblastic anemias: X-linked inheritance, dimorphic red cells, iron stains show ringed sideroblasts ≥15% of erythroid precursors

Hirschsprung disease: Congenital intestinal pseudo-obstruction. Absence of ganglion cells in the submucosal and myenteric nerve plexus. Nerve trunk hypertrophy is present. ACE stain and calretinin stain confirm the diagnosis

Holoprosencephaly: Cephalic disorder in which the prosencephalon (forebrain of the embryo) fails to develop into two hemispheres. Three types: alobar, semilobar, and lobar

Hydatid of Morgagni: Remnant of paramesonephric ducts, found in males

Hydrometrocolpos: Develops secondary to atresia of vagina and imperforate hymen

Hyperinsulinemic hypoglycemia: Seen in infants of diabetic mothers. Atypical islet cells, nesidioblastosis with marked proliferation of islet cells from pancreatic ducts. Changes may be focal or diffuse

Hypertrophic cardiomyopathy: Myocardial fibers are in disarray, short, stubby with boxcar hyperchromatic nuclei

Hypoplastic left heart complex: Most common congenital heart disease that is incompatible with extrauterine life. Mitral valve stenosis/atresia, small atretic LV with endocardial fibroelastosis, aortic stenosis, hypoplastic ascending aorta

Idiopathic infantile arterial calcification: Genetically inherited, extensive calcification and stenosis of large/medium-sized arteries, aorta, and coronary arteries involved, cardiac enlargement, myocardial necrosis. Mostly fatal by 6 months of age

Incontinentia pigmenti: Skin shows eosinophilic spongiosis and intraepidermal eosinophil containing vesicles

Infective endocarditis: In valvular damage or abnormality with high gradient turbulent flow. Consist of fibrin, platelets, and necrotic debris admixed with infectious organisms. Alpha-streptococcus and *Staphylococcus aureus* are the most common

INI-1 expression loss: Deletion or mutation of *INI1* gene on 22q11.2. CNS atypical teratoid/rhabdoid tumor, medullary

carcinoma of kidney, epithelioid sarcoma, renal rhabdoid tumor

Iniencephaly: Confluence of cranial and spinal cavities

Interstitial lung disease: Surfactant protein deficiency = SP-B, SP-C, and ABCA3 (most common) deficiency. Histologically, pulmonary alveolar lipoproteinosis and interstitial thickening of alveolar septa. In *ABCA3* mutations; EM shows distinctive small dense abnormal lamellar bodies

Intestinal duplication: Most common in ileum and colon, mesenteric border

Iron deficiency anemia: Nutritional deficiency, blood loss (fetomaternal hemorrhage, twin-to-twin transfusion). Microcytic-hypochromic anemia with increased ovalocytes and anisopoikilocytosis, elevated RDW, transferrin levels and total iron binding capacity (TIBC). Reduced serum iron, iron saturation, and serum ferritin levels

Ivemark syndrome: Two types—one type shows renal-pancreatic-hepatic dysplasia. The other type shows asplenia and visceroatrial heterotaxy but no liver disease

Jejunal and ileal atresias: Mesenteric vascular accidents during early development. The necrotic segment later gets resorbed and organized—"String of sausages"

Juvenile myelomonocytic leukemia (JMML): Myelodysplastic/myeloproliferative disease, monosomy 7. Proliferation of granulocytic/monocytic precursors, dysplasia in erythroid/megakaryocytic lines. Children ≤3 years of age. Peripheral blood monocytosis, blasts ≤20% of WBC in blood and bone marrow and no evidence of Philadelphia chromosome

Kartagener syndrome: Immotile cilia syndrome, sinusitis, bronchiectasis, situs inversus, male infertility. Defect in ciliary structure with absence of mucociliary transport. EM of cilia; absence of both inner and outer dynein arms, absence of spoke heads, absence of one or both central microtubules/central sheath

Kasabach-Merritt syndrome: Congenital giant cavernous hemangiomas, infantile hemangioendotheliomas, thrombocytopenia

Kawasaki disease: Also known as mucocutaneous lymph node syndrome. Clinically resembles scarlet fever. Lymph nodes show small vessel fibrin thrombi with associated patchy infarcts. Complicated by multisystem florid necrotizing arteritis and aneurysms of coronary arteries

Keratoconus: Degenerative disorder of eye in which there is non-inflammatory structural change within the cornea causing it to be thin and bulging anteriorly in a conical shape. Refractive errors and visual impairment. Autosomal recessive inheritance. May be associated with Ehlers-Danlos syndrome

Kikuchi-Fujimoto disease: Also known as histiocytic necrotizing lymphadenitis. Benign, necrotizing lymphadenitis (mostly cervical), self-limited, painless, and may be associated with fevers. Circumscribed para cortical necrotizing lesions with karyorrhectic debris, fibrin deposits, and plasmacytoid monocytes. Absence of neutrophils and plasma cells in infiltrate

Klinefelter syndrome: Most common form of male hypogonadism, small testes, oligospermia/azoospermia, gynecomastia. 47, XXY karyotype. Tendency to develop germ cell tumors in mediastinum, retroperitoneal, and pineal gland

Klippel-Feil syndrome: Short neck and reduced neck mobility due to abnormal cervical vertebrae

Klippel-Trenaunay-Weber syndrome: Hemangioma on an extremity with focal gigantism of affected part and bone deformity

Kostmann syndrome: Severe congenital neutropenia, with maturation arrest at promyelocyte or myelocyte stage. AR trait

LADD (lacrimoauriculodentodigital) syndrome: Partial to complete absence of salivary glands and lacrimal glands/puncta, ear, and dental anomalies and digital malformations

Langerhans cell-type malignant histiocytosis: Sheets of atypical histiocytes with pink homogenous cytoplasm, lobulated nuclei with central nuclear grooves, expression of CD1a and S100, prominent infiltrate of eosinophils

Large floppy ears: 5p deletion (cat cry) syndrome

Lead poisoning: Microcytic hypochromic anemia (lead interferes with porphyrin synthesis) with prominent basophilic stippling of erythrocytes on peripheral blood smears. Free erythrocyte protoporphyrin (FEP) levels in blood are extremely high

Limbal dermoid: Corneal solid choristoma of the cornea. Histologically comprised of non-keratinized epithelium, hair follicles, and sebaceous glands. Associated with Goldenhar syndrome

Lymphoblastic lymphoma: Majority derived from precursor T cells (T-LBL). Anterior mediastinal mass or cervical lymphadenopathy. Blasts have inconspicuous cytoplasm and fine nuclear chromatin. Immunophenotype is precursor T-cell type with expression of TdT. B-LBL is less common and exhibits precursor B-cell immunophenotype with expression of TdT and absence of surface IG but presence of cytoplasmic IG

Macrotia (large ears): Fragile X syndrome

Maffucci syndrome: Two or more enchondromas associated with hemangiomas in skin, soft tissue, or viscera. Commonly develop malignancies in viscera and in enchondromas

May-Hegglin anomaly: Triad of giant platelets, thrombocytopenia, and Dohle bodies in neutrophils (basophilic inclusions in cytoplasm)

McCune-Albright syndrome: Genetic disorder of bones, skin pigmentation, precocious puberty, and endocrine diseases

Meckel-Gruber syndrome: AR inherited lethal condition. Occipital meningoencephalocele, bilaterally enlarged multicystic kidneys, polydactyly, congenital hepatic fibrosis

Meconium ileus: Ileal obstruction from viscid and inspissated meconium. Manifestation of cystic fibrosis

Meconium periorchitis: In utero perforation of bowel with escape of meconium to tunica vaginalis and inflammatory reaction. Should be differentiated from a tumorous mass or torsion

Meconium peritonitis: Rupture of viscus in utero, release of meconium in peritoneum and marked foreign body giant cell reaction, keratinized epithelial cells, calcification with fibrosis

Mesonephric (Wolffian) ducts: Form the male genital tract (epididymis, ductus deferens, and ejaculatory ducts). Development is dependent on presence of testes that produce androgens and müllerian inhibitory substance (MIS). MIS causes regression of paramesonephric ducts also in males

Metastases of maternal neoplasm to fetus: Melanoma can metastasize from mother to fetus through placenta

Microcytic-hypochromic anemias: Reduced red cell counts and elevated red cell distribution width (RDW) is suggestive of iron deficiency anemia while normal to high red cell counts and normal/low RDW is consistent with thalassemia

Microtia (small ears): Lacking lobule are seen in Down syndrome or oculoauriculovertebral syndrome

Microvillous inclusion disease: AR disorder. Secretory diarrhea at birth or soon thereafter. Histology of small intestinal biopsy; total villous atrophy with lack of crypt hyperplasia, CD10-positive inclusions. EM; characteristic inclusions of microvilli in the cytoplasm of enterocytes

Miliaria: Pinpoint white papules on skin of forehead, cheeks, and nose. Contain keratinaceous and colloid material

Mixed lineage leukemias: *MLL* gene is found at chromosomal locus 11q23. *MLL* leukemias have sufficient expression of both myeloid and lymphoid markers on their blasts so that a specific lineage (myeloid or

lymphoid) cannot be assigned. Another type is when an ALL may express both B- and T-cell antigens simultaneously. The expression of markers may be simultaneous in the same blast population (biphenotypic) or may be present in two different blast populations of the same patient (bilineal)

MURCS association: Müllerian duct aplasia, renal agenesis/ectopia, cervicothoracic somite dysplasia, Klippel-Feil anomaly, deafness, short stature

Nanophthalmos: Microphthalmos (very small axial length of eye) with no major internal disorganization of the globe. There is a proportional, symmetric decrease in all the internal structures. Risk of developing glaucoma and patients are farsighted

Nasal glioma: Ectopic sequestered glial tissue, should be differentiated from basal encephalocele

Neonatal alloimmune thrombocytopenia (NAT): Transplacental crossing of maternal alloantibodies (against fetal platelets) with platelet destruction. May be seen in first pregnancy and there is risk of intracranial bleeding at birth. HPA-1a is the most common alloantigen

Neonatal necrotizing enterocolitis (NEC): More common in terminal ileum, cecum, and right colon. Transmural necrosis, distension, pneumatosis intestinalis, fibrosis, strictures, and obliteration of bowel

Nephrogenic rests: Abnormally persistent foci of embryonal cells that have capability to develop into nephroblastomas. May be perilobar or intralobar. Presence of nephrogenic rests in a patient with Wilms tumor is indicative of Wilms tumor in the contralateral kidney also

Neural tube defects: Increased maternal alpha-fetoprotein levels between 16 and 18 weeks' gestation and increased amniotic fluid acetylcholinesterase throughout pregnancy

Neuroblastoma: Most common malignant tumor of fetus and infant. N-myc and ras oncogenes are found. Deletion of chromosome 1p36

Non-compaction of the left ventricle: Grossly, the left ventricular myocardium shows deep trabeculations, spongy myocardium. May predispose to fatal cardiac arrhythmias

Normal bronchial morphology: Normal right bronchus is small and eparterial in relation to the right pulmonary artery. Normal left bronchus is long and hyparterial in relation to the left pulmonary artery

Normocytic anemias: Congenital hemolytic anemias (hemoglobinopathies, red cell enzyme defects, disorders of red cell membrane) and acquired hemolytic anemias (antibody mediated hemolysis and microangiopathic hemolytic anemias). Other causes include parvovirus B19 infection, pure red cell aplasia (Diamond-Blackfan anemia), and aplastic anemia

Ollier disease: Skeletal disease with two or more enchondromas. Tumors arise in medullary cavity, cortex, or surface of bone. May convert into chondrosarcoma

Oncogenes: Genes required for normal growth of cells, present in all the animal cells. When oncogenes are altered, unregulated growth occurs. Oncogenes impart certain properties to tumor cells: growth advantage, rapid proliferation, and ability to metastasize

Osteogenesis imperfecta: Osteochondrodysplasia with abnormal bone density. Inherited mesodermal defect with osteopenia, blue sclera and multiple bone fractures. Mutation of *COL1A1* gene

Osteopetrosis: Also known as marble bones. Osteoclast dysfunction with poor bone remodeling. Bones are dense and compact but brittle and prone to fractures

Otitis media: Due to aspiration of amniotic fluid through nasopharynx in asphyxiated babies. The fluid then reaches middle ear via Eustachian tube producing foreign body reaction, polypoidal lesions, otitis media, and squamous metaplasia of mucoperiosteum

Otosclerosis: Bone deposition around stapes causing fixation to oval window. Conductive hearing loss, AD, inner ear condition

Ovarian fibromas: May be associated with basal cell nevus (Gorlin) syndrome

Overgrowth syndromes: Include Beckwith-Wiedemann, Elejalde, Sotos, Perlman, Weaver, Proteus, Bannayan-Riley, and Cowden syndromes

Pachygyria: Rare and broad gyri on brain surface

Paramesonephric (müllerian) ducts: Form the female genital tract (fallopian tubes, uterus, and cervix). Development is not dependent on the presence of ovaries/ovarian hormones

Parvovirus B19 infection: Acute self-limited red blood cell aplasia due to transient arrest of erythropoiesis. There is reticulocytopenia and diminished hemoglobin. Bone marrow shows giant pronormoblasts with absence of later erythroid forms, eosinophilic viral nuclear inclusions surrounded by halo, absence of inflammatory reaction. Tropism of parvovirus for antigen P is seen on RBC precursors

Pendred syndrome: Deaf mutism, hypothyroidism, and probable peroxidase defect

Periarteritis nodosa: Multisystem, focal segmental necrotizing inflammation of small and medium-sized muscular arteries

Periventricular leukomalacia: Hypoxic-ischemic necrosis of the white matter, premature infants

Perlman syndrome: AR inheritance. Visceromegaly, islet cell hyperplasia, and Wilms tumor

Persistent pulmonary hypertension of the newborn (PPHN): Thickening of muscularis media of small pulmonary arteries and extension of smooth muscle into intraacinar arteries that normally are devoid of muscle

Peutz-Jeghers syndrome: Muco-cutaneous pigmentation and hamartomatous intestinal polyps which have a risk of malignancy in colorectal region. Mutation of *LKB1* gene

Pituitary adenomas: Commonly produce prolactin or ACTH

Polymicrogyria: Abnormal cortical pattern, focal or diffuse, excessive folding of all the layers. May be four layered or unlayered

Polysplenia bilateral left sidedness (left atrial isomerism): Multiple spleens, both lungs are bilobed with bilateral hyparterial bronchi. Better prognosis and defect mostly correctable with surgery

Porencephaly: Congenital cerebral defect with wide communication between the ventricles and surface of brain due to destructive process—"basket brain."

Postaxial polydactyly: Duplication of fifth digit

Posttransplant lymphoproliferative disease (PTLD): Lymphoid hyperplasia and lymphomas that arise in organ transplant recipients (2%–5%) and bone marrow transplant recipients (1%). Risk factors include immunosuppression and primary EBV infection. May arise in nodal or extranodal sites, predominantly B-lymphocytic origin; usually arise during the first posttransplant year. Histologically, range from hyperplastic lesions to atypical lymphoid lesions to lymphomas (NHL). May be polymorphic or monomorphic type and most commonly arise from B lymphocytes. Arise from recipient cells in solid organ transplant patients and from donor cells in bone marrow transplant patients

Preaxial polydactyly: Duplication of thumbs

Primary immunodeficiencies: Three major lethal primary immunodeficiencies in children are chronic granulomatous disease (CGD), X-linked agammaglobulinemia (XLA), and severe combined immunodeficiency (SCID)

Primary lymphoid organs: Bone marrow and thymus produce B and T lymphocytes, respectively

Primary pulmonary hypertension: Pulmonary angiogram shows thickened, short, and stubby vessels

Primary sclerosing cholangitis: Association with ulcerative colitis. Liver shows portal expansion, bile duct proliferation, onion skin fibrosis around bile ducts, neutrophilic infiltrate

Progeria: Accelerated premature aging both in general appearance and occurrence of atherosclerosis, arthritis, coronary heart disease, etc., in the first decade of life. Skin atrophy with absent hair follicles. Mutations in *LMNA* gene

Proteus syndrome: Asymmetric overgrowth, cerebriform connective tissue nevi, epidermal nevi, vascular malformations, dysregulated adipose tissue, lipomas, macrodactyly, macrocephaly, PTEN related

PTEN hamartoma tumor syndrome: Bannayan-Riley/Cowden syndrome have *PTEN* mutations with phenotypic overlap. High birth weight, hypotonia, mental deficiency, macrocephaly, pigmented macules on penile shaft. Multiple lipomas in subcutaneous tissue and hamartomatous polyps in GI tract

Pulmonary alveolar proteinosis: Surfactant protein deficiency. Alveoli filled with homogenous glassy eosinophilic debris which may show needle like spaces

Pulmonary interstitial glycogenosis (PIG): Expansion of interstitium with spindle-shaped cells containing glycogen in cytoplasm (PAS +)

Pulmonary sequestration: Mass of abnormal pulmonary tissue that does not communicate with tracheobronchial tree through a normally located bronchus. Blood supply is by anomalous systemic artery. Intralobar sequestration is within the visceral pleura of lung and extralobar sequestration lies outside the visceral pleura

Radial alveolar count: Number of alveolar spaces from terminal bronchiole to the pleura. Normal RAC is about 5–6 on average. Low counts indicate pulmonary hypoplasia

Ranula: Mucocele of the sublingual gland. Simple ranulas are retention mucoceles located above the mylohyoid muscle. Plunging ranulas are extravasation mucoceles in which mucus penetrates below the level of mylohyoid muscle

Rathke pouch cysts: Cyst of the remnant of Rathke pouch. Lined by ciliated epithelial cells with squamous metaplasia, collagenous wall

Renal tubular dysgenesis: Deficient tubular development in kidneys, glomeruli appear more crowded. The epithelium lining cortical tubules consists of cells lacking histologic features of proximal/distal convoluted tubules. Oligohydramnios and postnatal anuria

Rendu-Osler-Weber disease: Hemorrhagic telangiectasia, AD

Respiratory distress syndrome: Atelectatic lungs and alveolar ducts lined by hyaline membranes (eosinophilic, composed of necrotic epithelial cells and transudated blood constituents)

Retina: Several horizontal layers histologically, from outer to inner include retinal pigment epithelium, outer segments of photoreceptors, external limiting membrane, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer, nerve fiber layer, and internal limiting membrane

Retinopathy of prematurity (ROP): Vasoproliferative retinal disorder, premature infants. Risk factors are supplemental oxygen and low birth weight

Rhabdomyoma: Most common cardiac tumor in fetus and infant. Associated with tuberous sclerosis, typical "spider cells" histologically

Rieger anomaly: Anterior chamber dysgenesis syndrome of the eye; ectopia (displaced pupil), corectopia (deformed pupil), polycoria, iris atrophy, and opacification of cornea. May include other non-ocular anomalies

Rosai-Dorfman disease: Also known as sinus histiocytosis with massive lymphadenopathy. Self-limited disease with benign massive enlargement of lymph nodes. Expansion of sinuses in LNs with reactive histiocytes showing bland

nuclei and abundant cytoplasm containing engulfed lymphocytes (emperipolesis). Histiocytes express S100 and CD68

Sacrococcygeal teratoma: Most prone to develop malignancy (yolk sac tumor)

Scimitar syndrome: Venous connections of all lobes of right lung are anomalous and drain into IVC. On imaging, scimitar-shaped shadow of an anomalous pulmonary vein along right cardiac border

Secondary lymphoid organs: Spleen, lymph nodes, and extranodal lymphoid tissue are the sites of immune reaction and lymphoid proliferation

Severe combined immunodeficiency: Severe fatal primary immunodeficiency in which there is disturbed development of functional B and T lymphocytes due to mutations in multiple genes. Patients are vulnerable to severe recurrent infectious diseases.

Sickle-cell anemia: Qualitative hemoglobinopathy showing presence of HbS (mutation in which glutamic acid of β-globin chain at position 6 is replaced by valine). Clinically manifested by sequestration crisis, veno-occlusive crisis, splenic infarction, aplastic crisis, increased risk of *Salmonella* infection

Stickler syndrome: AD connective tissue disorder, *COL2A1* abnormality. Ocular (high myopia), orofacial, and general skeletal abnormalities. Association with Pierre-Robin anomaly

Streak ovaries in Turner syndrome: Composed of dense ovarian stroma lacking ova and derivatives

Sturge-Weber disease: Disorder of cephalic endothelial neural crest cells. Lymphovenous malformation in the region of trigeminal nerve distribution

Syringomyelia and syringobulbia: Cavities in the spinal cord and medulla, respectively

TAR: Inherited thrombocytopenia disorder with decreased number of megakaryocytes and bilateral absence of radii

Teratomas versus fetus in fetu: Teratomas lack well-defined vertebra or structural organization of tissue components

Testicular regression syndrome: 46, XY individuals. Rudimentary epididymis, nodule of fibrocalcific replacement of testis with hemosiderin deposition, vas deferens ends blindly. This nodule may be localized to scrotum, retroperitoneum, or iliac region. In early regression, fetal testicular dysgenesis occurs

Tethered cord syndrome: Various anomalies of the filum-terminale; absent, shortened, may contain disorganized cord tissue, hamartomas, lipomas

Tetralogy of Fallot: Infundibular pulmonary stenosis, VSD, overriding aorta, right ventricular hypertrophy

Thalassemic syndromes: Decreased synthesis of one of the two globin chains (α or β) of HbA. The α-*globin* gene resides on chromosome 16 and is more prevalent in Southeast Asia. The β-*globin* gene resides on chromosome 11 and is more prevalent in Mediterranean descent

Thanatophoric dysplasia-Type I: Most common form of lethal osteochondrodysplasia

Thyrocervical teratoma: Fetal and infant. Causes maternal dystocia and respiratory distress in newborn. Comprises prominent immature neuroglial tissue (has no bearing on prognosis)

Thyroglossal duct cyst: Develop anywhere along the course of thyroglossal duct from base of tongue to the neck, inferior to hyoid bone. Lined by columnar/respiratory/squamous epithelium. May show chronic inflammation and thyroid tissue in wall

Tracheoesophageal fistula: Most common type is in which proximal esophagus ends in a blind pouch and distal esophagus shows communication with trachea at the region of tracheal bifurcation

Transient myeloproliferative disorder of newborns: Associated with Down syndrome. Mutations of X-linked GATA-1. Presents with transient polycythemia, leukocytosis, and/or thrombocytosis. Blasts include myeloblasts, megakaryoblasts, and erythroblasts. Peripheral blood contains more blasts than bone

marrow. Spontaneous resolution of blood abnormalities in 1–2 months. Increased risk of developing acute megakaryoblastic leukemia

Type IA MEN (Wermer syndrome): Parathyroid hyperplasia/adenoma, parathyroid or GIT neuroendocrine hyperplasia/tumors, pituitary adenoma

Type IIA MEN (Sipple syndrome): C-cell hyperplasia/medullary thyroid carcinoma, pheochromocytoma, pituitary hyperplasia/adenoma

Type IIB MEN (Gorlin syndrome): C-cell hyperplasia/medullary thyroid carcinoma, pheochromocytoma, parathyroid hyperplasia/adenoma

Ulegyria: Small and shrunken gyri with enlarged sulci = mushroom-like appearance of gyri. Caused by hypoxic-ischemic accident

Vaginal adenosis and clear cell adenocarcinoma: Increased incidence is associated with in utero exposure to diethylstilbestrol (DES)

Von Hippel-Lindau disease: Hemangioblastosis in the cerebellum, retina, skin, bones, and viscera. Multiple angiomas in cerebellum surrounded by cyst. May become dysplastic

Von Meyenburg complexes: Biliary microhamartomas, associated with fibropolycystic diseases of liver. Multiple periportal nodules showing proliferation of irregular tortuous bile ducts embedded in fibrous stroma

Waardenburg syndrome: Partial albinism, deafness, Hirschsprung disease

WAGR syndrome: Wilms tumor, aniridia, gonadal dysgenesis, mental retardation

Walker-Warburg syndrome: Type II lissencephaly with agyric brain, thick meninges with milky appearance, small cerebellum, cortical dysplasia, encephalocele and hypoplastic olfactory bulbs

Williams-Campbell syndrome: Congenital bronchiectasis due to deficiency of bronchial cartilage distal to main segmental bronchi

Wiskott-Aldrich syndrome: X-linked disease with mutations of the *WASP* gene. Congenital thrombocytopenia, eczema, bloody diarrhea, and recurrent infections. Platelet abnormalities include small size, thrombocytopenia, decreased platelet specific α-granules, and defective platelet aggregation

X-linked agammaglobulinemia: Boys have severe deficiency of all immunoglobulins, mature B cells, and plasma cells. Susceptible to pyogenic infections of skin and sinopulmonary tract. There is absence of tonsils/adrenals and LNs are atrophic. Mutations of *Bruton tyrosine kinase* (*BTK*) gene

Bibliography

The following is a list of the major resources used in compiling this review course. Additional sources such as journal articles, individual lectures, and so on, have been omitted. The reader is encouraged to consult the listed references below for additional information, photographs, or for a detailed discussion of any of the topics covered in this course. The references listed here are not the only ones that are available in pathology; however, they simply represent what I personally found valuable. During my training, I particularly found that Potter's pathology textbook was outstanding for fetal and infant developmental pathology, and the text from Stocker and Dehner was priceless for the pediatric organ system pathology.

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Section A

Fetal and Infant Developmental Pathology

1 Basics of Molecular Biology and Perinatal Chromosomal Abnormalities

- Lately, molecular medicine has taken a substantial role in diagnostic medicine
- Many of the tests that were performed in the past for diagnosis have been replaced by molecular tests
- An understating of the basic molecular techniques is now essential in the practice of pathology

Applications of molecular medicine

GENETICS

- Routine diagnosis of carriers of various genetic disorders such as cystic fibrosis, fragile X syndrome
- Prenatal diagnosis of status of fetus in families with high risk of diseases

ONCOLOGY

- In high-risk families, detection of carriers of cancer-predisposing mutations like the breast cancer susceptibility gene *BRCA1* and the p53 (Li-Fraumeni syndrome) gene *TP53*, so that appropriate follow-up can be performed
- Certain mutations have an impact on diagnosis (e.g., C-MYC and Burkitt lymphoma), and others determine prognosis and treatment (e.g., N-MYC expression and neuroblastoma)

MICROBIOLOGY

- Polymerase chain reaction (PCR) techniques reduce diagnostic time for microbial assays considerably, compared to traditional methods like microbiological cultures
- PCR may also identify the genes for antibody resistance

MEDICOLEGAL

- Restriction fragment length polymorphisms (RFLPs) may help in identifying a suspect in a crime case with certainty
- Solving paternity issues

Techniques in molecular medicine

PURIFICATION OF DNA

- Purified DNA is required for many molecular techniques
- Cells are lysed → DNA extracted from nuclei → cell debris is removed through chloroform/phenol purification

RESTRICTION ENZYMES

- These enzymes recognize and cut DNA sequences with great specificity
- The enzymes can identify a point mutation if there is a difference of even a single nucleotide
- Restriction enzymes can recognize and cut sequences ranging from 4 to 12 nucleotide base pairs

SOUTHERN BLOTTING

- DNA extraction → purification → digestion → electrophoresis in agarose gel → transfer to a membrane (nylon or nitrocellulose) → hybridization with a probe (radioactive or enzyme-linked segments of DNA or RNA) to determine the presence or absence of DNA sequences of interest → radioactive probe is then read using a radiographic film
- A lengthy technique, diagnosis takes very long regardless of clinical urgency, large quantities of DNA are required

RESTRICTION FRAGMENT LENGTH POLYMORPHISM

- The RFLP technique is used to distinguish both the alleles of a gene of interest
- By distinguishing the four parental alleles, the carrier status of the fetal alleles can be determined
- In families where parents are carriers of autosomal recessive diseases, the homozygosity or heterozygosity of the fetus can be determined prenatally, by doing a chorionic villous biopsy
- Cutting the DNA of parents, affected children, and fetus with restriction enzymes
- In medicolegal cases, suspects can be discriminated with certainty by using a sufficient number of probes
- Determination of father in paternity testing. The implicated father should have all the other electrophoretic DNA bands of the child, which are not of maternal origin
- The length of restriction fragments varies from one allele to the other and is also due to point mutations
- Restriction fragment length polymorphism can also be demonstrated through PCR

DOT BLOT

- Does not require digestion or electrophoresis of DNA
- A drop of DNA is placed on a membrane and directly hybridized with a probe
- Multiple samples can be tested at once
- Much faster technique than Southern blotting

ALLELE-SPECIFIC OLIGONUCLEOTIDES

- Probes can be constructed to differ by only one nucleotide
- One probe recognizes the normal allele, and the other will recognize the mutant allele

DNA MICROARRAYS

- cDNA is used to identify and quantify the genes of interest
- Patient's DNA is labeled in green and the same quantity of control DNA is labeled in red
- Mixture is then hybridized onto the microarray
- If equimolar quantities of test and control DNA are present, there will be a yellow signal (equal combination of red and green)
- If the test DNA is in excess, signal will be green (trisomy 21, N-MYC amplification)
- If the control DNA is in excess, signal will be red (del p53, del 5p syndrome)

GENE EXPRESSION MICROARRAYS

- Determine the degree of expression of genes of interest
- DNA is digested with DNAse → residual RNA converted to cDNA using reverse transcriptase → cDNA is labeled in green → hybridized onto microarray → intensity of signal correlates with gene expression

SINGLE NUCLEOTIDE POLYMORPHISMS

- Study the differences involving only one nucleotide in a specific sequence, with probes specifically identifying these variations
- Assay of the whole genome through microarrays, rather than studying a single gene on a membrane (differential diagnosis [d/d] ASO)
- Useful for assays of trisomy, monosomy, and loss of heterozygosity (LOH) in tumors

FLUORESCENT IN SITU HYBRIDIZATION

- Identifies segments of chromosomes spread onto a slide using probes
- Chromosomes can either be in metaphase or interphase
- Quantitative fluorescence in situ hybridization (FISH) to determine the number of genes in a cell
- Several types of probes can be used

FUSION PROBES

- Detect balanced translocations, when two translocation partners are anticipated
- BCR-ABL translocation of Philadelphia chromosome in leukemia

BREAK-APART PROBES

- Series of two probes, each labeled in a different color
- In oncogenic translocation, one probe hybridizes to one segment immediately above the break point, and the other hybridizes immediately below that locus
- MLL gene translocation in leukemia

WHOLE CHROMOSOME PAINTING

- Multiple same color probes used to hybridize different portions of the entire length of a pair of chromosomes
- Metaphase spread is visualized and translocations studied

SPECTRAL KARYOTYPING

- Every chromosome is painted with a different color probe (22 colors for autosomes, 1 color for X chromosome, 1 color for Y chromosome)
- Can only be used in metaphase
- Powerful technology but very expensive

COMPARATIVE GENOMIC HYBRIDIZATION

- Technically complex diagnostic modality
- Test DNA labeled in red; control DNA labeled in green
- Both DNAs mixed in equimolar concentrations, hybridized to normal metaphase spread (chromosome-based CGH) or chips (chip-based CGH)
- Surplus of red signal in a chromosomal region = duplication in that region
- Surplus of green signal = deletion in that region
- Chip based better (cheaper, faster, and more sensitive) than chromosome based

NEWER GENERATION CHIPS

- Combine standard CGH (comparative genomic hybridization) and SNP (single nucleotide polymorphism) probes
- Used and being developed for a large variety of diseases
- Will revolutionize clinical genetics, oncology, pharmacology, and pathology in the future

NORTHERN BLOTTING

- Studies the mRNA rather than DNA
- Determines the genes that are transcribed or active in a tissue, gene expression profiling, etc.

WESTERN BLOTTING

- Studies the cellular protein expression through gel electrophoresis

POLYMERASE CHAIN REACTION

- Reveals presence or absence of small sequences of DNA
- DNA from cells suspended in solution containing primer nucleotides (A, T, G, and C) and DNA polymerase (Taq polymerase)
- At high temperature, dsDNA converted to ssDNA → cooled and annealed with primers → polymerase synthesizes the new strands of DNA → multiple cycles performed to increase the fragments of DNA exponentially → electrophoresis

NEXT GENERATION SEQUENCING

- Also known as massively parallel sequencing; millions of small fragments of DNA can be sequenced simultaneously, creating a massive pool of data
- Provides information on numerous genes at the same time
- Molecular profile of a tumor sample can lead to identification of an alteration suggesting best drug treatment/clinical trial (stratified/personalized medicine)

- Various sequencing techniques; pyrosequencing, Illumina, SOLID sequencing, Sanger sequencing
- Drawbacks; management/storage/reviewing/scientific interpretation of vast amount of generated computer data is needed

Comparison of PCR to Southern blotting

- PCR is fast, technically less complex, inexpensive
- Requires minute DNA quantities, amplifies short segments of DNA
- Large number of samples assayed simultaneously
- PCR can only be performed if the gene sequence is known (as primers are required)

Reverse transcriptase-polymerase chain reaction (RT-PCR)

- Modification of PCR
- Messenger RNA (mRNA) converted to cDNA with reverse transcriptase
- cDNA amplified with PCR
- Conveys information about gene transcription

Synopsis

DNA-based tests (Southern, PCR, CGH, and SNP)

- Detect the number of copies of a gene in a cell
- Detect whether the alleles are normal or not

Tests assessing gene expression (Northern, RT-PCR, Western, and RNA-based microarrays)

- Detect whether or not the gene is transcribed/active

Traditional cytogenetic analysis (the karyotype)

- Chromosomes visualized in prophase or early metaphase
- Included features are chromosome size, centromere position, and banding pattern
- Giemsa (G)-banding procedure applied
- Tissue sources: blood (T-lymphocytes), skin (fibroblasts), amniotic fluid (amniotic epithelial cells), and chorionic villous biopsy (trophoblasts)
- Successful cell culture inversely related to postmortem interval
- Very autolyzed stillborn fetuses; placenta may be used for tissue source

Karyotypic disorders

MOSAICISM

- Combination of cells with different chromosomal content

CONFINED PLACENTAL MOSAICISM

- Mosaicism confined to placenta, not affecting the fetus
- Discrepant results between chorionic villous sampling and amniocentesis
- Discrepant placental and fetal karyotypes
- Aneuploid population confined to the trophoblast (type I), chorionic stroma (type II), or both (type III)
- Mitotic non-disjunction in a trophoblastic cell; trisomy in trophoblast or placental stroma
- Most frequent mosaics = (trisomy:diploid) and (45X:diploid) combinations
- Rare disorder, may lead to intrauterine growth retardation (IUGR)

MOSAIC VARIEGATED ANEUPLOIDY

- Mitotic non-disjunction can lead to somatic aneuploidy
- Premature chromatid separation with mosaic variegated aneuploidy (PCS-MVA); several different aneuploid cell populations identified in different body tissues
- Neurological defects, ocular malformations, prone to neoplasia
- Mutations in *BUB1B* gene

AUTOSOMAL TRISOMIES

- Arise from errors during the first meiotic division (meiotic non-disjunction) in the maternal germline

- Most non-mosaic autosomal trisomies = early embryo demise
- Those that survive to term may be placental mosaics
- Trisomy 13, 18, and 21 are compatible with survival to term (high rate of embryonic or early fetal wastage)
- Associated with clinically defined syndromes
- Specific phenotypic features, multiple organ malformations, and mental retardation
- Trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome); worse prognosis than trisomy 21 (Down syndrome)

AUTOSOMAL MONOSOMIES

- Embryos (unless they are mosaic) die before implantation

SEX CHROMOSOME ANEUPLOIDIES

- Monosomy Y cannot exist (at least one X chromosome required for embryo survival)
- Monosomy X, extra copies of X and Y chromosomes; compatible with long-term survival

Monosomy X (Turner syndrome)

- Loss of maternal or paternal sex chromosome during postzygotic mitosis
- Pure 45X females (Turner syndrome) distinct features: Female genitalia, short stature, specific anomalies (cystic hygroma, coarctation of aorta, hypoplastic left heart, cubitus valgus, streak ovaries, horseshoe kidneys), normal-range intelligence
- Mosaic forms (45X/46XY); gonadal dysgenesis, ovotestis

Sex chromosome polysomy

- *Klinefelter syndrome (47XXY karyotype)*: Mild neurocognitive deficits, behavioral problems, hypogonadism, hypogenitalism
- *Super-males (47XYY)*: Aggressive behavior, mild dysmorphic features, mild cognitive deficits

POLYPLOIDY

- *Complete extra haploid set of chromosomes* = triploidy (69 chromosomes), tetraploidy (96 chromosomes)

Diandric triploid conceptions

- Extra set of chromosomes = paternal origin
- Dispermic fertilization of a single oocyte
- Normal fetal growth/moderate symmetrical growth restriction
- Partial molar transformation of placenta (large cystic villi/trophoblastic proliferation)

Digynic triploid conceptions

- Extra set of chromosomes = maternal origin
- Errors in first or second meiotic division
- Severe asymmetric fetal growth restriction
- Small placenta without molar transformation
- Diagnosis of triploidy confirmed faster and less expensively by flow cytometry

PARTIAL CHROMOSOMAL ANEUPLOIDIES

- Structural chromosomal anomalies result in partial duplication (trisomy) or deletion (monosomy) of portions of chromosomes
- Portions of chromosomes may be translocated, duplicated, or lost

TRANSLOCATIONS

Reciprocal translocations

- Between two heterologous chromosomes
- Balanced = two abnormal chromosomes but no net gain/loss of genetic material
- Individuals with balanced translocations are likely to be normal themselves
- Can transmit an unbalanced translocation to their offspring who will be partially monosomic and partially trisomic

Robertsonian translocation

- Translocations involving the acrocentric chromosomes (13, 14, 15, 21, and 22)

- Chromosomes break at centromere; long arms fuse to form a single chromosome, short arms fuse to form reciprocal product (ultimately gets lost)
- May be balanced or unbalanced (Down syndrome, Patau syndrome)

CHROMOSOMAL INSTABILITY DISORDERS

Fanconi syndrome

- Multigene disorder, aplastic anemia, IUGR
- Bilateral radial aplasia with medial deviation of wrist
- Congenital malformations overlap with anomalies of VACTERL (vertebral-anorectal-cardiac-tracheal-esophageal-renal-limb) association
- *FANCA*, *FANCC*, and *FANCG* genes involved

Some other syndromes

CRI-DU-CHAT SYNDROME

- Laryngeal hypoplasia
- 5p syndrome

ROBERTS SYNDROME

- *ESCO2*
- Shortened arm and leg bones, facial anomalies

FRAGILE X SYNDROME

- X-linked dominant with incomplete penetrance, males affected more
- Mental retardation and cognitive impairment
- *FMR1* gene with expansion of CGG trinucleotide repeat. Location Xq27.3

ATAXIA-TELANGIECTASIA

- *ATM* gene mutation

CHARGE SYNDROME

- *CHD7* gene mutation
- Coloboma, heart defect, choanal atresia, brain retardation, genital abnormalities, and ear abnormalities

Selected submicroscopic chromosomal anomalies

DIGEORGE SYNDROME (VELOCARDIOFACIAL SYNDROME)

- del 22q11.2 (hypercalcemia, thymus, and parathyroid hypoplasia, outflow tract defects of heart, anomalies of lower face
- AD trait
- Velocardiofacial and DiGeorge syndrome share craniofacial and conotruncal cardiovascular anomaly
- Deletion diagnosed by FISH or array-based CGH

TUBEROUS SCLEROSIS

- LOH on 9q34 (*TSC1*) and 16p13 (*TSC2*)

ALAGILLE SYNDROME

- del(20) at *JAG1* or *NOTCH2* gene (intrahepatic bile duct paucity and neonatal jaundice)

PRADER-WILLI/ANGELMAN

- Mutation in 15q11-13 region

MARFAN SYNDROME

- Mutations in *Fibrillin-1* gene on chromosome 15q21

DUCHENNE MUSCULAR DYSTROPHY

- Mutation of dystrophin gene at locus XP21

CAT EYE SYNDROME

- (+22p), ocular coloboma, malformed ear and preauricular tag

Subtelomeric deletions

- Diagnosed by FISH with subtelomeric-specific probes and array-based CGH
- Unexplained mental retardation or anomalies
- Deletion 1p36 syndrome

Prenatal diagnosis

DEFINITIVE PRENATAL DIAGNOSIS

- Invasive procedures (e.g., amniocentesis, chorionic villous sampling, etc.) to obtain tissue for cytogenetic studies (karyotype, FISH)

Screening methods

- Based on maternal serum markers (to avoid unnecessary costs/risks associated with prenatal diagnosis)

Integrated tests

- Quantitative measurement of pregnancy-associated plasma proteins in maternal serum; alpha-fetoprotein, unconjugated estriol, free beta-HCG, and inhibin-A
- Early second trimester demonstration of nuchal translucency on ultrasound

2 First and Second Trimester Embryo and Fetal Deaths

- Detailed examination of spontaneous abortion specimen/determination of accurate pathogenesis of pregnancy loss; helps in appropriate reproductive counseling of parents
- 10%–20% of pregnancies result in spontaneous abortions (SAs) in first trimester
- 1%–2% SAs after the first trimester
- Gestational age = developmental age + 2 weeks
- Presence of chorionic villi and/or embryonic/fetal tissue in endometrial curetting/washings; indicative of intrauterine pregnancy/products of conception

Stillbirth

- Delivery of deceased infant around 20 weeks of gestation
- Incidence of stillbirth at term gestation; 0.1%–0.5%
- 5%–10% of stillborn children have chromosomal anomaly
- 0.6%–0.9% of live-born infants have a chromosomal abnormality

Etiology of spontaneous abortions

CHROMOSOMAL ABNORMALITIES

- Most common cause especially in first trimester
- Trisomies (especially trisomy 16), triploidy, and monosomy X
- Cytogenetic analysis important in SA
- Trisomies caused by increased maternal age (due to defects in meiosis)

INFECTIONS

- HIV, parvovirus B19, listeriosis

MATERNAL FACTORS

- Antiphospholipid antibodies/other thrombophilia mutations, hypovolemic shock, fever, chorioamnionitis, retroplacental hemorrhage, uterine developmental anomalies, maternal nutrition/medication, maternal age

PLACENTAL CAUSES

- Intervillositis and perivillous fibrin deposition; immunological causes

Glossary of genetic terms

EMBRYO

- Conception until the end of the eighth week (all major organ systems develop by then)

FETUS

- Ninth week postconception until birth

CONFINED PLACENTAL MOSAICISM

- Different karyotype in placenta compared to other fetal tissues

EUCHROMATIN

- Genetically active

HETEROCHROMATIN

- Genetically inactive

MOSAICISM

- Variation in DNA sequence or chromosomal constitution among different cells of an organism

GERMINAL MOSAICISM

- Mosaicism within the germline, whereby a fraction of the eggs or sperms may contain a particular mutation or chromosomal aberration

SOMATIC MOSAICISM

- Variation in DNA sequence or karyotype among different somatic cells of an organism

HETEROPLASMY

- Different mitochondrial genomes in the same cell; mechanism by which proportion of altered mitochondria may increase in specific tissues to cause disease

IGF

- Insulin-like growth factor

INTRONS

- Non-coding intervening sequences between coding regions of genomic DNA

EXONS

- Coding regions of genomic DNA

LINKAGE

- Tendency of neighboring genes to segregate together in families

MITOSIS

- Process of somatic cell division that produces identical genomes in daughter cells

MEIOSIS

- Process of germ cell division that randomly allots one chromosome of each pair to a gamete

PROTO-ONCOGENE AND ANTI-ONCOGENE

- Equilibrium between expression of proto-oncogene and anti-oncogene at the cell and tissue levels determines their mitotic activity

GENOMIC IMPRINTING

- Differential expression of alleles derived from each parent
- A gene is said to be imprinted when allele received from one parent is transcribed more or less than that received from the other parent
- Gene with a complete maternal imprint has a complete inhibition of its maternal allele, expressing only paternal allele
- Parental imprints can be in some/all body cells
- Parental imprints may be complete/partial

PAX

- Family of nine developmental genes conserved across all the species that contain paired boxes

PC

- Postconception (from the time of fertilization of the zygote)

PCR

- Polymerase chain reaction by which the individual gene segments are amplified through sequential cycles

PHENOTYPE

- Individual physical traits or characteristics

GENOTYPE

- Set of genes in the DNA responsible for physical traits

PLICATION

- Folding of an embryo from flat to tubular structure

PMPs

- Peroxisomal integral membrane proteins

POINT MUTATIONS

- Nucleotide substitutions

REVERSE TRANSCRIPTASE

- Enzyme isolated from retroviruses that synthesize a complementary DNA copy (cDNA) from M-RNA using a 3' primer

ROBERTSONIAN TRANSLOCATION

- Non-reciprocal, joining of two chromosomes (homologous or non-homologous)
- A single recombined chromosome (composed of either two short or two long arms) is produced
- Involves acrocentric chromosomes (13, 14, 15, 21, and 22)
- May be balanced or unbalanced

BALANCED TRANSLOCATIONS

- Reciprocal translocations
- No phenotypic or clinical effects in the individual with translocation
- Reproductive risks with birth of an infant having unbalanced karyotype

UNBALANCED TRANSLOCATIONS

- Loss or gain of genetic material
- Trisomy or monosomy of one of the fused chromosomes occurs

TATA BOX

- DNA segment rich in thymine and adenine allowing initiation of transcription

TM

- Temperature that separates or melts a double-stranded nucleic acid

TRANSVERSIONS

- Purine-to-pyramidine or pyramidine-to-purine substitutions

TRISOMIES/MONOSOMIES

- Cells or tissues with extra or missing entire chromosome

UNIPARENTAL DISOMY

- Two copies of a chromosome pair derived from one parent, for example, Angelman syndrome and Prader-Willi syndrome

Uniparental heterodisomy

- Both the chromosomes of a single parent are represented

Uniparental isodisomy

- Two identical copies of the same parental chromosome are represented

KARYOTYPE

- Organization of all the individual chromosomes in the cell nuclei, from the largest to the smallest with the shorter arm oriented upward

ANEUPLOIDY

- Loss or addition of whole or pieces of chromosomes (always considered deleterious)

TRISOMY

- One whole extra chromosome, caused due to non-disjunction

NON-DISJUNCTION

- Failure of homologous chromosomes/ sister chromatids to separate properly during cell division

MONOSOMY

- Lack of one whole chromosome, caused due to anaphase lag

ANAPHASE LAG

- Delayed movement during anaphase where one homologous chromosome during meiosis or one chromatid in mitosis fails to be included in reforming nucleus

CHIMERA

- Single organism composed of genetically distinct cells derived from two separate zygotes

CHROMOSOMAL MOSAICISM

- Two or more chromosomally different cell lines derived from a single zygote in one individual

DEL

- Deletion

DUP

- Duplication

INSERTION

- Intrachromosomal or interchromosomal

INVERSION

- Two breaks—180-degree rotation. Paracentric (centromere not included) and pericentric (centromere included)

POLYPLOIDY

- More than two haploid sets of chromosomes
- 69 (triploidy), 92 (tetraploidy)

Characteristics of aneuploidy and polyploidy

DEFECTS OF GROWTH

- Embryonic growth disorganization (GD)
- Associated with chromosomal anomalies (trisomy, monosomy, triploidy, tetraploidy)
- Non-hereditary, sporadic, and non-recurrent
- Four types of growth disorganization;
  - *GD1 stage*: Anembryonic sac (empty gestational sac)
  - *GD2 stage*: Nodular embryo, 1–4 mm length (no landmarks, no external features of retinal pigment)
  - *GD3 stage*: Cylindrical embryo, up to 10 mm length (retinal pigment present, no other landmarks)
  - *GD4 stage*: Stunted embryo, 10–15 mm length, distorted body shape

DEFECTS OF BLASTOGENESIS (FIRST 28 DAYS OF DEVELOPMENT)

- Increased monozygotic twinning
- Higher frequency of mid-line anomalies, severe brain and heart anomalies

DEFECTS OF ORGANOGENESIS (29–56 DAYS OF DEVELOPMENT)

- Milder defects than blastogenesis
- Affects single rather than multiple parts of the body
- Meckel diverticulum, persistent urachus, atavisms (recurrence of a trait that is typical of an ancestral form, evolutionary throwback)

DEFECTS OF PHENOGENESIS (57–266 DAYS OF DEVELOPMENT, FETAL STAGE)

- Multiple minor anomalies
- Loss of family resemblance

DEFECTS OF POSTNATAL LIFE

- Neoteny (persistence of juvenile features in adult form), physiological development slowed
- Functional defects, dysplasia, altered hemostasis

Prenatal diagnosis and neonatal testing

TRIPLE SCREEN TEST

- Maternal blood screening test for alpha-fetoprotein (AFP), unconjugated estriol, and beta-HCG
- If positive; indicates high risk of Down syndrome, Edwards syndrome, or neural tube defects
- Performed at 15–18 weeks of gestation

AMNIOTIC FLUID

- Amniocentesis performed at 14 weeks' gestation
- Amniocytes; cytogenetic testing
- Increased amniotic fluid AFP and acetylcholinesterase; indicates open neural tube defects

CHORIONIC VILLUS SAMPLING

- Performed at 9–12 weeks of gestation
- Trophoblasts; cytogenetic testing
- Complication; transverse digital defects

PREIMPLANTATION GENETIC DIAGNOSIS (PGD)

- Performed at 6 days postconception
- Polar body biopsy, blastomere biopsy, blastocyst biopsy

PERIPHERAL BLOOD

- Lymphocytes

SKIN AND SOFT TISSUE

- Fibroblasts

Use of ancillary tests in perinatal pathology

TRADITIONAL CYTOGENETICS—FISH

- Interphase (touch prep, tissue sections, frozen tissue)
- Metaphase (cell culture)
- FISH tests the specific hypothesis about a particular portion of genome, for example, velocardiofacial syndrome del 22q11.2 (DiGeorge syndrome)

SUBTELOMERIC CHROMOSOMAL REARRANGEMENTS

- Detection of facioscapulohumeral muscular dystrophy, Alzheimer disease

COMPARATIVE GENOMIC HYBRIDIZATION (CGH)

- Technique that allows detection of loss/gain of DNA across entire genome
- No prior knowledge of specific chromosome abnormality
- Used to screen loss/gain of particular chromosomal regions

Confined placental mosaicism

- When cytogenetic abnormality is confined to the placenta only and not to the fetal tissue
- Fetus is mostly diploid in all types

TYPE 1

- When aneuploid cells are confined to the trophoblast with chromosomally normal stroma (most common)

TYPE 2

- When aneuploid cells are confined to the chorionic stroma

TYPE 3

- When aneuploid cells are confined to both trophoblast and the stroma

Autosomal trisomies

- Most frequently seen in spontaneous abortions

DOWN SYNDROME (TRISOMY 21)

- *Brain*: Small superior temporal gyrus and large middle temporal gyrus
- *Heart*: Atrioventricular canal defects (atrial septal defect and ventricular septal defect)
- *Hematological abnormalities*: Polycythemia, leukemia (congenital acute myeloid leukemia, acute lymphoblastic leukemia in childhood, acute megakaryocytic leukemia, transient myeloproliferative disorder of infancy)
- *Clinodactyly*: Curvature of fifth finger toward adjacent four fingers
- Single palmer crease and absence of middle crease in fifth finger

EDWARD SYNDROME (TRISOMY 18)

- Triangular facies, microcephaly, micrognathia, hypertelorism, horse-shoe kidney, rocker-bottom feet, overlapping second and third digits, clenched hands

PATAU SYNDROME (TRISOMY 13)

- Midline facial defects, cebocephaly (ocular hypotelorism and single nostril), alobar holoprosencephaly, aplasia cutis, postaxial polydactyly, appendiceal diverticula (dinosaur tail), fusion of spleen and pancreas

TRISOMY 16

- Common in embryos and fetuses that abort early during gestation

Sex chromosome polysomies

- 47XXX—Normal female
- 47XYY—Super male
- 47XXY—Klinefelter syndrome (tall males, gynecomastia, arachnodactyly, atrophic testicles with hypoplastic clusters of Leydig cells). Prone to develop teratomas
- 45X/45XY—Turner syndrome—monosomy X, present as hydrops fetalis (infantile female external genitalia, streak-gonads, co-arctation of aorta, rarely fertile). If mosaicism for Y chromosome → prone to develop gonadoblastoma

Triploidy

- Extra set of chromosomes in the cells

DIGYNIC

- Haploid set from mother
- IUGR (asymmetric), macrocephaly with small and thin limbs
- Placenta very small, hypoplastic with no features of partial mole
- Marked adrenal hypoplasia
- Failure of division during meiosis I or II
- Maternal serum shows decreased estriol and HCG
- Outcome: Spontaneous abortion/stillbirth

DIANDRIC

- Extra haploid set from the father
- Normal or mild symmetric IUGR
- Normal adrenal glands
- Large cystic placenta with features of partial hydatidiform mole
- Fertilization of normal oocyte by two spermatocytes
- Maternal serum shows increased AFP and HCG
- Outcome: Spontaneous abortion

Molar pregnancy

- Should be differentiated from hydropic abortion (degenerative changes)

COMPLETE HYDATIDIFORM MOLE

- Diploid genotype, 46XX or 46XY
- The nuclear genes are inherited from the father only (androgenesis)
- P57 (KIP2) immunostaining of cytotrophoblast and villus stroma = negative because of absence of maternal genome

PARTIAL HYDATIDIFORM MOLE

- Triploid genotype, 69XXY, 69XXX, or 69XYY
- Nucleus contains one set of maternal genes and two sets of paternal genes

- The P57 (KIP2) immunostaining of cytotrophoblast and villus stroma = positive because of maternal haploid genome contribution

Infections

LISTERIOSIS

- Listeria monocytogenes (Gram-positive bacilli)
- Consumption of unpasteurized milk products and processed meats
- Presence of small white abscesses on fetal skin, viscera, and placental villi

VIRAL INFECTIONS SUCH AS CYTOMEGALOVIRUS (CMV)

- Fetal viscera and placenta show lymphoplasmacytic infiltrate and CMV inclusions

Hydrops fetalis

- Common presentation is fetal death in second trimester
- Range of etiology is vast; chromosomal defects, infections, hemoglobinopathies, cardiac arrhythmias, metabolic disorders, and congenital pulmonary airway malformation

Twinning

- Monozygous twins more prone to intrauterine fetal demise due to vascular anastomosis leading to twin-to-twin transfusion syndrome and twin reversed arterial perfusion
- Increased umbilical cord entanglement

3 Congenital Anomalies and Malformation Syndromes

Definitions

CONGENITAL ANOMALY

- Also known as *birth defects*
- Structural/functional anomalies that occur during intrauterine life
- May be identified prenatally/at birth/later in life

SYNDROME

- Well-characterized constellation of major and minor anomalies that occur together in a predictable fashion
- Due to single underlying etiology (monogenic, chromosomal, mitochondrial, or teratogenic)
- For example, Down syndrome

SEQUENCE

- Group of related anomalies arising from a single major anomaly that alters the development of other surrounding or related tissues/structures

Potter sequence

- Oligohydramnios during pregnancy → talipes equinovarus, amnion-nodosum, pterygium, marked sinus webbing

Pierre Robin sequence

- Transient oligohydramnios in early pregnancy
- U-shaped cleft palate, micrognathia, retrognathia, glossoptosis, ear anomalies, and anomalies of oligohydramnios sequence
- Complicated by Stickler syndrome; blindness due to high myopia

ASSOCIATION

- Group of anomalies that occur more frequently together than would be expected by chance alone
- Do not have a predictable pattern of recognition and/or suspected unified underlying etiology

MURCS association

- Müllerian duct aplasia, renal aplasia, cervicothoracic somite malformation

CHARGE association

- Coloboma, heart defects, atresia choanae, retarded growth/development, ear anomalies

MALFORMATION

- Initiated in early developmental process
- Complex and far-reaching consequences
- High recurrence rate in future pregnancies
- For example, alobar holoprosencephaly

DEFORMATION

- Abnormal form or position of a part of the body
- Caused by a non-disruptive mechanical force
- Late in gestation; mechanical forces, caused due to lack of fetal movement
- For example, Potter-type facies due to oligohydramnios

DISRUPTION

- Morphological defect of an organ/part of an organ/larger region of the body
- Results from breakdown of/interference with an originally normal developmental process
- For example, amniotic bands

DYSPLASIA

- Intrinsic cellular architecture of a tissue is not maintained throughout growth and development
- For example, skeletal syndromes of short stature (dysplasia in developing bone/cartilage)

Causes of congenital anomalies

- Environmental teratogenic agents (15%), monogenic (15%), chromosomal (15%), multifactorial (55%)

TYPES OF DISRUPTION AFFECTING MORPHOGENESIS OF FETUS/EMBRYO

- Vascular, anoxia, infection, radiation, amniotic entanglement, teratogenic drugs

Teratogens

- Androgens (clitoral hypertrophy and labial fusion)
- Diethylstilbestrol (vaginal adenosis)
- Goitrogens and iodine (fetal goiter)
- Hyperthermia (anencephaly)
- Radio-iodine (fetal thyroidectomy)
- Tetracycline (teeth staining)
- Thalidomide (eye and ear malformation, limb reduction defects)
- Warfarin (nose hypoplasia, stippling of epiphysis)
- Fetal alcohol syndrome (telecanthus, absent philtrum and thin vermilion border of upper lip)

Vascular causes

Cutis verticis gyrate

- Thrombosis of sinus venosus with necrosis of cerebral cortex and collapse of the skull
- Thickening of the scalp with severe microcephaly

Gastroschisis

- Due to the premature ablation or disruption of ophthalmomesenteric artery

Subclavian artery supply disruption

- Poland sequence, Klippel-Feil syndrome, and Mobius defect
- Sternocleidomastoid muscle and breast hypoplasia

Amniotic disruption

- *Streeter band*: Constriction ring in the ankle due to amniotic disruption sequence

Miscellaneous syndromes

NOONAN SYNDROME

- Autosomal dominant
- No chromosomal anomaly, disorder of unknown cause
- Shares some features of Turner syndrome (cystic nuchal hygroma)

TWIN-TO-TWIN TRANSFUSION (TTT) SYNDROME

- Pale small donor; plethoric enlarged recipient

TWIN REVERSED ARTERIAL PERFUSION SEQUENCE (TRAPS)

- Acardiac co-twin

ZELLWEGER SYNDROME

- Cerebro-hepato-renal dysplasia

APERT SYNDROME

- Acrocephalosyndactyly
- First branchial arch affected
- *FGFR2* gene—two-point mutation

BRACHMANN-DE LANGE SYNDROME

- Growth deficiency, profound mental retardation
- Hirsutism
- Thin downward vermillion border

NEUROFIBROMATOSIS

- Congenital gigantism of toes

MECKEL-GRUBER SYNDROME

- Occipital encephalocele
- Cystic renal dysplasia (collecting ducts)
- Polydactyly

ROBERT SYNDROME (PSEUDOTHALIDOMIDE)

- Limb defects, micrognathia, hypoplastic ear
- *ESCO2* gene defect
- Prominent centromeres in metaphase spread

OVERGROWTH SYNDROMES

- Elejalde syndrome (fibroblasts complete the cycle in less than 63% of normal time)
- Beckwith Wiedemann (sporadic 85%, AD 10%–15%)
- *PTEN* mutations (Bannayan-Riley-Ruvalcaba/Cowden syndrome/Proteus syndrome)

Proteus syndrome

- Asymmetric overgrowth of body parts
- Cerebriform connective tissue nevi, epidermal nevi, vascular malformations, and dysregulated adipose tissue
- Somatic mosaicism hypothesis
- Prone to serous and mucinous ovarian tumors
- Children with increased body size and neoplasia; increased prevalence of tumors such as neuroblastoma, leukemia, Wilms tumor, astrocytoma, osteosarcoma

CRANIOFACIAL ANOMALIES

Anencephaly

- Open neural tube defect in the cephalic region
- Exposed mass of degenerating neural tissue in the skull floor

Rachischisis

- Complete spina bifida; cleft through the entire spinal cord
- Posterior neuropore of the neural tube fails to close by 27th day of gestation
- May occur in association with anencephaly

Encephalocele

- Mostly occipital and midline
- In amniotic-band disruptions—asymmetric encephalocele

Frontonasal dysplasia

- Median bony clefting of frontal or frontonasal region

Holoprosencephaly

- Developmental field defect–impaired midline cleavage of the embryonic forebrain
- *Alobar type*; prosencephalon fails to cleave sagittally into cerebral hemispheres, transversely into telencephalon and diencephalon and horizontally into olfactory tracts and bulbs
- Face predicts the brain 80% of the time; cyclops, arrhinia, proboscis, ethmocephaly, cebocephaly (blind-ended single nostril nose)

Craniosynostosis

- Process of premature sutural fusion

Plagiocephaly

- Asymmetric skull

Crouzon syndrome

- AD, craniosynostosis, maxillary hypoplasia, proptosis, and shallow orbits

Apert syndrome

- Craniosynostosis, mid-face hypoplasia, congenital deafness, symmetric syndactyly of hands and feet

Classic Pfeiffer syndrome

- Cloverleaf skull and syndactyly

Thanatophoric dysplasia

- Type 1 and 2 have a disproportionately large skull

Cleidocranial dysplasia

- Brachycephaly and absent clavicles

- Delayed closure of fontanels and sutures
- Wormian bones

Branchial arch syndrome

- *Hemifacial microsomia*: Affects oral, aural, and mandibular growth (mostly unilateral)
- *Goldenhar syndrome*: Oculo-auriculo-vertebral syndrome, epidural dermoids
- *Treacher Collins syndrome*: AD, bilateral zygomatic hypoplasia, down-slanting palpebral fissures, malformed ears, and micrognathia

Disorders of anterior thoracic and abdominal wall

- *Pectus excavatum*: Funnel chest
- *Pectus carinatum*: Pigeon chest
- *Ectopia cordis*: Abnormal location of heart either partially/totally outside thorax, due to abnormal development of septum transversum
- *Poland syndrome*: Unilateral absence or hypoplasia of pectoralis major muscle. May be associated with hypoplasia of breast, nipple, hand, or digit of that side
- *Jeune thoracic dystrophy*: Lethal in infancy—very long and narrow thorax with extreme pulmonary hypoplasia

Congenital abnormalities and developmental disorders of the breast

- *Amastia* (absence of breast), *Athelia* (absence of nipple), *Hypomastia* (small breast)
- Abnormal epithelio-stromal induction
- Exposure to radiation before puberty can cause breast hypoplasia and fibrosis in children
- *Accessory breast* (polymastia lies within the milk line)
- *Ectopic breast* (polymastia lies outside the milk line)
- *Macromastia*: Virginal breast hyperplasia. Mostly stromal proliferation but sometimes glandular also (unilateral or bilateral). Increased sensitivity of mammary adipocytes, fibroblasts, and epithelial cells to estrogen/progesterone
- *Gynecomastia*: Enlargement of breast in adolescent males. Klinefelter syndrome (47XXY). Induced by estrogen and treated by tamoxifen. Mastectomy if resistant

Abdominal wall defects

NORMAL EMBRYOLOGY

- At 6 to 10 weeks of development; physiological intestinal herniation occurs in the umbilical cord, which regresses at the 10th week
- At 5 to 8 weeks of development; omphalomesenteric duct/vitellointestinal/vitelline ducts normally get absorbed. If they fail to absorb then there is development of Meckel diverticulum. Complications include bleeding, perforation, peritonitis, bowel intussusception
- Umbilical cord attaches at the region of umbilical ring
- Right and left umbilical ligaments are obliterated bilateral umbilical arteries
- Normally at 33 weeks right umbilical vein atrophies in the placenta
- Round ligament is the obliterated umbilical vein

PATHOLOGICAL DISORDERS

Umbilical granuloma

- Drains small amount of serous and serosanguinous fluid

Umbilical hernias

- Direct: 5% of individuals have neither a round ligament nor umbilical fascia, closing the umbilical ring
- Indirect: When round ligament fails to cover the ring and it is only covered by umbilical fascia. By 5 to 6 years of age the hernia is mostly reduced spontaneously

Omphalocele/Exomphalos

- Viscera herniated into the umbilical cord through the umbilical ring

- Viscera is covered by amnion and peritoneum
- Abnormal karyotype—most frequent is trisomy 18
- Complication is peritonitis when amnion ruptures

Gastroschisis

- Defect is lateral to the umbilical ring; both the umbilical ring and the cord are normal
- Viscera are encased in a gelatinous mass (no sac)
- Defect to the right of the umbilical cord, liver not herniated
- Vascular etiology suspected
- Non-syndromic and non-lethal (unlike omphalocele)

Inguinal region

NORMAL EMBRYOLOGY

- In males, internal inguinal ring closes after descent of testis in scrotum through processus vaginalis, during the seventh and the eighth months of gestation
- Obliterated canal forms fibrous band while scrotal portion is lined by mesothelium
- Fluid-filled tunica vaginalis lies around the anterior portion of testis

PATHOLOGICAL DISORDERS

Indirect congenital inguinal hernia

- Failure of closure of processus vaginalis results in hernia (intestines and other viscera herniate)
- Common in cryptorchidism and prematurity
- Right-sided more common

Acquired indirect inguinal hernia

- Failure of upper portion of processus vaginalis to close
- Blind peritoneum lined sac (not lined by tunica vaginalis)

Littre hernia

- Meckel diverticulum in hernia sac

Hydrocele

- Failure of closure of only the lower end of processus vaginalis

Direct hernia

- Defect of abdominal wall (4%)
- Edge of rectus abdominis

Meconium peritonitis

- Due to in utero rupture of the bowel wall
- If there is a patent processus vaginalis, meconium leaks into scrotum and presents as hemiscrotal mass—*meconium periorchitis* (d/d neoplasm)

Cryptorchidism

- Risk of malignancy and infertility remains even after orchiopexy

Appendix testis

- Aka hydatid of Morgagni—vestige of the müllerian duct
- Located in the upper pole of testis
- Minute, sessile, oval structure
- Torsion of appendix testis reveals an edematous and congested testicular stroma leading to hemorrhagic infarction later

Amnion rupture sequence and limb body wall complex

- Normal amnion fuses with chorionic plate by 12 weeks postconception
- Failure of the amniotic membrane to fuse with chorion—strips of membrane floating within the amniotic cavity

LIMB BODY WALL DEFECT (LBWD)

- Defect develops earlier during gestation
- Thoracoabdominoschisis, exencephaly, or encephalocele with facial defects, limb defects
- Rupture leads to defect in the body stalk—very short umbilical cord
- Amnion and chorion are affected due to vascular disruption
- Traction by the short cord—scoliosis

- Vascular disruption—Diaphragmatic hypoplasia/aplasia
- Generally sporadic, but alcohol and smoking can predispose

AMNION RUPTURE SEQUENCE (ARS)

- Defect develops later during gestation
- Nature of defect depends on location of amniotic band
- Interference with normal development
- Clefts in ARS do not follow normal lines of closure, asymmetrical
- Amniotic surface of placenta absent/necrotic

BACK AND PERINEUM

Primary neurulation

- Conversion of neural plate into a cylindrical tube (between second and fourth week after fertilization)

Secondary neurulation

- Occurs beneath the epidermis
- Neural tube caudal to the site of caudal neuropore forms beneath the epidermis
- Open neural tube defects do not extend to the caudal sacrum
- Closed neural tube defects (tethered cords, lipomas) common in the terminal sacral region
- Caudal eminence is pluripotential and gives rise to teratomas

Hindgut derivatives

- Descending colon, rectum, urinary bladder, urethra, and lower vagina
- Cloaca (terminal part of hindgut) communicates with allantois via urachus
- Urachus involutes after fifth month of fetal life and persists as medial umbilical ligament
- Cloaca partitioned into rectum and urogenital sinus by urorectal septum (coronal sheet of mesoderm)

Rachischisis

- Defect in the spinal column involving the posterior part of the vertebrae

Spina bifida occulta

- Spinal cord defect, skin and subcutaneous tissue are intact

Spina bifida aperta

- Spinal cord defect, absent skin and subcutaneous tissue

Spondylothoracic dysplasia

- Dysplasia of the thoracic vertebra associated with fusion, branching, ectopia, or agenesis of adjacent ribs

Vertebral anal cardiac tracheoesophageal renal limb (VACTERL) association

- Associated with maternal diabetes mellitus/sporadic
- Differential diagnosis with Fanconi anemia (AR, overlapping features, diagnosed by chromosomal breakage studies)

Neurenteric cysts or fistulae

- Rare congenital cysts, in contact with central nervous system (CNS), lined by gastrointestinal/respiratory mucosa
- Intraspinal/extramedullary location
- Closed/occult spinal dysmorphisms without mass effect
- Lower cervical, thoracic, or thoracolumbar
- Associated anomalies; dermal sinuses, intradermal lipomas, tight filum terminale

Persistent cloaca

- Severe form of anorectal anomaly
- Any type of persistent connection between urinary bladder, vagina, and rectum
- Results from incomplete septation of embryonic cloaca by urogenital septum
- Association with talipes, scoliosis, and other deformities (intrauterine constraint perhaps from amnion involvement)
- *Males*: Ambiguous genitalia associated. Mostly a fistulous connection between bladder and rectum with imperforate anus
- *Females*: Bladder, vagina, and rectum all open into one common opening

Exstrophy of the bladder

- Anterior wall of bladder and overlying ventral body wall are defective
- Bladder lumen exposed inferior to umbilicus
- Bladder mucosa lined by squamous, columnar, and glandular structures
- Exstrophy-epispadias complex
- Patients with exstrophy may later develop neoplasia like adenocarcinoma and squamous cell carcinoma

Cloacal exstrophy

- Anterior wall of persistent cloaca absent
- Overlying portion of the abdominal wall absent
- Omphalocele, exstrophy, imperforate anus, spinal anomaly

Urachal anomalies

- *Urachal cyst*: Lined by transitional/cuboidal epithelium (versus vitelline remnants lined by intestinal epithelium)
- *Persistent urachus*: Urine through the umbilicus

Anorectal abnormalities

- Anal stenosis, imperforate anus

Prune-belly syndrome

- Triad of congenitally deficient abdominal musculature, urinary tract anomaly, and cryptorchidism in males
- Bladder outlet obstruction is cause of triad
- In fetus—taut and distended abdomen
- In infant—wrinkled and deflated abdomen

Caudal dysgenesis

- Caudal duplication (duplication of the pelvic organs, sacrum)
- Caudal dysplasia (sacral dysgenesis—dysplasia, hypoplasia, or absence of sacral vertebrae)

Currarino syndrome

- Partial sacral agenesis, presacral tumor (anterior meningocele, enteric cyst, presacral teratoma) and anorectal malformation

Sacral dysgenesis with lower extremity anomalies—Sirenomelia

- Associated with maternal diabetes mellitus
- Renal agenesis with imperforate anus and malformed external genitalia
- Single umbilical artery arising from abdominal aorta

Significant malformations in infants of diabetic mothers

- *CNS*: Microcephaly, anencephaly, holoprosencephaly
- *Craniofacial*: Cleft lip/palate, ear anomalies
- *Cardiovascular system*: Ventricular septal defect, transposition of great vessels, situs inversus, single umbilical artery
- *Gastrointestinal tract*: Malrotation of bowel, anal/rectal atresia
- *Genitourinary*: Renal agenesis, hypospadias, cryptorchidism, multicystic dysplasia
- *Skeletal*: Caudal agenesis, rib and/or vertebral anomalies
- *Hyperinsulinemia*, hyperglycemia, and macrosomia

4 Multiple Pregnancies and Conjoined Twins

- Twins constitute about 3% of births and 14% of perinatal deaths

Major complications of twin and multifetal pregnancy

- Preterm delivery, pregnancy-induced hypertension, hydramnios, premature rupture of membranes, and fetal death

Monochorionic monoamniotic placenta

- High risk due to risk of cord intertwining and double fetal death

Monochorionic (MC) twin pregnancies

- MC placentas have interfetal vascular anastomoses that can be of three types: arterio-arterial, arterio-venous, and venu-venous
- Vascular anastomosis and unequal sharing of MC placental parenchyma lead to the following adverse outcomes:
  - Twin-to-twin transfusion (TTT)
  - Twin reversed arterial perfusion (TRAP)
  - Severe growth discordance

Monozygotic twins

- Placenta may be monoamniotic-monochorionic, diamniotic-dichorionic, or diamniotic-monochorionic

Dizygotic twins

- Placenta is usually dichorionic (DC)

Diamniotic-dichorionic placenta

- May have separate or fused discs
- Fused type; dividing membranes have two amnions with a single interspersed chorion

Diamniotic-monochorionic placenta

- Septal membranes have two amnions (each having epithelium and stromal component)
- No interspersed chorion

Twin-to-twin transfusion prenatal

- Donor (stuck twin) is small, anemic, flexed, and has oligohydramnios
- Recipient is large, polycythemic, plethoric, and has hydramnios
- Transfusion occurs between 18 and 24 weeks of gestation

ACUTE TTT, PERINATAL

- Due to the clamping of first delivered twin (mostly recipient), blood from the MC placenta is available for venous return to the second-born twin (mostly donor)
- Larger twin is anemic, and the smaller twin is plethoric (due to reversed TTT)

MANAGEMENT OF PRENATAL TTT

- Laser coagulation of equatorial chorionic vessels that are potential sites of A-V anastomosis

Twin reversed arterial perfusion

- Special condition in MC twins

- One twin (pump twin) actively perfuses the co-twin (acardiac twin) via large arterio-arterial or venu-venous anastomosis
- Arterio-venous anastomosis not involved
- Arterial supply to placenta by pump twin is able to overcome blood pressure of the co-twin
- Pump twin perfuses the co-twin by reversed flow
- Postductal blood from pump twin is hypoxic, hypercarbic, acidotic, nutrient-poor and -rich in waste products
- Brain, heart, and the upper limbs of the co-twin do not tolerate the quality and quantity of blood flow and undergo ischemic necrosis

SECOND SUGGESTED MECHANISM

- Acardiac twin is constitutionally abnormal
- If this embryo was a singleton, it would have undergone spontaneous miscarriage
- Passive existence of acardiac twin due to pump twin

Note: TTT, TRAP, and cord complications occur mostly in MC-MA placentas

Note: TRAP occurs frequently in triplet pregnancies

Death of one fetus

- More complicated in MC twins (due to vascular anastomosis in placentas)
- Death in first trimester; dead fetus is completely absorbed—*vanishing twin*
- Death in second trimester; *fetus papyraceous* (fetus is dead and pressed flat against uterine wall due to growth of live twin). Surviving twin may have aplasia cutis/multiple small bowel atresias due to twin embolization syndrome
- Death in third trimester; severe hypoxic/hypotensive/ischemic pathology in survivor twin

NEED TO KNOW CHORIONICITY EARLY IN PREGNANCY

- In DC pairs, it is safe to allow the dying fetus to die, after which the co-twin can be left in utero until pulmonary maturity is reached

Discordances for major malformations

- Neural tube defect, holoprosencephaly, and sirenomelia may be intrinsic to the twinning process itself

Discordance for congenital heart disease in MC twins

- Results from unequal distribution of blood flow through placental vascular anastomoses

HOMP

- Higher-order multiple pregnancies
- MZ may show various combinations of DC and MC placentations

Conjoined twins (CTs)

- Relatively late twinning events when the body axes (primitive streak, notochord, neural tube) are molecularly specified and begin to be visible morphologically
- Occurs around day 14 postfertilization
- Body axes are mostly oriented toward each other
- Most common CTs have two almost complete notochordal axis
- Most common type is thoracopagus
- Most rare is craniopagus

Fetus in fetu

- Reduced and parasitic fetus showing vertebral segmentation and organogenesis (differential diagnosis from teratoma)
- Mostly located intra-abdominal, in the body of the autosite

5 Fetal Effusions and Hydrops Fetalis

Hydrops fetalis

- End-stage fetal disease; anemia, hypoproteinemia, and cardiac failure
- Subcutaneous edema/fluid accumulations in various body cavities
- Edema of placenta and polyhydramnios

ETIOLOGY

Immune causes

- Blood group isoimmunization (Rh blood group antigens)

Non-immune causes

- Metabolic storage diseases
- Large neoplasms (sacrococcygeal teratoma, angiomas)
- Parvovirus infection
- Chromosomal aneuploidies (Turner syndrome, trisomies)
- Congenital pulmonary airway malformation (CPAM) of lung
- Right-sided diaphragmatic hernia
- Twin-to-twin transfusion
- Congenital heart block
- Tachyarrhythmias
- Fetal infections-TORCHS (hydropic fetus and placenta, hepatosplenomegaly, hepatitis, myocarditis, purpura, plasma cell villitis in placenta)
- Urethral stenosis/atresia

Cystic hygroma/nuchal edema

- Large collections of lymph in thoracic duct due to jugulo-lymphatic misconnection
- Lymphatic vessel dysplasia
- Chromosomal aneuploidy (fetal Turner phenotype, trisomy 21)
- 45X fetuses have distended cervical and lumbar hygromas and deficient/absent peripheral lymphatics with generalized subcutaneous edema
- Noonan syndrome

Fetal hydrothorax

- In chylothorax/hydrothorax; protein levels and lymphocyte counts are high due to lymphatic obstruction
- Hydrothorax leads to pulmonary hypoplasia. Preventive measures include multiple sequential thoracentesis
- Associated with pulmonary lymphangiectasia

Fetal pericardial effusions

- Associated with hydrops fetalis, congenital pericardial teratoma

Fetal ascites

- Hydrops fetalis
- Urinary tract obstruction: posterior urethral valves, urethral atresia, ureterocele, ureteric obstruction, retroperitoneal neoplasia
- Intestinal perforation can lead to meconium peritonitis, ascites, peritoneal calcification
- Lysosomal storage diseases

6 Nutritional Disorders and Toxic Embryopathies

- In growing children, a deficiency of single or multiple nutrients may result in growth failure and cognitive and behavioral deficits
- Trace elements are essential for gene expression

Macronutrients

- Proteins, carbohydrates, fat, and water

Micronutrients

- Vitamins and minerals

Primary deficiencies

- Due to lack of intake

Secondary deficiencies

- Due to malabsorption or disorders of metabolism

Marasmus

- Severe undernutrition of multiple nutrients
- Non-edematous protein energy malnutrition

Kwashiorkor

- Undernutrition of proteins compared to calories
- Edematous protein energy malnutrition

Vitamin A

- Vitamin A is found in animal products (eggs and liver) and yellow, orange, and green leafy vegetables

VITAMIN A DEFICIENCY

- Night blindness, conjunctival xerosis, keratosis of mucosal surfaces and skin

HYPERVITAMINOSIS A

- Keratosis of skin (similar to deficiency), hyperostosis of bones, hydrocephalus and pseudotumor cerebri
- *Teratogenic*: In the infants of mothers who consume large amounts of retinoids for treatment of acne

The B vitamins

THIAMINE (VITAMIN B1) DEFICIENCY

- Wet beriberi (heart failure) and dry beriberi (affects nerves, muscles)
- Wernicke-Korsakoff syndrome (cerebral beriberi), clinical triad; confusion, ataxia, and nystagmus
- Death from thiamine deficiency is mostly due to cardiac failure

RIBOFLAVIN (VITAMIN B2) DEFICIENCY

- Sore tongue, cheilosis, angular stomatitis, seborrheic dermatitis

NIACIN DEFICIENCY (VITAMIN B3)

- Pellagra (diarrhea, dermatitis, dementia, and finally death)

- Prevalent in countries where corn (poor source of tryptophan) is the staple diet

PYRIDOXINE (VITAMIN B6) DEFICIENCY

- Microcytic hypochromic anemia, sideroblastic anemia, polyneuritis

FOLIC ACID DEFICIENCY (B9)

- Megaloblastic anemia, smooth red tongue, ulceration of buccal mucosa
- Neural tube defects increased in infants due to folate deficiency in their mothers during pregnancy
- Supplemental folate during preconception and early postconception periods recommended for prevention

VITAMIN B12 (COBALAMIN) DEFICIENCY

- Megaloblastic anemia, neurologic degeneration, pernicious anemia, and subacute combined degeneration of spinal cord

BIOTIN DEFICIENCY (VITAMIN B7)

- Non-specific dermatitis, alopecia

Vitamin C

VITAMIN C DEFICIENCY (SCURVY)

- Capillary fragility with petechial bleeding in skin, gums, and periosteum
- Fibroblasts and osteoblasts fail to produce intracellular matrix and osteoid

EXCESS VITAMIN C

- Oxaluria

Vitamin D

VITAMIN D DEFICIENCY (RICKETS)

- Infants and children with failure to mineralize growing bone and osteoid tissue
- Widening of metaphyses, hypocalcemic tetany, frontal bossing, bowing of legs, craniotabes (skull like ping-pong ball)

EXCESS VITAMIN D

- Hypercalcemia, metastatic calcification, growth failure, mental retardation, and renal failure

Vitamin E deficiency

BROWN-BOWEL SYNDROME

- Accumulation of brown ceroid pigment in muscularis propria of small bowel

Vitamin K deficiency

- Hemorrhagic disease of the newborn (bleeding in skin, gastrointestinal tract, and central nervous system)
- Breast milk contains very little vitamin K, hence supplementation needed

Essential fatty acid deficiency

- *Linoleic acid*: Deficiency in infants causes dermatitis and failure to grow

Iron

IRON DEFICIENCY

- Microcytic hypochromic anemia, glossitis, stomatitis, atrophy of gastric mucosa, splenomegaly, nail changes

EXCESSIVE DIETARY IRON

- Iron deposits; hemochromatosis; decreased function of liver, heart, kidney, and other organs

Zinc

ZINC DEFICIENCY

- Growth failure, diarrhea, acrodermatitis, hypogonadism

Copper

COPPER DEFICIENCY

- Anemia, neutropenia, defective elastin, collagen, myelin formation

COPPER EXCESS

- Wilson disease; cirrhosis of liver and Kayser-Fleischer rings, due to congenital lack of ceruloplasmin
- Menkes-Kinky hair syndrome

Iodine

IODINE DEFICIENCY

- Hypothyroidism, cretinism, and mental retardation

IODINE EXCESS

- Goiter and thyrotoxicosis

Selenium

SELENIUM DEFICIENCY

- Keshan cardiomyopathy; congestive cardiomyopathy due to combination of selenium deficiency and mutant strain of coxsackievirus
- Collagen vascular abnormalities

SELENIUM EXCESS

- Alopecia, garlic odor to breath, nail abnormalities

Calcium

CALCIUM DEFICIENCY

- Tetany, seizures, cardiac failure, osteomalacia

CALCIUM EXCESS

- Hyporeflexia, metastatic calcification, renal failure

Phosphorus

PHOSPHORUS DEFICIENCY

- Rickets

PHOSPHORUS EXCESS

- Tetany

Magnesium

- *Deficiency*: May result in tetany

Toxic embryopathies

COCAINE-ABUSING FEMALES

- Rupture of aneurysms and hypoplastic blood vessels
- Abruptio placentae, congenital anomalies, intracranial hemorrhage, cerebral infarction, increased perinatal morbidity

HYPERTHERMIA IN MOTHERS

- Neurogenic arthrogryposis in fetus

RUBELLA EMBRYOPATHY

- Bilateral congenital cataract

CONGENITAL SYPHILIS

- Copious nasal discharge

VARICELLA EMBRYOPATHY

- Extensive cutaneous facial scarring

ACCUTANE EMBRYOPATHY

- Ear anomalies

FETAL ALCOHOL SYNDROME

- Short palpebral fissures, mild ptosis, smooth philtrum area, and narrow vermilion border

- Fetus has no alcohol dehydrogenase and so the fetal alcohol levels persist even when the alcoholic mother's diminish

TETRACYCLINE EMBRYOPATHY

- Long-term tetracycline therapy; yellow pigmentation of teeth that darkens with age

PHENYTOIN (DILANTIN) EMBRYOPATHY

- Hypertelorism, prominent eyes, depressed nasal bridge, macrognathia, and microcephaly

TRIMETHADIONE EMBRYOPATHY

- Facial dysmorphism and ear anomalies

PREDNISONE EMBRYOPATHY

- Cleft lip and cleft palate

LSD EMBRYOPATHY

- Skeletal defects, including radial aplasia and microcephaly

SYMPATHOMIMETIC DRUGS EMBRYOPATHY

- Limb reduction defects

THALIDOMIDE EMBRYOPATHY

- Phocomelia

WARFARIN EMBRYOPATHY

- Nasal hypoplasia

DIABETIC EMBRYOPATHY

- Amelia, cleft lip, micrognathia, caudal dysplasia, sirenomelia

HYDANTOIN AND ALCOHOL

- Prenatal carcinogens; neuroblastoma

DIETHYLSTILBESTROL

- Prenatal carcinogen; clear cell adenocarcinoma of vagina

Etiology of sudden unexpected death in infants

MYOCARDITIS

- Coxsackie group B, *Toxoplasma gondii*
- Lymphocytes, plasma cells and histiocytes, necrosis of myocardial fibers

CONGENITAL AORTIC STENOSIS

HYPERTROPHIC CARDIOMYOPATHY

- Marked hypertrophy of individual myocardial fibers with enlarged hyperchromatic boxcar nuclei
- Autosomal dominant caused by genes: *MYH7, MYBPC3, TNNT2, TNN13*

TUBEROUS SCLEROSIS

Rhabdomyoma

- Finger-shaped subendocardial masses, up to 2 cm diameter
- Spider cells (glycogen filled)
- Masses disturb the conduction system of the heart → arrhythmias

RESPIRATORY CAUSES

- Bronchopneumonia
- Bronchiolitis—RSV (edema and thickening of the bronchiolar walls; incidence of death 1%)

CYSTIC FIBROSIS

- Inspissated mucus secretions (pink) in small and large bowel, bronchioles, and in the pancreas—mostly Caucasian ancestry

ADRENAL INSUFFICIENCY

- Addison crisis (hypercalcemia, hyponatremia, hyperkalemia, hypoglycemia, metabolic acidosis)

7 Congenital and Acquired Systemic Infectious Diseases

- Neonates and infants are more susceptible to infections (immune system is immature)
- Patients with splenectomy may develop fulminant septicemia (capsulated organisms like *Meningococci* and *Pneumococci*)
- Intrauterine infections may be causative of deleterious fetal outcomes
- Procalcitonin (PCT) is a specific biomarker for rapid diagnosis of bacterial infections/sepsis

Transmission

VERTICAL TRANSMISSION

- Transmitted from mother to child
- *Transplacental* (across the placenta) or *ascending* (through the maternal genital tract to amniotic sac), in utero
- *Intrapartum* (through maternal genitalia or gastrointestinal tract); during delivery
- Breastfeeding (HIV-1, HTLV-1, cytomegalovirus [CMV])

Viral infections

HERPES SIMPLEX VIRUS

- Acquired intrapartum from mother's infected birth canal
- Inclusions
  - Type A Cowdry (eosinophilic smaller nuclear inclusions with a halo)
  - Type B Cowdry (basophilic glassy, multinucleate, nuclear molding, and chromatin margination)
- Coagulative necrosis in liver, adrenals, scant inflammatory cells
- Acute hepatitis, meningoencephalitis, neurological symptoms

CONGENITAL CMV INFECTION

- Hepatosplenomegaly, ascites, calcifications in the brain
- "Blueberry muffin" lesions (extramedullary hematopoiesis in skin)
- Cytomegaly with nuclear and cytoplasmic inclusions
- Inclusions in endothelial cells, epithelial cells, histiocytes, and stromal cells
- Common cause of birth defects and disability (sensorineural deafness, mental retardation, microcephaly)
- Transplacental infection

VARICELLA-ZOSTER VIRUS

- Infants infected more than 5 days before delivery do not manifest symptoms (there is time for production and transfer of maternal antibodies)
- Tzanck smear of vesicular or pustular fluid = giant cells and intranuclear inclusions
- Reye syndrome = complication of chicken pox treated with salicylates

HIV (HUMAN IMMUNODEFICIENCY VIRUS)

- Less than 500 copies/mL of HIV-1 RNA level = minimal risk of maternal-fetal transmission
- HIV-2 causes slower progression to immune suppression

PNEUMOCYSTIS JIROVECII PNEUMONIA (PJP)

- Previously known as *Pneumocystis carinii* pneumonia (PCP)

- Fatal infection in infancy
- Fungal organism stains with GMS stain

MEASLES (RUBEOLA)

- RNA paramyxovirus of the genus Morbillivirus
- Reticuloendothelial (Warthin-Finkeldey giant cells)—in lymphoid tissue
- Epithelial giant cells—in epithelial tissue

EPSTEIN-BARR VIRUS

- Family of human herpes virus (HHV)

Epithelial cell infection

- *Lytic* (productive); full cycle of viral replication and release of infectious viral particles in circulation

Infection of B-lymphocytes

- *Latent* (non-productive); only a limited set of genes is expressed (EBV-Nuclear antigen and three latent membrane proteins [LMPs])

INFECTIOUS MONONUCLEOSIS

- Occurs in 10–19 year age group
- Para-cortical expansion and an atypical lymphoid infiltrate with multiple immunoblasts (mixture of T and B cells)
- CD8+ve cytotoxic T-lymphocytes (CD30+ve)
- In situ hybridization for EBV (EBER-probe)
- Heterophile antibodies elevated

EBV-ASSOCIATED TUMORS

- Lymphomas (Burkitt, HIV-associated immunoblastic lymphoma, and Hodgkin lymphoma)
- Nasopharyngeal carcinoma, lymphoepithelial carcinoma
- Posttransplant lymphoproliferative disease (PTLD)

PARVOVIRUS

- B19 parvovirus targets P antigen of erythroid precursors in bone marrow
- Fetal anemia, non-immune hydrops
- In postnatal infection; erythema infectiosum (fifth disease), aplastic anemia
- Distinctive intranuclear inclusions in erythroid precursors in fetal capillaries of placenta

MUMPS

- Lymphocytic parotitis, lymphocytic myocarditis, lymphocytic epididymo-orchitis

COXSACKIE VIRUS

- Hand-foot-and-mouth disease, myocarditis, aseptic meningitis

VIRAL HEMORRHAGIC FEVERS

- *Arbovirus* (virus transmitted by arthropods)
  - *Flavivirus*: dengue virus, hantavirus, Rift valley fever, West Nile virus
- Hemorrhage due to thrombocytopenia and DIC

ADENOVIRUS

- Immunocompromised host, intranuclear amphophilic/basophilic inclusions, smudge cells

HTLV (I&II)

- Breastfed babies, transmitted through breast milk
- Type I causes adult T-cell leukemia/lymphoma

Bacterial infections

STAPHYLOCOCCI

Staphylococcus epidermidis

- Coagulase negative
- Commensal of skin causing severe infections in immunosuppressed patients
- Associated with intravenous catheters/invasive procedures

Staphylococcus aureus

- Coagulase positive
- Catalase positive
- Toxic epidermal necrolysis, staphylococcal scalded skin syndrome, septic arthritis, endocarditis, bacteremia
- Presence of Mec A gene, associated with β-lactam antibiotic resistance (MRSA)
- For treatment of MRSA; macrolides, clindamycin, vancomycin

Staphylococcal scalded skin syndrome (SSSS)

- Very little tissue reaction (toxin mediated)

STREPTOCOCCI

Group A Streptococcus (GAS)

Streptococcus pyogenes

- Beta-hemolytic
- Direct tissue invasion of upper airways and skin (impetigo, erysipelas, cellulitis)
- Toxin elaboration (scarlet fever)
- Immune mediated (rheumatic fever and glomerulonephritis)

Group B Streptococcus (GBS)

Streptococcus agalactiae

- Beta-hemolytic
- Transmitted in utero and during delivery
- Early neonatal sepsis, meningitis, and pneumonia

Streptococcus pneumoniae

- Alpha-hemolytic
- Mostly asplenic patients—community-acquired pneumonia, meningitis, otitis media

NEISSERIA MENINGOCOCCI

- Fulminating meningitis and Waterhouse-Friderichsen syndrome (bilateral adrenal hemorrhage, necrosis, shock, and death)

ENTEROBACTERIACEAE

- *Escherichia coli*—purulent meningitis

HAEMOPHILUS INFLUENZAE

- Gram-negative coccobacilli
- Epiglottitis

PSEUDOMONAS

- Gram-negative bacilli
- Cystic fibrosis patients—necrotizing hemorrhagic pneumonia
- Skin—pyoderma gangrenosum

CITROBACTER SPECIES

- Neonatal sepsis—following surgical manipulation of the umbilical cord

LISTERIOSIS

- Infection acquired by eating infected meat, unpasteurized milk and cheese
- Gram-positive bacilli
- Second trimester abortion and premature delivery of newborn/stillbirth
- Lung abscess with minimal inflammation
- Brown-Hopps stain = rod-shaped bacteria

SYPHILIS

- Hydrops fetalis, barber-pole funisitis, Condylomata lata, bifid molars, ulcerative mucositis, snuffles (due to obstructive nasopharyngitis)
- CSF: VDRL positive, FTA-ABS-IgM positive

LYME DISEASE

- Deer-tick borne (*Ixodes scapularis*)
- Spirochete—*Borrelia burgdorferi*
- Erythema migrans
- *Ixodes scapularis* causes *Babesiosis* and *Ehrlichia* infections, also "piggyback infections"

CLOSTRIDIAL INFECTIONS

- Toxins produced by bacteria involved in disease pathogenesis

- Botulism (*Clostridium botulinum*), tetanus (*C. tetani*), gas-gangrene (*C. perfringens*), and pseudomonas colitis (*C. difficile*)

TUBERCULOSIS

- Mycobacterial disease is of three types
  - *Pulmonary tuberculosis: Mycobacterium tuberculosis*
  - *Disseminated: M. avium* infection in pediatric HIV infection
  - *Lymphadenopathy*: Atypical *Mycobacterium* usually *M. fortuitum, M. scrofulaceum, M. avium-intracellulare*
- Congenital—(transplacental) rare
- Deficiency of macrophages and dendritic cell function in children
- Children develop Th-2-type T-cell responses to mycobacterial infection; absent CD8+ve cell response and production of IL-K and IL-5 by CD4+ve cells
- *BCG vaccine*: May not prevent infection but reduces the chances of hematogenous spread/tubercular meningitis
- *Miliary tuberculosis*: Numerous bacilli disseminate through bloodstream causing simultaneous disease in two or more organs with millet-sized lesions. Tuberculin test may be negative
- Tuberculomas
- *Lab diagnosis*: Stains for acid-fast bacilli and polymerase chain reaction

Note: Congenital and perinatal TB usually elude diagnosis until autopsy

RICKETTSIAL DISEASES

Arthropod borne

Spotted fever group

- Tick borne
- RMSG (Rocky Mountain spotted group): *Rickettsia ricketsii*
- Rickettsial pox: *R. akari*

Typhus group

- Scrub typhus (*R. tsutsugamushi*—tick borne)
- Q-fever (*Coxiella burnetii*—tick borne)
- Epidemic typhus (*R. prowazekii*—louse borne)

Ehrlichiosis

- Tick bite

Mycoplasma and ureaplasma

- Smallest free-living micro-organisms lacking cell-wall peptidoglycans
- Inhabitants of female genital tract
- Atypical pneumonia (*Mycoplasma pneumoniae*)

Chlamydial infections

CHLAMYDIA TRACHOMATIS

- Rectum/vagina/female genital tract infected
- Inclusion conjunctivitis, pneumonitis
- *Trachoma:* Cytoplasmic inclusions in conjunctival epithelial cells

CHLAMYDIA PNEUMONIAE

- Atypical pneumonia

CHLAMYDOPHILA PSITTACI

- Ornithosis (zoonotic)
- Aerosol of infected birds

Actinomycotic infections

- *Actinomyces israelii* is filamentous bacteria
- Chronic suppurative inflammation
- Anaerobic Gram-positive bacteria, sulfur granules with peripheral clubbing
- Cervicofacial form common
- Usually immunosuppressed patients

Nocardiosis

- Gram-positive coccobacilli
- Obligate aerobes, weak acid-fast
- Stains—gram, acid-fast, silver methenamine
- Usually immunosuppressed patients

Fungal infections

- In utero—rare
- *Candida glabrata* and *Aspergillus*: Reach fetus through ascending transcervical route
- *Malassezia furfur*: In children on long-term parenteral alimentation using lipid emulsion

Endemic fungi

- Geographically defined
- All types produce lung infection
- Dimorphic fungi—yeast form in tissue
- Host response = granulomatous and suppurative
- Blastomycosis (Eastern United States), histoplasmosis (Ohio and Mississippi), coccidiomycosis (southwest)

Opportunistic

- Immunocompromised hosts
- Two yeast forms (*Candida* and *Cryptococcus*)
- Two mycelial forms (*Aspergillosis* and *Zygomycosis*)

CRYPTOCOCCUS

- Multiple budding yeasts with thick mucoid capsule showing clear halo
- Granulomatous inflammation and gelatinous mass
- Pneumonia, meningitis, and cutaneous lesions

ASPERGILLOSIS

- Dichotomously branching septate hyphae, uniform diameter of 7–8 μ
- Radial/sunburst appearance

ZYGOMYCOSIS (MUCORMYCOSIS)

- *Rhizopus*, *Mucor*, and *Absidia*
- Rhinocerebral and endobronchial infections
- Diabetic children
- Hyphae branch at right angle and diameter varies from 5 to 20 μ
- Aseptate hyphae (folds and wrinkles may mimic septation)

Protozoal infections

INTESTINAL PROTOZOA

- *Entamoeba histolytica*, *Giardia*, *Balantidium coli*, *Cryptosporidium*

EXTRA-INTESTINAL PROTOZOA

- *Naegleria fowleri*, *Toxoplasma gondii*, *Trichomonas vaginalis*, *Pneumocystis carinii*

BLOODBORNE PROTOZOA

- *Plasmodium*, *Leishmania donovani* (Kala-Azar), *Trypanosoma cruzi* (Chagas disease)

NEMATODES (ROUNDWORM)

- *Ascaris lumbricoides*, *Enterobius vermicularis*, *Necator americanus*, *Ancylostoma duodenale*, *Strongyloides stercoralis*

CESTODES (TAPEWORM)

- *Taenia solium* (larva causes cysticercosis), *T. saginatum*, *Hymenolepis nana*, *Diphyllobothrium latum*

TREMATODES (FLATWORM)

- *Schistosoma japonicum*, *S. mansoni*, *S. haematobium*

TOXOPLASMOSIS

- Protozoa, coccidia
- Definitive host is cat
- Disseminated—confined to the eyes and brain
- In tissues; both encysted and free forms exist
- *Cysts:* Are round to oval, 10–30 μ
- Stains—H&E, PAS, silver
- *Trophozoites:* Within cyst are tiny, densely packed 2 μ structures
- Granulomatous and suppurative reaction

ENTAMOEBA HISTOLYTICA

- Erythrophagocytosis

CUTANEOUS LEISHMANIASIS

- Intracellular within histiocytes
- Brown-Hopps stain—nucleus and kinetoplast

Infection-associated hemophagocytic syndrome

- Wide variety of infectious organisms are causative
- Severe acute systemic illness
- Proliferation of benign histiocytes with erythrophagocytosis (engulfed red blood cells)

8 Inborn Errors of Metabolism (IEM)

- Collective incidence of IEM; 1/1500
- Most metabolic diseases are autosomal recessive (AR), some are X-linked

Clinical symptoms in patients with IEM

- Non-immune hydrops fetalis, fetal ascites, sudden unexpected death in infancy
- Family history of early death in siblings, failure to thrive, lethargy, vomiting, shock, coma, seizures
- Hepatomegaly/splenomegaly, dysostosis-multiplex, cardiomyopathies and arrhythmias
- Skeletal abnormalities, macular and retinal changes, macroglossia, coarse facial features

Unusual odor produced in various IEM

- Maple syrup urine disease = burnt sugar
- Phenylketonuria = mousy
- Tyrosinemia, type I = cabbage, fishy
- Isovaleric academia/glutaric acidemia type II = sweaty feet
- Multiple carboxylase deficiency = cat urine

Lysosomal storage diseases

- Most commonly diagnosed metabolic disorder
- Symptoms begin in first month of life, progressive
- Autosomal recessive except for Hunter, Fabry, and Danon disease (X-linked recessive)
- Diagnosis by biochemical assay for deficient enzyme
- Leukocytes, fibroblasts, and amniocytes assessed for enzyme levels
- Electron microscopy studies detect morphological evidence of stored material

GAUCHER DISEASE

- Most common lysosomal storage disease
- Enzyme deficiency: Beta-glucosidase
- Accumulated substrate: Glucocerebroside
- Type I (reticuloendothelial storage), type II (infantile cerebral form), type III (adolescent form)
- Type I is most common, 80%
- Hepatosplenomegaly usually in second decade of life, bone pain, easy bruising, fever, and pneumonia
- Enlarged lipid-laden histiocytes (Gaucher cells) throughout reticuloendothelial system
- *E/M*: Glucocerebroside storage material = rod-shaped/tubular lipid-bilayer stacks, up to 4 μ diameter

FABRY DISEASE (ANGIOKERATOMA CORPORIS DIFFUSUM UNIVERSALE)

- X-linked disorder
- Renal failure, cardiac disease, and cerebrovascular disease
- Glomeruli show mesangial expansion by PAS positive material, pale-staining podocytes (visceral epithelial cells)
- *EM*: Epithelium expanded by osmiophilic, lamellated leaflets, and tubules (glycolipid and cholesterol storage)

NEURONAL CEROID LIPOFUSCINOSES (BATTEN DISEASE)

- Progressive encephalopathies, premature death

- PAS positive glycolipid in lysosomes of lymphocytes, skin cells, endothelial cells
- Central nervous system; cerebral/cerebellar atrophy, neuronal loss, and apoptosis
- *EM*: Infantile (granular bodies), late infantile (curvilinear bodies), juvenile (fingerprint bodies)

POMPE DISEASE (GLYCOGEN STORAGE DISEASE TYPE II, GSD-II)

Note: Explained in detail in the section of "Glycogen storage disease"

DANON DISEASE, X-LINKED VASCULAR CARDIOMYOPATHY AND MYOPATHY

- Mental retardation, hypertrophic cardiomyopathy, skeletal myopathy
- Death from heart failure
- X-linked dominant mutation *LAMP2* gene

MUCOPOLYSACCHARIDOSES

- Storage of undegraded glycosaminoglycans (GAG) in lysosomes
- Progressive psychomotor delay, coarse facial features, short stature, dysostosis multiplex
- Autosomal recessive disorders except Hunter syndrome (X-linked)
- Type I = Hurler syndrome, type II = Hunter syndrome
- Increased urinary GAG
- Peripheral blood leukocytes; vacuoles and metachromatic Alder-Reilly granules
- *EM*: Fibrillogranular lysosomal storage material

MUCOLIPIDOSES

I-cell disease (ML-II) and pseudo-Hurler polydystrophy

- Defective *N*-acetylglucosamine I-phosphotransferase activity
- Clinical features mimic MPS and sphingolipidoses
- PAS +ve and Hale's colloidal iron +ve vacuoles in fibroblasts, endothelial cells, and lymphocytes
- *EM*: Fibroblast cytoplasm expanded by numerous membrane-bound vacuoles containing fibrillar material
- ML-III shows similar but milder symptoms

OLIGOSACCHARIDOSES/ GLYCOPROTEINOSIS

- Clinical features similar to MPS
- Disorders of glycoprotein degradation
- Accumulation of glycoproteins and oligosaccharides in tissues
  - Alpha-mannosidosis
  - Beta-mannosidosis
  - Fucosidosis
  - Sialidosis (Mucolipidosis I)
  - Aspartyglycosaminuria

GANGLIOSIDOSES

- Lysosomal accumulation of glycosphingolipids (gangliosides)

GM1 gangliosidosis

- Deficiency of beta-galactosidase
- Accumulation of GM1 gangliosides in central nervous system (CNS)

GM2 gangliosidosis

- Defect in lysosomal hexosaminidase
- Accumulation of GM2 gangliosides in neurons

GM2 type I, Tay-Sachs disease, B variant

- Hexosaminidase A enzyme deficiency, accumulation of substrate GM2 ganglioside
- Ashkenazi Jews. Mental/motor deterioration begins in infancy, blindness, cherry red spot on macula, death by 2–3 years
- CNS and retina; enlarged cerebral gyri, narrow sulci, atrophy of cerebellum/brainstem
- Neurons ballooned with cholesterol, phospholipids, and GM2 gangliosides

GM2 type II, Sandhoff disease, O variant

- Absence of hexosaminidase A and B
- Clinically similar to Tay-Sachs disease

SPHINGOLIPIDOSIS

Niemann-Pick disease

- Sphingomyelinase enzyme deficiency, sphingomyelin substrate is accumulated
- Type A is common (infantile neuronopathic form of Niemann-Pick disease)
- CNS and visceral organs involved
- Hepatosplenomegaly in infancy, loss of mental/motor functions, and death by third year
- Ashkenazi Jews
- Brain atrophy, neuronal loss, gliosis, and demyelination
- 25–75 μ histiocytes in bone marrow, splenic pulp, and lungs
- Histiocytes have vacuolated cytoplasm, pale-yellow/tan on H&E
- Vacuoles positive for Sudan black B and oil-red-O
- Stored material composes lipofuscin, sphingomyelin, ganglioside, and cholesterol

METACHROMATIC LEUKODYSTROPHY (MLD)

- Deficiency of arylsulfatase A
- Accumulation of sulfated glycolipids in CNS/extraneural sites
- Excessive urinary sulfatides
- Metachromatic material accumulates in cells (stains with cresyl violet/toluidine blue)
- *EM*: Tuftstone inclusions

WOLMAN DISEASE AND CHOLESTEROL ESTER STORAGE DISEASE (CESD)

- Reduced/absent acid lipase
- Accumulated material = triglycerides and cholesterol esters
- Liver enlarged, greasy, bright orange, progresses to cirrhosis
- *EM*: Lipid droplets and cholesterol clefts
- CEST: Some residual acid lipase activity (disease is milder)

FARBER DISEASE (DISSEMINATED LIPOGRANULOMATOSIS)

- Acid ceramidase deficiency leading to accumulation of ceramide
- Symptoms in infancy; failure to thrive, deformed joints, respiratory insufficiency
- Multivisceral involvement, PAS positive storage material
- *EM*: Curvilinear membrane bound storage material = banana bodies (Farber bodies)

KRABBE DISEASE (GLOBOID CELL LEUKODYSTROPHY)

- Neurological symptoms
- Galactocerebroside beta galactosidase deficiency leading to accumulation of undigested psychosine
- Monocyte/macrophage cells in nervous system (globoid cells positive for PAS and acid-phosphatase)

CYSTINOSIS

- Cystinosin deficiency leading to accumulation of cysteine in multiple viscera
- Nephropathic form is most severe, kidneys involved
- Cysteine crystals in interstitium, glomeruli, and tubular cells
- Progressive interstitial fibrosis, swan-neck deformity of the proximal convoluted tubule, renal failure
- Unfixed frozen tissue shows rhomboid cysteine crystals by polarizing light
- Ophthalmologic demonstration of cysteine crystals

Aminoacidopathies

- Blockage of amino acid breakdown (due to enzyme deficiency) leading to accumulation of specific amino acids

PHENYLKETONURIA

- AR trait
- Phenylalanine hydroxylase absent leading to elevated phenylalanine/deficiency of tyrosine
- Deficiency of tyrosine (melanin precursor); patients are fair skinned/fair haired/blue eyes

- Excessive vomiting, mousy odor of sweat and urine
- If untreated with special diet, severe mental retardation/seizures
- Diagnosis: Tandem mass spectrometry (MS/MS) for blood phenylalanine levels

TYROSINEMIA TYPE I (HEPATORENAL TYROSINEMIA, CONGENITAL TYROSINOSIS)

- Fumarylacetoacetate hydrolase deficiency leading to accumulation of tyrosine
- Liver and kidney involved
- Failure to thrive, fishy odor, acute liver failure, cirrhosis, renal Fanconi syndrome
- Hepatocellular carcinoma at young age
- Liver transplantation recommended by 2 years of age (to prevent carcinoma)

TYROSINEMIA TYPE II (OCULOCUTANEOUS TYROSINEMIA, RICHNER-HANHART SYNDROME)

- Tyrosine aminotransferase deficiency
- Palmoplantar keratosis, corneal erosions, mental retardation
- No liver involvement

HOMOCYSTINURIA

- Cystathionine beta synthetase deficiency with increased level of homocysteine and methionine (serum and urine)
- CNS and multisystem disorder
- Thromboembolism, multifocal CNS infarction

NON-KETOTIC HYPERGLYCINEMIA (NKH)

- Error in glycine degradation
- Accumulation of glycine in all body fluids, tissues (including brain)
- No ketosis

MAPLE-SYRUP URINE DISEASE (MSUD, BRANCHED-CHAIN KETOACIDURIA)

- Accumulation of leucine, isoleucine, and valine in plasma
- Common among Mennonites
- Burnt sugar, maple syrup odor to urine, sweat, and saliva (sotolone induced)

Carbohydrate metabolism abnormalities

GALACTOSEMIA

- Deficiency of enzymes that convert galactose to glucose: GALT, GALK, and GALE
- Severe galactose intolerance (after milk feed)
- *Escherichia coli* sepsis (due to depressed neutrophil function)
- Extensive liver damage, CNS disorders, ovarian failure
- Diagnosis; red cell GALT assay

HEREDITARY FRUCTOSE INTOLERANCE (HFI)

- Fructose-1-phosphate aldolase deficiency leading to accumulation of fructose-1-phosphate
- Liver, kidney, and brain involved
- Liver shows steatosis, giant cell transformation, ductular proliferation, cholestasis, fibrosis, and necrosis

GLYCOGEN STORAGE DISEASE (GSD)

- Type 0
- Type I, von Gierke disease
- Glucose-6-phosphatase enzyme deficiency
- Massive hepatomegaly, cirrhosis, xanthomas, growth retardation, hypoglycemia, hyperlipidemia
- Pale liver cells, steatosis
- Increased glycogen storage in liver/kidney
- Hepatocellular adenoma that can evolve into HCC

Type II (Pompe disease)

Infantile

- Hypotonia, cardiomegaly
- Hepatomegaly mild/absent

- Death from cardiac/respiratory failure
- Distended lysosomes also contain acid-phosphatase
- Vacuolar myopathy = PAS +ve vacuoles in skeletal muscle and myocardium
- Cardiac myocyte enlargement leads to hypertrophic gross appearance of the myocardium
- Hepatocytes enlarged with vacuolar rarified cytoplasm
- *EM*: Lysosomal and extra-lysosomal glycogen storage

Childhood

- Predominant skeletal muscle involvement

Adult

- Slowly progressive proximal myopathy
- Respiratory insufficiency

Type 3 (Cori disease, limit dextrinosis)

- Debrancher enzyme deficiency

Type 4 (Anderson disease, branching enzyme deficiency)

- Amylopectinosis (brancher enzyme deficiency)
- Hepatosplenomegaly, cirrhosis, muscle wasting
- Liver resembles Lafora disease, progresses to fibrosis and cirrhosis
- Hepatocytes enlarged with cytoplasmic inclusions
- Inclusions have halo around them and are PAS +ve/diastase resistant
- Inclusions are green with colloidal iron, brown/blue with Lugol's iodine
- Inclusions removed by pectinase/α amylase

Type 5 (McArdle)

- Myophosphorylase deficiency

Type 6 (Her)

- Mosaic pattern of non-distended and distended hepatocytes

Other types are Type 7 (Tarui disease), Type 8, Type 9, and Type 10 (Fanconi-Bickel).

Disorders of nucleic acid metabolism

LESCH-NYHAN SYNDROME

- X-linked affects only males
- Hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency
- Purines accumulated in blood
- Uric acid levels increased
- Uric acid crystals in diaper (orange sand)
- Self-mutilation of fingers and lips

ADENOSINE DEAMINASE DEFICIENCY

- AR trait
- Recurrent severe multiorganism infections during infancy
- Lymph nodes, spleen, tonsils, appendix; depleted of lymphoid tissue

Fatty acid oxidation defects

ACYL-COA DEHYDROGENASE DEFICIENCIES

- Normally, acyl-CoA dehydrogenases (short chain, medium chain, long chain, and very long chain) catalyze conversion of fatty acids to their coenzyme A
- AR disorders
- Hypoketotic hypoglycemia, liver and skeletal muscle abnormalities, cardiomyopathy
- Sudden unexpected death in childhood

MCADD (medium-chain acyl-CoA dehydrogenase deficiency)

- Homozygous for A985G mutation
- Most common IEM (1 per 5000–8000 people)
- Infant may present with sudden death
- Family history with similar sibling death usually positive
- Dysmorphic facial features, enlarged/pale organs
- Deteriorated clinical status after symptom-free interval of hours/days
- Hypoketotic hypoglycemia following birth
- Symptoms may resemble Reye syndrome or SIDS

Long-chain acyl-CoA dehydrogenase deficiency

- Mothers of affected fetuses may develop HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts) during pregnancy

Glutaric-acidemia type II (multiple acyl-CoA dehydrogenase deficiency, MADD)

- Renal dysplasia and hepatic steatosis

Substrate transport defects

CARNITINE PALMITOYLTRANSFERASE (CPT)

- CPT catalyzes transport of carnitine and long-chain fatty acids into mitochondria
- Deficiency associated with myopathy, myoglobinuria, and weakness of respiratory muscles

CARNITINE DEFICIENCY

- Carnitine is a co-factor for transport of medium- and long-chain fatty acids across mitochondrial membranes
- Deficiency associated with muscle weakness, progressive cardiomyopathy, and recurrent acute hepatic encephalopathy

HYPERAMMONEMIAS/UREA CYCLE DISORDERS

- Urea cycle occurs in liver and intestine
- Converts toxic nitrogenous waste to water-soluble urea
- If defective, hyperammonemia, neurotoxicity, and cerebral edema
- High-protein diet/infections precipitate symptoms

ORNITHINE TRANSCARBAMYLASE (OTC) DEFICIENCY

- Most common urea cycle defect
- X-linked dominant
- Vulnerable to valproate-associated hepatotoxicity
- Pale water clear hepatocytes with lipid deposition
- Brain edematous with Alzheimer type II astrocytosis
- Other types are Carbamoyl Phosphate; Synthetase I Deficiency; Citrullinemia; Argininosuccinic Aciduria; Argininemia; Hyperornithinemia, Hyperammonemia, Homocitrullinuria (HHH disease); and Lysinuric Protein Intolerance (LPI).

Organic acidemias

- Enzyme deficiency blocks catabolism of amino acids, carbohydrates, and fatty acids
- Accumulation of organic acids
- Hepatomegaly, severe progressive encephalopathy, coma, seizure, and death
- Diagnosis: MS of urine
- Various types are Propionic Acidemia, Isovaleric Acidemia, Glutaric Acidemia Type I, and Methylmalonic Acidemia

Hyperlactinemia, lactic acidemia

- Lactic acidosis, chronic neurological dysfunction, structural abnormalities of the brain, hepatomegaly with steatosis
- The various examples are Pyruvate Dehydrogenase Deficiency and Pyruvate Carboxylase Deficiency

Peroxisomal disorders

- Peroxisomes have multiple metabolic biosynthetic and degradative functions
- Structurally, they are spherical, 0.1–1 μ in size and bound by a single lipid bilayer
- In disease, increased tissue and body fluid (very long-chain fatty acid [VLCFA])
- *EM*: Abnormal number/size of peroxisomes, trilaminate inclusions (due to VLCFA)

ZELLWEGER (CEREBROHEPATORENAL SYNDROME)

- Most severe peroxisomal disorder
- AR trait

- Metabolic abnormality, facial dysmorphism, severe hypotonia, failure to thrive, seizures, ocular/CVS malformation, renal cysts, calcific stippling of patella
- *EM*: Decreased/absent peroxisomes in liver and kidney

NEONATAL ADRENOLEUKODYSTROPHY

- AR trait
- Milder clinical course than that of Zellweger
- Hypotonia, craniofacial dysmorphism, adrenocortical atrophy, progressive dysmyelination of cerebral/cerebellar white matter
- *EM*: Reduced size/number of hepatic peroxisomes

INFANTILE REFSUM DISEASE

- Milder course than above two disorders
- Hypotonia, seizures, mental retardation, and liver fibrosis
- *EM*: Hepatic peroxisomes reduced in number and size

RHIZOMELIC CHONDRODYSPLASIA PUNCTATA TYPE I

- Impaired plasminogen synthesis and phytanic acid oxidation
- Proximal limb shortening and calcific stippling of hyaline cartilage

HYPEROXALURIA TYPE I

- Single peroxisomal enzyme deficiency
- High urine oxalate, progressive oxalate nephrocalcinosis, oxalate urolithiasis
- Calcium oxalate crystals in multiple sites, bone, soft tissue, eye, cardiac conduction system
- Renal failure, recurrent fractures, and cardiac arrhythmias

Metal metabolism abnormalities

NEONATAL HEMOCHROMATOSIS (NEONATAL IRON STORAGE DISEASE)

- AR trait
- Hepatic failure in neonate, liver injury may start in utero
- Widespread hepatocellular loss, giant cell/pseudoacinar transformation, regenerative nodules, acute/chronic inflammation, cirrhosis, coarsely granular hemosiderin accumulation in the hepatocytes (Prussian blue stain +ve)
- Kupffer cells do not show iron deposition
- Extrahepatic siderosis in multiple organs
- Demonstration of siderosis by biopsy of oral submucosal glands
- *EM*: Hemosiderin demonstration in hepatocytes

WILSON DISEASE

- Hepatolenticular degeneration
- Mutation of *ATP7B* gene
- Hepatic copper retention, lack of biliary copper excretion, and lack of copper incorporation into ceruloplasmin
- For diagnosis, hepatic copper content greater than 250 µgm/gm dry weight (normal level less than 50 µgm/gm dry weight)
- Low serum ceruloplasmin, Keyser-Fleisher rings in eye, destruction of basal ganglia/intact cortex (neuropsychiatric problems)

MENKES KINKY HAIR SYNDROME

- X-linked recessive trait
- Mutation of *ATP7A* gene
- Defective intestinal copper absorption = copper deficiency
- Hair show Pili torti (sparse, hypopigmented, twisted, brittle hair)
- Profound neurodevelopmental deterioration
- Secondary deficiency of multiple copper-dependent enzymes = phenotypic abnormalities
- Serum copper and ceruloplasmin levels low

Disorders of the endoplasmic reticulum

ALPHA-1-ANTITRYPSIN (A1AT) DEFICIENCY

- Prevalent in northern Europe

- A1AT is an acute phase reactant synthesized by hepatocytes
- Inhibits proteases in lung, thus preventing lung damage during inflammation
- Normal glycoprotein is PiMM genotype
- Point mutation in *SERPINA1* gene leads to PiZZ genotype
- Heterozygotes are PiMZ
- Variants have liver and lung disease with serum alpha-1-antitrypsin levels of less than 20% of normal levels
- Misfolded PiZZ protein gets accumulated in ER of hepatocytes, increasing hepatic levels of protein
- Serum levels of A1AT are low causing lung damage
- Periportal hepatocytes accumulate globules that are PAS positive and diastase resistant, positive for specific immunostain
- Replacement therapy with purified A1AT is helpful for the lungs but not for liver (because hepatic injury is caused by increased A1AT rather than deficiency)
- Treatment is liver transplant

CONGENITAL DISORDERS OF GLYCOSYLATION (CDG)

- Group of multisystem disorders caused by abnormal glycosylation of N-linked oligosaccharides
- AR trait
- Two types are CDG-I and CDG-II
- Severe olivopontocerebellar atrophy, pleural and pericardial effusions, obstructive cardiomyopathy, cirrhosis

Lipid metabolism disorders

SMITH-LEMLI-OPITZ SYNDROME

- Deficiency of 7-dehydrocholesterol reductase
- Reduced plasma cholesterol
- Bilateral ptosis, micrognathia, microcephaly, cystic kidney, mental retardation, and hypotonia
- Reduced myelination of nervous system and pancreatic enlargement with pancreatic islet cell nuclear hyperchromasia

CONRADI-HÜNERMANN SYNDROME (CDPX2)

- X-linked dominant disorder of sterol metabolism
- Chondrodysplasia punctata, limb anomalies, joint contractures, ichthyosiform skin lesions, short stature
- Serum cholesterol levels normal

CHILD SYNDROME (CONGENITAL HEMIDYSPLASIA, ICHTHYOSIS, AND LIMB DEFECTS)

- Rare X-linked dominant disorder of sterol metabolism
- Ipsilateral visceral abnormalities

SUDDEN DEATH IN INFANTS WITH INBORN ERRORS OF METABOLISM

- Deterioration in clinical status after an interval of hours to days
- Family history of similar sudden death (particularly sibling)
- Dysmorphic features, enlarged spleen/ liver/ heart, pale and fatty organs, cerebral edema
- Fatty acid oxidation defects (especially MCADD) = hypoketotic hypoglycemia at birth

Autopsy of child with suspected inborn errors of metabolism

- Autopsy should be done as soon as possible (preferably within 2 hours after death)
- Autopsy should include photography, radiography, histology, histochemistry, ultrastructure, fibroblast culture, toxicology, biochemical analysis, and DNA analysis
- Urine should be collected by catheterization and frozen at –20°C for amino/organic acid analysis
- Spotting a few drops of whole blood onto filter paper (Guthrie card); for analytical assays
- DNA analyzed by collecting whole blood in EDTA and keeping at room temperature until DNA is extracted

- Vitreous humor collected in fluoride tube and stored at –20°C for glucose/electrolyte analysis
- Bile is the only analyzable fluid when the interval between death and autopsy is long
- 1 cm^3 of tissues like brain, liver, muscle, kidney, and other viscera should be snap frozen in liquid nitrogen, wrapped in foil, and stored at –70°C
- Fresh frozen muscle is tissue of choice for diagnosis of mitochondrial respiratory chain disorders
- LCAD and MCAD in liver are stable for 100 hours after death (refrigerated body) and 5 years after death (if tissue kept at –70°C)
- Fibroblasts from skin used for studies of DNA, enzyme, metabolites, and for karyotyping
- Cultivated fibroblasts cryopreserved indefinitely for future studies

Mitochondrial disorders

- Heterogeneous group of neuromuscular/multisystemic disorders due to altered mitochondrial metabolic function
- Impaired respiratory chain function and oxidative phosphorylation
- Tissues and organs dependent on aerobic metabolism are affected the most
- Mitochondria contain their own genome—a small, circular, double-stranded DNA called mtDNA
- Mitochondria depend on nucleus for supply of many OXPHOS proteins and also for factors that replicate/repair/maintain mtDNA
- Mutation of genes encoded by either nuclear DNA (NDNA) or mitochondrial DNA (mtDNA) cause mitochondrial diseases
- Ptosis, ophthalmoplegia, exercise intolerance, increased lactate levels, abnormal brain MRI
- More than 2% subsarcolemmal mitochondrial aggregates (larger than 4 µ in depth) support a diagnosis of mitochondrial myopathy (SDH histochemistry)
- *EM*: Mitochondrial alterations including abnormal number/altered crystal structure
- Diagnosed by molecular genetic testing or by muscle biopsy for respiratory chain function

MITOCHONDRIAL DNA DEFECT (mtDNA)

- Inherited maternally
- Manifested usually in later childhood/adult life

Disorders with mitochondrial DNA rearrangements

Chronic progressive external ophthalmoplegia (CPEO) with ragged red fibers

- Slowly progressive ptosis, ophthalmoplegia, proximal limb weakness
- Sporadic with deletions/duplications of mDNA
- Muscle biopsy shows ragged red (modified trichrome) and COX-negative fibers

Kearns-Sayre syndrome (KSS)

- Severe mitochondropathy, retinitis pigmentosa, external ophthalmoplegia, and heart block beginning before 20 years of age
- Muscle biopsy shows ragged red (modified trichrome) and COX-negative fibers

Pearson marrow pancreas syndrome

- Bone marrow failure, pancytopenia, sideroblastic anemia, pancreatic failure, and sepsis
- Death in early childhood

Point mutations in the genes encoding mitochondrial tRNA

MELAS

- Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
- Common respiratory chain disorder
- Muscle biopsy; ragged red fibers with numerous COX-negative fibers

MERRF

- Myoclonic epilepsy with ragged red fibers

- Muscle biopsy; ragged red fibers with numerous COX-negative fibers

NUCLEAR GENE DEFECT

- Inherited as AD or AR traits
- Manifested usually in infancy/early childhood
- Abnormalities in nuclear genes related to oxidative phosphorylation
- Complex I—complex V deficiencies

Point mutations in nuclear DNA encoding OXPHOS complex structural subunits

Leigh syndrome

- Also known as subacute necrotizing encephalopathy
- Necrotizing brain lesions and hypertrophic cardiomyopathy
- Infantile onset

OTHER DISORDERS

Defects of inner mitochondrial membranes

Barth syndrome

- Defect in *TAZ* gene that encodes the protein tafazzin, which incorporates cardiolipin (an essential part of inner mitochondrial membrane)
- X-linked disorder
- Skeletal myopathy, dilated CMP with abnormal left ventricular compaction and neutropenia

9 Pediatric Forensic Pathology

- The forensic pathologist is responsible for ensuring that proper medicolegal death investigation is performed during the process of death certification
- Deaths to be reported to medical examiner/coroner include
  - All sudden or unexpected deaths
  - All child deaths outside hospital
  - Deaths in emergency room
  - All unnatural deaths

Sudden infant death syndrome (SIDS)

- Most deaths occur between 1 and 4 months of age
- Sudden unexpected death of an infant/unexplained cause
- Mostly occurs during sleep
- No evidence of child abuse
- No evidence of thymic stress effect
- Lack of concordance among twins/non-genetic
- Sleeping position and sleeping surface important (prone versus supine)
- Large parents, intoxicated and sedated—risk of overlying
- Maternal cigarette smoking—risk factor
- Prevalence of long QT-syndrome gene variants; bradycardia, prolonged QT interval, alteration of Na+/K+ channels
- Metabolic disorders in SIDS—medium-chain Acyl-CoA dehydrogenase deficiency (MCADD)
- *Microscopic autopsy findings*
  - Petechiae in thymus, visceral pleura, and epicardium
  - Pulmonary congestion and edema
- Increased hypoxanthine levels in vitreous

PREVENTION

- Supine sleeping position (back to sleep)
- Use pacifiers, avoid hypoxemia
- *Haemophilus influenzae* vaccine at 2 months of age—diminished frequency of SIDS

Munchausen syndrome by proxy

- Parent/caregiver creates/fakes illness in child to gain attention from medical providers
- Perpetrator assumes sick role by proxy and all its benefits
- No motivation of financial gain/perpetrator is sound in mind
- Considered physical abuse
- May be fatal; children may undergo unnecessary medical procedures/treatment (mortality rate may be 9%)
- Important to rule out genuine illness in child

Neonaticide

- Killing of a baby in first 28 days of life
- By definition, fetus should have been born alive/reached viable gestational age (24–28 weeks)
- In postpartum death; lungs are aerated (floating test) and gastrointestinal tract shows air

IMPORTANT TO RULE OUT

- *Death in utero*: Should show signs of maceration (skin slippage, red brown discoloration of umbilical cord stump, loss of basophilia of renal cortex cell nuclei)

- *Intrapartum injuries*: Birth injuries (caput succedaneum, cephalhematoma). Lungs show primary atelectasis in death in utero/intrapartum injuries

Neglect

- Most common child maltreatment
- Act of commission/omission by caregivers endangering physical, mental, emotional, or developmental health of child

Accidental causes of death in children

DROWNING

- No definite postmortem test/finding indicates death due to drowning
- Diagnosis of exclusion (history and circumstantial evidence)

ACCIDENTAL STRANGULATION

- Interruption of blood flow to brain rather than occlusion of airway
- Ligature furrow in neck skin (yellow-brown with waxy base)
- Displays suspension point

HOUSE FIRE DEATHS

- Smoke inhalation—Black carbonaceous material adherent to laryngeal mucosa/airways
- Cherry red discoloration of viscera
- Carboxyhemoglobin saturation above 10%
- May be accidental (hazards in sleeping quarters) or homicide

Death due to physical abuse

- Head injury and abdominal injury; most common
- A history that does not match physical findings is suspicious of abuse

CUTANEOUS EVIDENCE OF PHYSICAL ABUSE

- Fatally abused child may demonstrate no signs of external injury
- Healthy active preschool toddler may show wear and tear injuries over lower extremities, elbows, forearms (not a sign of abuse)
- Contusions on face in infant, injuries in recessed or protected areas such as submental space, philtrum, buttocks, and so on; suspicious for inflicted injuries
- Pattern injuries suspicious for inflicted injury by an object (e.g., belt)
- Yellow discoloration of a bruise may indicate that it is at least 18 hours old
- Accidental scald burns often are asymmetric and show small satellite "splash burns"
- Inflicted scaffolding burns are symmetric and show immersion pattern/glove or stocking distribution
- Abusive contact burns; shape of burn delineates causative object (cigarette, clothing iron)

Gunshot wounds

CONTACT RANGE GUNSHOT WOUND

- Muzzle stump on skin at the entrance point
- Gases, soot, and gunpowder are deposited at entrance
- Stippling/tattooing surrounding the wound (due to burnt gunpowder particles)—indicates distance up to 2′ range
- In contact gunshot wound of the head; skin laceration at entrance, due to expansion of soft tissue and skin tearing
- *Abrasion collar*: Produced at entrance site (when bullet encounters the skin and indents it)

INTERMEDIATE RANGE (CLOSE RANGE) GUNSHOT WOUND

- Soot/gunpowder deposited
- Stippling/tattooing surrounding the wound (due to burnt gunpowder particles)—indicates distance up to 2′ range

- No muzzle imprint/no laceration
- Wound may be irregular (provides information about range of the fire/path of projectile)

EXIT WOUND

- Irregular and stellate
- No abrasion/no burnt powder/no soot
- Usually bigger than entrance wound
- Bone "bevelling" that is oriented away from entrance wound

Cause of death

PROXIMATE CAUSE (UNDERLYING CAUSE)

- Disease or injury that initiates the events terminating in death
- Without this, the end result would not have occurred

IMMEDIATE CAUSE

- Complications/sequelae of underlying cause
- There may be one or more immediate causes, and they may occur over a prolonged interval
- Ultimate responsibility of death is that of underlying cause

Mechanism of death

- Physiological derangement or biochemical disturbance

Manner of death

- Natural, accidental, homicide, suicide, or undetermined

Chain of custody

- Procedure established to verify the possession of an object; from the time it is collected until it is offered as evidence in court

Wounds (antemortem versus postmortem)

ANTEMORTEM WOUNDS

- Polymorphonuclear cells appear in 4–8 hours
- Hemosiderin = 2–3 days
- Granulation tissue = 3 days
- Scar formation = 1 week

POSTMORTEM WOUNDS

- No changes

Intrathoracic petechiae

- Found more frequently in SIDS

Pulmonary siderophages

- Increased in asphyxiation

Drowning

- *Wet drowning*: Aspiration of liquid
- *Dry drowning*: No aspiration of liquid
- Hemorrhage of petrous bone—seen in drowning death
- Hot tub drowning—*Pseudomonas* infection

Hypothermia

- Less than 35°C body temperature
- Pink lividity of internal tissues

Head injuries

SUBDURAL HEMORRHAGE

- Damage to the bridging veins
- Marker of rotational acceleration of head
- Acute subdural hemorrhage (less than 3 days old)
- Chronic subdural hemorrhage (more than 10 days old)

EPIDURAL HEMORRHAGE

- Trauma to meningeal artery
- *Lucid interval*: Temporary improvement in patient's condition after traumatic brain injury, after which the condition deteriorates
- Large epidural hemorrhage is uncommon due to firm adherence of the dura to the skull

SCIWORA

- Spinal cord injury without radiographic abnormality
- Unique abnormality in children under 8 years of age—traumatic myelopathy

RETINAL HEMORRHAGE

- Superficial nerve fiber intraretinal hemorrhage is *flame/splinter* shaped
- Deep retinal hemorrhage is *dot/blot* shaped

BETA-AMYLOID PRECURSOR PROTEIN

- Used for the detection of diffuse axonal injury in head trauma

TIN EAR SYNDROME

- Unilateral ear bruising, ipsilateral cerebral edema, and hemorrhagic retinopathy

AXONAL SPHEROID

- In the brain (retraction ball)
- Eosinophilic globule, indicator of brain injury
- Detected by silver stain

Abusive rib fractures

- Antero-posterior squeezing results in posterior and lateral fractures
- Ribs show callus formation

Abdominal trauma

- May lead to perforation, hemorrhage, and peritonitis

Impetigo contagiosa

- Skin lesion shows vesicles in the upper layers of the epidermis
- Mimics abusive cigarette burns

Miscellaneous terminology

- *Abrasion, ecchymosis, and laceration*: Blunt force injury
- *Incision*: Sharp force injury that is longer than it is deep
- *Stab wound*: Sharp force injury that is deeper than it is long
- *Neonaticide*: Killing of an infant within 28 days of birth
- *X-ray (Faxitron)*: Diagnoses the putrefactive gases in soft tissue of decomposed abandoned dead children
- *Pattern injuries*: Fly swatter, belt, and so on, are continuous injuries and are indicative of abuse
- *Untrained CPR*: May cause fractured ribs

Autopsy Checklist

Specimen	Storage Recommendation
Urine	–70°C for amino acid and organic acid analysis
Blood	EDTA and heparinized (–70°C) serum should be stored in acid washed tubes
Vitreous	Send for electrolyte, urea, nitrogen, creatinine, glucose analysis
Skin and pericardium	Store in sterile tissue transport media after cleaning with alcohol. Store at –70°C if immediate culture is not available
Other tissues: Brain, kidney, heart, muscle, liver, spleen	• 1 mm^3 cubes stored in 4% glutaraldehyde for EM • 1 cm^3 cubes stored in liquid nitrogen for biochemistry assays or Oil-Red-O stain • Fresh or frozen tissue for DNA analysis • *Liver*: MCAD and LCAD enzymes are stable up to 100 hours if the body is frozen at –70°C and stable up to 5 hours if body is refrigerated
Special Studies • *Iron-morphometry*: Lungs → in possible cases of suffocation • *Iron and trichrome* → in wound healing, subdural hemorrhage • *Beta-amyloid precursor protein* → in cases of head trauma analysis	

10 Perinatal Pathology

- Perinatal period is the interval extending immediately before and after birth. Depending on the definition it starts from 20th to 28th week of gestation extending up to 1 to 4 weeks after birth.

Complications of perinatal care

CHORIONIC VILLOUS SAMPLING

- 9–12 weeks of gestation—transverse digital defects

PERINATAL TRANSFUSION

- Antibody-screened and seronegative blood should be used for transfusion; to protect against viral infections
- Graft versus host disease (GVHD) is a complication of blood transfusion (especially in immunodeficient patients)
- Blood and leukocytes should be irradiated before transfusion (to inactivate T cells)

BREECH EXTRACTION

- Most harmful to the fetus: Multiple birth injuries may be caused

CAPUT SUCCEDANEUM

- Subcutaneous edema and hemorrhage (extends over suture lines)

SUBGALEAL HEMORRHAGE

- Hemorrhage between scalp aponeurosis and periosteum of the skull

CEPHALHEMATOMA

- Hemorrhage between surface of calvarial bone and the periosteum (does not extend over suture lines)

MASSIVE SUBDURAL HEMORRHAGE

- Complication of high forceps delivery
- Caused by tear in tentorium cerebelli or rupture of bridging veins

INTRAVENTRICULAR AND PARENCHYMAL HEMORRHAGE

- Mostly caused by hypoxia in preterm infants (germinal matrix hemorrhage)

EPIDURAL HEMORRHAGE

- Due to rupture of middle meningeal artery

BRACHIAL PLEXUS INJURY

- Fifth and sixth cervical root—*Erb palsy*
- Seventh/eighth cervical and first thoracic—*Klumpke paralysis*

FIBROMATOSIS COLLI

- Injury to sternocleidomastoid muscle (*torticollis*)—Atrophy of the muscle and fibrosis

ENDOTRACHEAL TUBE

- Intubation causes obstruction by mucus and other tracheal secretions
- Necrotizing tracheobronchitis

PERSISTENT LOCALIZED PULMONARY INTERSTITIAL EMPHYSEMA

- Complication of continuous positive airway pressure/mechanical ventilation
- Overdistended air spaces and dissection of gas in lobular septa
- Pseudocysts lined by giant cells

CENTRAL CATHETERS

- Bloodstream infection, endocarditis, thrombosis, cardiac rupture, and tamponade

HEATED INFUSION BAGS

- Skin burns may be caused in a hypothermic child (after application of heated infusion bags)

ECMO (Extracorporeal membrane oxygenation)

- Used in infants who have a mortality risk of 80% or higher
- *Indications*: Severe air leak syndrome, respiratory distress syndrome (RDS), pulmonary hypertension, persistent interstitial pulmonary emphysema, sepsis, diaphragmatic hernia, B-surfactant deficiency, congenital heart defect, meconium aspiration pneumonia
- *After 2 days*: Intra-alveolar and interstitial hemorrhage, hyaline membrane formation, hyperplasia of type 2 alveolar cells and bronchial epithelial cells
- *After 1 week*: Interstitial fibrosis and calcification
- *Complications*: Hemorrhage, neurological damage, hypertension, hypercalcemia, infection, renal failure, thromboembolism

Intravenous alimentation aka total parenteral nutrition (TPN)

- Injury due to the metabolic nature of fluid and apparatus delivering the infiltrate
- *Liver injury*: Canalicular and ductular cholestasis, ductular proliferation, portal fibrosis
- *Lung injury*: Pulmonary lipid embolism
- *Malassezia furfur* organisms can develop in the TPN (increased fat in the fluid)

Umbilical vein/artery catheterization

- Complicated by thrombosis of abdominal aorta and iliac arteries
- Infarcts of kidney, bowel, and gangrene in lower limb

Medications used in newborn

PROSTAGLANDIN SYNTHETASE INHIBITORS

- Used to inhibit labor/prolong pregnancy
- *Complications*: Oligohydramnios, fetal and neonatal oliguria/anuria, pulmonary hypertension

INDOMETHACIN

- Used to promote closure of patent ductus arteriosus (PDA) in small preterm infants
- *Complications*: Necrotizing enterocolitis, bowel perforation, and intracranial hemorrhage

PROSTAGLANDIN E

- Maintain the patency of PDA in congenital heart disease (tetralogy of Fallot, pulmonary stenosis, and pulmonary hypertension)
- *Complication*: Gastric outlet obstruction

Miscellaneous terms and definitions

Hypotelorism

- Distance between the two inner canthi of the eyes is very small

Hypertelorism

- Distance between the two inner canthi of the eyes is very large

Low-set ears

- If the upper tip of the ear is below the level of ipsilateral palpebral fissure

Micrognathia

- Small or undersized lower jaw

Macrognathia

- Abnormally large lower jaw

AUTOPSY-RELATED TERMS

Standard thoracic/abdominal incision

- Y-shaped

Blood culture

- Taken from right atrium or inferior vena cava

Lung culture

- Taken from right or left lower lobe

Tissue for cytogenetics

- Fibroblasts are viable up to 24–48 hours after death

Rokitansky technique

- Removal of the thoracic and abdominal viscera en bloc

Routine brain samples

- Cerebrum, hippocampus, basal nuclei, cerebellum, brainstem, and spinal cord

11

Placental Pathology

Normal development

- Blastocyst implanted in gestational endometrium by seventh postovulatory day
- Trophoblasts transport maternal substrates to fetus and ensure adequate tissue remodeling of the uterus
- Intermediate trophoblasts invade endometrium and myometrium
- Endovascular trophoblasts grow into arteries, form cellular plugs, invade arterial walls, destroy endothelium, media, and replace them with fibrinoid material
- At term, mature/intermediate/terminal villi; increase in number, diminish in size, display increased syncytial knots/vasculosyncytial membranes
- Term placental weight is about 450 gm

Normal placental anatomy at term

- Mature placenta composed of four components:
  - Chorionic plate and vascularized fetal connective tissue
  - Villous trophoblasts and intervillous space
  - Basal plate and underlying maternal uterine vasculature
  - Placental membranes (amnion, chorion, and decidua)

Placenta of multiple pregnancy

DIAMNIOTIC-DICHORIONIC

- If embryo division occurs prior to blastocyst formation
- Dividing membranes thick/opaque, contain two amnions/single chorion

DIAMNIOTIC-MONOCHORIONIC

- If embryo division occurs between blastocyst formation and amniogenesis
- Dividing membranes thinner/translucent, contain two amnions/no chorion

MONOAMNIOTIC-MONOCHORIONIC

- If embryo division after amniogenesis
- Absent dividing membranes, placental disc shows no cleavage plane

MONOZYGOTIC PLACENTA

- Division of a single fertilized ovum resulting in identical twins
- Can be any type (diamniotic-dichorionic, diamniotic-monochorionic, monoamniotic-monochorionic)

DIZYGOTIC PLACENTA

- Fertilization of two separate ova, twins are genetically different
- Mostly diamniotic-dichorionic (two separate discs or single fused disc)

MONOCHORIONIC PLACENTAS

- Vascular communications; surface arterial-arterial combined with deep parenchymal artery-artery, vein-vein, and artery-vein
- Twin-to-twin transfusion (TTT) syndrome: Large deep artery-vein anastomoses and paucity of counterbalancing surface artery-artery anastomoses

Anomalies of placenta

PLACENTA EXTRACHORIALIS

- Insertion of membranes into the disc away from disc edge
- Complete or partial
- Chorionic plate smaller than placental disc

Circumvallate

- Membrane folded back upon itself (partial or complete)
- Associated with antepartum/postpartum hemorrhage, premature rupture of membranes (PROM), second trimester abortions

Circummarginate

- Thinning of placental membranes on fetal surface
- No folded membrane
- No morbidity and no clinical significance

VARIATION IN LOBATION

- Accessory lobe/bilobed, lobes of unequal size
- Clinically insignificant, though sometimes may cause postpartum hemorrhage

PLACENTA ACCRETA

- Abnormal attachment of entire/part of placenta to uterine wall after delivery
- Total or partial absence of decidua basalis
- Associated with placenta previa, cesarean section scars, prior dilation and curettage

Accreta

- Villi attached to endometrium without decidua; most common

Increta

- Villi within the myometrium

Percreta

- Full thickness penetration of chorionic villi in uterine wall
- Uterine rupture; hemopericardium

PLACENTA PREVIA

- Abnormally implanted placenta in lower uterine segment/cervix
- Associated with antepartum bleeding, PROM, premature labor

PLACENTOMEGALY

- Large for gestational age placenta (weight >650 gm)
- Hemolytic disease of the newborn
- Non-immune hydrops (chromosomal disorders, infections, maternal diabetes mellitus [DM], Beckwith-Wiedemann syndrome)

AMNION NODOSUM

- Nodules (tiny pinpoint) on amniotic surface of placenta
- Composed of squamous cell aggregates derived from fetal skin and vernix caseosa
- Associated with oligohydramnios sequence

MECONIUM STAINED PLACENTA

- Green-stained umbilical cord and placental membranes
- Vacuolated pigment-laden macrophages in chorionic vessels/umbilical vessels with apoptosis of peripheral vascular smooth muscle (vascular necrosis)
- Indicative of fetal distress, hypoxic-ischemic injury

PLACENTAL DYSMATURITY

- Also known as distal villous dysmaturity
- Enlarged distal villi, numerous central capillaries, increased villous stroma, diminished syncytiotrophoblastic knots, paucity of vasculosyncytial membranes
- Associated with maternal uncontrolled DM, maternal obesity, hypercoiled umbilical cord, chromosomal abnormalities
- May lead to intrauterine fetal demise (IUFD)

Placental vascular lesions

MATERNAL VESSELS

Decidual arteriopathies

Acute atherosis

- Prevalent in severe pre-eclampsia, maternal DM, anti-phospholipid antibody syndrome
- Prominent intimal macrophage proliferation
- Fibrinoid degeneration/medial necrosis of uterine arteries/arterioles
- Changes noted after 18 weeks' gestation

Mural hypertrophy

- Medial hypertrophy of maternal arterioles
- Increased prevalence in chronic hypertension, DM, or pre-eclampsia
- Defective non-trophoblast related remodeling of spiral arteries during early pregnancy
- Thickness of arteriolar smooth muscle exceeds two-third of the total diameter
- May be associated with acute atherosis

Villous changes associated with maternal perfusion

- Leads to fetal growth retardation/pre-term delivery
- Increased villous syncytial knots (due to increased trophoblast turnover), intervillous fibrin deposits (due to circulatory stasis), and villous agglutination (due to foci of trophoblast necrosis)
- Changes noted after 24 weeks' gestation

Villous infarction

- Ischemic necrosis of villous parenchyma due to cessation of maternal vascular flow
- Multiple infarcts at term/any infarct in premature infant = indicative of underlying maternal vascular disease
- Fetal growth retardation, pre-eclampsia, pre-term labor, maternal anti-phospholipid antibodies, chronic hypertension
- Infarts are wedge shaped, dark red (fresh less than 1 day old), or pale yellow (remote)
- Collapse of intervillous space, villous agglutination, ischemic necrosis of trophoblastic cell layer

Perivillous fibrin deposition

- Fibrinoid matrix envelops distal villi
- Preservation of space between villi (no villous agglutination)
- Massive perivillous fibrin deposition (maternal floor infarction) = leads to IUGR, stillbirth, preterm delivery
- Prevalent in maternal hypertension, anti-phospholipid antibody syndrome

Abruptio placentae

- Rupture of spiral arteries leading to central retroplacental hemorrhage
- Indentation/rupture of basal plate, irregular intraplacental hemorrhage, villous stromal hemorrhage
- Risk factors: Maternal hypertension, trauma, vasoactive drugs

Marginal abruption

- May be acute or chronic
- Marginal venous rupture
- Pre-term delivery/second trimester abortion/vaginal bleeding
- Association with circumvallate placenta

FETAL VESSELS

Fetal thrombotic vasculopathy (FTV)

- Thrombotic occlusion of chorionic plate or major stem villous vessels
- Prevalent in umbilical cord entanglement/abnormalities, maternal DM, thrombophilic conditions (anti-phospholipid antibody syndrome, clotting disorders)
- Adverse fetal outcomes; neonatal encephalopathy, cerebral palsy, disseminated intravascular coagulation (DIC)
- More than 15 affected villi per section of villous parenchyma
- Hyalinized avascular villi, stromal vascular karyorrhexis (hemorrhagic endovasculitis), organized thrombi in major fetal vessels, fibromuscular sclerosis of the vessels

Partial/chronic/intermittent umbilical cord obstruction

- Scattered small foci of avascular villi (near basal plate and distal villi)

- Intimal fibrin cushions in large fetal veins
- Ectasia of fetal veins (chorionic plate and stem vessels)

Intervillous thrombi

- Feto-maternal hemorrhage
- Parenchymal hematomas surrounded by villi
- Significant in ABO incompatibility

Villous capillary proliferations

CHORANGIOSIS

- More than 10 capillaries in at least 10 terminal villi in at least three low power fields of placenta
- Indicative of chronic placental hypoperfusion/low-grade tissue hypoxia
- Associated neonatal morbidity/mortality

CHORANGIOMA

- Benign hemangioma of placenta (1%)
- Large tumor associated with high-output congestive heart failure
- Well-circumscribed mass of small capillaries lined by benign endothelium

CHORANGIOMATOSIS

- Non-expansile vascular proliferation in normal stem villi
- Proliferation of capillaries and the surrounding pericytes
- Stromal fibrosis
- Diffuse/multifocal, can involve several non-contiguous areas of placenta
- Associated neonatal morbidity/mortality

MESENCHYMAL DYSPLASIA

- Placental vascular anomaly involving varying combinations of small and large fetal vessels
- Increased villous stroma, cavitated edematous cisterns
- Associated with Beckwith-Wiedemann syndrome

Gestational trophoblastic disease

COMPLETE MOLE (CM)

- Large for gestational age uterus, vaginal bleeding, spontaneous abortion with passage of molar tissue
- Elevated HCG levels, bilateral ovaries may show theca-lutein cysts
- Diploid karyotype (46XX) = both chromosomes are androgenic
- Diffuse circumferential trophoblastic proliferation, uniform dilation of avascular villi, central cisterns (grape-like clusters), absent fetal parts/cord/membranes
- Spontaneous regression in most, after evacuation
- A few develop either invasive mole or choriocarcinoma (2%)
- Strong HCG and p53 immunopositivity
- P57 kip2 (cyclin-dependent kinase inhibitor) is negative

PARTIAL MOLE (PM)

- Missed abortion
- HCG levels normal or slightly high
- Chorionic villi display biphasic populations; dilated villi mixed with normal villi
- Polarized trophoblastic proliferation, less villous edema, no cistern formation, fetal tissue may be present
- Triploid karyotype (mostly 69 XXY or 69 XXX)
- HCG (weakly +ve), p53 +ve and p57kip2 is +ve (paternally imprinted and expressed from maternal alleles)

INVASIVE MOLE (CHORIOADENOMA DESTRUENS)

- Uterine bleeding and persistently elevated HCG after evacuation of mole
- Molar villi extend into myometrium
- Uterine perforation, villi may embolize to other organs with hemorrhagic complications
- No metastases

PLACENTAL SITE TROPHOBLASTIC TUMOR (PSTT)

- Abnormal proliferation of intermediate trophoblasts
- Solitary nodule in myometrium
- Spindle/polyhedral mononuclear cells deeply invade the myometrium
- Absence of villi/cytotrophoblasts
- Mostly benign, risk of uterine rupture
- 10%–15% are malignant, may metastasize to distant organs

CHORIOCARCINOMA

- Highly malignant tumor
- 50% of cases associated with previous history of complete mole
- Other cases associated with spontaneous abortion, normal pregnancy, or ectopic pregnancy
- Tumor is necrotic and very hemorrhagic
- Highly atypical syncytiotrophoblasts and cytotrophoblasts
- Absent chorionic villi
- Markedly elevated serum HCG

Placental inflammation

INFECTIOUS CAUSES

Amniotic fluid infection (chorioamnionitis)

- Ascending infection from organisms in genital tract or bloodborne infection
- Bacteria, mycoplasma, or fungal infections
- Gram-negative bacilli, group B streptococci or *Staphylococcus aureus*
- Pre-term labor, maternal fever, fetal/maternal tachycardia, foul-smelling discharge
- Grade I (neutrophils in subchorionic fibrin), Grade II (neutrophils in both amnion and chorion), Grade III (necrotizing chorioamnionitis)

Funisitis

- Infection of the umbilical cord
- *Candida albicans* infection may cause microabscesses on surface of umbilical cord

Chronic deciduitis

- Prevalence is 3% at term
- Accompanies acute chorioamnionitis, TORCH infections, villitis of unknown etiology (VUE), maternal vascular disease
- Lymphoplasmacytic infiltrate in decidua

Placental malaria

- Diffuse infiltration of intervillous space by histiocytes, fibrin, malarial pigment, and parasitized red cells
- Rare cause of recurrent reproductive failure

Congenital infections and TORCH group

- TORCHS is an acronym for feto-placental infections caused by *Toxoplasma gondii*, Others (Epstein-Barr virus, varicella-zoster virus, *Treponema pallidum*), rubella virus, cytomegalovirus, herpes simplex viruses, and syphilis
- Multifocal chronic placental inflammation
- Associated with hydrops fetalis, hepatosplenomegaly, IUGR, petechiae, central nervous system damage and placental villitis (infectious)
- *Syphilis*: Histiocytic villitis with villous edema
- *CMV*: Plasma cell villitis with villous fibrosis
- Lymphoplasmacytic inflammatory infiltrate noted in umbilical cord, membranes, all villi
- *Screening tests:* "TORCH titer" test, IgG, IgM antibodies, polymerase chain reaction on fetal blood or amniotic fluid from amniocentesis

Toxoplasmosis

- Microcephaly, periventricular calcification, myocarditis, and chorioretinitis

Rubella

- *Fetal rubella syndrome*—cataracts, deafness, patent ductus arteriosus
- Worse prognosis if infection occurs before 8 weeks of gestation

CMV

- Jaundice, hepatitis

Herpes

- Prematurity/stillbirth, pneumonitis, hepatosplenomegaly

Congenital syphilis

- Hydrops fetalis with IUGR, pneumonia alba, Hutchinson's incisors, saddle nose, saber shin

Listeria

- Fetal septicemia, placental abscess

Parvovirus

- Hydrops, congenital anemia

NON-INFECTIOUS CAUSES

Villitis of unknown etiology (VUE)

- Prevalent in 5%–10% of pregnancies
- Patchy chronic lymphocytic infiltrate seen in villous stroma (less than 25% villous affected)
- Maternal T lymphocytes react to fetal macrophages in the villous stroma
- Focal/patchy nature of villous infiltrate (d/d infectious villitis)
- Small group of less than 10 villi involved
- Adverse outcomes include IUGR, cerebral palsy, fetal neurological impairments, recurrence of VUE

Obliterative fetal vasculopathy

- Associated condition with VUE
- Marked perivascular chronic inflammation involving stem villi leading to vascular occlusion/avascular villi

Lesions of umbilical cord

- Hypercoiling (more than two to three coils per 10 cm)
- Long umbilical cord (UC) (>70 cm)
- UC entanglements/UC knots (true versus false)
- Membranous/furcated umbilical cord insertion (Battledore placenta)
- Decreased Wharton jelly
- Encirclement of UC by amniotic bands

Placental changes in IUFD

- Morphological changes similar to FTV but seen diffusely throughout placenta
- Early demise (24–48 h) shows nuclear karyorrhectic debris in blood vessels and villous capillaries
- Later morphological changes include vascular septation, avascular villi, villous fibrosis, calcification

Section B

Systemic Organ Pathology

12 Breast

Embryology/development/anatomy

- Modified sweat gland
- Development begins during fourth week of intrauterine life
- By term, 15–20 lactiferous ducts form
- Progressive branching of this system forms ductal-lobular architecture
- Mammary gland of newborn rudimentary but responsive to maternal hormones
- In newborn, mammary glands clinically palpable, composed of secretory ducts and edematous stroma
- Female pubertal breast enlargement (thelarche) due to accumulation of fat and ductal lobular units
- Male breast tissue hormonally unstimulated and contains ducts without lobular development

Congenital anomalies

AMASTIA

- Congenital absence of breast
- Failure of pectoral portion of mammary ridges to develop
- Often clinical manifestations of Poland syndrome (aplasia of pectoral muscles)

ATHELIA

- Absence of nipple

SUPERNUMERARY NIPPLE

- *Polythelia*, accessory nipple
- Mostly arise along embryonic mammary line
- Small pigmented macule with tiny umbilication
- Morphologically contains components of normal nipple
- Sometimes hyperplastic duct epithelium, capillary proliferation, pilosebaceous units, bundles of smooth muscle

ACCESSORY BREAST TISSUE

- More common in Native American population
- Mass in axilla or vulva
- Unremarkable breast ducts and subareolar structures

BREAST ASYMMETRY

- Between Tanner stages 2 and 4
- May persist in some young adults
- Correctable by augmentation mammoplasty
- Unilateral breast enlargement in neonates; in response to maternal and placental hormones

Breast lesions

FIBROCYSTIC CHANGES

- Mid to late adolescence
- Cysts and masses with variable size
- Correlates with menstrual cycle
- Perimenstrual tenderness
- Stromal fibrosis with variable cellularity, cystic dilation, apocrine metaplasia, adenosis, and usual ductal hyperplasia

Fibrous mastopathy

- Localized, ill-defined fibrous proliferation of breast stroma
- Fibrous end of fibrocystic spectrum

Type I

- More common in young females
- Prominent acinar tissue with scant concentric collagen bundles

Type II

- Partial replacement of the acini by irregularly distributed collagen

Type III

- Almost complete replacement of acinar tissue by collagen

Pseudoangiomatous stromal hyperplasia (PASH)

- Fibrous mastopathy with myofibroblastic differentiation
- Anastomosing small, slit-like spaces mimicking vascular spaces in a background of dense collagenous fibrosis

PAPILLARY DUCT HYPERPLASIA

- Presents as a mass
- Gross cut surface: Cysts with papillary excrescences
- Three patterns: *True papilloma, sclerosing papilloma,* and *papillomatosis*
- Fronds of epithelial cells in single or multiple layers with fibro-vascular stromal cores
- *Sclerosing papilloma*: Radial scar-like lesion, mimics carcinoma

DIABETIC MASTOPATHY

- Long-standing type I diabetes
- Late adolescence, firm mass in one or both breasts
- Lymphocytic lobulitis, ductitis, perivasculitis, and dense keloidal fibrosis
- Commonly recurs

JUVENILE PAPILLOMATOSIS

- Postpubertal, firm, discrete solitary mass at breast periphery
- Gross cut surface; several variably sized cysts (1 mm – 2 cm); *Swiss cheese breast*
- Apocrine metaplasia, usual ductal hyperplasia, papillomas, cysts, and dilated ducts (with lipid-laden macrophages in lumen), microcalcifications
- Sometimes atypical ductal hyperplasia
- Recurs if surgical margins positive

INFECTIONS

- Any age
- Etiology: Foreign bodies, trauma, nipple piercing, epidermal cyst infection
- Often *Staphylococcus aureus*, sometimes *Mycobacterium*
- Acute and chronic inflammation, abscess, granulomas, squamous metaplasia
- Incision and drainage for abscess treatment

FAT NECROSIS

- Previous surgery or trauma
- Nodules with gritty yellow cut surface
- Chronic inflammation, lipophages, fibrosis, dystrophic calcification

GYNECOMASTIA

- Idiopathic enlargement of breast in males
- Most common breast abnormality in adolescent boys
- Imbalance between estrogen and androgen, disordered end-organ response
- Bilateral, if underlying endocrine abnormality associated
- *Pseudogynecomastia*: Breast enlargement due to other tissues like muscle enlargement, obesity, diffuse neurofibromatosis, pseudoangiomatous stromal hyperplasia (PASH)
- Subareolar mass, rubbery, white, ill-defined, mixed with adipose tissue
- *Early phase*: Ductal epithelial hyperplasia, papillary and cribriform pattern, myoepithelial hyperplasia, cellular and edematous stroma
- *Late phase*: Less epithelial proliferation, more collagenous stroma

JUVENILE HYPERTROPHY AND MACROMASTIA

- Spontaneous, massive, painful, deforming, and rapid growth of female breast

- Onset at menarche, unilateral/bilateral
- Secondary to increased sensitivity to gonadal hormones
- Probably autoimmune etiology
- Grossly, no discrete mass, homogenous tan-yellow cut surface
- Irregular ductal proliferation, epithelial hyperplasia, edematous stroma, PASH may be associated
- Treated with antiestrogen therapy or surgical reduction

FIBROADENOMA

- Common, adolescent females
- Painless, slow growing, well circumscribed, freely mobile, size range 2–4 cm
- Rubbery, bulging, and lobulated cut surface
- Biphasic proliferation of epithelial, myoepithelial, and stromal elements
- Intracanalicular and pericanalicular subtypes

TUBULAR ADENOMA

- Variant of fibroadenoma
- Small packed tubules, lined by epithelial and myoepithelial cells, minimal stromal component

LACTATIONAL ADENOMAS

- All ducts show lactational changes
- Glands are closely aggregated and are actively secreting
- Seen during or shortly after pregnancy

JUVENILE FIBROADENOMA

- Also known as cellular or giant fibroadenoma
- Overlapping features with benign phyllodes tumor
- Rapidly enlarging, size >5 cm
- More common in African Americans
- Differs from typical fibroadenoma by having a more hypercellular stroma and more epithelial hyperplasia
- Intracanalicular, pericanalicular, and leaf-like pattern (clefts lined by hyperplastic epithelium)
- Stromal cells lack atypia, rare mitotic figures
- Benign but recurrent

PHYLLODES TUMOR (CYSTOSARCOMA PHYLLODES)

- Regarded as low-grade malignancy
- Rapidly enlarging discreet circumscribed mass
- Tan-gray bulging and clefted cut surface
- Low-grade spindle cell stroma, mitotically active
- Mitotic rate determines survival
- Stromal cellularity and mitotic activity concentrated around ducts
- Sarcomatous component may resemble myofibroblasts, undifferentiated sarcoma, rhabdomyosarcoma, liposarcoma
- Favorable prognosis: 10-year survival 90%
- Recurs commonly, rare metastases

NIPPLE DUCT ADENOMA

- Rare lesion in children
- Rapidly enlarging unilateral subareolar mass
- Erosion of overlying skin/nipple discharge
- Sclerosing papillomatosis, papillomatosis and adenosis
- Differential diagnosis with syringocystadenoma papilliferum (extension to skin surface, exuberant plasma cell infiltrate)

HAMARTOMA

- Fibrous or adipose tissue stroma, normal lobules/ducts (breast within a breast)

SECRETORY CARCINOMA

- Also known as juvenile carcinoma
- Very rare, may also be seen in boys
- Indolent clinical behavior
- Balanced t(12; 15) translocation creating *ETV6-NTRK3* gene fusion (also seen in cellular mesoblastic nephroma and infantile fibrosarcoma)
- Size range: 1–2.5 cm

- Lobules of tumor cells separated by thick bands of connective tissue
- Extracellular secretions and intracytoplasmic vacuoles
- Association with juvenile papillomatosis

OTHER BREAST CANCERS

- Second malignant tumors; in long term survivors of other childhood tumors
- Inherited mutations of *P53* and *BRCA* genes

MESENCHYMAL LESIONS

Lipoma

- Rare

Fibromatosis

- Spindle cells arranged in broad sheets with thin-walled open blood vessels (positive for CD34 and beta-catenin)
- May spread to surrounding soft tissue
- Differential diagnosis with PASH and nodular fasciitis, which are myofibroblastic lesions (positive for vimentin and smooth muscle actin)

Vascular tumors

- Infantile or capillary hemangioma
- Regress/involute with fibrosis

Granular cell tumor

- Benign tumor
- Sheets of large polygonal cells with abundant pale granular cytoplasm, central vesicular nuclei, prominent nucleoli
- PAS +, diastase resistant, S100 +

Hematopoietic lesions

- These lesions include Burkitt lymphoma, granulocytic sarcoma, Rosai-Dorfman disease

13 Female Reproductive System

General

- Process of sexual development divided into various phases

CHROMOSOMAL SEX

- Genetic sex determined by XX and XY genotypes

GONADAL SEX

- Development of ovaries or testes
- Sex-determining region on Y chromosome
- Gonadal sex predominantly dependent on sex-determining region Y (SRY)

PHENOTYPIC SEX

- Ductal system and external genitalia
- Regulated by müllerian inhibiting substance (MIS)/anti-müllerian hormone (AMH) (secreted by Sertoli cells)
- Regulated by steroid hormones of testis and ovary
- Disorders of sex development (DSDs) get initiated in utero and final phenotypic changes occur at time of puberty

Embryology

- Primordial germ cells (PGCs) reach genital ridge at 4–5 weeks of gestational life
- Indifferent gonad derived from mesothelium lining the posterior abdominal wall, underlying mesenchyme and PGCs
- Up to 6 weeks, indifferent gonad remains bipotential and indistinguishable between male and female
- Expression of SRY necessary to initiate testicular development
- Timing of SRY expression crucial for normal development; otherwise ovary formed in XY embryo
- Ovarian germ cells undergo active mitotic division up to birth
- Germ cells enter meiosis at 12th week of gestation and commit to become oocytes
- Primordial follicle formed when oocyte surrounded by granulosa and theca cells
- During prepubertal years, oocytes and primordial follicles gradually decrease in number/ovarian stroma increases
- Mesonephric (wolffian) ducts in female embryo begin to disappear by week 10
- *Gartner ducts*: Mesonephric remnants in broad ligament, uterus, or vagina
- *WNT4*, *HOXA* genes essential for normal müllerian development
- If female fetus exposed to an increase in androgens before 10–12 weeks' gestation, ambiguous external genitalia resembling phenotypic male
- If androgens increase after week 20, the only effect is enlarged clitoris

Premature ovarian failure

- Deficiency of sex steroid production
- High gonadotropin levels and amenorrhea any time before 40 years of age
- Turner syndrome, fragile X, Swyer syndrome (XY gonadal dysgenesis)
- Infections, autoimmune disorders, treatment of childhood tumors

Acquired abnormalities and other lesions

- Infections common in premenarchal girls; HPV, HSV, syphilis, molluscum contagiosum

CONDYLOMA ACUMINATA

- HPV type 6 or 11
- Hyperkeratosis, parakeratosis, acanthosis, dyskeratosis, and koilocytosis (raisinoid nuclei) of squamous epithelium
- Laryngeal papillomas in infants of mothers with condyloma acuminata (due to HPV exposure during vaginal delivery)
- Transmission: Perinatal, autoinoculation/heteroinoculation, sexual abuse

HERPES

- Nuclear ground glass inclusions
- Infected cells exhibit multinucleation, nuclear molding, and chromatin margination

SYPHILIS

- *Chancre*: Shallow ulcer
- Perivascular infiltrate, plasma cells, lymphadenopathy, plaques (*condyloma lata*)
- Spirochetes (detected by Warthin starry silver stain, fluorescent conjugated antibodies)

MOLLUSCUM CONTAGIOSUM

- Pox virus
- Large intracytoplasmic inclusion bodies

CHLAMYDIA TRACHOMATIS

- Salpingitis, endometritis; leading to infertility
- Infection of vulva and vagina leads to lymphogranuloma venereum
- Cell culture is diagnostic

CHANCROID

- *Haemophilus ducreyi*

GRANULOMA INGUINALE

- Calymmatobacterium granulomatis
- Vacuolated histiocytes contain encapsulated bacilli = Donovan bodies

BEHÇET SYNDROME

- Autoimmune etiology
- Triad: Oral ulcers, vulvar ulcers, and ophthalmologic inflammations

Miscellaneous entities

- Lichen sclerosis, bullous diseases, Crohn disease

Tumors of the female genital tract

BENIGN TUMORS/CYSTS

Bartholin cyst

- Located in vagina/labia
- Lined by squamous/urothelial epithelium, inflamed
- May be caused by sexually transmitted organisms

Cysts of Gartner duct

- Vaginal inclusion cyst
- Non-mucinous
- Arises from vestigial remnants of mesonephric duct

Cysts of canal of Nuck

- Inguino-labial swelling, hydrocele
- Cyst wall is fibrovascular and is lined by mesothelial cells

Müllerian cyst

- Arises from remnants of müllerian ducts
- Mucin secreting, lined by columnar epithelium

Hidradenoma papilliferum

- Benign tumor of apocrine sweat gland origin
- Tubules and acini with intact myoepithelial cells

MALIGNANT TUMORS

Embryonal rhabdomyosarcoma

- Most common

Botryoid embryonal

- Vaginal discharge, bleeding, grape-like mass at introitus
- Tumor cells round to spindle shaped
- Cambium cell layer underneath vaginal epithelium
- Cervical embryonal rhabdomyosarcoma: Islands of mature metaplastic cartilage
- Loss of heterozygosity at 11p15
- Positive for muscle markers; desmin, MyoD1, myogenin, and myoglobin
- Rule out other small, round, blue cell tumors: Embryonal rhabdomyosarcoma (RMS) negative for PGP9.5, CD99, WT1, CD45
- Positive for desmin and myogenin (less frequently positive as compared to alveolar RMS)
- Treatment: Primary chemotherapy followed by local excision

Endodermal sinus tumor (yolk sac tumor)

- Good prognosis with chemotherapy

Clear cell adenocarcinoma

- Vaginal tumor
- Manifested in daughters whose mothers took diethylstilbestrol during pregnancy

HPV condyloma

- HPV types 6 and 11

Ovarian tumors

BENIGN/CYSTIC LESIONS

- Congenital cysts lined by luteinized cells
- Acquired cysts lined by granulosa cells
- Follicular cysts (in prepubertal girls): Incidental or associated with pseudoprecocious puberty
- Juvenile hypothyroidism: Multicystic ovaries/galactorrhea

Polycystic ovary syndrome (PCOS)

- Incidence 3%–8%
- Primary or secondary amenorrhea, delayed puberty
- Anovulatory cycles, unopposed estrogen influence
- Enlarged ovaries, multiple follicular cysts underneath ovarian cortex
- Medullary stromal hyperplasia

Endometrioma

- Hemorrhagic cyst lined by plump cuboidal epithelial cells
- Compressed endometrial stroma, hemosiderin pigment, inflammatory cells underneath

Massive edema of ovary

- Torsion of mesovarium
- Restriction of lymphatic and venous drainage

OVARIAN NEOPLASMS

Germ cell tumors

- More common in children compared to adults

Mature teratoma

- Most common (40%–60% of all childhood ovarian neoplasms)
- Cystic or solid
- Cystic type resembles benign dermoid cyst
- Uncontrolled growth of tissue from one or more of the three embryonic layers (ectoderm, mesoderm, and endoderm)
- Malignant transformation very rare, karyotypically normal
- *Struma ovarii*: Contains mostly thyroid tissue. Thyroglobulin and TTF-1 positive

Immature teratoma

- Intermediate malignancy
- Malignant ones always contain component of endodermal sinus tumor: Increased serum alpha-fetoprotein (AFP)
- Frequent non-recurrent abnormalities in tumor
- Grading based on: Quantity of immature neuroectoderm
  - Primitive neuroepithelium limited to one low power field/slide = Grade I

- Primitive neuroepithelium up to three low power fields/slide = Grade II
- Primitive neuroepithelium more than three low power fields/slide = Grade III

Gliomatosis peritonei

- Small nodules of mature glial tissue implants on peritoneal surface
- Solid mature and immature teratomas
- Do not affect staging or prognosis

Ovarian dysgerminoma

- Most common malignant germ cell tumor of ovary
- Biological counterpart of testicular seminoma
- Mutation is i(12p)
- Nested uniform neoplastic cells with distinct cell outlines, round nuclei, prominent nucleoli
- Brisk lymphocytic infiltrate in tumor parenchyma
- Scattered multinucleated syncytiotrophoblasts
- Positive for PLAP, OCT4, CD117
- Highly radiosensitive tumors

Endodermal sinus tumor

- Aka yolk sac tumor
- Serum AFP levels used for monitoring tumor recurrence/metastases
- Various subtypes: Reticular, solid, microcystic patterns
- Coarse chromatin, cytoplasmic vacuoles, hyaline bodies
- *Schiller-Duvall bodies* diagnostic: Central vascular core lined by tumor cells, a space, and then an outer rim of tumor cells
- Positive for AFP, negative for OCT4
- Mutation is i(12p)

Embryonal carcinoma

- Rare tumor but may be a minor component in mixed germ cell tumor
- Glandular, papillary, solid subtypes
- Large, overlapping nuclei, prominent nucleoli, amphophilic cytoplasm, individual cell necrosis
- Positive for CK+, OCT4, CD30. Negative for epithelial membrane antigen (EMA)

Ovarian choriocarcinoma

- Rare but may be minor component in mixed germ cell tumor
- Hemorrhagic tumors, medium-sized cytotrophoblasts, multinucleated syncytiotrophoblastic
- No chorionic villi
- HCG positivity in syncytiotrophoblasts

Gonadoblastoma

- Arise in dysgenetic gonads, phenotypic females with 46XY karyotype
- Small nodules within streak gonads
- Eosinophilic hyaline bodies, germ cells, stromal cells of Sertoli-granulosa cell type, hyalinization, laminated calcifications
- *TSPY* gene involved

Ovarian sex-cord stromal tumors

- Ovarian stromal cells: Granulosa, theca, interstitial, fibroblasts
- May contain testicular stromal cells: Sertoli cells
- Precocious puberty (mostly before 9 of years age)
- Virilization (mostly after 9 years of age)
- Positive for inhibin, calretinin, and CD99
- Negative for EMA

Juvenile granulosa cell tumors

- Solid, yellow tumors with fibrous bands
- Solid sheets of luteinized cells with interspersed irregular follicles resembling large Graafian follicles
- Mitotically active, mild cytologic atypia
- Absent nuclear grooves and absent Call-Exner bodies (d/d from adult granulosa cell tumor)
- Better prognosis than adult tumors

Adult-type granulosa cell tumors

- More rare than juvenile subtype
- Various histological subtypes: Microfollicular, macrofollicular, diffuse, trabecular
- Nuclear grooves and Call-Exner bodies always present

Sex-cord tumors with annular tubules (SCTAT)

- Rounded epithelial nests, cells with abundant pale eosinophilic cytoplasm, multiple hyaline bodies
- No germ cells
- Association with Peutz-Jeghers syndrome

Sclerosing stromal tumors

- Lobules of spindle-shaped cells separated by edematous stroma
- Lipid-containing signet ring-like cells scattered in between

Sertoli-Leydig cell tumors of ovary

- Virilizing tumors
- Varying proportion of Sertoli, Leydig, and indifferent stromal cells
- Classified by degree of differentiation: Well, intermediate, and poorly differentiated
- May contain heterologous elements

Epithelial neoplasms

- Arise from ovarian surface epithelium, multipotential (mucinous, serous, endometrioid, mesenchymal)
- Classified into benign, borderline, or malignant
- Borderline: Complex architecture, papillary processes, loss of nuclear polarity, mitoses, cytologic atypia (lack invasion into underlying stroma)
- Malignant (invade into underlying stroma)

Serous neoplasms

- Epithelial cells are ciliated columnar to cuboidal (resemble epithelial cells lining the fallopian tube)

Mucinous neoplasms

- Epithelial cells are mucin containing (resemble epithelial cells lining the endocervix)

Small cell tumors

- Very aggressive tumors
- Paraendocrine hypercalcemia
- Poorly differentiated small cells with hyperchromatic nuclei and scant cytoplasm
- Positive for EMA, WT1, and chromogranin

14 Male Reproductive System and Disorders of Sexual Development

Testes

EMBRYOLOGY/ANATOMY/PHYSIOLOGY

- Gonadal development starts with formation of urogenital ridge
- Urogenital ridge composed of mesonephros and gonadal ridge
- Normal male differentiation depends on expression of *SRY* gene on Y chromosome
- In absence of *SRY* gene, an ovary is formed
- *SRY* expressed (transiently) by celomic-derived somatic cells in testicular stroma
- *SRY* expression activated by WT1
- In gonadal blastema, celomic epithelial cells express *SOX9* and anti-müllerian hormone (AMH)
- By the sixth to eighth weeks of embryonic life, celomic epithelial cells start to organize into tubular structures forming primordial sex cords
- Fibrous tunica albuginea is formed at eighth week of gestation
- Morphology of seminiferous tubules unchanged from birth to puberty
- Testicular development complete by eighth week of embryonic life (abdominal organ at this time)
- AMH appears at 12th–16th weeks; helps in regression of müllerian duct and upper vagina
- Testosterone peaks at 12th–16th week; helps in differentiation of wolffian ducts, epididymis, vas deferens, and seminal vesicles
- Rete-testis develops from mesonephric remnants in proximity of seminiferous cords
- At 8th–15th weeks, transabdominal phase of testicular descent occurs (dependent on androgen expression)
- Gubernaculum (caudal ligament of testis) helps in migrating the testis down to inguinal region
- At 28th–35th weeks, inguino-scrotal phase of testicular development, mediated by gubernaculum and dependent on androgen expression

AT PUBERTY

- Sertoli cells stimulated by luteinizing hormone and follicle-stimulating hormone, acquire adult phenotype
- Tight junctions (blood-testis-barrier) formed between Sertoli cells
- Sertoli cells secrete fluid, seminiferous tubules, acquire lumina
- AMH (anti-müllerian hormone) production stops
- Germ cells enter meiosis and enter tubular luminal compartment
- Spermatogenesis begins
- Sertoli cells express androgen receptor

CONGENITAL ANOMALIES

Cryptorchidism/undescended testis

- Unilateral/bilateral testes fail to migrate to base of scrotum
- Incidence increased in premature males at birth
- Processus vaginalis mostly patent
- Atrophic seminiferous tubules with irregular contour
- Thick basement membranes, lack of spermatogenesis
- Sertoli cell only pattern in testis

Prepubertal macroorchidism

- Idiopathic, McCune-Albright syndrome, fragile X syndrome

Testicular regression syndrome

- Irreversible destruction of one/both testes during fetal life in an XY individual
- Variable hormonal deficiencies and developmental anomalies (based on stage at which testicular damage occurred)
- Etiology: Genetic, intrauterine infection, testicular infarction

Other anomalies

- Agonadism, anorchidism, testicular agenesis, rudimentary testes, hypoplastic testes

ACQUIRED DISORDERS

Testicular torsion

- Medical emergency, most common cause of testicular infarct
- Delayed repair (if done after 8 hours): Testicular viability lost, permanent ischemic injury
- Three grades of testicular injury
- Grade III: Fully developed hemorrhagic infarction of testis, necrosis of seminiferous tubular cell layer

Epididymoorchitis

- Bloodborne infections cause orchitis
- Infections ascending through sperm excretory ducts cause epididymitis
- Predisposing factors: Trauma, hematological spread, urinary tract infection, urologic abnormalities
- Etiologic agents: *Escherichia coli*, chemical epididymitis, mumps virus, coxsackie B virus
- Granulomatous-orchiepididymitis (tuberculosis in endemic regions)

Testicular microliths

- Microliths develop in cryptorchid testes
- Inside the seminiferous tubules
- These tubules are devoid of germ cells
- Hypersecretion of laminin/collagen IV by Sertoli cells, followed by mineralization
- Bad prognosis

TESTICULAR NEOPLASMS

- Most common are the germ cell tumors followed by sex-cord stromal tumors
- Juvenile granulosa cell tumor: Most common in newborns
- Rhabdomyosarcoma: Most common paratesticular tumor

Germ cell tumors

Differences between Prepubertal and Postpubertal Germ Cell Tumors

Prepubertal	*Postpubertal*
Contain only one histologic type (teratoma or yolk sac tumor)	Mixed histology of seminomatous and nonseminomatous counterparts
Do not occur in cryptorchid testis	Associated with cryptorchid testis, somatosexual ambiguity syndromes, and so on
Lack the intratubular germ cell neoplasia component	Invariably contain intratubular germ cell neoplasia
Diploid (teratoma) or aneuploid (yolk sac tumor)	Hypertriploid (seminoma) or hypotriploid (nonseminoma) or may have mutations of short arm of chromosome 12: i(12p), and so on
May be either benign or malignant	Mostly always malignant

Yolk cell tumor

- Median age of presentation: 16–18 months
- Associated with an increase in serum AFP levels
- Not hormonally active
- Metastases at time of presentation common (hematogenous or lymphatic)
- Various histologic subtypes: Microcystic, reticular, endodermal sinus pattern, polyvesicular vitelline, hepatoid
- Meshwork of vacuolated cells with eosinophilic hyaline globules, Schiller-Duval bodies
- Positive for AFP, SALL4
- PLAP positive or negative
- OCT4-ve

Teratoma

- Tissues from different germ cell layers/varying proportions (endoderm, mesoderm, and ectoderm)
- Nodular firm, cystic, and solid cut surface
- Mature elements resemble normal postnatal tissue derived from three germ layers
- Immature elements: Embryonal type of neuroectodermal or other tissue

Fetus in fetu

- Extensive maturation/organization of a teratoma
- Type of pathologic monozygotic twinning
- May show vertebral body development
- Excellent prognosis

Epidermoid cyst

- Benign tumor of ectodermal origin
- Lack components of other germ cell layers
- Cyst contains flaky, yellow-white keratinous material
- Lined by keratinized squamous epithelium
- Confined to testicular parenchyma
- Enucleation has excellent prognosis

Intratubular germ cell neoplasia

- Neoplastic proliferation of germ cells within the seminiferous tubules
- Precursor lesion (carcinoma in situ)
- Large cells with irregular nuclei, vacuolated cytoplasm, coarse chromatin, and prominent nucleoli
- Not reliably detected in at-risk prepubertal patients
- Tumor cells line basal portion of tubules
- Positive for PLAP, OCT4, CD117

Embryonal carcinoma

- Common component in mixed GCT, but rare in pure form
- Sheets of large undifferentiated pleomorphic cells with prominent nucleoli and atypical mitoses, necrosis
- May show primitive gland or papillary formations
- Positive for OCT4, CD30, CK, PLAP, AFP
- Negative for EMA

Seminoma

- Sheets/aggregates of uniform cells with clear cytoplasm, well-defined cell borders, large regular nuclei, prominent nucleoli
- Neoplastic cells resemble primitive germ cells
- Tumor infiltrated by lymphocytes
- Positive for PLAP+, OCT4+, CD117+

Choriocarcinoma

- Rare as pure form but may be a component of mixed GCT
- Syncytiotrophoblasts and cytotrophoblasts
- No chorionic villi
- Hemorrhage and necrosis
- Positive for HCG

Mixed germ cell tumor

- Combination of two or more germ cell tumors
- More common in postpubertal testis
- Adjacent testis may show intratubular germ cell neoplasia

Sex-cord stromal tumors

- Composed of specialized supportive components of male and female gonad
- Prepubertal and postpubertal testis

Leydig cell tumor

- Precocious puberty, increased levels of testosterone
- More common with Klinefelter syndrome, cryptorchidism
- Sheets of large polygonal cells, abundant granular eosinophilic cytoplasm
- Lipofuscin pigment, crystals of Reinke
- Positive for vimentin, inhibin, calretinin, Melan-A
- May be seen in adrenogenital syndrome or Nelson syndrome

Sertoli cell tumor

- Genetic or syndromic associations (androgen insensitivity syndrome, Peutz-Jeghers syndrome)
- Precocious puberty, increased estradiol levels, gynecomastia

- Sertoli cells in various stages of differentiation
- Tubular, retiform, or solid growth pattern
- Cells are round/oval/elongate, uniform without pleomorphism
- Positive for vimentin and CK

Large cell calcifying Sertoli cell tumor

- Variant of SCT
- Cords/sheets of large polygonal cells, abundant myxohyaline stroma
- Large areas of calcification

Juvenile granulosa cell tumor

- Most frequent congenital testicular tumor
- Most common in early infancy
- Hormonally inactive
- Associated with dysgenetic gonads, or structural abnormalities of Y chromosome
- Solid and cystic pattern
- Cysts lined by proliferated granulosa cells internally and theca cells externally
- Interfollicular areas: Nodules and sheets of tumor cells, mitotically active
- Positive for vimentin, CK, S100, Inhibin

Gonadoblastoma

- Associated with mixed gonadal dysgenesis with ambiguous genitalia and presence of Y chromosome
- Nests of large/pale germ cells, admixed with sex-cord cells (with small dark and angular nuclei)
- Hyalinized nodules of basement membrane-like material surrounded by tumor cells
- Prominent calcification

Sex-cord stromal tumor with annular tubules

- Association with Peutz-Jeghers syndrome

Epididymis, spermatic cord, and paratesticular tissues

CONGENITAL ANOMALIES

- Complete absence of vas deferens (most common), epididymis, seminal vesicle
- Selective atresia, ectopia, cysts, diverticula
- Embryonal remnants of müllerian ducts (in hernia sac); tubular structures, narrower than vas deferens, no smooth muscle in wall
- Cystic fibrosis: Aplasia/hypoplasia of vas deferens/epididymis
- Congenital absence of bilateral vas deferens: Defects in *CFTR* gene
- Heterotopic tissue in paratesticular region (splenogonadal fusion tissue, immature renal, testicular, adrenal tissue)

VARICOCELE

- Dilatation of veins in pampiniform plexus of spermatic cord (adolescent boys)

HYDROCELE

- Fluid accumulation in processus vaginalis/tunica vaginalis

MECONIUM PERIORCHITIS

- Large solitary/multinodular paratesticular mass along spermatic cord
- In utero perforation of gastrointestinal tract → meconium leak in peritoneal cavity → tunica albuginea via processus vaginalis
- Fibrous tissue, macrophages, foreign body giant cells with brown bile pigment, cholesterol clefts, dystrophic calcification

PARATESTICULAR TISSUE TUMORS

Malignant mesothelioma

- Resemble pleural and peritoneal counterparts
- Range from well-differentiated (tubulepapillary architecture) to completely undifferentiated forms (solid diffuse growth pattern)
- Mesothelial cells positive for CK5/6, calretinin

Desmoplastic small round cell tumors

- Small round cells with epithelial growth pattern

- Desmoplastic stroma
- Positive for keratin and desmin
- Chromosomal abnormality t(11;22)(p13;q12) resulting in gene fusion *EWS-WT1*

Rhabdomyosarcoma

- Most common paratesticular sarcoma in children
- Embryonal more common
- Desmin and myogenin immunoreactive

Melanotic neuroectodermal tumor

- Tumor of facial/skull bones, but may be found in epididymis
- Melanin-containing epithelioid cells
- Small neuroblast-like cells
- Cellular stroma
- Benign but locally recurrent

Adenomatoid tumor

- Tubules and cords of low cuboidal/flat mesothelial cells in fibrotic stroma
- Positive for CK5/6 and calretinin

Miscellaneous tumorous lesions

- Nodular mesothelial hyperplasia, hemangioma, juvenile xanthogranulomatosis

Penis

HYPOSPADIAS

- Abnormal opening of urethral meatus on ventral surface of penis
- Associated with chordee (abnormal ventral curvature of penis)

EPISPADIAS

- Abnormal opening of urethral meatus on dorsal surface of penis

CUTANEOUS VIRAL INFECTIONS

- Papillomavirus causes bowenoid papulosis, condyloma acuminata (HPV-16)

BALANITIS XEROTICA OBLITERANS

- Thick white plaque on prepuce, glans, and meatus
- Keratotic and atrophic epidermis, slight liquefactive degeneration of basal cell layer
- Thick subepithelial hyalinized acellular material
- Dense lymphoplasmacytic infiltrate below hyalinized zone

PENILE NEOPLASMS

- Very rare in children

Prostate

CONGENITAL ANOMALIES

- Hypoplasia of prostate and dilation of prostatic urethra in prune-belly syndrome
- Fibroepithelial polyps of posterior urethra

ACQUIRED ANOMALIES

Rhabdomyosarcoma

- Mostly embryonal type

Disorders of sexual development (DSD)

- Any congenital condition presenting with atypical development of chromosomal, gonadal and/or anatomical (genital) sex
- DSDs get initiated in utero and final phenotypic changes occur at puberty
- Prevalence of germ cell tumors increased with DSD (especially patients containing Y chromosome in their genome)

DYSGENETIC GONAD

- Seen in patients with DSD
- Streak gonads; fibrous tissue only or ovarian stroma intermixed with abnormally developed sex-cord-like structures containing primitive germ cells

CLASSIFICATION OF DSD

Normal sex chromosomes

Female pseudohermaphroditism

- Elevated androgens in females
- 46XX, DSD

- Adrenogenital syndrome
- Maternal virilization
- Maternal ingestion of androgenic hormones

Male pseudohermaphroditism

- Diminished androgens in males
- 46XY, DSD
- Testicular regression syndrome
- Gonadotropin-Leydig cell defects
- Steroid hormone deficiencies (testosterone/DHT)
- Androgen insensitivity syndrome (testicular feminization syndrome)
- Persistent müllerian duct syndrome

Abnormal sex chromosomes

When sexual ambiguity frequently exists

- Mixed gonadal dysgenesis (45X/46XY, MGD)
- True hermaphrodite (ovotesticular DSD)

When sexual ambiguity infrequently exists

- Pure gonadal dysgenesis (46,XY)
- Klinefelter syndrome(47,XXY)
- Turner syndrome(45,XO)
- XX-male syndrome

Three types of sex

- Chromosomal
- Gonadal
- Phenotypic

SRY

- Sex-determining region on Y chromosome
- Gonadal sex predominantly dependent on SRY

Phenotypic sex

- Development of ductal system/external genitalia regulated by müllerian inhibiting substance (MIS/AMH)
- Anti-müllerian hormone (AMH) secreted by Sertoli cells
- Phenotypic sex determined by steroid hormones of the testis (testosterone/DHT) and ovary (estrogen/progesterone) also

DEFECTS OF WILMS TUMOR (WT1) SUPPRESSOR GENE

- WT-KTS isoform required for cell survival and proliferation in bipotential gonad (both males and females)
- Mutation of this gene associated with genital and kidney defects, increased risk for Wilms tumor and mental retardation
- Three syndromes: WAGR, Denys-Drash, and Frasier

15 Skin

Embryology

- Epithelial structures (epidermis, pilosebaceous units, sweat glands); derived from *ectoderm*
- Mesenchymal structures (dermis, vessels, smooth muscle, nerves); derived from *mesoderm*
- Melanocytes, Merkel cells, and perineural cells; derived from *neural-crest derivatives*
- Mast cells and Langerhans cells; derived from *mesenchymal precursors of bone marrow*
- Skin development starts as single layer of cells in a 3 week embryo with progressive stratification of epidermis
- Cornification of epidermis completed during sixth month of pregnancy
- Dermal modification and formation of adnexal structures; throughout third trimester and beyond
- Fetal skin biopsies increasingly being used in diagnosis of genodermatoses (congenital diseases of skin)
- Understanding of skin embryology important to determine timing/interpretation of biopsy
- Different types of skin biopsies: punch, shave, excision, scrape prep (for vesicular/pustular lesion), and curettage

Specimen processing

DIRECT IMMUNOFLUORESCENCE (IF)

- Bullous diseases
- Biopsy the perilesional skin
- Michel fixative transport medium
- Frozen sections incubated with antibodies against IgG, IgA, IgM, C3, C1q, and fibrinogen
- Evaluated with IF microscope

ELECTRON MICROSCOPY (EM)

- Used for undifferentiated neoplasms, metabolic disorders, various types of epidermolysis bullosa
- Fixative is 2% glutaraldehyde

CYTOGENETIC TESTING

- Skin and subcutaneous tissue used
- Sterile specimen placed in RPMI transport medium

Congenital diseases (genodermatoses)

- Cutaneous involvement and underlying genetic defect

APLASIA CUTIS CONGENITA

- Congenital absence of skin
- Single or multiple lesions, scalp involved
- Full-thickness skin defect
- If healed, scarring present

ICHTHYOSIS

- Epidermal disorders, dryness and scaling of skin
- Flexor surfaces spared, extensor surfaces involved
- Moderate hyperkeratosis, reduced/absent granular layer, follicular plugging
- Ichthyosis vulgaris, lamellar ichthyosis, X-linked ichthyosis
- CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects)

Fetal harlequin ichthyosis

- The infant at birth encased in thick, fissured, scaly crust
- Crust interferes with normal fetal development, can be fatal

Collodion baby

- Infant encased in keratinous membrane (sheds after 1–2 weeks)

DARIER DISEASE

- Also known as *keratosis follicularis*
- Papillomatous epidermal hyperplasia, suprabasal acantholysis
- Dyskeratotic cells (corps ronds) and parakeratosis (corps grains)
- Face, neck, upper trunk, oral mucosa

HAILEY-HAILEY DISEASE

- Usually appears in late teens to early twenties
- Vesicles in neck, groin, and axillae
- Suprabasal acantholysis, dilapidated brick wall appearance

POROKERATOSIS

- Keratotic papules, plaques, and keratotic ridges
- Coronoid lamella (column of parakeratosis, overlying dyskeratotic keratinocytes)
- Most pronounced features noted in porokeratosis of Mibelli

RESTRICTIVE DERMOPATHY

- Prematurity, rigid and tense skin, perineal abnormalities, fixed facial expression, skin denudations
- Thick/hyperkeratotic epidermis, flattening of rete ridges, thin dermis, poorly developed adnexal structures

ECTODERMAL DYSPLASIA

- Dysplasia of all structures derived from ectoderm
- Hypoplasia of hair, sebaceous glands, apocrine and eccrine glands

FOCAL DERMAL HYPOPLASIA

- X-linked dominant inheritance
- Multisystem disorder; developmental skin defects with ocular, dental, and skeletal system abnormalities
- Thinned out dermis with thin fibrils of collagen admixed with adipocytes

EPIDERMOLYSIS BULLOSA

- Bullous lesions develop spontaneously or after minor trauma

Simplex

- Good prognosis, blisters heal without scarring
- Cleavage plane suprabasal in epidermis
- Cockayne syndrome

Junctional

- Bad prognosis
- Blistering begins at birth and fatal by 2 years of age
- Cleavage plane at lamina lucida of basement membrane at dermo-epidermal junction
- Similar changes in mucosa of urinary/respiratory/gastrointestinal tract

Dystrophic

- Recessive form has bad prognosis (ulcerations and erosions)
- Cleavage plane in papillary dermis, below basement membrane

INCONTINENTIA PIGMENTI

- X-linked dominant condition, mostly females
- Vesicles/bullae on extremities
- Heal with formation of verrucous/hyperkeratotic lesions, hyperpigmented lesions
- *Vesicular stage*: Eosinophilic spongiosis
- *Hyperpigmented stage*: Numerous melanophages in dermis

ACRODERMATITIS ENTEROPATHICA

- Defective zinc absorption by intestines
- Triad of dermatitis, diarrhea, and alopecia in infancy
- Similar changes in zinc deficiency states
- Vesiculobullous lesions (acral/periorofacial)

Acquired vesiculobullous diseases

LINEAR IGA BULLOUS DERMATOSIS

- Tense bullae lower part of trunk, prepubertal children
- Subepidermal blisters with neutrophils/eosinophils
- *Direct IF*: Linear IgA at basement membrane zone
- No association with gluten-sensitive enteropathy

DERMATITIS HERPETIFORMIS

- Pruritic papulovesicular symmetric eruption
- Scalp and extensor surface of body
- Associated with gluten-sensitive enteropathy
- Subepidermal bullae filled with neutrophils, eosinophils, and fibrin
- *Direct IF*; IgA granular deposits at the tips of dermal papillae

HERPES GESTATIONIS

- Autoimmune bullous disease
- Transmitted from pregnant mother to neonate
- Subepidermal bulla with eosinophils
- *Direct IF*: Linear deposits of C3 and IgG at basement membrane

ERYTHEMA MULTIFORME, STEVENS-JOHNSON SYNDROME, AND TOXIC EPIDERMAL NECROLYSIS (TEN)

- Life threatening, fluid loss and sepsis
- Includes widespread epidermal necrosis, bullous formations
- Skin and mucosa
- May be related to viral infections, drugs
- Vacuolar alteration of basal cell layer, necrotic keratinocytes
- Dermal perivascular infiltrate of lymphocytes
- TEN: Full-thickness epidermal necrosis, subepidermal bulla formation

Vesiculopustular diseases

ERYTHEMA TOXICUM NEONATORUM

- Transient macula-pustular rash, self-limiting
- First 24–48 hours after birth
- Eosinophils in pilosebaceous units

TRANSIENT NEONATAL PUSTULAR MELANOSIS

- Self-limiting, black infants
- Superficial sterile pustules → rupture and heal with hyperpigmented macules
- Pustules contain neutrophils

ACROPUSTULOSIS OF INFANCY

- Pustules on palms, black infants, self-limiting, infancy
- Pustules contain neutrophils

Eczematous dermatitis

- Erythematous scaling vesicular lesions, serum crust
- Children with atopic predisposition
- Epidermal spongiosis, intraepidermal vesicles
- Mixed moderate dermal perivascular inflammation
- Other types of allergic dermatitis with similar histology are nummular, atopic, contact, and dyshidrotic dermatitis

Papulosquamous dermatoses

PSORIASIS VULGARIS

- Plaque and guttate types more common in children
- Pruritic scaling, symmetric lesions

- Scalp, face, and extensor aspect of extremities
- After removal of scale, pinpoint area of bleeding = *Auspitz sign*
- Confluent parakeratosis, Munro-microabscesses, regular elongation of rete ridges
- Thin supra-papillary plates, dilated vessels in rete ridge, mild perivascular infiltrate

SEBORRHEIC DERMATITIS

- Early infancy, adolescents
- Erythematous scaly lesion
- Scalp, face, diaper area
- Morphologic features overlap between psoriasis and spongiform dermatitis

LICHEN PLANUS

- Pruritic self-limiting eruption
- More common in South Asian children
- Flat-topped violaceous papules on flexor aspect extremities, back
- May be seen in oral mucosa, nails, hair
- Hyperkeratosis, hypergranulosis, irregular epidermal hyperplasia, sawtooth rete ridges, vacuolization of basal cell layer and colloid bodies
- Band-like lymphohistiocytic infiltrate at dermo-epidermal junction

PITYRIASIS ROSEA

- Acute self-limiting eruption, adolescents
- Herald patch on trunk (single, large, scaling plaque)
- Viral etiology (HHV-7 and parvovirus)
- Focal parakeratosis, focal epidermal spongiosis
- Extravasated erythrocytes in papillary dermis, mild perivascular lymphohistiocytic infiltrate in superficial dermis

PITYRIASIS RUBRA PILARIS

- Chronic popular eruption around follicles
- Mild epidermal hyperplasia, alternating parakeratosis and hyperkeratosis
- Follicular plugging, mild perivascular dermal inflammation
- Keratoderma of palms, cephalic involvement

PITYRIASIS LICHENOIDES

- PLEVA, also known as Mucha-Habermann disease (pityriasis lichenoides et varioliformis acuta)
- Milder chronic form
- Eruption mostly self-limiting, trunk and extremities
- Parakeratosis, spongiosis, necrotic keratinocytes, neutrophilic epidermal infiltrate, ulceration
- Interface and deep dermatitis

PAPULAR ACRODERMATITIS OF CHILDHOOD

- Self-limiting disease
- Association with various viruses (Hep B, EBV)

LICHEN SCLEROSUS

- White flat plaques/papules
- Anogenital region
- Hyperkeratosis, epidermal atrophy
- Papillary dermal sclerosis, lymphocytic band below papillary dermis
- Overlapping features with morphea

Infectious diseases

BACTERIAL INFECTIONS

Impetigo

- Most common bacterial infection in children

Non-bullous (impetigo contagiosa)

- *Staphylococcus aureus*
- Vesiculopustular lesions on exposed parts of body
- Subcorneal pustule filled with Gram-positive cocci
- May be superimposed on other pre-existing skin conditions

Bullous impetigo

- *S. aureus*
- Start as small vesicular lesions progressing to flaccid bullae

- Cleavage plane at/just below granular cell layer
- Bullous cavity contains scant/no inflammatory cells
- Superficial dermis contains neutrophilic infiltrate
- Localized form of staphylococcal scalded skin syndrome (SSSS)

Staphylococcal scalded skin syndrome

- Caused by epidermolytic toxin of *S. aureus*
- Exfoliative toxin ETB causes generalized SSSS
- ETA toxin causes bullous impetigo
- Abrupt onset of fever, erythema, and large flaccid sterile bullae
- Bullae rupture with peeling of sheets of epidermis: Scalded appearance
- Similar to bullous impetigo, but no dermal inflammation
- Good prognosis with complete recovery in 2–3 weeks

Toxic shock syndrome

- TSS toxin-I and enterotoxins produced by *S. aureus*
- Acute life-threatening multisystem disorder, fever, generalized rash, hypotension
- Non-specific histologic findings

Ecthyma

- Group A beta-hemolytic streptococci
- Ulcerative dermatitis, dense neutrophilic infiltrate

Ecthyma gangrenosum

- *Pseudomonas aeruginosa*, immunocompromised children
- Necrotizing vasculitis at base of cutaneous ulcer
- Scant neutrophilic infiltrate

Erysipelas

- Superficial cellulitis of skin
- Group A beta-hemolytic streptococci
- Dermal edema, diffuse neutrophilic infiltrate

VIRAL INFECTIONS

Human papillomavirus

- Papovavirus
- Verruca vulgaris (common wart), verruca plantaris, verruca palmaris, condyloma acuminata
- HPV 6 and 11 cause benign or low-grade lesions
- HPV 16 type is oncogenic
- Epidermal hyperplasia, papillomatosis, hyperkeratosis, parakeratosis, hypergranulosis, koilocytosis
- Condyloma acuminata (anogenital warts): Prenatal mode of transmission (maternal history of warts) or due to sexual abuse

Molluscum contagiosum

- Poxvirus
- Discrete dome-shaped umbilicated papules
- Epidermal hyperplasia with surface invagination
- Intracytoplasmic, large eosinophilic round inclusion bodies: Molluscum bodies
- Thin crescentic nuclei
- Numerous lesions in immunocompromised hosts

Herpes virus infection

- HSV (type I is orofacial and type II is genital)
- CMV, varicella-zoster virus, HHV-6-8 and EBV
- Primary infection by varicella-zoster virus causes chicken pox
- Herpes-zoster caused by reactivation of virus from dorsal root ganglion (immunocompromised hosts)
- Vesicular lesion in dermatomal distribution
- Intraepidermal vesicles, multinucleation of keratinocytes, intranuclear ground-glass inclusions

FUNGAL INFECTIONS

Superficial infections

- Dermatophytosis (tinea), *Pityrosporum* and *Candida*
- Fungal diagnosis made by culture/biopsy/KOH preparation

Deep mycosis

- Sporotrichosis, chromoblastomycosis, histoplasmosis, coccidioidomycosis, blastomycosis, and cryptococcosis
- Suppurative/granulomatous inflammation of dermis/subcutaneous tissue
- Pseudoepitheliomatous hyperplasia of epidermis

INFESTATIONS

Scabies

- *Sarcoptes scabiei*
- Contagious vesiculopustular eruption
- Distal extremities and genitalia
- Perivascular mixed dermal infiltrate with eosinophils
- Mite/eggs identified in parakeratotic layer of skin

Noninfectious inflammatory dermatoses

ACUTE FEBRILE NEUTROPHILIC DERMATOSIS

- Also known as *Sweet syndrome*
- Violaceous skin plaque-like lesions
- Underlying malignancy/inflammation
- Diffuse dermal neutrophilic infiltrate, no vasculitis

Noninfectious granulomatous dermatoses

GRANULOMA ANNULARE

- Asymptomatic ringed papules (dorsum of hands/feet)
- Upper dermal zones of myxoid collagen degeneration surrounded by palisaded histiocytes

NECROBIOSIS LIPOIDICA

- Associated with diabetes mellitus
- Palisaded granulomatous inflammation around degenerated collagen, plasma cell infiltrate
- Involves entire dermis and extends to subcutaneous tissue

JUVENILE RHEUMATOID ARTHRITIS

- Palisading granulomas around fibrinoid collagen degeneration
- Arthritis, elevated serum rheumatoid factor

SARCOIDOSIS

- Multisystem disorder, red-yellow cutaneous plaques
- Non-caseating granulomas
- Epithelioid cells, scant/absent lymphocytes

Panniculitis

- Inflammation of fat
- Lobules of fat (*lobular panniculitis*) or fibrous septa (*septal panniculitis*)

ERYTHEMA NODOSUM

- Symmetric tender erythematous subcutaneous nodules, extensor surface of lower legs
- Septal pattern of panniculitis, fibrosis, and granulomatous inflammation
- Associated with inflammatory bowel disease, tuberculosis, streptococcal infection, coccidioidomycosis
- Self-limiting

SUBCUTANEOUS FAT NECROSIS OF NEONATES

- Cheeks, buttocks, shoulders in neonates
- Lobular pattern of panniculitis: Fat necrosis, infiltration by macrophages and multinucleated giant cells (contain lipid and calcium deposits)

SCLEROMA NEONATORUM

- Diffuse involvement of fat cells by radially arranged crystals of lipid
- No inflammation
- Poor prognosis/fatal

Vasculitis

- Primary vascular disorder or secondary to underlying systemic disorder (collagen vascular disease)
- Damage to vessel wall: Fibrinoid necrosis, perivascular inflammation, extravasation of red cells

LEUKOCYTOCLASTIC VASCULITIS

- Henoch-Schönlein purpura
- Follows streptococcal upper respiratory infection in children
- Purpuric rash lower extremities, arthralgia, arthritis, abdominal pain, and hematuria
- Self-limiting, resolves in a few weeks

LYMPHOCYTIC VASCULITIS

- Insect bite reaction, PLEVA, lymphomatoid papulosis and collagen vascular diseases
- Benign pigmented purpuras (lichen aureus, Schamberg-Majocchi purpura)
- Superficial perivascular lymphocytic infiltrate, extravasated red blood cells, hemosiderin laden macrophages

Folliculitis and perifolliculitis

ACNE

- Acne vulgaris, adolescents, face, trunk/back
- Intrafollicular hyperkeratosis, sebum secretion, blockage of follicular infundibula, comedones formation
- Neonatal acne = transient eruption

EOSINOPHILIC PUSTULAR FOLLICULITIS

- Infants, scalp/forehead
- Subcorneal pustule with eosinophils

Systemic diseases with cutaneous manifestations

LUPUS ERYTHEMATOSUS

- Malar rash, oral ulcers, photosensitivity, alopecia, discoid lupus erythematosus
- Mild hyperkeratosis, epidermal atrophy, vacuolization of basal cell layer
- Interface dermatitis with extension around blood vessels and adnexa
- *Direct IF*: Continuous granular deposit of C3, IgG along dermo-epidermal junction of skin

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

- Mild/variable inflammation, thick hyalinized collagen bundles in dermis/subcutaneous fat

Graft-versus-host disease

- Response seen in immunocompromised hosts after receiving immunocompetent donor cells
- After stem cell transplant or after transfusion of non-irradiated blood in immunocompromised children
- Maculopapular eruption, exfoliative
- Basal cell vacuolization, keratinocyte necrosis surrounded by lymphocytes (satellite necrosis), epidermal necrosis
- Subepidermal bullae, dermal hyalinization of collagen

Metabolic diseases

CALCINOSIS CUTIS

- Localized dystrophic or systemic metastatic type
- Subepidermal calcific nodules in heals of infants after repeated needle sticks
- Tumoral calcinosis in soft tissue around joints

MUCOPOLYSACCHARIDOSES

- Lysosomal enzyme deficiency → abnormal accumulation of mucopolysaccharides in multiple organs including skin
- Skin thick and inelastic

Skin tumors/tumor-like conditions

EPIDERMAL NEVI

- Proliferation of epidermal keratinocytes
- Hyperkeratosis, papillomatosis, epidermal acanthosis
- Normal adnexal structures
- In epidermal nevus syndromes; associated central nervous system, skeletal and renal system defects

EPIDERMAL INCLUSION CYST

- Dermal nodule lined by keratinizing stratified squamous epithelium
- Intact stratum granulosum
- Cyst lumen filled with lamellar keratin
- Multiple cysts in Gardner syndrome

TRICHILEMMAL CYST

- Lined by keratinized epithelium devoid of granular cell layer
- Cyst lumen filled with pilar keratin

DERMOID CYST

- Developmental cysts, located along lines of embryonic suture closures
- Locations: periorbital, midline nose, neck, scalp
- Cysts lined by keratinizing stratified squamous epithelium and adnexal structures
- Lumen contains lamellar keratin, sebum, and hair
- Midline cysts may contain sinus tract; evaluate radiologically before excision

ERUPTIVE VELLUS HAIR CYST

- Anterior chest, face, extremities, trunk
- Lined by squamous epithelium with laminated keratin
- Multiple hair in lumen

STEATOCYSTOMA MULTIPLEX

- Axilla, sternum, arms
- Cysts lined by two to three cell layer thick stratified squamous epithelium
- Covered by thick homogenous eosinophilic cuticle

ADNEXAL TUMORS

Follicular Neoplasms

- Tumors with follicular differentiation most common

Pilomatrixoma (calcifying epithelioma of Malherbe)

- Most frequent
- First and sixth decades of life
- Hard dermal/subcutaneous nodule, head and neck
- Basaloid cells, ghost cells, calcified/ossified stroma, foreign body giant cell inflammation

Trichoepithelioma

- Papules on face (flesh colored)
- Germinative cells in cellular fibrotic stroma

Trichoblastoma

- Less well-differentiated form of trichoepithelioma

Eccrine neoplasms

Syringoma

- Papules on face
- Small solid nests/tubules of epithelial cells, some tadpole shaped
- Confined to upper half of dermis

Sebaceous and apocrine neoplasms

Nevus sebaceous of Jadassohn

- Hamartomatous lesion
- Yellow plaques located in scalp, forehead, or face
- Epithelial hyperplasia, mild papillomatosis, numerous sebaceous lobules, malformed small hair follicles
- Ectopically placed apocrine glands

BASAL CELL NEVUS SYNDROME

- Also known as Gorlin-Goltz syndrome
- Autosomal dominant

- Multiple jaw tumors, skeletal anomalies, intracranial calcifications, medulloblastoma, multiple basal cell carcinomas

MELANOCYTIC NEOPLASMS

Congenital melanocytic nevi

- Giant (bathing trunk pattern), large and small in size
- Verrucous epidermal hyperplasia, coarse hair
- Junctional, compound, or intradermal
- Melanocyte nests located periadnexal, perivascular
- Individual melanocytes infiltrate collagen bundles, deeper dermis, and subcutaneous fat
- Giant nevi in head/neck; associated with leptomeningeal melanocytosis/melanoma
- Congenital nevi have higher risk of transformation to melanoma

Acquired melanocytic nevi

- Symmetrical, circumscribed, small in size
- Nests of monomorphic melanocytes, which show maturation with depth
- Junctional, intradermal, or compound

Spitz nevus

- Also known as spindle and epithelioid cell nevus
- Occurs in children before 14 years of age
- Pink, small symmetric
- Spindle or epithelioid cell nests surrounded by clefts, Kamino bodies, mitotic figures, pagetoid epidermal spread
- Considerable nuclear and cytologic pleomorphism
- May be junctional, compound, or intradermal
- Pseudoepitheliomatous epidermal hyperplasia
- Difficult to differentiate from melanoma sometimes

Halo nevi

- Located in back
- Zone of depigmentation around the nevus
- Dense lymphocytic infiltrate destroys the melanocytes and produces depigmented halo around nevus
- Common in patients with vitiligo; similar immunologic mechanism

Blue nevus

- Children older than 10 years
- Blue-gray papules
- Dendritic melanocytes with dense melanin pigment, nests/fascicles, extend into reticular dermis
- Variant is cellular blue nevus

Clark dysplastic nevus

- Positive family history of melanomas and dysplastic nevi
- Broad junctional/compound nevi, bridging of rete ridges by melanocytes, lamellar fibroplasias, cytologic atypia
- Features mimicked by nevi in very young children, nevi located in genitalia/conjunctiva/palms/soles

Malignant melanoma

- Rare in children
- Congenital melanoma may be due to transplacental metastasis from mother
- Similar clinical/histologic features as adults
- Prognosis depends on maximum thickness of lesion (Breslow depth)

MESENCHYMAL NEOPLASMS

Neurothekeoma

- Benign tumors of nerve-sheath origin
- Whorls of spindle/epithelioid cells, myxoid matrix in dermis
- Positive staining for CD3, vimentin, CD10
- Negative for S100

Solitary/plexiform neurofibroma

- Neurogenic tumor
- Positive for S100

Vascular tumors

Hemangiomas

- May be congenital, variable size

- Head and neck most common sites
- Mostly regress spontaneously
- Thin-walled capillary proliferation, lobular clusters of spindle cells
- Infantile/juvenile hemangioma; GlUT-1 positive

Pyogenic granuloma

- Also known as lobular capillary hemangioma
- Rapidly growing, pink/red papule
- Located in finger or gums mostly
- Polypoid, ulcerated, inflamed stroma, epidermal collarette overlying lesion

Tufted hemangioma

- Well-defined foci of closely set capillaries in dermis/subcutaneous tissue

Myogenic tumors

Congenital infantile myofibromatosis

- Birth or within the first year of life
- Solitary or systemic (poor prognosis)
- Nodular cutaneous/subcutaneous mass
- Biphasic morphology, central hemangiopericytoma-like proliferation
- Peripheral fascicular proliferation of fibroblasts/myofibroblasts

Cutaneous myofibroma

- Similar features as infantile myofibromatosis, but it is well circumscribed

Infantile digital fibromatosis

- Dome-shaped papules on fingers/toes of infants
- Lateral and dorsal aspects of distal/middle interphalangeal joints
- Fibroblasts surrounded by collagen
- Perinuclear, small round inclusion bodies (contain actin) resembling erythrocytes
- Inclusion bodies stain red with Masson trichrome stain
- Benign tumor, mostly regresses with time

Giant cell fibroblastoma

- Also known as juvenile dermatofibrosarcoma protuberans
- Both share same cytogenetic abnormality
- Proliferation of infiltrating spindle cells in dermis/subcutaneous tissue, moderate nuclear pleomorphism
- Pseudovascular spaces lined by multinucleated cells
- CD34 and CD99 positive
- Locally recurrent, no metastases

Hematopoietic neoplasms

Mast cell diseases

- Solitary mastocytoma; present at birth and regresses spontaneously in a few years
- Urticaria pigmentosa; diffuse maculopapular rash, 3–9 month infants, regresses by puberty
- Diffuse mastocytosis; systemic with poor prognosis
- Wheal formation (Darier sign)
- Infiltrate of monomorphic, mononuclear mast cells with bland nuclei and abundant pale to amphophilic cytoplasm (fried egg appearance)
- Stain with CD117, Giemsa (metachromatic granules), toluidine blue, Leder stain

Histiocytoses

Langerhans cell histiocytosis (LCH)

- Langerhans histiocytes positive for S100 and CD1a
- Letterer-Siwe disease (acute disseminated with visceral involvement, infancy)
- Hand-Schüller-Christian disease (chronic multisystem disease with osseous involvement but less visceral, early childhood)
- Focal disease with one or more bone involvement (eosinophilic granuloma, late childhood and adults)
- Cutaneous manifestation, scalp and anogenital region most common
- Diffuse infiltrate of Langerhans histiocytes in papillary dermis, abundant pale cytoplasm and reniform nucleus, multinucleated histiocytes and eosinophils

Juvenile xanthogranuloma

- Yellowish/red papular lesions
- Diffuse infiltrate of histiocytes, cytoplasmic lipidization, Touton giant cells, lymphocytes, and eosinophils

- Proliferating histiocytes positive for all macrophage markers except CD1a and S100
- Benign lesions, rarely systemic

Sinus histiocytosis with massive lymphadenopathy

- Also known as Rosai-Dorfman disease
- Papules and nodules
- Histiocytes show emperipolesis of lymphocytes
- Histiocytes are S100 positive

Leukemia and lymphoma

- Anaplastic large cell leukemia, lymphomatoid papulosis, angiocentric cutaneous T-cell lymphoma

Miscellaneous cutaneous conditions

BLUEBERRY MUFFIN BABY

- Congenital viral infections, dermal extramedullary hematopoiesis, hemolytic disease of newborn, blue bleb rubber nevus syndrome, twin-to-twin transfusion, metastasis from neuroblastoma, leukemia, choriocarcinoma, rhabdomyosarcoma

DERMAL MANIFESTATIONS OF TUBEROUS SCLEROSIS

- Angiofibroma, fibromas, shagreen patch, leaf-shaped hypopigmentation

16 Soft Tissue

Tumors

VASCULAR TUMORS

Benign

Lobular capillary hemangioma

- Also known as pyogenic granuloma
- Capillaries arranged in lobules, intervening dense fibrotic stroma, infiltrated with inflammatory cells, epidermal collarette
- Raised erythematous nodule, ulceration

Juvenile hemangioma

- Also known as infantile hemangioma
- Lobular arrangement of capillaries, intervening normal stroma (no densely fibrotic bands)
- Spontaneous involution with fibrosis, apoptosis, and very few residual capillaries
- Positive staining with GLUT1

Congenital hemangiomas

- GLUT1 negative

Rapidly involuting congenital hemangiomas (RICH)

- Tumor fully grown at birth, regresses rapidly (by 1 year)

Non-involuting congenital hemangiomas (NICH)

- Tumor fully grown at birth, does not regress, grows proportionately with child

Epithelioid hemangiomas

- Small vessels lined by epithelioid endothelial cells
- Accompanying lymphocytic infiltrate
- Skeletal muscle hemangiomas

Glomus tumors

- Arise from modified smooth muscle cells of glomus body
- Paraspinal, subungual, retroperitoneal
- Basophilic round cells beneath intact endothelium
- Positive for smooth muscle actin (SMA) stain

Glomangioma

- Resemble cavernous hemangioma

Glomangiomatosis

- Angiomatosis with excess glomus cells

Glomangiomyoma

- Features of glomus tumor and angioleiomyoma

Intermediate grade

Hemangioendotheliomas

- Soft tissue, bone, viscera
- Poorly canalized cords/nests of endothelial cells in myxohyaline background
- Stain positively with CD31, CD34, and factor VIII-related antigen

Kaposiform hemangioendothelioma

- Multiple masses in head/neck, extremities, intestinal tract, and retroperitoneum
- Spindle cell proliferation
- Mixed venous and lymphatic malformation
- Thrombocytopenia
- Stain positively with factor VIII-related Ag, D2-40, SMA
- Does not harbor HHV-8
- Associated with Kasabach-Merritt syndrome, lymphangiomatosis

Malignant

Kaposi sarcoma

- Lymph node-based disease or extranodal
- Immunocompromised children
- Soft tissue, oral cavity, gastrointestinal tract, lung
- Low-grade, spindle cell lesion, entrapped erythrocytes
- Immunoreactive with CD31, CD34, HHV-8

Epithelioid hemangioendothelioma

- Similar histology as benign counterpart
- Soft tissue, liver
- More cytologic atypia, infiltrative tumor
- Metastatic rate is 20%

Angiosarcomas

- Extremely rare in children

VASCULAR MALFORMATIONS

- Conglomeration of vessels of variable caliber
- Lumina show thrombi in different stages of organization
- Simple slow flow: Capillary, lymphatic, venous
- Simple fast flow: Arterio-venous

Syndromes associated with vascular malformations

Von Hippel-Lindau syndrome

- Hemangioblastoma of cerebellum, renal cell carcinoma

Blue rubber bleb nevus syndrome

- Multifocal venous malformations affecting skin and gastrointestinal tract

Maffucci syndrome

- Multiple enchondromas, hemangiomas, and lymphangiomas
- Higher risk of central nervous system (CNS), pancreatic, and ovarian malignancies

Proteus syndrome

- Overgrowth of bone, skin, and other tissues
- Vascular malformations and risk of pulmonary embolism

Sturge-Weber syndrome

- Hemangioma in distribution of trigeminal nerve

Kasabach-Merritt syndrome

- Thrombocytopenia due to sequestration of platelets in lesion
- Vascular malformation with lymphatic channels, positive staining with D2-40

Gorham-Stout syndrome

- Vanishing bone syndrome

Osler-Rendu-Weber syndrome

- Hereditary hemorrhagic telangiectasia and arterio-venous malformations

LYMPHATIC TUMORS

Cystic lymphangioma (hygroma)

- Slow flow malformation
- Soft-tissue mass in neck/surrounding structures
- *Gorham-Stout syndrome*: Bone involvement by lymphangioma leads to vanishing bone syndrome
- Variably sized lymphatic spaces lined by endothelium
- Positive staining with D2-40
- Turner syndrome and Noonan syndrome

FIBROUS, MYOFIBROBLASTIC, AND PERICYTIC TUMORS

- Composed of spindle-shaped cells

Scars, keloids, and fasciitis

- Reactive fibrous/myofibroblastic process
- Healing and repair
- Cytologic atypia in fibroblasts after radiation therapy

Hypertrophic scar

- Nodular fibroblastic proliferation in dermis

Keloid

- Pink eosinophilic glassy collagen
- Abnormality in wound healing process, more prevalent in Africans

Nodular fasciitis

- First two decades of life
- Head and neck region
- Rapidly growing mass, <3 cm, non-recurrent
- Circumscribed, non-encapsulated, glistening cut surface
- Spindle cell areas forming short fascicles, interspersed by less cellular areas and mucoid-myxomatous extracellular material
- Mitotic figures (none atypical), mild cytologic atypia, interstitial hemorrhage, and scattered inflammatory cells
- Positive staining for vimentin and SMA

Cranial fasciitis

- Related to nodular fasciitis
- Infancy
- Cranium, may compress underlying brain

Myositis ossificans

- Mostly males, first two decades
- History of trauma
- Thigh, abdomen, buttocks
- Circumscribed intramuscular mass (10–15 cm)
- No anaplasia, no atypical mitoses
- Three zones
  - Central zone: Proliferating plump myofibroblasts, histiocytes, and blood vessels
  - Middle zone: Immature osteoid
  - Outer zone: Mature bone

Fibrodysplasia ossificans progressiva

- AD disorder
- Progressive transformation of soft tissue to heterotopic bone
- *ACVR1/ALK2* mutation

Infantile myofibromatosis (myofibroma)

- Most frequent fibrous tumor of childhood
- Cutaneous/subcutaneous nodule, less than 3 cm
- Head/neck/extremities
- Spontaneous regression
- Non-encapsulated nodular mass, central hemorrhage
- Centrally, hemangiopericytoma-like histology (CD34+)
- Peripherally, spindle-shaped cell fascicular proliferation (SMA+)

Myopericytoma

- Combination of myofibroblasts and pericytes
- Blood vessels surrounded by collarettes of spindle cells

Infantile fibromatosis

- Lipofibromatosis (subcutaneous)
- Located in between muscle fibers or deeper desmoid fibromatosis
- Stain positively with CD34

Fibrous hamartoma of infancy

- Less than 2–3 years of age
- Subcutaneous tumor; trunk, axilla, inguinal regions, extremities
- Bland mature spindle cells, mature adipose tissue, small bundles of immature spindle cells

Inclusion body fibromatosis (infantile digital fibroma)

- Small nodular mass located in digits and toes (sparing big toe/thumb)
- Desmoid-type fibromatosis
- Eosinophilic paranuclear inclusions of actin (stain red with trichrome)

Desmoid-type fibromatosis (desmoid tumor, musculoaponeurotic fibromatosis)

- Association with Gardner syndrome and familial adenomatous polyposis (FAP)
- Spindle fibroblasts/myofibroblasts in collagenous, pale myxoid background
- Infiltrative margins, scattered lymphoid nodules at interface with normal tissue
- Surgical margins important due to very high recurrence rate
- Sporadic/familial desmoids have nuclear expression of beta-catenin

Gardner-nuchal fibroma

- Paucicellular collagenized mass
- Poorly circumscribed, plaque-like growth
- Subcutaneous/deep-seated, posterior truncal/paraspinal region
- Nuclear positivity for beta-catenin and cyclin -D1

Palmer-plantar fibromatosis

- Poorly circumscribed spindle cell tumors
- Bland collagenous stroma

Juvenile hyaline fibromatosis

- Painful papulonodular lesion of skin/soft tissue
- AR inheritance
- Dense hypocellular nodules of collagen
- Rounded stromal cells in lacunar spaces (resemble cartilage)

Calcifying aponeurotic fibromatosis

- Poorly circumscribed mass, distal extremities
- Infiltrative spindle-shaped fibroblasts in hyalinized stroma, granular calcifications
- Highly recurrent

Juvenile nasopharyngeal angiofibroma

- Adolescent males, epistaxis
- Polypoidal mass, spindle to stellate cell proliferation, intervening vascular spaces, pushing borders
- Associated with FAP, positive nuclear expression for beta-catenin

Fibromatosis colli

- Lower one third of SCM muscle
- Spontaneous regression in most
- Infiltrative borders
- Morphology similar to desmoid-type fibromatosis

Inflammatory myofibroblastic tumor

- Inflammatory pseudotumor
- Intermediate grade
- Common locations: Lung, bladder, gastrointestinal tract, multifocal
- Associated constitutional symptoms: Fever, weight loss, failure to thrive
- Dense spindle cell proliferation (myofibroblasts), extensive infiltration by lymphocytes and plasma cells
- Paucicellular histology with scattered inflammatory cells
- No anaplasia/atypical mitoses/necrosis
- Stain positive for vimentin, SMA, AlK-1
- ALK-1 positive staining; better prognosis

Adult-type fibrosarcoma

- Diagnosis of exclusion
- Positive staining for vimentin and CD34

Congenital infantile fibrosarcoma (CIFS)

- First 2–3 years of life
- Extremities, intestines
- *ETV6-NTRK3* gene fusion, t(12;15)
- Same translocation shared by cellular mesoblastic nephroma and secretory breast carcinoma also
- Uniform to primitive appearing spindled fibroblasts in fascicular/non-fascicular pattern
- Treated with chemotherapy

Low-grade fibromyxoid sarcoma

- Slow growing, lower extremity/trunk
- Alternating pattern of cellular to less cellular myxoid areas
- Hyalinizing giant rosettes
- Diffusely positive for vimentin and focally positive for epithelial membrane antigen (EMA)

Solitary fibrous tumor and hemangiopericytoma

- Intermediate-grade, rarely metastasizing tumors
- Fibroblastic-myofibroblastic neoplasms
- Bland spindle cell proliferation in collagenous stroma
- Positive staining for vimentin and CD34

Dermatofibrosarcoma protuberans and giant cell fibroblastoma

- Both share the same translocation: t(17;22)
- Dermatofibrosarcoma protuberans (DFSP) arises in mid-deep dermis and extends into subcutaneous tissue/deep fascia
- Both tumors show proliferation of spindle cells, pale myxoid stroma
- Scattered floret like giant cells in cleft-like spaces
- Pigmented DFSP = Bednar tumor
- Positive staining for vimentin and CD34

FIBROHISTIOCYTIC TUMORS

Benign fibrous dermatofibroma

- Proliferation of bland spindle-shaped fibroblasts and histiocytes

- Grenz zone present
- Stain positively with vimentin and factor XIIIa
- Stain negatively with CD34

Juvenile xanthogranuloma

- Xanthomatous histiocytes and Touton giant cells

Giant cell tumor (GCT) of tendon sheath

Nodular tenosynovitis

- Localized subtype
- Small nodule in finger or wrist
- Bland mononuclear cells and multinucleated giant cells

Extra-articular villonodular tenosynovitis

- Diffuse subtype
- Composed of bland mononuclear cells only

Pigmented villonodular synovitis

- Knee joint, chronic joint effusion
- Papillary synovial tissue, hemorrhage, hypercellular stroma, hemosiderin pigment laden histiocytes

Angiomatoid fibrous histiocytoma

- Low-grade malignant tumors, slow growing
- Extremities and trunk
- Spindle-shaped cells, cytologic atypia, brisk mitotic activity
- Blood-filled spaces, lymphoid nodules
- Positive staining with vimentin, CD99, desmin, CD68, and EMA
- *EWSR1-ATF1* translocation
- Low rate of metastasis, local recurrence

Plexiform fibrohistiocytic tumor

- Low-grade malignant tumors
- Lower dermis/subcutaneous tissue
- Forearm, lower extremity, trunk
- Nodular pattern, nests of histiocytes, spindled fibroblasts in collagenous stroma
- Scattered osteoclast like giant cells, lymphocytic inflammatory infiltrate
- Positive for CD68
- Locally recurrent, low metastatic rate

ADIPOCYTIC (LIPOMATOUS) TUMORS

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN)

- Germline mutation in tumor suppressor gene located on 10q
- Proteus syndrome; formation of hamartomatous growths

Macrodystrophia lipomatosa and macrodactyly

- Overgrowth of an extremity/digit
- Overgrowth of fat layers (below dermis), hamartomatous growth of fibrous, vascular, neural tissue
- Macrodactyly; lipofibromatous hamartoma of median nerve

Congenital intraspinal lipoma

- Neural tube defect, midline of lower back
- Lobules of mature fat admixed with neural tissue
- Differential diagnosis with Currarino syndrome (sacral anomalies, tethered spinal cord or lipoma, presacral teratoma and various anorectal anomalies, point mutations in *HLXB9* homeobox gene)

Lipomas

- Less frequent than in adults

Angiolipoma

- Tender nodules, forearm
- Mature fat, small peripheral capillaries, fibrin thrombi

Lipoblastoma

- Up to 10 years of age
- Fat cells in all stages of differentiation, myxoid change, no atypia
- Delicate arborizing capillary network, mast cells, lobular architecture
- Fat cells show positive staining with S100
- *PLAG1* gene amplified/rearranged (8q13)

Myxoid liposarcoma

- Most common liposarcoma in children
- Diffuse architecture, primitive spindle/round cells, lipoblasts, myxoid background, lacy vasculature
- Positive for S100 in fat cells

- CHOP/FUS or CHOP/EWS rearrangement (CHOP on 12q13)

Hibernoma

- Lobulated yellow-brown tumor mass
- Younger than 20 years of age
- Extremities, head/neck
- Adipocytes are eosinophilic, fine cytoplasmic vacuoles

Arrhythmogenic right ventricular cardiomyopathy

- Fatty infiltration and replacement of right ventricle of heart by fat

PERIPHERAL NERVE SHEATH TUMORS (PNST)

Neurofibroma

- Most common PNST in children
- Association with NF1 (multiple cutaneous, subcutaneous, and deep soft-tissue masses)
- Non-encapsulated, diffuse, and plexiform subtypes
- Wavy spindle cells
- Focally positive for S100 stain

Schwannoma

- Sporadic or associated with NF2
- NF2; bilateral involvement of eighth cranial nerve by schwannoma
- Diffuse staining with S100
- Encapsulated tumors
- Cellular spindle cell pattern with Verocay bodies (Antoni A)
- Hypocellular myxoid foci (Antoni B)

Malignant peripheral nerve sheath tumor (MPNST)

- Sporadic or complication of NF1
- Plexiform NF more prone to malignancy
- Spindle cell sarcoma with fascicles of neoplastic cells
- If associated with small collections of rhabdomyoblasts; triton tumor
- Positive staining with vimentin, S100, CD57

Perineurioma

- Soft-tissue mass arising in major nerve/brachial plexus
- Positive staining with CD34, vimentin, EMA
- Negative staining with S100

Nerve sheath myxoma (neurothekeoma)

- Negative staining with S100

Granular cell tumor (GCT)

- Neural (S100+ve)
- Non-neural (S100–ve); congenital epulis on alveolar border of maxilla/mandible in neonates
- Nests of granular cells, pale/eosinophilic granular cytoplasm
- Positive staining with CD68, S100 (neural variant), alpha-inhibin

Glioneuronal heterotopia

- Head/neck region
- Heterotopic glial tissue in fibrous background
- Nasal gliomas

PERIVASCULAR EPITHELIOID CELL NEOPLASM (PECOMA)

- Immunophenotyping similar to angiomyolipomas of kidney and sugar tumor of lung
- Immunopositive for SMA, HMB-45, and microphthalmic transcription factor
- Arise in soft tissue and viscera
- Epithelioid cells with abundant pink eosinophilic/clear cytoplasm

GASTROINTESTINAL STROMAL TUMOR (GIST)

- Soft tissue of extremities
- Mutations of kit (tyrosine receptor kinase) or PDGFR1
- Positive staining with CD117, CD34
- Stomach/small intestine most common sites
- Association with Carney triad
- Spindle/epithelioid cells mixed morphology

SKELETAL AND SMOOTH MUSCLE NEOPLASMS

Rhabdomyoma

- Benign tumors of skeletal muscle
- Located in soft tissue (head/neck) or in heart
- Cardiac tumors; multifocal pale small masses in ventricles

- May be congenital (diagnosed by prenatal ultrasound), fetal hydrops, or hypoplastic left heart syndrome
- Enlarged neoplastic myocytes, spider cells
- Positive staining with desmin

Focal myositis

- Inflammatory mass in deep soft tissue of extremities
- Surrounding skeletal muscle shows degenerative/regenerative changes

Smooth muscle tumors

- Leiomyoma of soft tissue, smooth muscle hamartoma
- Rare tumors

Rhabdomyosarcoma (RMS)

- Metastasize to regional lymph nodes, bone marrow, and lungs
- RMS may be associated with other tumors; ectomesenchymoma (RMS+ PNET), triton tumor (RMS+ MPNST)
- In uterine cervix RMS shows heterologous cartilage

Embryonal RMS

- Younger children/infants
- Genitourinary, head/neck
- Neoplastic cells variable in size/shape, nuclear hyperchromasia, atypical mitoses scattered larger tumor cells with abundant eosinophilic cytoplasm
- Sarcoma botryoides (cambium layer of small primitive tumor cells underneath epithelial surface)
- Spindle cell variant (better prognosis)
- Positive staining with vimentin, MyoD1, myogenin, desmin
- Molecular genetics: LOH on 11p15.5

Alveolar RMS

- Older children/adolescents
- Soft tissue of extremities
- Less-frequent subtype, worse prognosis
- Uniform small tumor cells attached to fibrovascular stroma, septal growth pattern
- Loose sheets of tumor cells with intervening multinuclear tumor cells
- Positive staining for vimentin, diffuse nuclear positivity for desmin, myoD1, and myogenin
- Molecular genetics; *PAX3-FKHR*, t(2;13), and *PAX7-FKHR*, t(1;13)
- *PAX3* is more common; carries a worse prognosis

Ectomesenchymoma

- Rare tumor
- Combination of mesenchymal elements: Rhabdomyosarcoma and neuroectodermal
- Head/neck, external genitalia

SARCOMAS OF UNCERTAIN HISTOGENESIS

Ewing sarcoma-primitive neuroectodermal tumor (EWS-PNET)

- EWS fusion partner with FLI1
- Many non-random translocations t(11; 22)
- Located in soft tissue of extremities, chest wall, paraspinal region, viscera
- Second decade of life
- Nested lobular pattern of monotonous round/polygonal cells
- Central round nuclei, finely vacuolated/clear glycogen-containing cytoplasm
- Positive staining for vimentin (perinuclear cytoplasmic/dot like) and CD99 (membranous pattern)

Desmoplastic small round cell tumor

- EWS fusion partner with WT1, t(11;22)
- Most common location abdomen
- Nests of undifferentiated small cells in fibrous stroma
- Positive staining with vimentin, cytokeratin (perinuclear), desmin, WT1

Clear cell sarcoma of soft tissue (malignant melanoma of soft parts)

- EWS fusion partner with *ATF1*, translocation t(12;22)
- Phenotypically melanoma-containing melanosomes
- Does not have mutation of BRAF4 kinase (d/d cutaneous melanoma)
- Located in lower extremities, near tendon sheath/aponeurosis
- Adolescent/older children

- Spindled/epithelioid/polygonal cells in fibrous hyalinized background
- Multinucleated giant cells, nuclear pseudoinclusions
- Positive staining with S100, HMB45, Melan-A, CD99

Extraskeletal myxoid chondrosarcoma

- t(9;22), CHN-EWS fusion
- Proximal lower extremity
- Adolescent/older children
- Multilobulated architectural appearance
- Nests of spindled/high-grade round cells
- Myxoid/mucoid background, no cartilage
- Positive staining for vimentin and NSE
- Negative staining for S100 and CD99

Myoepithelial tumor of soft tissue

- Extremities, adolescent children
- Histology overlaps with extraskeletal myxoid chondrosarcoma
- Positive staining for AE1/AE3, EMA, S100

Malignant rhabdoid tumor

- INI-1 del confirmed by FISH
- Most aggressive tumors
- Visceral primary sites: Liver, kidney, and central nervous system
- Soft-tissue primary sites: Head, neck, and mediastinum
- Filamentous eosinophilic cytoplasmic inclusions in rhabdoid cells
- Positive staining for EMA, vimentin
- Negative staining for *BAF47* (due to inactivated *INI1* gene)

Atypical teratoid rhabdoid tumor (ATRT)

- Malignant rhabdoid tumor found in CNS
- SMA is consistently positive
- *INI1* negative

Carcinoma with t(15;19) translocation

- Midline carcinoma of children/young adults
- Very lethal/aggressive tumor with *NUT* rearrangement t(15;19), *NUT-BRD4* oncogene
- Unknown etiology, rare tumor
- Superior vena cava syndrome (if tumor located in mediastinum)
- Sheets of undifferentiated cells, hemorrhage, necrosis, apoptosis, mitosis
- Squamous differentiation may be present
- Positive staining for cytokeratin, EMA

Alveolar soft part sarcoma

- Der(17)t(X; 17), *ASPL-TFE3* fusion gene
- Similar to Xp11.2 translocation-type renal cell carcinoma in children
- Deep soft tissue of proximal lower extremity, head/neck
- Nests of uniform polygonal tumor cells, prominent nucleoli, surrounded by delicate stromal envelopes
- Pale granular cytoplasmic staining by PAS
- Positive staining with vimentin, *TFE3* (nuclear positivity is diagnostic)

Epithelioid sarcoma

- Adolescents/young adults
- *Classic (distal type)*: Slow-growing nodule in hand/forearm, superficial dermal location
- *Proximal (axial type)*: Immunophenotype/genotypic features similar to malignant rhabdoid tumor, very aggressive clinical course, located in deep soft tissue
- Mantle of epithelioid cells, central necrosis/hyalinization
- Differential diagnosis with necrobiosis lipoidica (CD68+)
- Positive staining with vimentin, cytokeratin, EMA
- *INI1* loss

Synovial sarcoma

- t(X;18) translocation, fusing *SYT* and *SSX1/SSX2*
- Peripheral soft tissue of extremities
- Ankle common site
- Second decade
- Classic biphasic pattern of gland formation in spindle cell background, dystrophic calcification
- Positive staining for spindle cell component; vimentin (diffuse)
- Positive staining for epithelial component; EMA(diffuse), CK7(Individual tumor cells), Bcl2, CD99
- Nuclear TLE1 staining is diagnostic
- If tumor size is >5 cm, indicates bad prognosis

17 Skeletal System

- Normal endochondral ossification; chondrocytes arranged in regular columns at epiphyseal growth plate zone, cartilage-bone junction straight/uniform

Congenital disorders

OSTEOCHONDRODYSPLASIAS

- Genetic skeletal disorders affecting normal development of bones/soft tissue; affect stature of the individual
- Defects of growth of tubular bones/spine
- Disorganized development of fibrous/cartilaginous portions of skeleton
- Disorders in bony density/cortical diaphyseal structure/metaphyseal modeling

Classification

FGFR3 (Achondroplasia group)

- Short limbs with larger trunk
- Achondroplasia and hypochondroplasia are non-lethal
- Hypochondrodysplasia (thanatophoric dysplasia, TD types 1 and 2); most common and lethal
- TD type I = curved femur and humerus
- TD type II = craniosynostosis and cloverleaf-like skull; straight, very short femur

Decreased bone density group

- Seven types of osteogenesis imperfecta
- Mutation in *COL1A1, COL1A2, CRTAP,* or *LEPRE* genes
- These genes are involved in collagen type I synthesis/assemblage (occurs in osteoblasts)

Osteogenesis imperfecta type 2

- Second-most lethal skeletal dysplasia in frequency (perinatal lethal type)
- Severe osteopenia, blue sclera, short/bowed extremities
- Diminutive thorax, crumpled/collapsed long bones (especially femur)
- Soft cranium with intracranial hemorrhage
- Cause of death in all forms; severe pulmonary hypoplasia

Type 2 collagen group

- Lethal achondrogenesis type 2
- Gene; *COL2A1*

Miscellaneous skeletal diseases

SHORT RIB SYNDROME WITH POLYDACTYLY

- Group 7 disorder; Majewski syndrome
- Severe secondary pulmonary hypoplasia, fatal
- Growth plate shows; irregular columnization of chondrocytes, disordered bone maturation, retention of central cartilage

METATROPHIC DYSPLASIA

- Shortened long bones, trumpet-like flaring of metaphysis

ACHONDROGENESIS TYPE IB

- Sulfation disorder
- Severe micromelia, cystic hygroma, hydrops fetalis

RHIZOMELIC CHONDRODYSPLASIA PUNCTATA

- X-linked dominant
- Dystrophic calcification, cystic degeneration of epiphysis
- Peroxisomal disorder (Zellweger)

OSTEOPETROSIS

- Autosomal recessive
- Osteosclerosis, increased bone density
- Absence of medullary canal
- Thickened bony trabeculae, retained central cartilage
- Absence of bone marrow/hematopoiesis

MUCOPOLYSACCHARIDOSIS

- Chondrocytes have distended, finely vacuolated cytoplasm

TERATOGENS AND SKELETAL ABNORMALITIES

- *Thalidomide*: Phocomelia
- *Valproic acid and other anti-epileptics*: Limb reduction defects, polydactyly
- *Retinoids*: Lower limb defect
- *Cyclophosphamide*: Craniosynostosis
- *Warfarin*: Short limbs and stippled calcification of epiphysis
- *Aminopterin*: Craniosynostosis, oligodactyly, syndactyly

Acquired disorders

METABOLIC AND NUTRITIONAL CONDITIONS

Scurvy

- Lack of vitamin C prevents hydroxylation of lysine and proline → inadequate formation of extracellular collagenous matrix
- Proliferation of fibroblasts (instead of bone formation)
- Subperiosteal hemorrhage, microfractures, osteopenia of medullary bone

Rickets/osteomalacia

- Lack of calcium prevents adequate mineralization of bone matrix
- Maternal vitamin D deficiency, hereditary defects in vitamin D activation or phosphate resorption by renal tubules, calcium malnutrition
- Disruption of enchondral ossification and persistence of cartilage in metaphysis

Hyperparathyroidism

- Due to chronic renal failure
- Associated with skeletal abnormalities and four gland hyperplasia
- Bone biopsy; osteoclastic and osteoblastic activity with medullary fibrosis
- Brown tumor of hyperparathyroidism resembles giant cell reparative granuloma morphologically

Pseudohypoparathyroidism

- Functional resistance to *PTH* due to mutation in gene *GNAS*
- Albright hereditary osteodystrophy type IA has maternal inheritance and type IB has paternal inheritance

Primary hyperoxaluria I

- Mutation in *AGT* gene
- Autosomal recessive disorder
- Deposition of oxalate crystals in medullary space
- Osteoblastic/osteoclastic activity in trabecular bones

Tumor and tumor-like conditions

MATRIX PRODUCING AND ASSOCIATED TUMORS

Osteoid osteoma

- Benign bone-forming neoplasm
- Limited growth potential, usually <1 cm
- Proximal femur, tibia
- Progressive pain, worse at night, usually relieved by NSAIDs
- Imaging: Well-demarcated oval lucency, central calcification, reactive sclerosis
- Nidus composed of calcified osteoid, anastomosing bony trabeculae, fibrovascular stroma, spicules lined by osteoblasts
- Del 22q13.1 and del 17q

Osteoblastoma

- Rare osteogenic neoplasm similar to osteoid osteoma
- Size > 1 cm
- Pain, swelling, tenderness

- Appendicular skeleton, vertebrae, jaws
- Imaging: Well demarcated, lucent with ossification, reactive sclerosis
- Anastomosing trabeculae, lined by osteoblasts in loose stroma, sheets of bony matrix, immature bone, osteoblasts in clusters
- Osteoblasts polygonal in shape, round to oval nuclei, no cytologic atypia

Osteoma

- Benign tumors of sinuses, jaw, orbit, nasal cavity
- May produce facial distortion
- Imaging: Well demarcated, dense compact bone
- Dense compact bone, broad trabeculae of lamellar bone
- May show osteoblastoma-like areas in between

Fibrous dysplasia

- Non-neoplastic disorder, causing bone maturation arrest at woven bone stage
- Monostotic or polyostotic
- Curvilinear trabeculae (Chinese letters) of metaplastic woven bone in hypocellular, fibroblastic stroma
- No osteoblastic rimming
- No atypia or mitotic activity

McCune-Albright syndrome

- Polyostotic fibrous dysplasia
- Associated endocrine disorder (precocious puberty in girls, hyperthyroidism, Cushing, hyperparathyroidism)
- Jawbones, skull, ribs, long bones (pathological fractures)
- Defect in medulla
- Missense Gsα mutations in *GNAS1* (20q13)

Osteofibrous dysplasia

- Benign fibro-osseous process of tibial/fibular cortex
- Related to adamantinoma
- Spindle cell stroma with trabeculae of woven bone (lined by prominent osteoblastic rimming)
- Cytokeratin stain positive in spindle cells (not seen in FD)

Ossifying fibroma

- Benign fibro-osseous tumor of craniofacial skeleton
- Psammomatoid and trabecular patterns

Trabecular type

- Maxilla and mandible
  - Spindle cell stroma with a hint of osteoid
  - If *with osteoid*: Myositis ossificans is in differential diagnosis
  - If *without osteoid*: Nodular fasciitis is in differential diagnosis
  - If *woven bone trabeculae*: Fibrous dysplasia is in differential diagnosis

Psammomatoid type

- Broader age group
- Multiple uniform calcified ossicles embedded in cellular fibrous stroma
- Orbit and paranasal sinuses

Hyperparathyroidism jaw tumor syndrome

- AD with mutations in *HRPT2* gene
- Hyperparathyroidism and ossifying fibroma in jawbones

Osteosarcoma

- Most common malignant bone tumor in pediatric age group
- Arises from metaphysis in long bones (femur, humerus, tibia)
- Imaging: Codman triangle (periosteal elevation), bone formation
- Sarcomatous stroma, bone production by tumor cells
- High-grade malignant osteoblasts with lace-like osteoid matrix
- Depending on state of underlying bone, primary or secondary (post radiation, Paget disease, infarction, osteomyelitis, prosthesis, pre-existing benign tumors)
- If less than 90% tumor ablation by chemotherapy, poor overall response and bad prognosis
- Various subtypes: Osteoblastic, chondroblastic, fibroblastic, telangiectatic, small cell, giant cell

Small cell osteosarcoma

- In addition to small cells there are large pleomorphic malignant cells, osteoid matrix

Osteochondroma

- *EXT1* and *EXT2* gene mutations in multiple hereditary exostosis

Chondroma

- Also known as enchondroma: Solitary central intramedullary tumors
- After 8–10 years of age
- Maffucci (multiple enchondromas/vascular lesions) and Ollier disease (multiple enchondromas)
- Growth through intertrabecular spaces, expansion, and infiltration
- Chondrocytes may show nuclear enlargement and atypia with differential diagnosis of chondrosarcoma (very rare in pediatric age group)

Chondroblastoma

- Tumor arises in epiphyses of long bones
- Fibrochondroid stroma, embedded polygonal mononuclear cells, nuclear grooves, chicken-wire calcification, nodules of cartilage, osteoclast-like giant cells
- Positive for S100

Chondromyxoid fibroma

- Giant cells, chondroid stroma, lobulated
- 6q13 rearrangements

Chest wall hamartoma

- Cystic, solid, hemorrhagic appearance
- Cartilage, bony trabeculae, cystic and hemorrhagic foci

Myxoid chondrosarcoma

- Multinodular pattern, cords of tumor cells in myxoid matrix
- Low to intermediate grade
- Positive for S100 and vimentin

NON-MATRIX–PRODUCING TUMORS AND CYSTS

Aneurysmal bone cyst (ABC)

- Neoplastic lesion involving genetic translocation
- Imaging: Eccentric lucent metaphyseal lesion, internal septation fluid-fluid levels
- Cystic spaces filled with erythrocytes and fibrin, separated by thick septa and multinucleated giant cells
- Septa may have bony trabeculae, spindle cells, giant cells, and lace-like calcification

Unicameral bone cyst (UBC)

- Adolescent males
- Proximal femur/humerus
- Intramedullary cysts, unilocular
- Pathological fracture of bone
- Non-specific, fibrovascular lining with granulation tissue, hemosiderin pigment, calcospherites, giant cells
- Recurs after curettage

Giant cell tumor

- Skeletally mature individual, infrequent in prepubertal child
- Distal femur and proximal tibia
- Uniform osteoclast-like giant cells, groups/sheets, intervening spindle cell stroma

Giant cell reparative granuloma (GCRG)

- Age 10–25 years, females
- Jawbones, orbit, paranasal sinuses
- Familial cherubism; multiquadrant tumor in jawbones
- Scattered multinucleated giant cells in loose/compact fibrous stroma
- Resembles brown tumor of hyperparathyroidism

PRIMARY VASCULAR NEOPLASMS

Cavernous hemangiomas/venous malformations

- Craniofacial bones and vertebrae
- Thin-walled vascular spaces, scant intervening stroma, luminal thrombi, papillary endothelial hyperplasia (Masson lesion)

- Endothelial cells positive for CD34
- Stain negatively for GLUT-1 and D2-40

Gorham-Stout disease

- Also known as vanishing bone disease
- Humerus, pelvis, scapula involved
- Pleura (chylothorax)
- Maldevelopment of lymphatics, abnormal proliferation of lymphatic vessels in bones leading to bone loss
- Positive staining for CD105 (endoglin)

FIBROUS SPINDLE CELL TUMORS OF BONE

Non-ossifying fibroma

- Also known as metaphyseal fibrous defect
- Pain and pathological fracture
- Distal femur and proximal tibia
- Imaging: Metaphyseal radiolucency, well demarcated
- Bland uniform spindle cell proliferation, interspersed giant cells, xanthomatous histiocytes

Desmoplastic fibroma

- Similar to intraosseous desmoid-type fibromatosis
- Mandible and femur
- Bland spindle cells separated by pale collagenized stroma, mitotic figures
- High recurrence rate

Myofibromas

- Rare in bones
- Nodules of bland spindle cells
- Positive staining for smooth muscle actin

Cranial fasciitis

- Fibroproliferative lesion resembling nodular fasciitis
- Local growth erodes inner and outer table of skull
- SMA stain positive

Congenital pseudoarthrosis

- Congenital tibial dysplasia
- Associated with *NF1*

Fibrosarcoma

- Metaphysis of long bones
- Imaging: Differentiate from fibroblastic variant of osteosarcoma

Adamantinoma

- Anterior diaphysis of tibia, well-circumscribed lesion
- Second decade
- Morphologically mimics osteofibrous dysplasia
- Bland spindle cell stroma, trabeculae of woven bone and clusters of bland epithelial cells with peripheral palisading
- Osteoblastic lining seen around bony trabeculae
- Recur locally but no metastasis
- Classic pattern (in adults/rarely children) = basaloid, squamoid, pseudoglandular cells in myxoid stroma, may metastasize

ROUND CELL NEOPLASMS

Ewing sarcoma/primitive neuroectodermal tumor (PNET)

- Second-most common pediatric malignant bone tumor
- Imaging: Intramedullary, diaphyseal/metadiaphyseal
- Tumor cells in sheets with no matrix
- Neoplastic cells: Round, uniform, small with hyperchromatic nuclei, vacuolated to clear cytoplasm (glycogen)
- Stain positively with PAS, CK, vimentin, CD99 (membranous), caveolin, FLI-1
- FISH: EWS break apart, t(11;22) (q24;q12)

Melanotic neuroectodermal tumor of infancy

- Head and neck region: Maxilla, mandible, skull, brain/meninges
- Larger epithelioid cells; glandular architecture, pigmented, positive for HMB45
- Smaller cells; primitive, positive for neuroendocrine markers

Large B cell lymphoma

- Positive for CD20, *BCL6*

Metastases from a nasopharyngeal carcinoma

- Positive for CK, CD45

Langerhans cell histiocytosis (LCH)

- Cells have abundant eosinophilic cytoplasm, folded nucleus, no processes
- Infiltrate of Langerhans cells, eosinophils, Charcot-Leyden crystals, giant cells
- Stain positive for C1a, S100
- Stain negative for CD45
- Birbeck granules on EM
- *Unifocal LCH*: Eosinophilic granuloma
- *Multifocal LCH*: Hand-Schuler-Christian disease
- *Acute disseminated LCH*: Letterer-Siwe disease

Chordoma

- Lower spine, sacrococcygeal region
- Malignant tumors arising from fetal notochord
- Cords and lobules of physaliferous cells (vacuolated, bubbly cytoplasm) in fibromyxoid stroma
- Stain positive for S100, CK, vimentin, EMA

Infective/inflammatory conditions of bones

OSTEOMYELITIS

- Acute (neutrophils), subacute (mixture of neutrophils, lymphocytes, and plasma cells), chronic (lymphocytes, plasma cells, and macrophages)
- Necrotic bone (sequestrum) and new bone formation (involucrum)

Acute osteomyelitis

- Bacterial infection (*Staphylococcus aureus*); methicillin-resistant *S. aureus* (MRSA) or methicillin sensitive
- In children with sickle cell disease = Salmonella
- Tuberculous osteomyelitis is hematogenous, anterior portion of vertebral body (caseating granulomas)
- Non-tuberculous mycobacterial infection in immunocompromised children (cystic fibrosis)

Subacute osteomyelitis

- Brodie abscess (lytic lesion surrounded by osteosclerosis)

NON-BACTERIAL OSTEITIS

- Auto-inflammatory disorder, chronic recurrent multifocal osteomyelitis
- Upper anterior chest wall, bones of feet
- Mixed neutrophilic infiltrate, irregular bony trabeculae, mosaic lines
- Marrow fibrosis, chronic inflammation

Miscellaneous conditions of bone

ROSAI-DORFMAN DISEASE

- Emperipolesis, background contains plasma cells, eosinophils, and histiocytes
- Histiocytes are positive for S100

INFANTILE CORTICAL HYPEROSTOSIS

- Familial or sporadic
- Mutation in *COL1A1* gene
- Infants and toddlers, waxing/waning condition
- Soft-tissue swelling, inflammation, self-limited course
- Subperiosteal new bone formation, structural loss of cortical bone

OSTEONECROSIS

- Also known as aseptic/avascular necrosis
- Complication of chronic corticosteroids and hemoglobinopathies (sickle cell disease)
- Osteonecrosis of femoral head; seen in Legg-Calvé-Perthes disease and Gaucher disease

Synovium

- Involved by infectious, metabolic, or autoimmune conditions

ACUTE SYNOVITIS

- Pyogenic infection of joint space
- Infiltration of interstitium by neutrophils
- Knee and hip joint common

CHRONIC SYNOVITIS

- Diffuse/nodular infiltrate of lymphocytes, plasma cells, mast cells
- Hyperplasia of synovial cell lining, papillary architecture

Juvenile rheumatoid arthritis

- Chronic arthritis, ANA common
- Systemic onset, oligoarthritis, involves large joints
- Papillary synovial hyperplasia, lymphoplasmacytic infiltrate, lymphoid follicles and germinal centers, multinucleated giant cells, fibrin and hemosiderin

HEMOPHILIC ARTHROPATHY

- When factor VIII and IX levels <1% of normal
- Knee, ankle, and elbow joint common
- Infiltrates of lymphocytes, histiocytes, prominent hemosiderin deposits (synovial lining cells and histiocytes)

GRANULOMATOUS SYNOVITIS

- Sarcoidosis

HISTIOCYTIC SYNOVITIS

- CD68 positive multinucleated giant cells and foamy macrophages
- Non-tuberculous mycobacterial synovitis, arthropathy

TUMEFACTIVE LESIONS

- Synovial chondromatosis, synovial lipomatosis, pigmented villonodular synovitis, giant cell tumor of tendon sheath, ganglion cyst

OSTEOARTHROPATHY

- Degenerative joint disease
- Occurs as a result of other diseases; metabolic disorder, osteonecrosis, abnormal skeletal development

18 Nervous System

Introduction

- Nervous system contains different types of neurons
- Small granular neurons (<15 μ) and large pyramidal neurons (10–100 μ)
- Acutely necrotic/ischemic/dead neurons: Pyknotic shrunken or karyorrhectic nuclei and red eosinophilic cytoplasm
- Damage to axons causes accumulation of cytoskeletal filaments = axonal spheroids (stained with β-APP)
- Astrocytes are present throughout brain (connective tissue of brain)
- Gray matter (protoplasmic astrocytes), white matter (fibrillary astrocytes)
- Gliosis; hyperplasia/hypertrophy of astrocytes in response to injury/insult to brain
- Long-standing gliosis associated with Rosenthal fibers/eosinophilic granular bodies (pilocytic astrocytoma and Alexander disease)
- Oligodendroglia (responsible for myelination) have round regular nuclei, indistinct cytoplasmic processes
- Insults affecting oligodendroglia produce demyelination (detected with Luxol-fast blue stain)
- Oligodendroglia contain abnormal nuclear inclusions in progressive multifocal leukoencephalopathy (PML)
- Ependymal cells are ventricular lining cells (cuboidal/columnar)
- Microglia are inflammatory/antigen-presenting cells derived from bone marrow monocytes (phagocytose necrotic debris)

Increased intracranial pressure/ edema/hydrocephalus

- Mass lesions/increased intracranial pressure; shift/herniation of brain tissue from one compartment to another
- Most common are subfalcine, transtentorial (uncal), and tonsillar herniations

CEREBRAL EDEMA

- Accumulation of fluid in brain parenchyma
- Flattening of gyri/narrowing of sulci, narrow slit-like ventricles
- Pale and vacuolated parenchyma

Trauma

BIRTH TRAUMA

- Birth trauma due to difficult delivery/use of forceps can cause various injuries
- *Caput succedaneum*: Hemorrhage in subcutaneous connective tissue
- *Cephalhematoma*: Hemorrhage in subperiosteum
- *Erb paralysis*: Brachial plexus (C5-6 nerve roots) injury (traction forces during delivery)
- *Klumpke paralysis*: Damage to C8-T1

INFANCY AND CHILDHOOD

- Accidental or non-accidental
- Fatal craniospinal injury; mostly hypoxic-ischemic brain injury leading to cerebral edema and death
- Injury to vital cardiorespiratory center located in brainstem

INFLICTED INJURY IN INFANTS

- Epidural, subdural, subarachnoid hemorrhage, or cerebral contusions
- Cerebral edema, related to global hypoxic-ischemic encephalopathy (HIE) is the immediate cause of death
- HIE morphology: Neuronal necrosis, parenchymal vacuolization, microglial activation, myelin pallor

Embryology

- Neurulation is the formation of a neural tube
- *Primary neurulation*: Fusion of neural folds forming rostral neural tube
- *Secondary neurulation*: Canalization of solid mass of cells forming caudal neural tube
- Fusion of both primary and secondary neurulation forms complete spinal cord
- After formation of neural tube, axial skeleton is formed thus encasing central nervous system (CNS)
- Cranial vault/occiput develop from endochondral bone formation
- Facial bones/skull base develop from membranous bone

Congenital anomalies

NEURAL TUBE DEFECT

- Defective neural tube; normal closure during 3–4 weeks of gestation

Craniorachischisis

- Complete failure of neural tube closure, exposure of brain and spinal cord to amniotic fluid
- Most severe neural tube defect

Anencephaly

- Defect limited to cranial and cervical regions
- Most of the brain replaced by area cerebrovasculosa

Myelomeningocele

- Lumbosacral region defect mostly
- Herniation of spinal cord/meninges through associated vertebral defect
- Spinal cord lesion open or closed

HERNIATION THROUGH AXIAL MESODERMAL DEFECTS

- Neural tube closure is proper
- *Encephalocele*: Herniation of portions of the brain
- *Meningocele*: Herniation of all the three layers of meninges
- *Meckel-Gruber syndrome*: Occipital encephalocele, cystic renal dysplasia, ductal plate malformation of liver

TAILBUD DEFECTS

Tethered cord syndrome

- Traction on distal cord elements
- Lower limb motor/sensory deficits
- Pain and neuropathy of urinary bladder
- Thickened filum-terminale, spinal lipoma, other abnormalities of lumbosacral region
- Treatment is surgical de-tethering

HOLOPROSENCEPHALY

- Most severe type is alobar
- Associated with Smith-Lemli-Opitz, infants of diabetic mothers, trisomy 13, agenesis of corpus callosum, single fourth ventricle
- Brainstem and cerebellum normal

AGENESIS OF CORPUS CALLOSUM (ACC)

- Aicardi syndrome (partial/complete agenesis, retinal abnormalities, infantile spasms)
- Non-ketotic hyperglycemia (inborn error of metabolism)

LISSENCEPHALY TYPES I AND II

- Diffuse smooth cerebral surface, absence of gyration
- Cerebral gray matter is thick, paucity of white matter
- *Lissencephaly I*
  - Caused by disrupted neo-cortical cell migration

- Malformed four-layered cerebral cortex
- Developmental delay, mental retardation and seizures

- *Lissencephaly II*
  - Excessive migration of neuroglial precursors
  - Associated with autosomal recessive syndromes (Walker Warburg, Fukuyama)
  - Triad of cerebral, ocular, and muscle diseases

PACHYGYRIA

- Focal agyric abnormalities

POLYMICROGYRIA

- Cortical malformation
- Neocortical gray matter ribbon is very thin/excessively folded/fused/unlayered
- Risk factors: TORCH, intrauterine ischemia, metabolic diseases (Zellweger), family history

MALFORMATIONS OF CORTICAL DEVELOPMENT (FOCAL CORTICAL DYSPLASIA)

- Epileptogenic
- Focal thickening of gray matter, blurring of gray-white matter
- Delamination and columnar disorganization
- *Dysmorphic neurons*: Large, neurofilament rich, atypical coarse Nissl substance, thick dendritic processes, maloriented
- *Balloon cells*: Abnormal cells with abundant glassy eosinophilic cytoplasm, eccentrically placed vesicular nucleus, prominent nucleoli
- Dysmorphic neurons have neuronal, glial, or hybrid features (positive for GFAP and neuronal markers)
- FCD type I: Disorganized and delaminated cortex
- FCD type II: Delaminated cortex and dysmorphic neurons. IIA = without balloon cells. IIB = with balloon cells
- FCD type III: Cortical delamination associated with other principal lesion (hippocampal sclerosis, epileptogenic tumors, vascular malformations, cerebral traumatic lesion of early life)

ANTENATAL DISRUPTIVE LESIONS OF BRAIN

- Hypoxic/ischemic/infectious insult to brain

Porencephaly

- Focal transmantle necrosis of cerebrum
- Mostly in territory of middle cerebral artery
- Ventricle communicates with subarachnoid space
- Polymicrogyria, gliosis, calcification seen at rim of defect

Basket brain

- Bilateral middle cerebral artery defect
- Cingulate gyrus intact

Schizencephaly

- Non-traumatic cleft in cerebrum

Microcephaly

- Small head

Micrencephaly

- Small brain

BUDD-CHIARI MALFORMATION

Chiari I

- Herniation of tonsils through foramen magnum
- Syringomyelia

Chiari II

- Small posterior fossa
- Herniation of vermis through foramen magnum
- Lumbar myelomeningocele
- Tectal beaking: "S"-shaped kinking of medulla into dorsal spinal cord
- Vitamin A deficiency in mother

Chiari III

- Occipital cervical encephalocele

DANDY-WALKER MALFORMATION

- Cystic dilatation of fourth ventricle, hydrocephalus
- Cerebellar vermis small/hypoplastic/absent
- Large posterior fossa
- Elevation of tentorium and related dural sinuses
- Maternal isotretinoin usage is risk factor

Infectious disease

BACTERIAL INFECTIONS

Acute meningitis

- Neonatal meningitis caused by group B streptococcus and *Escherichia coli*
- Infants/young children infected by *Haemophilus influenzae* type B
- Older children by *Streptococcus pneumoniae* and *Neisseria meningitidis*
- Cerebrospinal fluid (CSF) exam: Granulocytic pleocytosis, increased proteins, decreased glucose
- Identification of organisms on Gram stain
- Long-term effects: Fibrosis, gliosis (leading to cranial nerve palsies), hydrocephalus

Cerebral abscess

- Children with CHD at risk for hematogenous bacterial spread/cerebral abscess
- Other risk factors: Penetrating head injuries, neurosurgical procedures, immunocompromised hosts

VIRAL INFECTIONS

- Signs of meningismus and fever
- Lacks neurologic dysfunction
- Viral cultures are positive
- Echovirus (coxsackie A and B) and enterovirus common
- Other viruses: HSV, CMV, VZV, HIV
- Perivascular and leptomeningeal lymphocytic infiltrate
- Diagnosis of fetal infection: Viral cultures, polymerase chain reaction of amniotic fluid, fetal IgM serology

FUNGAL INFECTIONS

- Immunocompromised hosts
- *Cryptococcus neoformans*, *Candida albicans*, *Aspergillus* species

PARASITIC INFECTIONS

Toxoplasmosis

- Intracellular protozoan (*Toxoplasma gondii*)
- Definitive host is cat
- Congenital infection through transplacental spread
- Immunocompromised children (reactivation of dormant infection)
- Sabin tetrad = seizures, chorioretinitis, cerebral calcifications, and hydrocephalus
- Encysted bradyzoites in brain easily identified compared to extracellular tachyzoites
- Imaging: Multiple ring-enhancing lesions

Neurocysticercosis

- CNS disease; when humans are intermediate hosts (after eating pork contaminated with *Taenia solium* oocysts)
- Oocysts develop into larvae → invade gastrointestinal tract → disseminate hematogenously → reside in CNS/muscle
- Scolex has characteristic suckers/hooklets

Vascular disorders

- Congenital or acquired disorders
- Premature infants mostly affected

HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE)

- Global insult to body (cardiac arrest/septic shock)
- Gray and white matter may be involved
- Cerebral swelling, dusky gray matter, loss of gray and white matter junction, cerebral atrophy
- Parenchymal edema, vacuolization, microglial activation, foamy macrophages
- Neuronal cytoplasmic eosinophilia, pyknotic angulated nuclei, karyorrhexis

- Vascular proliferation, gliosis, and calcium deposits
- Vascular watershed regions susceptible to HIE
- Sulcal cortical depth involved leading to ulegyria (mushroom-like)
- HIE in prenatal life leads to malformations; polymicrogyria, schizencephaly

PERIVASCULAR LEUKOMALACIA (PVL)

- White matter damage in premature infants
- 24–35 weeks' gestational age, most prone
- Other causes: intrauterine infection, feto-maternal cardiorespiratory instability
- Periventricular coagulative necrosis, cystic degeneration, mineralization, and gliosis
- Long-term sequelae: Cerebral palsy, cognitive disorders, epilepsy

GERMINAL MATRIX HEMORRHAGE (GMH)

- Infants less than 28 weeks' gestational age
- Risk factors: Prematurity, sepsis, respiratory compromise, intrauterine growth retardation (IUGR), hypothermia
- Germinal matrix has neuroglial precursors and is a site of fibrinolytic activity
- Grade I: Confined to germinal matrix
- Grade II: Intraventricular hemorrhage (ventricle normal in size and less than 50% involved with hemorrhage)
- Grade III: Intraventricular hemorrhage (ventricle dilated and entirely filled with hemorrhage)
- Grade IV: Parenchymal extension of hemorrhage

PEDIATRIC STROKE

- Infarction
- Risk factors: Diabetes, congenital heart disease (CHD), thrombophilia, smoking, hypertension, oral contraceptive use

VASCULAR ANEURYSM

Berry aneurysm

- Circle of Willis
- Saccular aneurysm
- Wall attenuated, media and internal elastic lamina replaced by fibrosis, atherosclerosis

VASCULAR MALFORMATIONS

Arterio-venous malformation (AVM)

- Veins, arteries, hybrid vessels (arterialized veins) with intervening gliotic brain tissue fragments

Cavernous hemangiomas

- Hyalinized veins of variable caliber arranged in back-to-back pattern
- No intervening parenchyma

Vein of Galen aneurysm

- Associated AV fistula

Meningioangiomatosis

- Meningovascular malformation/hamartoma
- Proliferation of meningothelium, hyalinized fibrosed vessels, perivascular spindle cells
- Surrounding brain has gliosis and dysmorphic neurons
- Seizures and headache

Lysosomal storage disease

NEURONAL LIPIDOSIS

- Neuronal cytoplasm distended by lipofuscin-like storage material (neuronal ceroid lipofuscinosis)

LEUKODYSTROPHIES (KRABBE AND METACHROMATIC)

- Abnormality in myelin formation and metabolism
- Bilateral, symmetrical white matter disease, involves all parts of CNS
- Rostral fibers involved in Alexander disease and metachromatic leukodystrophy (MLD)
- Caudal fibers involved in Krabbe leukodystrophy (KLD) and adrenoleukodystrophy (ALD) (Luxol fast blue stain)

MUCOPOLYSACCHARIDOSIS/ HURLER SYNDROME

- Build-up of glycosoaminoglycans
- Intellectual disability

Mitochondrial diseases

- Mitochondria are known as "power houses of cell"; provide energy by ATP and electron transport chain
- Dysfunction of electron transport chain results in cell death (due to energy deprivation/free radical toxicity/apoptosis)

ENCEPHALOMYOPATHIES

- Skeletal muscle, cardiac muscle, and brain affected
- Blood/CSF lactate and lactate/pyruvate, ratio increased

MELAS

- Metabolic encephalopathy, lactic acidosis, and stroke
- Maternally inherited disorder
- Adenine to guanine point mutation at nucleotide

MERRF

- Maternally inherited disorder
- Point mutation at adenine to guanine

LEIGH DISEASE

- Subacute necrotizing encephalopathy
- Nuclear DNA mutation
- Inherited in AR pattern

KEARNS-SAYRE SYNDROME

- Mostly ophthalmic findings
- Neuronopathy—RRF and spongy myelinopathy
- Mitochondrial myopathy

Note: *Ragged red fibers*; Gomori's trichrome stain (dark red). Succinic dehydrogenase stain (dark blue). *EM*: Rectangular para-crystalline arrays resembling a parking lot

Vitamin deficiencies

- Wernicke-Korsakoff syndrome: Vitamin B1 (thiamine) deficiency
- Subacute combined degeneration: Vitamin B12 (cobalamin) deficiency

Epilepsy

- Disorders causing dysfunctioning of neocortex

MESIAL TEMPORAL SCLEROSIS

- Ammon horn sclerosis (hippocampal sclerosis)
- Isolated or in association with other temporal lobe diseases (neoplasm, vascular malformation, cortical dysplasia)
- Atrophy of hippocampal formation, dilatation of adjacent inferior temporal horn of lateral ventricle
- Neuronal loss/gliosis most prominent in CA1 and CA3 hippocampal subregions
- Dysmorphic neurons

Neurodegenerative cerebellar disorders

FRIEDREICH ATAXIA

- Autosomal recessive progressive limb and gait ataxia, multisystem disorder
- Expanded GAA intronic nucleotide repeat, chromosome 9
- Spinal cord shows symmetric degeneration in dorsal column, corticospinal tracts, and spinocerebellar tracts
- Neuronal loss in dorsal root ganglion, loss of large myelinated fibers in peripheral nerves

SPINAL MUSCULAR ATROPHY

- Autosomal recessive
- Rounded, atrophic, and elongated skeletal muscle fibers
- Type I more common

AUTISM

- Duplication of chromosome 15q11-q13
- Linkage between GABA beta3 and autism
- Insistence on sameness

Neoplasia

GLIOMAS

Pilocytic astrocytoma

- Most frequent pediatric brain tumors
- Posterior fossa, cerebellum, and hypothalamus
- Seen in relation to optic pathway (NF1)
- Imaging: Cystic lesion with enhancing mural nodule
- World Health Organization (WHO) grade I
- Sharp tumor/normal brain interface
- Biphasic solid/microcystic architecture
- Spindle-shaped cells, bipolar hair-like processes
- Smaller cells with short cytoplasmic processes
- Rosenthal fibers (RF) and eosinophilic granular bodies (EGB)
- Positive staining with GFAP, low MIB-1 index

Pilomyxoid astrocytoma

- Variant of PA, more infiltrative
- Located in hypothalamus
- WHO grade II
- Round/ovoid cells in mucoid/myxomatous background, perivascular pseudorosettes

Anaplastic astrocytoma

- WHO grade III
- Enlarged, hyperchromatic, irregular tumor nuclei, scant cytoplasm
- Nuclear atypia, high mitotic activity
- Diffusely infiltrative

Glioblastoma multiforme

- WHO grade IV
- Cytologic atypia, mitotic activity, endovascular proliferation, geographic necrosis with pseudopalisading

Ependymomas

- Posterior fossa tumor
- Perivascular pseudorosettes
- *EM*: Zipper-like intercellular junctions, microvilli
- Positive staining with GFAP, EMA, and CD99

Pleomorphic xanthoastrocytoma

- Temporal lobe, epileptogenic tumor
- WHO grade II
- Positive for CD34

Oligodendroglioma

- In children, del1p19q is absent
- Bad prognosis
- Tumor cells have fried egg appearance

EMBRYONAL TUMORS

Medulloblastoma

- Posterior fossa
- Defect is i(17q)
- Gorlin syndrome and *PTCH* gene association
- WHO grade IV
- Small, round, blue cell tumor, high grade
- Positive for synaptophysin
- Large cell anaplastic medulloblastoma has prominent cell wrapping

ATRT (Atypical teratoid rhabdoid tumor)

- *HSNF5* gene—22q11 mutations/deletions
- Loss of nuclear expression of INI-1/BAF47
- Tumor cell nuclei negative for INI-1 (non-neoplastic lymphocytes/endothelial cells retain positivity)
- Triad stain positivity: Vimentin, SMA, and EMA

Medulloepithelioma

- Rare embryonal tumor
- Mimics embryonic neural tube
- Tubular/papillary epithelial growth pattern
- Positive for vimentin and nestin
- Neoplastic epithelium has external limiting membrane
- Divergent differentiation

Ependymoblastoma

- Multilayered true rosettes
- Positive for vimentin and S100

Hemangioblastoma

- Von Hippel-Lindau syndrome
- Positive for vimentin, NSE, inhibin A, and GFAP
- Negative for epithelial markers

TUMORS RELATED TO THE THIRD VENTRICLE/SUPRASELLAR SPACE

Craniopharyngiomas

- Tumor of sellar region
- Wet keratin, adamantinomatous epithelium, squamoid cells lining cysts
- Papillary pattern is less common in children

Intracranial germinoma

- Biphasic histology; mitotically active epithelioid cells and reactive lymphocytes
- CD117 stain; membranous positivity

Pineocytoma

- Bland, uniform cells
- Pinocytic rosettes (larger than Homer-Wright rosettes)

Pineoblastoma

- Small, round, blue cell primitive tumor
- Homer-Wright rosettes

NEURONAL AND MIXED GANGLIONEURONAL TUMORS

- Slow-growing, low-grade tumors
- Clinically present with seizures

Ganglioglioma

- WHO grade I
- Epileptogenic tumor
- Mixture of glial cells and numerous neoplastic neurons
- Vacuolated and bi-nucleated neurons
- Eosinophilic granular bodies, perivascular lymphocytic cuffing, microcalcifications
- GFAP stain positive in glial portion
- Neu-N stain positive in ganglion cells
- CD34 stain highlights tumor cells with highly ramifying cytoplasmic processes

Dysembryoplastic neuroepithelial tumor (DNET)

- WHO grade I
- Glioneuronal/hamartomatous tumor
- Cortically based temporal lobe lesions
- Floating neurons and oligodendroglial like cells (S-100+)
- Cortical dysplasia adjacent to tumor (disorganized and dyslaminated cortex)

Desmoplastic infantile glioneuroma (DIG)

- WHO grade I

Dysplastic infantile astrocytoma

- WHO grade I

Dysplastic gangliocytoma of the cerebellum

- Also known as Lhermitte-Duclos disease
- WHO grade I
- Associated with Cowden syndrome
- Abnormal architecture of cortex (flipped inside out)
- Cerebellar cortex replaced by two layers; outer layer composed of parallel arrays of myelinated axons, inner layer composed of abnormal smaller/larger neurons
- Germline mutations in *PTEN* gene
- Patients prone to gastrointestinal and breast malignancies

CHOROID PLEXUS TUMORS

- Lateral ventricle; common site
- Normal choroid plexus cells: Bumpy hob nailing of surface

Choroid plexus papilloma

- WHO grade I
- Epithelial hob nailing lost, more cellularity of tumor than normal choroid plexus

Choroid plexus carcinoma

- WHO grade III
- Cytologic atypia/mitotic activity
- Bad prognosis

- Positive staining for CK, S-100 (mostly carcinoma)
- Negative staining for EMA

MENINGIOMA

- Uncommon tumors in children (compared to adults)
- Slow growing, derived from arachnoid cap cells
- Grade I: Meningothelial, fibroblastic, transitional, angiomatous, psammomatous
- Grade II: Atypical, choroid, clear cell
- Grade III: Anaplastic, papillary, rhabdoid
- Round, well-circumscribed, dura based
- Lobulated architecture, meningothelial whorls, uniform round cells, intranuclear inclusions, psammoma bodies
- Stain positive with vimentin and EMA stains

Cancer predisposing neurocutaneous syndromes

- *NF1*: Neurofibromas (diffuse, nodular, plexiform), optic/hypothalamic gliomas, diffuse astrocytomas
- *NF2*: Bilateral vestibular schwannomas, schwannomas, multiple meningiomas, meningioangiomatosis
- *Ataxia-telangiectasia*: Cerebellar degeneration, intracranial hemorrhage, cytomegaly, nuclear atypia, lymphomas
- *Nevoid basal cell carcinoma syndrome (Gorlin)*: Desmoplastic medulloblastoma, meningioma
- *VH-Lindau*: Hemangioblastoma of cerebellum
- *Cowden (PTEN)*: Lhermitte-Duclos disease
- *Li-Fraumani*: Gliomas, choroid plexus tumors
- *Turcot*: GBM, medulloblastoma
- *Retinoblastoma*: Bilateral retinoblastoma and pineoblastoma (ectopic intracranial retinoblastoma) = trilateral retinoblastoma

19 Ophthalmic Pathology

- Major anomalies during ocular development result from interference during organogenesis (between fourth and eighth embryonic weeks)

Eyelid

NORMAL ANATOMY

- Movable folds of tissue that cover and protect globe anteriorly and help lubricate eye
- Orbicularis muscle closes the eyelids
- Levator palpebrae muscle elevates the upper lids
- Meibomian glands are holocrine sweat glands

VASCULAR ABNORMALITIES OF EYELID

- Capillary hemangioma, nevus flammeus, choroidal hemangioma

INFLAMMATORY ABNORMALITIES OF EYELID

Pyogenic granuloma

- Lobular proliferation of capillaries
- Granulation tissue in intervening stroma

Chalazion

- Occlusion and rupture of meibomian glands of eyelid
- Lipo-granulomatous inflammation; foreign body giant cell reaction to sebaceous products of glands

Juvenile xanthogranuloma

- Non-Langerhans cell histiocytosis
- Mononuclear lipidized/non-lipidized cells and Touton giant cells

Molluscum contagiosum

- Poxvirus infection of skin epithelium (of eyelid)
- Multiple, elevated, non-tender, umbilicated nodules
- Acanthosis, prominent intracytoplasmic inclusions in squamous epithelial cells

Sty or hordeolum

- Abscess of adnexal units of eyelid skin

Preseptal cellulitis

- Bacterial infection of subcutaneous tissue of eyelid; anterior to orbital septum
- *Haemophilus influenzae* and *Streptococcus* species

NEOPLASTIC LESIONS OF EYELID SKIN

Xeroderma pigmentosa

- Autosomal recessive defect in DNA repair system of body
- Exposure to UV light can cause squamous cell carcinoma, basal cell carcinoma, malignant melanoma

Basal cell nevus syndrome (Gorlin-Goltz)

- Affected individuals are prone to develop basal cell carcinoma of skin

Neurofibromatosis type I (NF-I)

- Autosomal dominant (AD)
- Neurofibromas in eyelid skin
- Optic pathway glioma

Conjunctiva

NORMAL CONJUNCTIVA

- Thin, movable mucus membrane lining inner surface of eyelids and sclera

- Composed of non-keratinizing squamous epithelium (2–5 cell layers thick), goblet cells on the surface
- Highly vascularized substantia propria
- *Palpebral conjunctiva* lines inner surface of eyelids
- *Bulbar conjunctiva* lines surface of globe

INFLAMMATORY CONDITIONS OF CONJUNCTIVA

Chlamydia trachomatis

- Causes trachoma
- Early stages: Follicular conjunctivitis
- Late stages: Entropion and corneal scarring due to eyelashes
- Leads to blindness

Ligneous conjunctivitis

- All mucus membranes of body including conjunctiva, show subepithelial fibrin deposition
- Systemic reduction in levels of plasminogen

CONGENITAL ANOMALIES OF CONJUNCTIVA

Episcleral osseous choristoma

- Represents embryonic rests of bone in episcleral tissue
- Mature bone surrounded by mature fibrous tissue

Limbal dermoid

- Solid choristoma mass with surface epithelium resembling epidermis, dermis, and adnexal structures
- Underlying dense fibrous tissue

Neuronal ceroid lipofuscinosis

- Neurodegenerative diseases showing accumulation of lipo-pigments within cells
- Disruption of cellular function
- Intracellular "curvilinear and fingerprint bodies" on EM

Melanocytic abnormalities of conjunctiva

Hypermelanosis of conjunctiva

- More than average number of typical melanocytes

Melanosis of episcleral/scleral tissue/nevus of Ota

- Risk factors for melanoma in ipsilateral uveal tract or deep orbital tissue

Melanocytic nevus of conjunctiva

- Nevus associated with abnormal development of conjunctival epithelium
- Solid nests of squamous cells/cysts lined by squamous epithelium, in substantia propria
- Pleomorphic spindle shaped/epithelioid melanocytes
- Melanocytes may occur in epithelium of inclusion cysts and mimic lymphatic spread of melanoma

Malignant melanoma of the conjunctiva

- Rare in children

Squamous cell carcinoma of conjunctiva

- Rare in children

Cornea

NORMAL CORNEA

- Outer protective coat located in center of anterior pole of eye
- Transparent and refracts light
- Consists of five layers (from anterior to posterior): Non-keratinizing squamous epithelium, Bowman layer (acellular type I collagen), stroma, Descemet membrane (thick basement membrane of endothelial cells), and endothelium

SURGICAL PROCEDURES OF CORNEA

- Various methods used to decrease corneal thickness
- Photorefractive keratectomy and laser in situ keratomileusis (LASIK)

- These procedures used to reduce refractive error of myopia

DEVELOPMENTAL ABNORMALITIES OF CORNEA

- *Microcornea:* Horizontal diameter less than 9 mm at 1 year of age
- *Macrocornea*: Horizontal diameter more than 11.5 mm at 1 year of age
- *Cornea plana*: Flattened cornea
- *Pete anomaly*: Failure of separation of cornea from crystalline lens

INFLAMMATORY CONDITIONS OF CORNEA

Herpes simplex keratitis

- After systemic body infection, HSV virus is retained in Gasserian ganglion
- Virus periodically travels via sensory peripheral nerves to infect cornea
- Linear branching ulcer of cornea (dendritic figure)
- May cause corneal rupture
- Lymphocytic infiltration, vascular proliferation, foreign body granulomatous reaction

Acanthamoeba keratitis

- Acanthamoeba is a protozoa found in soil and water
- Invades cornea due to microabrasion of cornea, especially in contact lens wearers
- Necrotizing keratitis and scarring
- Encysted forms identified by PAS stain

DYSTROPHIC CONDITIONS OF CORNEA

- Metabolic abnormalities of cornea that cause clinically detectable corneal opacities
- AD (except macular corneal dystrophy)
- Progressive, recur in corneal graft, bilateral

Congenital hereditary endothelial dystrophy (CHED)

- Opaque cornea due to edema, which is secondary to endothelial dystrophy

Map-dot-fingerprint dystrophy

- Excessive production of basement membrane material by corneal epithelial cells
- Epithelium loosely adherent

Fuchs endothelial dystrophy

- Common in older age groups
- Corneal endothelium not able to dehydrate cornea, and stroma becomes thick/opaque
- Descemet membrane thickened focally or diffusely
- Loss of endothelial cells

Keratoconus

- Acquired localized stromal thinning of cornea, usually inferonasal quadrant
- Abnormal activity of matrix metalloproteases, secreted by corneal keratinocytes
- Corneal hydrops, rupture, corneal opacities
- Distinct focal breaks in Bowman membrane and scarring
- Treated by penetrating keratoplasty

CORNEAL DEGENERATION

Band keratopathy

- Degeneration of anterior cornea
- Chronic anterior uveitis/keratitis
- Dystrophic calcification of stroma/Bowman membrane
- Marked vision loss

Crystalline lens

STRUCTURE OF CRYSTALLINE LENS

- Lens develops from lens vesicle (derivative of surface ectoderm)
- Anterior portion of vesicle composed of low columnar epithelium forming the anterior epithelium of adult lens
- Posterior wall of vesicle composed of cells that lengthen substantially to form lens fibers
- Succeeding fibers after cell division keep getting arranged in concentric layers

- Oldest and deepest fibers lose their nuclei
- Lens encased by lens capsule (produced by epithelial cells)

DEVELOPMENTAL ABNORMALITIES OF CRYSTALLINE LENS

Ectopia lentis

- Dislocation of lens resulting from zonular rupture
- May be congenital or acquired (trauma)
- Several systemic disorders: Marfan syndrome (subluxates temporally and superiorly), homocystinuria (subluxates medially and inferiorly), and hyperlysinemia

The vitreous

STRUCTURE OF VITREOUS

- Clear, gel-like structure (contains mostly water) that is found between lens and retina
- Molecular constituents: Heterotypic collagens, glycosaminoglycans, and non-collagenous structural proteins

Optic nerve

STRUCTURE OF OPTIC NERVE

- Optic nerve is a tract of central nervous system and not a peripheral nerve
- Refers only to anterior portion of the tract between retina and optic chiasm (50 mm in length)
- Surrounded by dura, arachnoid, and pia mater
- Nerve has organization similar to white matter of the brain
- Axonal fibers surrounded by oligodendrocytes and not Schwann cell sheaths

The orbit

STRUCTURE OF ORBIT

- Anatomic space lying between orbital bones
- Contains eye, extraocular muscles, vessels, nerves, and connective tissue
- Volume of adult orbit is about 30 cc
- Bony orbit composed of ethmoid, frontal, lacrimal, maxillary, palatine, sphenoid, and zygomatic bones
- Optic nerve, ophthalmic artery, and sympathetic nerves transmitted from posterior orbit through optic foramen to middle cranial fossa

Lesions of orbit

Dermoid cyst

- Cystic choristoma containing benign dermal elements
- Lined by keratinized stratified squamous epithelium
- Contain adnexal elements

Epidermoid cyst

- No adnexal elements

Langerhans cell histiocytosis (LCH)

- Granulomatous inflammatory infiltrate
- CD1a positive Langerhans histiocytes

Lymphangioma

- Vascular channels of various sizes
- Separated by fibrous septa containing lymphocytes
- Stain positively with D2-40 immunostain

Inflammatory pseudotumor of orbit

- Pleomorphic inflammation (predominance of plasma cells)
- Fibrovascular proliferation, fat necrosis

Tumors of lacrimal gland

- Most common tumor is pleomorphic adenoma
- Most common malignant tumor is adenoid cystic carcinoma

The eye

STRUCTURE OF EYE

- Two functional compartments of eye are anterior segment and posterior segment

Anterior segment

- Anterior segment includes lens and structures anterior to lens
- Anterior segment includes two fluid chambers: Anterior chamber and posterior chamber
- The two chambers are divided by iris and communicate via pupil
- Aqueous humor is a transparent fluid that fills both chambers (formed by ciliary body)

Posterior segment

- Space behind the lens
- Consists of retina, choroid, and vitreous
- Composes 80% of ocular volume

MAJOR ANOMALIES OF EARLY DEVELOPMENT

Cyclopia

- Consequence of development of single optic vesicle
- Lethal condition
- Rudimentary tubular nose (proboscis) above the fused/single globe

Synophthalmus

- Less severe condition resulting from fusion of paired optic vesicles
- Eyes are relatively well differentiated in anterior segment
- Posterior segment less well organized

Anophthalmos

- Absent eye tissue

Microphthalmos

- Small disorganized globe

Nanophthalmos

- Microphthalmos
- No major internal disorganization of globe

Cryptophthalmos (ablepharon)

- Embryonic lid folds fail to develop
- Conjunctiva, cornea, and lid folds replaced by skin
- Skin is continuous from eyebrows to cheek

Primary aphakia

- Congenital absence of lens
- Failure of lens vesicle formation/degeneration of vesicle

Coloboma

- Occurs inferonasally usually
- Failure of closure of optic fissure at fifth embryonic week
- Atypical colobomas occur in regions other than inferonasal area
- Cystic coloboma (associated with microphthalmos) results from faulty closure of optic fissure and imperfect alignment of optic vesicle walls
- Coloboma of lens is secondary to coloboma of ciliary body (region of absence of zonules)
- Lens appears notched

Neoplasms of eye

RETINOBLASTOMA

- Most common primary intraocular neoplasm of children
- Clinical presentation with leukocoria and/or strabismus
- Majority of cases are bilateral
- Median age of diagnosis is 12–24 months
- Strong tendency to invade optic nerve and brain
- Growth pattern in eye; endophytic/exophytic/diffusely infiltrating
- Small, round, undifferentiated retinoblastoma cells with hyperchromatic nuclei and scant cytoplasm
- Flexner-Wintersteiner rosettes, Homer-Wright rosettes, pseudorosettes, and fleurettes
- Extensive necrosis and calcification
- Direct extension through the sclera and invasion of the optic nerve; bad prognosis
- *Retinoblastoma* gene (*RB* gene); tumor suppressor gene, located at 13q14
- Loss/inactivation of both normal alleles of *RB* gene

- Hereditary retinoblastoma arises from single somatic mutation in cell that previously carried a germline mutation
- Sporadic retinoblastoma arises from two somatic mutations in the same cell; "two hit hypothesis of Knudson"

Spontaneously regressed retinoblastoma

- Clinically seen in "unaffected" family members of a newly diagnosed patient
- Asymptomatic clinically

Trilateral retinoblastoma

- Bilateral retinoblastoma plus pineoblastoma
- Risk of developing it is 5%–15% in a patient with bilateral retinoblastoma

MEDULLOEPITHELIOMA

- Rare congenital tumor
- Arises from non-pigmented ciliary epithelium
- May be benign or malignant
- Interlacing sheets, cords, and rosettes of medullary epithelium
- Intraocular extension in malignant forms
- Teratoid medulloepitheliomas contain heterotopic elements

MALIGNANT MELANOMA

- Uveal in location
- Rare in children
- Similar to adult tumors

OPTIC NERVE GLIOMA

- Juvenile pilocytic astrocytoma
- Fusiform enlargement of optic nerve
- Associated with NF1
- Biphasic pattern; fibrillary and mucoid stroma
- Rosenthal fibers
- Surgical resection of optic nerve/enucleation

MENINGIOMA OF OPTIC NERVE

- Arises in arachnoid sheath of optic nerve
- Meningotheliomatous or transitional type

ORBITAL RHABDOMYOSARCOMA

- Embryonal more common than alveolar

METASTATIC TUMORS

- Acute leukemia, myeloid sarcoma (may be bilateral and cause proptosis)
- Burkitt lymphoma, neuroblastoma, Ewing sarcoma

Glaucoma

- Buphthalmos; enlarged eye with raised intraocular pressure
- Ruptures in Descemet membrane, corneal edema, cupping of the optic nerve
- Developmental (congenital/infantile) glaucoma may be primary or secondary

PRIMARY

- Usually bilateral
- AR
- Developmental anomaly of angle structures

SECONDARY

- Associated with other ocular or systemic disorders

Miscellaneous conditions

- Wilson disease: Kayser-Fleischer ring
- GM2, type I, gangliosidosis (Tay-Sachs disease): Cherry red spot in the retina

OCULAR TRAUMA

- Neural retinal hemorrhages (splinter, flame shaped, blob); newborns due to mechanical rise in pressure of skull during labor/obstetrical instrumentation
- Tears in Descemet membrane due to obstetric forceps

CHILD ABUSE (BATTERED BABY SYNDROME)

- Hemorrhages in vitreous and subdural area of optic nerve, conjunctiva and lid
- Retinal trauma: Tears, detachments, schisis, and folds
- Most ruptures found at corneal sclera limbus (thin region)

SYMPATHETIC OPHTHALMIA

- Bilateral granulomatous inflammation of uveal tract
- Appears 5 days to many years following trauma to one/both eyes
- Autoimmune response

PHTHISIS BULBI

- Eye condition occurring months to years following trauma
- Small, shrunken, and cuboidal in shape
- Advanced ocular degeneration/disorganization, fibrosis, and calcification

20 Neuromuscular Diseases

Normal muscle development

- Undifferentiated mesenchyme → myoblasts → myotubes (central nuclei) → myofiber (mature muscle fiber having peripheral nucleus, cross striations, and basal lamina)
- Myotubes are replaced by myofibers at 18–20 weeks' gestation
- Normal ratio of type I/type II is 2/3 in most biopsy sites
- Deltoid, soleus, and rectus abdominis; type I fibers predominate
- Type I are slow-twitch fibers and type II are fast twitch
- Myofibrillar ATPase at pH 4.6 stains type I fibers dark, type II fibers light, and type IIC fibers intermediate
- Normally, type IIC fibers mostly disappear in the fetus during the third trimester of pregnancy
- Persistence of type IIC fibers indicates delayed myofiber maturation
- After 3 months of postnatal life, size of type I fibers = type II fibers
- From 3 months of age to puberty the size of type I fibers keeps increasing in both sexes

Features of maturational delay in muscle morphology in term newborn

- Persistent type IIC fibers, type I myofiber hypotrophy, type I myofiber predominance, persistence of myotubes (central nuclei), satellite cells, Wohlfart B fibers

Muscle biopsy

- Quadriceps for proximal muscle weakness/myopathy
- Gastrocnemius for distal muscle weakness/neuropathy
- Timing of biopsy dictated by disease severity
- Creatine kinase (CK), family history, nerve conduction studies, and EMG help to determine if muscle/nerve biopsy will be informative

Muscle biopsy triage

- Formalin-fixed paraffin-embedded (FFPE) sections stained with hematoxylin and eosin for morphologic study
- Snap frozen sections utilized for histochemical staining, quantitative biochemistry, and DNA studies
- EM studies after fixation in 2.5% glutaraldehyde (especially useful in mitochondrial myopathy and storage diseases)

Clinical and laboratory findings

- Signs of in utero muscle weakness: Weak fetal movements, short umbilical cord, pulmonary hypoplasia, polyhydramnios, non-immune hydrops, long thin myopathic facies, thin diaphragm
- Serum CK levels elevated in conditions causing myofiber degeneration
- Cardiomyopathy and arrhythmias may be associated with Pompe disease, muscular dystrophies
- Mitochondrial myopathies: Weakness, lactic acidosis, congenital cataracts, and hypertrophic cardiomyopathy

MALIGNANT HYPERTHERMIA

- Certain myopathies prone to this potentially life-threatening condition during general anesthesia

- Triggered by muscle relaxant succinylcholine/volatile anesthetics

ARTHROGRYPOSIS

- Twisted extremities due to contracture of joints
- Caused by absent/restricted fetal movements

CARDIOMYOPATHY ASSOCIATED WITH SKELETAL MYOPATHIES

- Hypertrophic or dilated CM
- Glycogen storage diseases especially type II (Pompe disease)
- Mitochondrial disorders: Leigh syndrome, Barth syndrome
- Lipid disorders: Defects in oxidation of long-chain fatty acids

FLOPPY INFANT

- Hypotonia
- Hyperextensibility

Muscular dystrophy

CONGENITAL MUSCULAR DYSTROPHY (CMD)

- Progressive weakness and loss of muscle mass
- Gene mutations interfere with proteins needed to form muscles
- Manifested in neonatal period
- Autosomal recessive
- Deficiency of cytoskeleton proteins (dystrophin-associated proteins)
- Infantile polymyositis associated with deficiency of merosin
- Muscle eye brain (MEB) disorders associated with hypotonia, weakness, contractures, mental retardation, central nervous system (CNS), and ocular abnormalities
- Fukuyama-CMD, Finnish-CMD, Walker-Warburg syndrome (abnormal glycosylation of alpha-dystroglycan)
- Laminin alpha-2 (merosin deficient) CMD (MDC1A) is the most common of all forms (progressive weakness and elevated serum CPK)
- Intermixed pattern of myofiber degeneration, atrophy, hypertrophy, necrosis, regeneration, and interstitial fibrosis
- Dystrophin immunostaining is normal in all forms of CMD (d/d Duchenne muscular dystrophy)
- No fiber type disproportion and no specific structural changes associated with congenital myopathies (nemaline rods, central cores, myotubes)

X-LINKED DYSTROPHINOPATHIES (DMD AND BMD)

- Also known as Xp21 dystrophies
- X-linked recessive conditions, male children affected
- Deficiency of membrane-associated protein dystrophin
- DMD (Duchenne) is most common muscular dystrophy, average age of onset is 3–5 years
- BMD (Becker) is a milder disease than DMD with lesser degree of dystrophin deficiency; average age of onset 12 years
- Delayed walking until 18 months or later, waddling gait, hip and shoulder weakness, difficulty running, climbing
- Gowers sign (crawl up on oneself)
- Pseudohypertrophy of calf muscles (fibro-fatty infiltration of muscle)
- Elevated CPK levels at birth and continue to rise to 3 years of age
- Death secondary to respiratory insufficiency, infections, and cardiac involvement
- Many cases sporadic with no family history of affected members
- Intermixed pattern of myofiber atrophy/hypertrophy, hypercontracted large dark opaque fibers, myofiber necrosis, endomysial fibrosis
- Diagnosis: Dystrophin immunostaining of biopsy/quantitative dystrophin analysis

Myotonic dystrophy

- Children and adults
- Average age of onset 20–25 years
- Progressive myotonia (inability to normally relax a contracted muscle)

CONGENITAL INFANTILE MYOTONIC DYSTROPHY

- Severely hypotonic infant, bilateral facial weakness, involvement of intercostal/diaphragmatic muscles, respiratory insufficiency
- Mother always affected
- Congenital cases always maternally transmitted
- Family history of intellectual impairment, cataracts, cardiac conduction defects, muscle weakness/wasting
- Inherited as autosomal dominant trait
- Gene located on chromosome 19q13.3
- Expansion of trinucleotide CTG triplet repeats
- Severe myofiber hypotrophy of type I, II, or both
- Myofiber immaturity: Fetal myotubes with central nuclei, lack of myofibril ATPase staining centrally, lack of peripheral oxidase staining, incomplete myofiber type differentiation, fiber type disproportion
- Subsarcolemmal location of acid phosphatase activity

Metabolic myopathies

GLYCOGEN STORAGE DISEASE

- Skeletal muscle involvement is mild in most lysosomal enzyme deficiency diseases except Pompe disease (severe muscle involvement)
- Type II GSD (Pompe disease) is most common
- Type V, McArdle disease (myophosphorylase deficiency); VII, Tarui disease (phosphofructokinase deficiency), IX, X, and XI: manifest as exercise intolerance, muscle cramps, rhabdomyolysis, and myoglobinuria

Pompe disease

- Deficiency of acid maltase
- Floppy infant
- Involvement of striated/cardiac muscles, macroglossia, cardiac/hepatic enlargement
- Non-obstructive HCM due to storage of glycogen within cardiac muscle fibers
- Death due to cardiac/respiratory failure
- Inherited as autosomal recessive trait, chromosome 17
- Vacuolar myopathy
- PAS stain reveals glycogen storage/sensitive to diastase reaction
- Storage of undegraded glycogen/neutral lipids within myofibers
- Positive acid phosphatase staining
- *EM*: Free cytoplasmic and intralysosomal glycogen

Danon disease

- Lysosomal GSD with normal acid maltase
- Vacuolar myopathy, cardiomyopathy, mental retardation
- LAMP-2 deficiency
- X-linked dominant

Mitochondrial myopathies

- Impairment of respiratory chain function
- Also known as mitochondrial oxidative phosphorylation (OXPHOS) defects
- Respiratory chain made of five complexes: Types I–IV of mitochondrial electron transport chain and type V (ATPase synthetase complex)
- Mitochondrial function depends on information derived from nuclear DNA (nDNA) and mitochondrial DNA (mtDNA)
- MtDNA exclusively maternally derived
- Mitochondrial myopathies clinically heterogeneous
- Muscle, kidney, heart involved
- Ragged red fibers (RRFs); reddish granular staining on modified Gomori trichrome stains of frozen sections (subsarcolemmal or diffuse)
- Oxidative NADH-trichrome stain and specific mitochondrial stain SDH: Mirror the staining of modified Gomori trichrome stain
- More than 2% subsarcolemmal mitochondrial aggregates (larger than 4 μ in depth) support a diagnosis of mitochondrial myopathy (SDH histochemistry)
- SDH activity absent in complex II deficiency (nuclear encoded). SDH stain is unaffected by mt(DNA) mutations

- Combined cytochrome c oxidase and SDH staining: Identifies individual RRF that are COX-negative (confirm mDNA mutation)
- Stains identifying triglyceride accumulation (oil red O, Sudan Black, and Nile Red) increased in RRF indicating mitochondrial myopathy
- Focal lack of COX activity within myofibers: KSS and MELAS syndromes
- *EM*: Abnormal number/size/internal morphology of mitochondria
- Large mitochondria with abnormal inclusions: Spiral and "parking lot" paracrystalline structures (deposits of CK)
- Enzyme biochemistry and genetic analysis

Lipid myopathies

- Skeletal muscles supplied with energy by mitochondrial oxidation
- Defect in CPT enzyme system produces impairment of transport of LCFA (long-chain fatty acids) into mitochondria
- Autosomal recessive trait
- Severe systemic disorder: Hypotonia, hypoglycemia, failure to thrive, CM, CNS abnormalities, hyperammonemia, and sudden death
- MCAD (medium-chain acyl Co-A dehydrogenase) deficiency: most common
- Primary carnitine deficiency and CPT II deficiency are also forms of lipid myopathies
- Accumulation of lipid (triglycerides) within type I myofibers
- Positive with oil red O and Sudan Black stains
- *EM*: Accumulation of lipid subsarcolemmal/parallel rows within myofibers, increase in mitochondrial size/number
- Specific diagnosis by biochemical analysis

Neurogenic diseases

ACUTE/INFANTILE SPINAL MUSCULAR ATROPHY (TYPE I/ WERDNIG-HOFFMAN DISEASE)

- Autosomal recessive pattern
- Linked to chromosome 5
- Degeneration of neurons in anterior horn of spinal cord
- Denervation, weakness/atrophy of skeletal muscles
- Symmetrical weakness, hypotonia, proximal more than distal, pectus excavatum
- Death from respiratory failure
- *EMG*: Neurogenic changes, mild slowing of motor nerve conduction
- Grouped myofiber hypertrophy and atrophy
- Atrophic myofibers have rounded edge instead of sharp angular shapes
- Hypertrophic fibers usually type I
- Alkaline phosphatase positive myofibers due to myofiber regeneration (indicative of progressive neuromuscular process)
- Histogram curve twin-peaked

Peripheral neuropathy

- Skin biopsy/muscle biopsy contain nerve twiglets helping in diagnosis

SURAL NERVE BIOPSY

- Evaluation of hereditary neuropathies and storage disorders
- Nerve teasing studies to differentiate between segmental demyelination and primary axonal degeneration

HEREDITARY NEUROPATHIES

Dejerine-Sottas disease

- HMSN (hereditary motor and sensory neuropathy) type III
- Infancy, weakness, hypotonia, loss of tendon reflexes
- Hypertrophic neuropathy, reduction of large myelinated nerve fibers
- Onion bulb Schwannian hypertrophy
- Similar changes in Charcot-Marie-Tooth disease (HMSN type I)
- EM studies for evaluation of myelinated axons

Metabolic diseases

- Lysosomal storage diseases, metachromatic leukodystrophy, Krabbe disease, Fabry disease, neuronal ceroid lipofuscinoses

EM STUDIES

- Skin/muscle biopsies: Suggest storage disorder; further confirmed by appropriate biochemical studies
- Krabbe disease → curved tubular/prismatic inclusions of galactocerebroside
- Metachromatic leukodystrophy (MLD) → tuftstone prismatic lamellae of sulfatide
- Fabry disease → myelin figures/parallel lamellae of glycosphingolipid galactosylceramide (endothelium and nerves)

BIOCHEMICAL ANALYSIS

- Enzyme assays on fibroblast culture/leukocyte specimens
- Krabbe disease → galactocerebroside beta-galactosidase
- MLD → arylsulfatase A
- Fabry disease → alpha-galactosidase A
- Neonatal adrenoleukodystrophy (NALD) → very long-chain fatty acids (fibroblasts and leukocytes)

Myasthenia gravis

- Autoimmune disorder manifesting as skeletal muscle weakness/fatigability
- May be acquired or congenital
- Histochemistry of muscle may be normal or may show type II atrophy
- Autoantibodies destroy the acetylcholine receptors at neuromuscular junction

Congenital myopathies

- Primarily disorders of muscle
- Myopathies are due to mutations of contractile/structural/other proteins of muscle
- Structural abnormalities of myofibers
- Accumulation of abnormal proteins in sarcoplasm

NEMALINE ROD MYOPATHY

- Slowly progressive or severe
- Progressive hypotonia, weakness, dysmorphic facial features, chest deformities, normal intelligence
- Death from respiratory failure, recurrent pulmonary infections, CM
- Normal CPK levels
- EMG studies normal/myopathic/neurogenic features
- *EM*: Type I myofibers contain subsarcolemmal needle-shaped thread like structures
- Modified Gomori trichrome: Subsarcolemmal reddish purple rods
- Type I myofiber predominance/hypotrophy

CENTRONUCLEAR (MYOTUBULAR) MYOPATHY

- Congenital/late onset/adult forms of disease
- Similar morphological features as nemaline rod myopathy
- Serum CPK is normal
- EMG: Myopathic findings
- Myotubular pattern: Myofibers resemble fetal myotubules
- Central nuclei/central basophilic granular staining (due to mitochondria and autophagic vacuoles)
- ATPase stain: Perinuclear halo due to lack of myofilaments
- NADH-trichrome stain: Oxidative mosaic pattern due to oxidative enzyme activity in center of myofibers

CENTRONUCLEAR MYOPATHY ASSOCIATED WITH FIBER SIZE DISPROPORTION

- Myofiber size disproportion such as type I hypotrophy with predominance of type I fibers
- Pattern of fiber size disproportion can be variable with type II hypotrophy or mixed

CENTRAL CORE DISEASE

- Infancy to adulthood manifestation
- Floppy infant, normal intelligence, risk of malignant hyperthermia, rarely associated with CM
- Serum CPK normal
- *EMG*: Normal/may show myopathic changes
- Cores seen as central areas of smudging (due to lack of normal sarcoplasmic reticulum pattern)
- NADH-trichrome: Target cells usually show pale single and central cores of staining, cores may be eccentric or multiple
- ATPase: Marked predominance of target fibers
- Modified Gomori trichrome: Cores seen as solid, central smudged area
- Cytochrome oxidase: Mimics pattern of oxidative stain (NADH-Tr); central area devoid of mitochondrial activity

CONGENITAL FIBER-TYPE DISPROPORTION

- Uniform clinical/histopathologic features
- Floppy infants, generalized weakness, hypotonia, contractures, facial dysmorphia, respiratory failure
- CPK and EMG usually normal
- CFTD type I more common than type II
- Hypotrophy and predominance of type I myofibers, indicating persistent fetal morphology/maturational delay of myofibers
- Type I hypotrophic fibers are at least 12% smaller than type II fibers
- Type I predominance indicates more than 55% fibers show type I histochemical staining
- Confirmed by ATPase stain

Inflammatory myopathy

DERMATOMYOSITIS

- Autoimmune myositis in children
- Perivascular endomysial lymphocytic infiltration
- Systemic vasculopathy
- Perifascicular myofiber atrophy
- Scattered myofiber degeneration/regeneration/atrophy
- Alkaline phosphatase activity in perifascicular connective tissue

FOCAL MYOSITIS

- Self-limited, undetermined cause
- Local skeletal muscle mass/swelling/tender/lower extremity
- Histologically florid; degeneration/regeneration of muscle fibers, interstitial lymphocytic infiltration, fibrosis

JUVENILE DERMATOMYOSITIS (JDM)

- Selective fiber atrophy at periphery of fascicles
- Mononuclear cell perivenulitis
- Endomysium contains CD68+ve macrophages, T cells, and rarely B cell
- Acute intimal arteriopathy
- Occlusive changes in chronic arteriopathy; ischemic damage to the gut/skin/muscle

POLYMYOSITIS

- Multifocal muscle fiber necrosis
- No features of JDM
- Arthritis/arthralgias, no rash
- Positive for RF/ANA

21 Mandible and Maxilla

Normal anatomy/embryology

- Close proximity of mandible/maxilla to oral cavity; enclose the odontogenic apparatus
- Odontogenic structures: Combined ectodermal and mesodermal origin
- Epithelium; also known as ameloblasts, forms the enamel of tooth
- Stroma; also known as odontoblasts, forms the dentin of tooth
- Primitive embryonic tissue from early fetal development forms primary and permanent teeth

Odontogenic cysts

- Epithelium-lined cysts common in jaws
- Derived from remnants of odontogenic epithelium
- Lined by hyperplastic to thin squamous or cuboidal epithelium

INFLAMMATORY CYSTS

Periapical (radicular cyst)

- Most frequent jaw cyst
- Apex of tooth root, maxillary molars
- Aftermath of long-standing dental inflammatory disease

Residual cyst

- Cyst attached to apex of tooth and noted after tooth extraction
- Lined by stratified squamous epithelium, ulcerated, wall has mixed inflammatory infiltrate, giant cells, cholesterol crystals, and dystrophic calcification
- Treated with curettage

DEVELOPMENTAL CYSTS

Dentigerous cyst

- Originates from crown of unerupted permanent tooth (impacted third molar tooth)
- Lined by thin layer of non-keratinized stratified squamous epithelium
- Dense inflammatory infiltrate in collagenous stroma
- May recur, treated with complete removal

Odontogenic keratocyst (OKC)

- Males, posterior mandible
- Aggressive cyst
- Lined by parakeratotic squamous epithelium with corrugated/verrucous surface
- Prominent basal cell layer
- High recurrence, treated with complete removal
- If multiple OKC, evaluate for Gorlin syndrome (nevoid basal cell carcinoma)

Gingival cyst of newborn

- Minute cysts, most newborns, disappear within weeks
- Stratified squamous epithelium lined inclusion cysts

Eruption cyst

- Gingival swelling above an unerupted primary tooth
- Cyst shows subacute inflammation, hemorrhage, lined by thin non-keratinized stratified squamous epithelium

Lateral periodontal cyst

- Cyst formation of remnants of dental lamina
- Develops in alveolar bone between teeth
- Lined by very thin squamous epithelium

Calcifying epithelial odontogenic cyst

- Also known as Gorlin cyst
- Prominent basal palisading and large masses of keratinized ghost cells (resembles craniopharyngioma)

Non-odontogenic cysts

MEDIAN ANTERIOR PALATINE CYST

- Cyst formation of embryologic remnants of incisive canal (canal joins nasal and oral cavities)
- Most common non-odontogenic cyst
- Lined by respiratory/oral epithelium

Odontogenic tumors

- May be neoplastic or hamartomatous
- Derived from odontogenic epithelium, ectomesenchyme, or mixed

BENIGN

Adenomatoid odontogenic tumor

- Also known as adenoameloblastoma
- Females, anterior maxilla
- Arises from epithelium of dental lamina complex
- Odontogenic epithelium with duct-like structures
- Cellular connective tissue stroma
- Surgical excision is curative

Calcifying epithelial odontogenic tumor

- Mandibular premolar-molar region
- Associated with embedded tooth
- Sheets of small to polyhedral cells eosinophilic squamoid cells, scant stroma, calcific spherules

Squamous odontogenic tumor

- Well-defined nests of monotonous clear squamoid cells
- Well-differentiated, surrounded by dense collagenous stroma

Odontogenic fibroma

- Fibrous tissue, odontogenic epithelial rests (more than myxoma)
- Females, anterior maxilla

Odontogenic myxoma

- Tooth germ origin, related to missing teeth
- Loose stellate cells with long cytoplasmic processes, strands of odontogenic epithelium
- Vimentin positive, negative for S100
- Posterior mandible

Cementoma

- Multiple, asymptomatic, females
- Incisors of mandible, apices of teeth
- Resembles fibrous dysplasia

Ameloblastic fibroma

- Thin strands/buds of odontogenic epithelium, reversed nuclear polarity
- Immature cellular connective tissue stroma
- No enamel or dentin

Odontoma

- Originate in alveolar ridge of mandible/maxilla
- Enamel origin

Complex odontoma

- Incidental, females, benign
- Molar region of mandible
- Poorly differentiated lesions
- Variable calcification, dentin, enamel/cementum; not enough to form an actual tooth

Compound odontoma

- More differentiated lesion than complex odontoma
- Benign, anterior mandible
- Resemble multiple misshapen teeth

Ameloblastic odontoma

- Prominent epithelial tissue, dental hard and soft tissue (enamel and dentin)
- A form of immature complex odontoma
- Benign but locally recurrent

BORDERLINE TUMORS

- Invasive tumors, may recur

Ameloblastoma

- Also known as adamantinoma
- Most common epithelial odontogenic tumor
- Mandible, molar region, cystic change
- Recurrent frequently, complete excision recommended
- Follicular and plexiform patterns

Follicular

- Outermost epithelium resembles ameloblasts
- Tall columnar cells with polarization of nuclei away from basement membrane
- Central portion of epithelial island has loose network of cells resembling stellate reticulum
- May show squamous metaplasia (acanthomatous)
- No dentin or enamel formation

Plexiform

- Irregular nests/cords of epithelial cells with minimal stroma

Clear cell odontogenic tumor

- Nests of clear cells surrounded by mature collagen

MALIGNANT

Ameloblastic carcinoma

- Architecturally resemble ameloblastoma
- Malignant cytologic features (cytologic atypia and mitotic activity)
- Basaloid staining of tumor cells
- Metastasizes to lungs/central nervous system

Ameloblastic fibrosarcoma

- Morphologically resembles ameloblastic fibroma
- Malignant sarcomatous features: Cytologic atypia, increased cellularity, atypical mitoses, diminished epithelial component
- Painful, local extension/recurrence

22 Endocrine System

- Pineal gland, pituitary gland, parathyroid glands, thyroid gland, adrenal glands, hypothalamus, islets of Langerhans (pancreas)
- Diffuse network of neuroendocrine cells distributed in respiratory/gastrointestinal tract

Pineal gland

ANATOMY AND EMBRYOLOGY

- Small, cone-shaped structure 50–150 mg
- Attached to posterior border of third ventricle in brain
- Develops at seventh week of gestation
- Increases in size from birth to 2 years
- Nests of chief cells; pinealocytes (immunoreactive for synaptophysin, chromogranin, and NFP), lobular pattern
- Interstitial astrocytes (immunoreactive for S100 and glial fibrillary acidic protein [GFAP])
- Calcifications develop after 5 years of age
- Major hormone; melatonin (circadian rhythm regulation/gonadal steroidogenesis)

CONGENITAL ANOMALIES

Pineal agenesis

- Associated with other midline central nervous system syndromes (absence of corpus callosum)

Pineal cysts

- Glial cysts, symptomatic if more than 1 cm (vertigo, headaches, visual disturbances)
- Cysts are lined by ependymal cells, contain reactive astrocytes

NEOPLASMS

- *Parinaud syndrome* (upward gaze paralysis and convergence nystagmus), due to compression of dorsal midbrain visual structures by tumors of pineal gland

Germ cell tumors

- Most common tumor of pineal gland
- Germinomas, teratomas, mixed germ cell tumors

Pineal parenchymal tumors

- Positive for synaptophysin, chromogranin, NFP, retinal S-antigen

Pineoblastoma

- Primitive neuroectodermal tumor, small blue cell tumor
- Homer-Wright rosettes, necrosis, hemorrhage
- First decade of life
- WHO grade IV

Trilateral retinoblastoma

- Bilateral hereditary retinoblastoma associated with pineoblastoma
- Aggressive neoplasm

Pineocytoma

- Circumscribed, lobulated tumor
- Uniform cells, no pleomorphism
- Homer-Wright and pineocytomatous rosettes
- Second decade of life
- WHO grade I

Pineal parenchymal tumor of intermediate differentiation

- Features of both pineoblastoma and pineocytoma
- WHO grade II

Other tumors

- Astrocytomas, rhabdoid tumors (*INI1* germline mutation)

Pituitary gland

ANATOMY AND PHYSIOLOGY

- Located posterior to optic chiasm in sella turcica (small concavity in sphenoid bone)
- Connected to hypothalamus by narrow stalk
- Weighs 100 mg at birth and 500–600 mg at adolescence
- Anterior part red-brown (*adenohypophysis*)
- Posterior part smaller, gray-white (*neurohypophysis*)

Adenohypophysis

- Three types of cells (per staining pattern); chromophobes, acidophils, and basophils
- Cell and their respective hormones are somatotrophs (growth hormone), lactotrophs (prolactin), thyrotrophs (TSH), corticotrophs (ACTH), gonadotrophs (FSH/LH)
- Positive staining for CK7/CK8 and their respective hormones

Neurophypophysis

- Secretes oxytocin/vasopressin hormones
- Cells are GFAP+

CONGENITAL ANOMALIES

Agenesis

- Infants of diabetic mothers
- Associated neural tube defects
- Other midline and craniofacial anomalies

Hypopituitarism

- Diminished/absent one or more anterior pituitary hormones
- Gene mutations, midline/craniofacial anomalies
- Associated central nervous system malformations; holoprosencephaly, Chiari malformation

Anencephaly

- Anterior pituitary tissue within mass of cerebrovasculosa tissue
- Hypoplastic adrenal glands

Ectopia

- Ectopic location in roof of nasopharynx or pharyngeal pituitary

Cysts

Rathke cleft cyst

- Lined by ciliated epithelium, fluid in lumen
- Compression of intrasellar/suprasellar structures
- Symptomatic with pituitary dwarfism

Empty sella syndrome

- Defect in diaphragm covering sella turcica
- Extension of arachnoid tissue in sella
- Increased cerebrospinal fluid pressure; compression of pituitary and impression of empty sella
- Secondary causes: Atrophy, tumor, infarction, previous hypophysectomy

Miscellaneous cysts

- Craniopharyngioma cyst, arachnoid cyst, dermoid cyst

ACQUIRED DISORDERS

Inflammatory and infiltrative disorders

- Infectious (syphilis, mycobacteriosis), storage disorders
- Manifest as visual field defects, hypopituitarism, diabetes insipidus

Lymphocytic hypophysitis

- Autoimmune disorder
- Lymphocytes, plasma cells, eosinophils, macrophages, fibrosis

Granulomatous hypophysitis

- Tuberculosis, sarcoidosis, Langerhans cell histiocytosis (LCH)

Xanthogranulomatous inflammation

- Cholesterol granulomas
- Idiopathic

Vascular lesions

- Pituitary apoplexy = hemorrhagic infarction of pituitary adenoma
- Sheehan syndrome = pituitary infarction in mothers due to intrapartum hypotension
- Pituitary ischemia = sickle cell crisis

Pituitary hyperplasia

- Non-neoplastic proliferation
- McCune-Albright syndrome, gigantism, primary hypothyroidism, pregnancy

Pituitary adenoma (PA)

- Monoclonal neoplasm of adenohypophysis
- 15–19 years of age
- ACTH-producing tumors more common before puberty (microadenomas <10 mm)
- Prolactinomas and GH secreting tumors more common after puberty (macroadenomas >10 mm)
- Effacement of pituitary parenchyma by diffuse infiltrate of a single population of cells
- Positive staining for specific hormone that is produced by neoplastic cells
- Positive staining for chromogranin/synaptophysin/NSE
- Negative for type IV collagen matrix

Craniopharyngiomas

- Arise from Rathke pouch remnants
- Calcified suprasellar mass/cyst
- Benign but locally recurrent
- Dark-brown fluid, cholesterol crystals, keratinous debris
- Epithelial cell lobules, palisading cells around cysts, wet keratin
- Dystrophic calcification, xanthogranulomatous inflammation, cholesterol clefts

Miscellaneous

- LCH, Rosai-Dorfman disease, salivary gland rests

Parathyroid glands

ANATOMY/PHYSIOLOGY/EMBRYOLOGY

- Four in number, 4–6 mm diameter each
- Located in vicinity of thyroid gland or embedded in thyroid gland
- Two inferior glands arise from third pharyngeal pouch
- Two superior glands arise from fourth pharyngeal pouch
- Arise in fifth gestational week
- At birth, combined weight of all four glands is 5–10 mg
- Solid, cellular, mainly chief cells before puberty
- After puberty oxyphil cells/adipocytes also appear

CONGENITAL ANOMALIES

Supernumerary parathyroid glands

- More than four parathyroid glands
- Cause of persistent/recurrent hyperparathyroidism

Ectopic parathyroid

- Within thymus/thyroid/remote sites

Agenesis-hypoplasia

- *DiGeorge syndrome* (del 22q11.2) = Parathyroid hypoplasia, hypocalcemia, anomalies of aortic arch, hypoplasia of thymus/thyroid, and abnormal facial development

ACQUIRED DISORDERS

Hypercalcemia

- Increased parathyroid hormone (PTH) secretion by parathyroid adenoma or hyperplasia
- Metastatic calcifications in multiple organs
- Other causes of hypercalcemia may be secondary to malignancy, vitamin D excess (sarcoidosis, tuberculosis, granulomatous conditions), drugs

Primary hyperparathyroidism

- Most common cause: Parathyroid adenoma
- Other causes: Parathyroid hyperplasia due to MEN1, MEN2a, fibro-osseous jaw tumors (mutation of *HRPT2* gene)
- Subperiosteal phalangeal bone resorption genu-valgum, bone cyst formation

- Hypercalcemia, hypercalciuria, nephrolithiasis
- Increased serum PTH (differentiates primary hyperparathyroidism) from other causes of hypercalcemia)

Secondary hyperparathyroidism

- Multiglandular hyperplasia secondary to hypocalcemia
- Hypocalcemia may be due to renal failure, vitamin D deficiency, malabsorption, rickets

Parathyroid adenomas

- Weight is 40–60 mg
- Nodular proliferation of chief cells, diminished fat, increased mitotic activity, no capsule
- Compressed out normal glandular tissue seen at periphery of adenoma
- Intraoperative determination of serum PTH level distinguishes between adenoma (levels come back to normal after removal) and hyperplasia (levels remain raised)

Parathyroid carcinoma

- Very rare in children
- Germline *HRPT2* mutations

Hypocalcemia

- Multifactorial causes: Hypoparathyroidism, pseudohypoparathyroidism (resistance to parathyroid hormone = Albright hereditary osteodystrophy), mitochondrial DNA defects, dietary imbalances

Hypoparathyroidism

- Previous parathyroidectomy, del 22q11.2, autoimmune, infiltrative disorders
- Parathyroid transplant before thyroidectomy recommended as a preventive measure

Thyroid gland

ANATOMY/PHYSIOLOGY/EMBRYOLOGY

- Development starts at third week of gestation
- Proliferation of endodermal cells on floor of pharynx
- Bi-lobed gland with isthmus, mid-anterior neck
- Adult weight (15–20 g) reached by 15 years of age
- Follicular cells secrete thyroid hormones
- Peripheral levels of thyroxine (T4) control secretion of TSH by pituitary (regulated by the hypothalamic thyrotropin-releasing hormone by a feedback mechanism)
- C cells (parafollicular cells) acquired by thyroid when ultimobranchial body incorporated in thyroid gland
- C cells derived from neural crest
- C-cell *hypoplasia* seen in DiGeorge syndrome
- C-cell *hyperplasia* seen in medullary thyroid carcinoma (MTC) in MEN2a, MEN2b, and familial MTC due to germline mutations in *RET* gene

CONGENITAL ANOMALIES

Dysmorphism/dysgenesis

- Inherited defects in enzymes responsible for thyroid hormone synthesis
- Congenital hypothyroidism: Raised TSH levels, thyroid hyperplasia, and dyshormonogenetic goiter
- Dysgenesis, hemigenesis, hypoplasia, or ectopic location
- Mutations in genes responsible for thyroid development

Ectopia

- Lingual thyroid
- Thyroid follicles interspersed between skeletal muscle fibers of tongue
- Hypoplastic thyroid

Thyroglossal duct cyst (TDC)

- Failure of thyroglossal duct to involute during fetal life
- Located midline anterior neck, overlying hyoid bone
- Cyst lined by ciliated columnar/coboidal epithelium/squamous metaplasia
- Surrounded by dense fibrous stroma, lymphoid tissue, and may show thyroid follicles
- May be infected, abscess formation, fistula
- Cysts may be diagnosed throughout life

Branchial cleft anomalies

- Lesions derived from incomplete obliteration of branchial cleft apparatus
- Cysts/sinuses/fistula/cartilage
- Located in anterolateral neck, preauricular region, angle of mandible
- Lined by squamous epithelium/columnar/respiratory epithelium
- Fibrotic wall with lymphoid follicles, heterotopic cartilage
- May be infected secondarily

ACQUIRED DISORDERS

- Goiter: Diffuse/nodular enlargement of thyroid

Chronic lymphocytic thyroiditis

- Adolescent females, euthyroid/hypothyroid
- Elevated serum thyroid peroxidase and antithyroglobulin antibodies (Hashimoto thyroiditis)
- Sporadic/associated with HLA types DR3, DR4, and DR5
- Gland enlarged, nodular, tan-gray, resembles lymph node
- Lymphoid follicles with germinal centers, scattered infiltrate of plasma cells
- Diminished/atrophic thyroid follicles, fibrosis

Hyperplasia

Simple non-toxic goiter

- Adolescent females, no hyperthyroidism
- Thyroid follicles of variable size, macrofollicles with colloid in lumen, cystic degeneration, fibrosis, hemorrhage, stromal inflammation

Adenomatous hyperplasia

- Dominant nodule with uniform follicles

Multinodular hyperplasia

- Dyshormonogenetic goiter
- Pendred syndrome (goiter with hearing loss)

Diffuse hyperplasia with clinical hyperthyroidism (Graves disease)

- Autoimmune disorder of thyroid, adolescent girls
- Hyperthyroidism, ophthalmopathy (exophthalmos), and dermopathy (pretibial myxedema)
- Anti-TSH receptor antibodies, elevated serum T3 and T4, decreased serum TSH
- Symmetrical diffuse enlargement of thyroid gland, red-brown (increased vascularity)
- Follicular cells are tall columnar, cell crowding, intrafollicular papillary infoldings
- Pale watery colloid, scalloping, lymphoid infiltrate in stroma

Papillary thyroid carcinoma (PTC)

- Most common thyroid carcinoma in children
- Mutations involving *RET* genes
- *RET/PTC1* = classic PTC
- *RET/PTC3* = radiation-induced PTC/follicular variant of papillary carcinoma
- Most cases are sporadic
- Familial cases in *MEN1*
- Classic papillary pattern/follicular variant/sclerosing variant
- Nuclear features diagnostic in all types: Crowded, overlapping nuclei, nuclear grooves, optically clear, nuclear pseudo inclusions
- Psammoma bodies, squamous metaplasia, desmoplastic stroma, lymphocytic infiltrate
- Stain positively for cytokeratins, thyroglobulin, TTF1
- Regional lymph nodes commonly involved by metastases
- Excellent prognosis

Follicular neoplasms of thyroid

Follicular adenoma

- Thin complete/interrupted capsule
- Follicles have monotonous architecture

Follicular carcinoma

- Thick fibrous capsule, transcapsular invasion
- Capsular microvascular invasion (adherence of tumor cells to vascular endothelium)
- Extensive capsular sampling/endothelial markers help in diagnosis
- Stain positively for TTF-1 and TG

- Difficult to subclassify follicular lesions of thyroid (follicular variant of papillary carcinoma, follicular thyroid carcinoma, follicular adenoma, and dominant adenomatous nodule) on frozen section

Medullary thyroid carcinoma (MTC)

- Familial; *RET* mutations, *MEN2a,* and *MEN2b*
- Tumor is small, microscopic, multifocal, always associated with diffuse C-cell hyperplasia
- Neoplastic cells rounded/spindled, fine chromatin, conspicuous nucleoli
- Stroma is fibrotic with amyloid
- Hyperplastic C cells and MTC seen as bulging growth in colloid of follicles
- However, MTC shows interstitial infiltration and aggregates of neoplastic cells
- C cells/MTC stain positive for calcitonin, chromogranin, synaptophysin, and CEA
- Negative for TTF-1 and thyroglobulin

Cervical thyroidal teratoma

- Congenital tumors, present during infancy
- Large size, compress upper airways, surgical treatment necessary
- Mature and immature (neuroepithelium) components
- Nodal gliomatosis common

Adrenal glands

ANATOMY/PHYSIOLOGY/EMBRYOLOGY

- Combined weight: 4–6 g in children
- Outer cortex (secretes steroids) and inner medulla (contains chromaffin cells, secretes catecholamines)
- Cortex subdivisions: *Zona glomerulosa* (secretes mineralocorticoids), *zona fasciculata* (secretes glucocorticoids), and *zona reticularis* (secretes androgens)
- During fetal life, subcapsular provisional fetal cortex (bright yellow cortical rim), involutes after birth
- Zona fasciculata: Major part of cortex, large lipid-laden cells, cortisol provides negative feedback on pituitary to stop further ACTH secretion

CONGENITAL ANOMALIES

- Unilateral adrenal agenesis (mostly with ipsilateral renal agenesis)
- Adrenal fusion (horseshoe adrenal glands)
- Renal-adrenal fusion (accreta)
- Disc-shaped adrenals (renal agenesis)
- Ectopic adrenal glands

Wolman disease

- Inborn error of acid lipase A deficiency
- Adrenals enlarged, bright yellow, contain lipid-laden foamy macrophages, accumulate cholesterol, triglyceride
- Necrosis and calcification

Adrenoleukodystrophy (ALD)

- Defective fatty acid beta oxidation
- Peroxisomal disorder, accumulation of very long-chain fatty acids
- Inflammatory demyelination of axons, loss of oligodendrocytes, atrophy of adrenals

Adrenal cytomegaly

- Enlarged cytomegalic cells in adrenal fetal cortex
- Stillborn/premature/newborns
- BW syndrome
- Cytomegalic cells are two to three times larger, hyperchromatic pleomorphic nuclei, nuclear pseudo inclusions, vacuolated cytoplasm

Congenital adrenal hypoplasia

- Decreased maternal estriol levels
- Combined adrenal weight <2 g
- Three distinct histological patterns: Cytomegalic (most common), anencephalic, and miniature

Congenital adrenal hyperplasia

- Adrenogenital syndrome
- Autosomal recessive
- Primary adrenal insufficiency/ambiguous genitalia

- 21-Hydroxylase deficiency (CYP21A2); most common
- 11-β-Hydroxylase deficiency (CYP11B1)
- 17-α-Hydroxylase deficiency (CYP17A1)
- Diminished cortisol production → no negative feedback → persistent ACTH secretion → synthesis of cortisol precursors
- Diagnosed prenatally, by maternal chorionic villus sampling in first trimester
- Neonatal screening by 17-hydroxyprogesterone to detect 21-hydroxylase deficiency
- Classic salt-wasting form: Hyponatremia, hyperkalemia, acidosis, shock, and death
- Increased androgen production, female pseudohermaphroditism, virilization of male and female infants
- Bilateral hyperplasia of adrenals, increased weight, cerebriform appearance, compact eosinophilic cells in zona fasciculata
- TART (bilateral testicular adrenal rest tumor) with male infertility associated

Primary pigmented (micronodular) adrenocortical disease

- Associated with Carney complex (*PRKAR1A*) and Cushing syndrome
- Multiple small pigmented nodules in adrenal cortex

Adrenocortical hyperplasia

- Beckwith-Wiedemann syndrome (BWS), multiple autoimmune syndrome (MAS), *MEN1*

Adrenocortical insufficiency

- Congenital (ALD, congenital adrenal hypoplasia, congenital adrenal hyperplasia)
- Acquired (infections, drugs, autoimmune disorders, adrenal hemorrhage)

ACQUIRED DISORDERS

Adrenal cysts

- Epithelial, endothelial, pseudocysts, parasitic

Bacterial fungal parasitic and viral infections

- Congenital intrauterine infections (HSV, CMV, varicella-zoster virus, histoplasmosis, tuberculosis)

Adrenal hemorrhage

- Intrauterine asphyxia, birth trauma, underlying coagulopathy, extracorporeal membrane oxygenation (ECMO), umbilical artery catheterization
- Spontaneous resolution with calcifications after birth

Waterhouse-Friderichsen syndrome

- Bilateral adrenal hemorrhagic necrosis, circulatory collapse, coagulopathy, petechial rash
- Etiology: Meningococcal infection
- Risk factors: Congenital asplenia/splenic atrophy with sickle cell anemia

Calcifications

- Wolman disease
- Resolving adrenal hemorrhage

ADRENAL NEOPLASMS

Adrenal cortical neoplasms (ACNs)

- Adrenocortical adenoma (AA) and adrenocortical carcinoma (ACC)
- Two peak age distributions = infantile and adolescent
- Associated with BWS, Li-Fraumeni syndrome, Carney complex
- Most common clinical manifestation is Cushing syndrome
- Size/weight of tumor distinguishes between AA and ACC
- Histological factors not reliable for prognosis
- Tumor cells positive for vimentin, inhibin, calretinin, Melan-A, synaptophysin, and NSE
- No difference on IHC between AA and ACC
- Chromogranin not immunoreactive with adreno-cortical neoplasms (d/d pheochromocytoma and paraganglioma)

Prognostic risk groups for ACNs in children

- Low risk (adenomas) confined to adrenal gland and weigh <200 g
- Intermediate risk (atypical adenomas) confined to the adrenal gland and weigh between 200 and 400 g

- High risk (ACC) weigh >400 g, metastatic spread to distant organs/direct gross invasion into adjacent organs like liver, kidney, spleen

Peripheral neuroblastoma (NB)

- Tumors of neural crest origin: Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma
- *Predominant sites*: Adrenal medulla (most common), extra-adrenal retroperitoneum, posterior mediastinum, paravertebral region from neck to pelvis
- Stage IV NB metastasizes to bone marrow (paratrabecular aggregates of tumor cells) and bone
- Stage IV metastasizes to skin, liver, and bone marrow
- Congenital NB may show tumor cells in chorionic villus capillaries of placenta
- Increased serum/urinary levels of homovanillic acid (HVA) and vanillylmandelic acid (VMA)
- Positive staining with NSE, NB84, PGP9.5, synaptophysin, chromogranin, CD57, NFP, NCAMS, and tyrosine hydroxylase
- Undifferentiated neuroblastoma: Positive only for vimentin and PGP9.5
- 17q gain is most frequent mutation
- Metaphase chromosomal spread shows numerous "double minutes"
- Positive for *MYCN* on fluorescence in situ hybridization
- *MYCN* amplification and 1p36 deletion; associated with adverse outcome

Neuroblastoma (Schwannian stroma-poor)

- *Undifferentiated subtype*: Resembles small, round, blue cell tumors. No neuropil. Tumor cells have irregular demarcation by fibrovascular septa
- *Poorly differentiated subtype*: Most common form of NB. May show neuropil, Homer-Wright rosettes
- *Differentiating subtype*: 5%–49% of cells have an appearance of differentiating neuroblast. Abundant neuropil formation. Tumor cells separated by thin fibrovascular septa. No significant schwannian stroma development

Ganglioneuroblastoma

- *Intermixed (Schwannian stroma rich)*: Same appearance as schwannoma. Extensive schwannian stromal development (occupying more than 50% of tumor tissue). Pockets of naked neuropil, tumor cells in various stages of neuronal differentiation
- *Nodular (stroma predominant/stroma rich and stroma poor)*: Grossly/histologically, tumor has appearance of ganglioneuroma with one or more nodules having the appearance of neuroblastoma (friable, hemorrhagic, necrotic cut surface)

Ganglioneuroma (Schwannian stroma predominant)

- *Maturing subtype*: Scattered maturing ganglion cells/neuroblasts (≥50%)
- *Mature subtype*: Fully mature ganglion cells, surrounded by satellite cells

Prognostic distinction

Based on three morphologic criteria and age:

- Schwannian stroma development (stroma poor, stroma rich, and stroma predominant)
- Grade of neuroblastoma differentiation (undifferentiated, poorly differentiated, and differentiating)
- Mitotic Karyorrhectic Index = on a count of 5000 cells; low (<100 cells), intermediate (100–199 cells), and high (200 cells or more)

Favorable histology

Favorable histology (FH) neuroblastomas fall into an age-appropriate maturational sequence:

- Neuroblastoma (Schwannian stroma-poor) poorly differentiated subtype. The MKI can be intermediate—up to 1.5 years of age
- Neuroblastoma (Schwannian stroma-poor) differentiating subtype. The MKI should be low—up to 5 years of age
- Ganglioneuroblastoma intermixed, and ganglioneuroma → FH (any age group)

Pheochromocytoma

- Neural crest origin
- Syndromic association (BWS, VHL, *MEN2a*, *MEN2b*)

- Pheochromocytoma arises from chromaffin cells of adrenal medulla
- Paraganglioma arises from extra-adrenal paraganglia
- Elevated catecholamines: Hypertension, sweating, palpitations, tachycardia
- Nesting (zellballen), trabecular, or solid pattern
- Cytoplasm eosinophilic to basophilic, granular
- Stain positive for chromogranin, vimentin, synaptophysin
- Sustentacular cells positive for S100
- 50% of pheochromocytomas and paragangliomas are malignant

Hypothalamus

- Secretes anti-diuretic hormone (ADH)
- *Syndrome of inappropriate ADH*: Increased ADH, causes hyponatremic-isovolemic condition
- *Diabetes insipidus*: Decreased ADH production (central) or nephrogenic (kidney response is defective)
- Osmolarity = measure of solute concentration in fixed solvent volume
- Calculation of predicted serum osmolarity: 2Na + Glucose/18 + BUN/2.8 + other osmolarities
- Normal range of serum osmolality = 285–295 mOsm/kg

23 Kidney and Lower Urinary Tract

Embryology

- Differentiation of kidney involves epithelial-mesenchymal interactions
- Renal and genital systems develop from common mesodermal ridge
- Metanephros (permanent renal system) ascends to lumbar region by eighth week of gestation
- Nephrons develop from caudal end of metanephric blastema
- Renal excretory system (collecting ducts, calyces, pelvis, and ureter) develops from ureteric bud
- Subcapsular nephrons formed last in the fetus and comprise nephrogenic zone

Congenital malformations of kidney

- Congenital anomalies of kidney responsible for end-stage renal failure in many cases

OLIGOHYDRAMNIOS SEQUENCE (POTTER PHENOTYPE)

- Causes: Bilateral renal agenesis, cystic renal dysplasia, obstructive uropathy, polycystic kidney disease
- Low-set deformed ears, beaked nose, receding chin, lower limb positional deformity, growth retardation, pulmonary hypoplasia
- When associated with renal agenesis = Potter syndrome

RENAL ECTOPIA

- May result in hydronephrosis (due to obstruction) reflux or malrotation

RENAL FUSION

- Horseshoe kidney (lower poles fused)
- Located lower than normal position
- Associated with Turner syndrome
- Prone to develop calculi/neoplasia (carcinoid)

RENAL AGENESIS/HYPOPLASIA

- Genitourinary malformations/lower body defects

BILATERAL RENAL AGENESIS

- Associated with many other congenital anomalies
- Adrenals disc shaped (no molding by kidneys)
- Pulmonary hypoplasia
- Sporadic or associated with hereditary renal adysplasia

UNILATERAL RENAL AGENESIS

- Compatible with normal life but high risk of hypertension/proteinuria/renal insufficiency
- Associated malformations of genitalia

RENAL HYPOPLASIA

- Normal renal shape but absolute number of nephrons reduced (inadequate branching of ureteric bud)
- Segmental renal hypoplasia (Ask-Upmark kidney) = localized atrophic scarring due to reflux nephropathy

RENAL TUBULAR DYSGENESIS

- Hypoplasia of proximal convoluted tubules
- Fetal and neonatal oliguria, late-onset oligohydramnios

- Abnormality of renin-angiotensin-aldosterone system
- Associated skull ossification defects, neonatal respiratory/renal failure

RENOMEGALY

- Kidney enlargement due to increase in number/size of nephrons
- Associated with growth disorders (hemihypertrophy)

RENAL DUPLICATION

- Two separate pelvises in same kidney
- Partial/complete duplication of ureter
- Associated with vesicoureteral reflux

HYDRONEPHROSIS

- Obstruction of ureteral-pelvic junction
- Dilation of renal pelvis/calyceal system, atrophy of parenchyma, fibrosis, chronic inflammation
- Possible renal dysplasia

Renal dysplastic cystic diseases

MULTICYSTIC

- Renal dysplasia with multiple unilateral/bilateral cysts

POLYCYSTIC

- Hereditary AD/AR kidney disease with cysts

RENAL DYSPLASIA

- Sporadic mostly
- Associated uretero-pelvic/any other level obstruction
- Enlarged/hypoplastic distorted kidneys, variably sized cysts (irregular distribution in kidney)
- Cortex and medulla involved
- Disorganized renal parenchyma: Dysplastic tubules surrounded by collarette of condensed mesenchyme
- Islands of immature cartilage
- Renal function diminished/absent/renal failure

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE (ARPKD)

- Onset during infancy
- Polycystic kidney and hepatic disease gene (*PKHD1*)
- Fibrocystin and polyductin proteins involved
- Cystic dilatation of collecting ducts
- Massively enlarged symmetric reniform kidneys
- Radially arranged collecting duct cysts (1–2 mm) under the capsule in cortex
- Rounded cysts in medulla
- Normal glomeruli and tubules seen between cysts
- Oliguria, oligohydramnios
- Associated congenital hepatic fibrosis (ductal plate malformation)

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

- Adult onset
- More common than ARPKD
- *PKD1* and *PKD2* genes involved
- Polycystin 1 and 2 proteins involved
- Prognosis worsened if manifested during infancy
- Enlarged/normal-sized kidneys
- Cysts vary in size (up to 3 cm), both cortex and medulla
- Any part of nephron may become cystic

MEDULLARY CYSTIC DISEASE

Medullary sponge kidney

- Sporadic, developmental disorder
- Cystic malformation of papillary collecting ducts in renal medulla
- Bouquet of flowers on intravenous pyelography
- Symptomatic if complicated by renal stones/infection/hematuria

Juvenile nephronophthisis-medullary cystic kidney disease (MCKD) complex

- *NHPH1* gene; nephrocystin gene product
- Juvenile nephronophthisis = onset in children and autosomal recessive
- MCKD = adult onset and autosomal dominant
- Chronic sclerosing tubulointerstitial disease, cysts at corticomedullary junction (1–15 mm diameter), secondary glomerular sclerosis
- Major cause of end-stage renal disease

CORTICAL CYSTS

Glomerulocystic kidney disease (GCKD)

- AD inheritance
- Cystic dilation of Bowman space and atrophy of glomerular tufts
- Cysts <1 cm in size, located in cortex

Simple cysts

- Cortical, unilocular, lined by cuboidal cells

CYSTS ASSOCIATED WITH SYNDROMES

Tuberous sclerosis

- AD trait
- Systemic malformation syndrome
- *TSC1* gene (hamartin) and *TSC2* gene (tuberin)
- Cortical cysts lined by exuberant hyperplastic epithelium, eosinophilic granular cytoplasm

Von Hippel-Lindau disease

- Renal cysts lined by hyperplastic epithelium
- Clear cytoplasm, hobnail nuclei
- Risk for renal cell carcinoma (RCC)

Meckel-Gruber syndrome

- Cortical/medullary cysts

Glomerular diseases (glomerulopathies)

- Examination of gross specimen of renal biopsy with dissecting microscope to assess specimen adequacy
- In the cortex, glomeruli appear as red dots
- In the medulla, vasa recta appear as linear striations

GLOMERULAR LESIONS TERMINOLOGY

- *Focal*: Involvement of only some of the glomeruli, by the lesion
- *Diffuse*: Involvement of almost all of the glomeruli, by the lesion
- *Segmental*: Involvement of part of a glomerulus, by the lesion
- *Global*: Involvement of almost the entire glomerulus, by the lesion
- *Mesangial proliferation*: More than three mesangial cells per peripheral mesangial area
- *Crescent*: Proliferation of glomerular epithelial cells and inflammatory cells that fill part (segmental) or all (circumferential) of Bowman space. May be cellular/fibrocellular/fibrous

NEPHROTIC SYNDROME

- Conditions causing mainly heavy proteinuria

Minimal change disease

- Hematoxylin and eosin (H&E) and immunofluorescent (IF) findings are normal
- *EM*: Foot process effacement, microvillous transformation of epithelial cells

Focal segmental glomerulosclerosis

- H&E shows glomerular tuft sclerosis
- IF is normal
- *EM*: Podocyte foot process effacement, mesangial sclerosis
- African American boys

Membranous glomerulonephritis (GN)

- Rare in children
- Diffuse thickening of capillary walls with short spikes extending from outer surface of capillary (silver stain positive)
- *IF*: Granular staining for IgG and C3 along capillary walls
- *EM*: Subepithelial deposits, foot process retraction

Diabetic/obesity-related GN

- Nodular mesangial sclerosis, hyaline caps, capsular drops, atherosclerosis

Other causes

- Nail patella syndrome, collagen type III glomerulopathy, Pierson syndrome

GLOMERULOPATHY WITH MAINLY HEMATURIA WITH/ WITHOUT PROTEINURIA

IgA nephropathy

- Hematuria and nephrotic range proteinuria

Berger disease

- Nephropathy after upper respiratory/gastrointestinal infection
- Focal segmental/global mesangial hypercellularity
- *IF*: Confluent mesangial granular deposits of IgA

Henoch-Schönlein purpura nephritis

- Similar morphological and IF findings as Berger disease
- More severe glomerular disease (including crescents)

Basement membrane nephropathy

Alport syndrome

- Family history of hematuria progressing to end-stage renal disease
- X-linked or AR inheritance
- Sensorineural deafness and hereditary nephritis
- Defect in type IV collagen involved in BM structure
- *E/M*: Thick/thin/irregular basement membrane, splitting of lamina-densa (basket-weave pattern), thinning of BM (less than 150 nm)
- Mutations in *COL4A1-A6* genes

Thin basement membrane nephropathy

- Benign familial hematuria
- Isolated hematuria with normal kidney function
- Family history of hematuria with AD inheritance
- *EM*: Diffuse thinning/attenuation of glomerular basement membrane (<250 nm)

GLOMERULOPATHIES WITH NEPHRITIC SYNDROME

- Hypertension, impaired renal function, hypocomplementemia
- Cellular casts, proteinuria, and hematuria

Postinfectious GN

- Acute GN following skin/throat infection with Group A streptococcus
- Glomerular hypercellularity, accentuation of lobular architecture, thick capillary walls
- *IF*: Coarse capillary granular staining for IgG and C3
- *EM*: Subepithelial hump-like deposits
- Good prognosis, mostly complete recovery

MPGN-I

- Diffuse uniform glomerular changes
- Enlarged glomeruli, hypercellular, prominent lobulation
- Mesangial hypercellularity, increased matrix
- Diffuse marked thickening of glomerular capillary walls
- Silver stain: Florid double contour (tramtracks) of capillary walls
- *IF*: Coarse granular C3 staining along capillary loops/periphery of mesangium
- *EM*: Subendothelial deposits

MPGN-II

- Dense-deposit disease
- *EM*: Electron-dense material along glomerular capillary basement membrane
- *IF*: Linear global ribbon-like C3 deposits in capillary walls/hollow rings in mesangium of C3

Lupus nephritis

- Hematuria, proteinuria, and hypertension
- Similar histology as MPGN
- *IF*: Immune deposits in all compartments; glomeruli/tubules/interstitium/blood

vessels (subendothelial, subepithelial, and mesangial)
- "Full-house" pattern of IgG, IgM, IgA, C3, and C1q deposits
- *EM*: Fingerprint deposits/tubuloreticular aggregates within endothelial cells

Crescentic glomerulonephritis
- Etiology: idiopathic, immune complex diseases, post-infectious GN, various vasculitis, Goodpasture syndrome
- Crescents are initially cellular and later organize into fibrocellular forms; project into the glomerular space and may compress the glomerular tufts
- Bad prognosis and patients usually progress to end-stage renal disease

Goodpasture syndrome
- Pulmonary-renal syndrome caused by anti-GBM antibody = Goodpasture syndrome
- These antibodies attack alpha-3 subunit of type III collagen
- GN associated with hemoptysis
- *IF*: Linear staining for IgG on GBM with patchy linear staining for C3

CONGENITAL NEPHROPATHIES
- Congenital nephrotic syndrome
- Manifestation of nephrotic syndrome in first year of life

Finnish type (CNF)
- Nephrotic syndrome within first 3 months of life
- Most prevalent in Finland
- *NPHS1/NPHS2* gene mutation (reduced protein nephrin/podocin)
- Autosomal recessive, steroid resistant
- Infants small for gestational age, enlarged placenta, massive proteinuria in utero, polyhydramnios, elevated AFP, placentomegaly
- Tubular ectasia (dilatation of proximal tubules)
- Interstitial inflammation, mesangial hypercellularity, glomerular sclerosis
- Bad prognosis, end-stage renal failure

Diffuse mesangial sclerosis type
- Nephrotic syndrome between 3 and 11 months
- *WT1* mutation
- Sometimes *PLCE1* mutations
- Early onset nephrotic syndrome, rarely at birth
- Increased mesangial matrix, secondary tubulointerstitial changes, diffuse mesangial Denys-Drash syndrome
- Bad prognosis

Tubulointerstitial diseases
- Tubular loss and interstitial fibrosis: Correlates with deteriorating renal function/progressive renal failure

ACUTE TUBULAR NECROSIS
- Mitotically active and swollen tubular epithelial cells, ectasia of tubular lumina
- Loss of brush border, necrosis/desquamation

Ischemic
- Etiology: Renal hypoperfusion (from shock, sepsis, trauma)

Toxic
- Antibiotics (aminoglycoside, amphotericin-B), antineoplastic drugs (cisplatin)

INTERSTITIAL NEPHRITIS
- Inflammation of renal interstitium
- Etiology: infection, drugs, obstructive/reflux uropathy, immunologically mediated metabolic diseases, hereditary diseases, cellular rejection in renal allograft

Pyelonephritis
- Hematogenous/ascending bacterial infection
- Both interstitium and collecting system involved

Renovascular diseases

HEMOLYTIC UREMIC SYNDROME

- Common cause of renal failure in childhood
- Hemolytic anemia, thrombocytopenia, and acute renal failure
- *Escherichia coli* O157:H7 serotype, linked to postdiarrheal HUS
- Thrombotic microangiopathy (TMA)
- Fibrin thrombi/fragmented red blood cells occlude glomerular capillaries/arteriolar lumina

RENAL ARTERY STENOSIS

- Medial fibromuscular dysplasia with aneurysm formation
- Girls in second/third decade of life

RENAL CORTICAL NECROSIS

- Coagulative necrosis due to sudden loss of renal perfusion

Renal neoplasms

WILMS TUMOR

- *WT1* locus on 11p13 (WAGR and Denys-Drash syndrome)
- *WT2* locus on 11p15 (Beckwith-Wiedemann syndrome)
- Bulging nodular yellowish variegated tumor
- 2–4 years of age
- Originates from metanephric blastema
- Triphasic pattern; blastema (densely packed primitive cells), epithelium (primitive/abortive tubules and glomeruli), stroma
- Heterologous elements (skeletal muscle, cartilage) in stroma
- Unfavorable histology = nuclear anaplasia and multipolar mitotic figures
- Unfavorable histology implies resistance to therapy
- Blastema positive for WT-1, vimentin and negative for synaptophysin
  - Refer to Appendix for Children's Oncology Group (COG) staging of Wilms tumor

CYSTIC NEPHROMA

- Unilateral multilocular cyst of kidney
- Multiple thin-walled cysts
- Cysts lined by cuboidal/flat cells and benign spindle cell stroma
- No immature elements

CYSTIC PARTIALLY DIFFERENTIATED WILMS TUMOR

- Stroma surrounding the cysts has immature tubules/glomeruli/blastemal tissue

NEPHROBLASTOMATOSIS

- Diffuse persistent foci of nephrogenic tissue
- Potential of developing into Wilms tumor

Perilobar nephroblastomatosis

- Massive enlargement of kidneys
- Blastema has compact/nodular configuration, discrete interface with adjuvant parenchyma
- Associated with hemihypertrophy and Beckwith-Wiedemann syndrome

Intralobar nephroblastomatosis

- Blastema/immature tubules blend with surrounding kidney
- Increased risk of progression to Wilms tumor
- Associated with WAGR and Denys-Drash syndrome

CONGENITAL MESOBLASTIC NEPHROMA

- Stromal neoplasm of early infancy

Classic pattern

- Intersecting bundles of uniform bland spindle cells, minimal atypia

Cellular pattern

- High cellularity, areas of necrosis
- Hemangiopericytoma-like vessels
- Higher risk for recurrence
- Chromosomal translocation t(12;15)(p13;q25)
- *ETV6-NTRK3* gene fusion (same genetic aberration as CIFS and secretory carcinoma of breast)

CLEAR CELL SARCOMA OF KIDNEY

- Also known as bone metastasizing renal tumor of childhood
- Peak incidence at 2 years of age
- No syndromic association
- Plexogenic pattern = 6–10 cell wide cords separated by capillary network of vessels
- Nuclei have optically clear appearance (similar to papillary carcinoma of thyroid)
- Cytoplasm pale/clear
- Positive for vimentin, CD99, CD56

MALIGNANT RHABDOID TUMOR

- Highly malignant tumor of infancy
- Sheets of large atypical/loosely cohesive mononuclear cells, prominent nucleolus
- Intracytoplasmic hyaline inclusions
- Mutations/deletions of *HSNF5/INI1* gene located on chromosome 22q11
- Positive for vimentin, CK, EMA, desmin, and NF
- Loss of nuclear staining for *INI1* and *BAF47*
- High risk for metastases

RENAL CELL CARCINOMA

- Associated with Von Hippel-Lindau syndrome

Translocation associated

- XP11.2 and *APSL-TFE3* fusion
- Papillary variant most common in children
- Distinct cell borders, abundant clear cytoplasm separated by fibrovascular stroma
- Tumor cells negative for EMA, CK, CAM5.2, and vimentin (in contrast to other RCC)
- Positive nuclear reactivity to TFE3 proteins

OSSIFYING RENAL TUMOR OF KIDNEY

- Infant boys
- Renal pelvis, resembles calculus
- Spindle cells in calcified osteoid matrix
- Excellent prognosis

EWING SARCOMA

- *EWS/FLI1* fusion product, t(11;22)
- Pseudorosettes; small, blue cell tumor; entrapped tubules
- Positive for CD99, FLI1

RENAL MEDULLARY CARCINOMA

- Sickle cell carrier, HbS
- 11p15.5 mutation
- Positive for cytokeratin, negative for nuclear *INI1*
- Highly malignant tumor, desmoplastic stroma with marked inflammation

ANGIOMYOLIPOMA

- Tuberous sclerosis
- *TSC1* and *TSC2* genes
- Positive for HMB-45, Melan A, SMA

INFLAMMATORY MYOFIBROBLASTIC TUMOR

- ALK rearrangement, t(2;5)
- Positive for ALK, vimentin, SMA, desmin

Diseases of the ureters

CONGENITAL MALFORMATIONS OF URETER

Ureteral agenesis

- Coexists with renal agenesis

Ureteral duplication

- Two ureteric buds/branching of ureteric bud
- Associated duplication of renal pelvis/duplex kidney

Ureteral ectopia

- More frequent in girls
- Urinary tract infection
- Dysplasia/hypoplasia of ipsilateral kidney

Ureterocele

- Congenital cystic dilation of distal intravesical portion of ureter
- Vesicoureteral reflux/urinary tract infections

- Diagnosed prenatally by ultrasound

Ureteral obstruction

- Ureteropelvic junction/vesicoureteral junction
- Caused by stenosis, valves, functional obstruction
- Results in hydronephrosis, hydroureter, multicystic renal dysplasia

Vesicoureteric reflux

- Retrograde flow of urine from kidneys
- Caused by short intravesical ureters, poorly formed trigone, ectopic ureteral orifice
- Results in recurrent infection, hypertension, and renal failure

Diseases of bladder and urethra

CONGENITAL LESIONS

Agenesis

- Associated with renal agenesis, malformations (sirenomelia, caudal regression syndrome)

Hypoplasia

- Associated with renal dysplasia

Duplication

- VACTERL (vertebral-anorectal-cardiac-tracheal-esophageal-renal-limb)

Bladder exstrophy

- Associated anomalies: Epispadias (urethral orifice on upper surface of penis), bifid clitoris in girls, cloacal exstrophy (bladder divided in two parts by central exstrophic bowel)
- Open symphysis pubis (whole posterior wall of bladder may be exposed)
- Risk of adenocarcinoma/squamous cell carcinoma

Obstructive lesions

- Posterior urethral valves in boys (most common cause of bladder outlet obstruction)

Prune-belly syndrome

- Boys affected
- Triad syndrome: Absence/hypoplasia of abdominal wall musculature (lax and wrinkled wall), cryptorchidism, urinary tract anomalies
- Fetal ascites and Potter phenotype

Megacystic microcolon

- Massive abdominal distension due to largely dilated bladder (non-obstructed)
- Intestinal hypoperistalsis syndrome with microcolon
- No mechanical outlet obstruction
- Normal ganglion cells in bowel

Urachal remnants

- Urachus connects urinary bladder to allantoic duct
- Normally it should be a solid cord by 4 months' gestation
- If fully/partially patent, fistula, sinus, or cysts between bladder and umbilical cord

ACQUIRED LESIONS

Cystitis

- Uncomplicated cystitis in healthy children; *E. coli*
- Indwelling catheters; *Staphylococcus aureus*
- Infections after instrumentation of urinary tract; coagulase negative staphylococci and *Candida*

Granulomatous cystitis

- Etiology; chronic granulomatous disease (congenital anomaly of phagocytic NADPH), tuberculosis, schistosomiasis, fungal infections

Cystitis cystica and glandularis

- Chronic proliferative cystitis
- Cystic structures in submucosa
- Lined by transitional or glandular epithelium, respectively

Interstitial cystitis

- Hunner ulcer
- Urinary solute (potassium) permeability in bladder mucosa increased → irritation and inflammation

Eosinophilic cystitis

- Food allergy, parasites, drugs, bronchial asthma
- Eosinophilic inflammation of bladder wall

Malakoplakia

- Chronic inflammation/granulomas
- Michaelis-Gutmann bodies (laminated calcospherites)
- Positive with von-Kossa, iron, and PAS stains

Hemorrhagic cystitis

- BK virus (bone transplant patients), adenovirus (type 11), *E. coli*, *Candida*, cyclophosphamide drug
- Cytologic atypia and risk of neoplasia

TUMORS OF BLADDER AND URETHRA

Inflammatory myofibroblastic tumor

- Also known as pseudosarcomatous tumor
- *ALK* rearrangement t(2;5)
- Positive staining for *ALK*, vimentin, SMA, desmin

Rhabdomyosarcoma

- Embryonal RMS polypoid, grape like gross appearance
- Densely packed small primitive tumor cells underneath mucosa = cambium cell layer
- Good overall prognosis

24 Cardiovascular System

Congenital malformations

- Heart is recognizable at 15 weeks of gestation
- Complex developmental process: Simple tube converted to four-chambered structure by septation and looping
- Genetic and environmental factors involved
- Most common chromosomal abnormality for congenital heart disease (CHD): 22q11 deletion of diGeorge/velocardiofacial syndrome
- In normal heart, systemic and pulmonary circulation are separate functioning as two parallel circuits
- Shunting and obstruction to flow are the main pathologies in CHD
- If shunt is from left → right = increased pulmonary blood flow, congestive heart failure, pulmonary hypertension
- If the shunt is from right → left = cyanosis
- Right-sided obstruction = decreased pulmonary blood flow and cyanosis
- Left-sided obstruction = decreased systemic blood flow
- Severe obstruction = blood flow occurs across ductus arteriosus (normally ductus closes at 1–2 days after birth)

SEPTAL MALFORMATIONS

Atrial septal defects (ASDs)

- Atrial septum made up of septum primum, endocardial cushions, and septum secundum
- In fetal life, blood flows from right to left atrium via foramen ovale
- Normally, foramen ovale closes during first year of life
- ASD is of four types: Septum primum defect, septum secundum defect (most common), sinus venosus defect, and coronary sinus defect
- *Single atrium*: Complete absence of atrial septum
- *Premature closure of foramen ovale*: Imperforate foramen = restricted uterine mixing of blood, hydrops fetalis, hypoplastic left heart syndrome

Ventricular septal defects (VSDs)

- Ventricular septum has four components: Inlet, trabecular, outlet, and membranous
- VSD is most common CHD
- Four different types of VSD: Perimembranous, outlet, inlet, and muscular defect
- Symptomatic when pulmonary vascular resistance falls at 2–6 weeks after birth
- Left-to-right shunt → congestive heart failure, pulmonary hypertension

Malformation of atrioventricular septum

- AV septum separates right atrium from left ventricle
- Endocardial cushion defects = partial or complete AV canal

MALFORMATIONS OF CONUS AND TRUNCUS

- Conotruncal structures of heart represent outflow region of developing heart

Transposition of great vessels

- Aorta arises from RV and pulmonary artery arises from LV

Complete transposition

- Most common form
- Transposed aorta to right of PA (D-transposition)
- Internally, AV concordance with ventriculoarterial discordance
- Accelerated pulmonary hypertension (due to massive pulmonary outflow)

Corrected transposition

- Less common form
- Also known as ventricular inversion
- Transposed aorta to the left of PA (L-transposition)
- Internally, AV and ventriculoarterial discordance (blood flow anatomically corrected)

RA → LV (right sided) → PA
LA → RV (left sided) → Aorta

Double outlet ventricle

- *DORV*: Both major vessels arise from RV
- *DOLV*: Both major vessels arise from LV
- Both forms of double outlet ventricles usually accompanied by VSD
- VSD serves as outflow tract for other ventricle (the one without double outlet)
- Subclassified according to location of VSD
- DORV is more common than DOLV

Persistent truncus arteriosus

- Single arterial trunk arising from single semilunar valve and supplying the aorta, pulmonary arteries, and coronary arteries
- Truncal valve in fibrous continuity with mitral valve
- Congestive heart failure and pulmonary HT

Aortopulmonary window

- Defect in vessel wall between ascending aorta and main pulmonary artery

MALFORMATIONS OF VENTRICULAR INFLOW TRACTS

Tricuspid atresia

- Tricuspid valve completely absent or an imperforate fibrous membrane
- No outlet for RA except for ASD or patent foramen ovale
- Very rudimentary and small RV
- Cyanosis/murmur in newborn

Ebstein malformation

- Common cause of isolated tricuspid stenosis/regurgitation
- Adherence of tricuspid valve leaflets to RV
- Atrialization of portion of RV
- Associated multiple cardiac anomalies
- Cyanosis/murmur in newborn

Mitral atresia

- Absence of left AV connection
- Blood from LA finds an outlet through patent foramen ovale or ASD
- LV is diminutive

Floppy mitral valve

- Myxomatous degeneration, collagen degeneration, and mucopolysaccharide deposits on valve, no inflammation
- Late systolic "click" on auscultation
- Associated with pectus excavatum, Marfan, or Ehlers-Danlos syndrome

Double inlet ventricle

- Left and right AV valves open into dominant LV
- Associated VSD (rudimentary RV communicates with LV)

MALFORMATIONS OF VENTRICULAR OUTFLOW TRACTS

Tetralogy of Fallot (TOF)

- Infundibular pulmonic stenosis, VSD, aortic valve dextroposition, right ventricular hypertrophy
- Most common cyanotic CHD
- Right-to-left shunt
- Associated DiGeorge or trisomy 21

Aortic valvular stenosis

- Bicuspid valve is most common
- May be asymptomatic in childhood
- Stenosis progresses and needs surgical intervention
- Endocardial fibroelastosis and subendocardial ischemic damage
- Complications: Bacterial endocarditis, arrhythmias, ischemic myocardial damage, sudden cardiac death
- Treated with balloon valvotomy, valve replacement

Aortic atresia

- Hypoplastic heart syndrome
- Male predominance

Hypoplastic left heart syndrome

- Underdevelopment of left side of heart
- Atresia of aortic valve/mitral valve
- RA, RV, and the right AV valve dilated and enlarged
- Obstruction of PA/patent ductus arteriosus (for adequate systemic blood flow)
- Endocardial fibroelastosis and myocardial hypertrophy
- Associated coarctation of aorta
- Incompatible with life unless staged surgical repair (Norwood repair)/cardiac transplantation in neonatal life

Multistage Norwood repair

Stage I
(Blalock-Taussig shunt)

- Initial palliative surgery at age 1–3 weeks
- Establishes unobstructed systemic blood supply
- Pulmonary blood flow and pressure is regularized

Stage II
(Bi-directional Glenn procedure)

- Intermediate palliation at age 4–6 months
- Reduces RV load
- SVC and right pulmonary artery anastomosis

Stage III
(Fontan variant procedure)

- Definitive repair at age 18 months–2 years
- Complete separation of pulmonary artery and systemic venous blood
- Tunnel anastomosis between IVC and right PA

MALFORMATIONS OF AORTIC ARCH SYSTEM

Ductus arteriosus

- Normally, ductus is patent in utero (due to low oxygen levels and increased prostaglandin levels)
- Normally, ductus closes within 15 hours after birth (term normal weight neonates)
- In PDA, remains patent beyond 2–3 weeks of life
- PDA is thin-walled, smooth intima
- Intact internal elastic lamina, paucity of internal elastic cushion
- Complicated by left-to-right shunt and congestive heart failure

Coarctation of aorta

- Area of narrowing in upper thoracic aorta, juxtaductal
- Composed of fibroelastic tissue and smooth muscle
- Upper extremity hypertension
- Decreased pulse and blood pressure in lower extremity

Aortic arch branching abnormalities

- Left aortic arch with aberrant right subclavian artery
- Right-sided aortic arch
- Vascular rings; malformations of aortic arch structures that encircle and compress trachea and esophagus

MALFORMATIONS OF CORONARY ARTERIES

- Anomalous origin of left coronary artery from pulmonary trunk
- Inadequate blood supply to left ventricle by anomalous coronary artery (pulmonary trunk is low pressure vessel)
- Anterolateral myocardial infarction, early death
- Clinical course determined by collateral vessels

MALFORMATIONS OF VENOUS SYSTEM

Persistent left superior vena cava

- Absence of innominate vein
- LSVC enters coronary sinus in AV sulcus

Interruption of inferior vena cava with azygous continuation

- Infrahepatic interruption of IVC by azygous continuation

- Absence of IVC between renal and hepatic veins
- Associated other CHD and polysplenia

Partial anomalous pulmonary venous return

- Blood from one to three pulmonary veins drains into right atrium or SVC
- Associated sinus venosus, ASD
- *Scimitar syndrome*
  - Anomalous pulmonary venous drainage to IVC
  - Associated multiple anomalies: Right lung hypoplasia, dextrocardia, systemic arterial supply to lung, defective bronchial anatomy
  - On plain chest x-ray; anomalous vein seen as a tubular structure parallel to right heart border as a Turkish sword ("scimitar")

Total anomalous pulmonary venous return

- All four pulmonary veins drain into systemic circulation
- Associated with pulmonary venous obstruction and severe pulmonary hypertension
- Medial hypertrophy of pulmonary arteries and veins, intimal proliferation and arterialization of pulmonary veins

Cor triatriatum

- Left atrium partitioned by fibromuscular shelf
- Pulmonary venous compartment separated from atrial appendage and mitral valve orifice
- Results in pulmonary venous compression

MALFORMATIONS OF POSITION AND SITUS

Dextrocardia

- Heart located in right side of chest with apex pointing to right
- May be seen with situs inversus

Dextroposition

- Heart displaced to right side of chest with apex pointing to left

Ectopia cordis

- Heart located partially/totally outside chest
- Thoracic/thoracoabdominal

Situs ambiguous (heterotaxia)

- Heart sidedness determined by morphology of atrial appendage

Asplenia

- Bilateral right-sidedness

Polysplenia

- Bilateral left-sidedness

MYOCARDIAL DISEASE

- Cardiomyopathy (CMP) is disease of myocardium associated with cardiac dysfunction

Primary CMP

HCMP (hypertrophic)

- Massive cardiomegaly with increased weight, thickened left ventricular free wall/interventricular septum
- Concentric (symmetric) or asymmetric
- Myocyte hypertrophy, interstitial fibrosis, myocyte disarray
- In infants, restriction of both right and left ventricular outflow
- AD disorder
- Mutated myosin binding protein C (MYBPC3) and cardiac beta-myosin heavy chain (MYH7)

Arrhythmogenic right ventricular dysplasia (ARVD)

- Partial or massive transmural replacement of right ventricular myocardium by fibrofatty tissue
- Myocardial disarray leading to ventricular arrhythmias

Non-compaction of ventricular myocardium

- Persistence of spongy myocardium (more common in LV)
- Similar pattern seen in early embryonic stages of heart development
- Fine trabecular meshwork of ventricular myocardium with intervening endocardium lined sinusoids
- Endocardial fibroelastosis

- Arrhythmias, congestive heart failure, systemic thrombi
- Gene involved is tafazzin (*TAZ*) on chromosome Xq28

Dilated cardiomyopathy (DCMP)

- Common endpoint of multiple underlying conditions
- Heart enlarged and heavy, biventricular/all four chambers, dilatation and poor contraction
- Lymphocytic myocarditis, interstitial fibrosis
- Underlying neuromuscular diseases

Restrictive CMP

- Stiff heart wall due to fibrotic/infiltrative disorders
- Ventricular diastolic volume decreased

Endocardial fibroelastosis

- Association with various CMP
- Subendocardial proliferation of fibroelastic tissue, opaque endocardium
- Association with mumps/adenovirus infection in utero

Myocarditis (inflammatory cardiomyopathy)

- Inflammatory infiltrate composed of neutrophils, lymphocytes, plasma cells, macrophages, giant cells, eosinophils
- Associated myocardial damage (vacuolization, necrosis, debris, frayed edges)
- Sudden cardiac death, acute heart failure
- Viral myocarditis most common (Coxsackie B virus, detected by polymerase chain reaction, serology)
- Bacterial (streptococci, staphylococci, *Neisseria*)
- Protozoal (*Trypanosoma cruzi*, Chagas disease; *Toxoplasma gondii*, toxoplasmosis)

Giant cell myocarditis

- Rapidly progressive, death or cardiac transplant
- Second decade
- Autoimmune disease—Association with inflammatory bowel disease
- Infiltrate of giant cells, mixed inflammatory cells (no granulomas)

Secondary CMP

Glycogen storage disease (GSD)

- AR disorder
- Deficiency of enzymes involved in degradation of glycogen
- Type II (Pompe disease)
  - Lysosomal—Bound glycogen in heart and skeletal muscle
  - Myocyte distension with vacuolated and lacy cytoplasm due to accumulation of glycogen (PAS positive)

Danon disease

- X-linked dominant disorder
- *LAMP-2* gene mutation
- Muscle weakness, cardiomyopathy, cardiac failure, mental retardation
- Myocytes have PAS and acid phosphatase positive membrane bound inclusions

Mucopolysaccharidoses

- AR lysosomal storage defect
- Defective intralysosomal degradation of acid mucopolysaccharides
- *Type I (Hurler syndrome)*: Valves and endocardium of all four chambers thickened, mitral valve nodules

Hereditary hemochromatosis

- Juvenile form: Mutation of genes hemojuvelin or hepcidin
- Adult form: Mutation of *HFE* gene
- Manifested as cardiac arrhythmias and DCMP

Mitochondrial electron transport chain disorders

- Mitochondrial enzyme deficiencies caused by mtDNA or nDNA mutations
- Cardiac myofiber filled with pools of mitochondria
- *EM*: Closely packed stacks of mitochondrial cristae
- DCMP or HCMP

NEUROMUSCULAR DISORDERS

Muscular dystrophies

- X-linked recessive

- Mutation in dystrophin gene: Duchenne and Becker forms

Myotonic dystrophy

- DCMP, interstitial/epicardial fibrosis, conduction defects

Congenital myopathies

- Myofibrillar myopathy (abnormal desmin), DCMP, central core disease

Friedreich ataxia

- GAA trinucleotide repeat expansion in frataxin gene
- HCMP

Barth syndrome

- Inherited in X-linked manner
- Females are carriers and males affected
- *TAZ* gene mutation
- Cardiomyopathy (mostly dilated), non-compaction of left ventricle, neutropenia, skeletal myopathy, prepubertal growth delay, facial dysmorphism (infants/toddlers)

INFANT OF DIABETIC MOTHER CARDIOMYOPATHY

- HCMP
- Resolves by 12 months, transient and rarely fatal

ISCHEMIC MYOCARDIAL NECROSIS

- Myocyte necrosis (cytoplasmic eosinophilia and nuclear pyknosis), marginal neutrophilic infiltrate, dystrophic calcification
- Ischemia damages papillary muscles/ventricular subendocardium

SYSTEMIC ARTERY DISEASE

Arteriopathy

Idiopathic infantile arterial calcifications

- Deposition of calcium hydroxyapatite in and around internal elastic lamina
- Intimal fibrous proliferation, reactive inflammatory response in arteries
- Coronary arteries frequently involved
- Heart failure, ischemic heart injury, non-immune hydrops

Fibromuscular dysplasia

- Non-inflammatory disorganization and fibrosis of large muscular arteries
- Duplication and fragmentation of internal and external elastic lamina
- Renal hypertension in childhood

ANEURYSMS

Marfan syndrome

- Dilatation and dissection of ascending aorta in Marfan syndrome
- Cystic medial degeneration with accumulation of mucopolysaccharides
- Mutation in fibrillin-1 gene

Ehlers-Danlos syndrome

- Thin-walled vessels with decreased elastic/collagen tissue
- Aortic dilatation, dissection, and rupture
- Mutation of *COL3A1* gene

Menkes steely hair syndrome

- Defective intestinal absorption of copper and reduced activity of copper-dependent enzymes (lysyl oxidase)
- Impaired formation of extracellular matrix
- Diminished vessel wall strength
- Mutation of *ATP7A* gene

Atherosclerosis

- Familial hypercholesterolemia
- Mutation in gene encoding low-density lipoprotein
- Aorta, coronary arteries, and cardiac valves involved
- Deposition of foam cells, fibrosis, and cholesterol clefts
- Valve stenosis/insufficiency

Vasculitis

- Inflammation of vessels

Kawasaki disease

- Mucocutaneous lymph node syndrome
- Japan, acute febrile exanthematous illness, cervical lymphadenopathy, bilateral conjunctivitis

- Very young children
- Coronary artery aneurysm with myocardial infarction

Takayasu arteritis

- Also known as pulseless disease
- Young women, southeast Asia and Mexico
- Chronic granulomatous inflammation of vessel wall, fibrosis, thrombosis, vessel occlusion, aneurysm formation

Endocardial diseases

- Endocarditis; inflammatory cells within endocardium

NON-INFECTIVE ENDOCARDITIS

- Rare in childhood
- Endothelial/endocardial injury → turbulent blood flow → nidus for platelet aggregation and thrombus formation
- Warty, nodular vegetations (fibrin, entrapped platelets, erythrocytes, and few leukocytes)
- Etiology: Intracardiac catheters, hypercoagulable states, malignancy, burns, DIC

INFECTIVE ENDOCARDITIS

- Congenital heart defects, prosthetic valves, shunts; nidus for infection
- Fever, malaise, new/changing heart murmur, positive blood culture, demonstration of vegetations on echocardiogram
- *Streptococcus viridans*, *Staphylococcus aureus*, fungal organisms
- Vegetations on atrial surface of AV valves and ventricular surface of outflow valves
- Vegetations composed of fibrin, polymorphonuclear cells, bacterial colonies/fungal organisms, necrotic material, platelets, and calcification

INFLAMMATORY/ AUTOIMMUNE DISORDERS

Systemic lupus erythematosus (SLE)

- Double-stranded DNA antibody
- Pericardial effusion/thickening, mesothelial proliferation, necrosis, fibrinous exudates, inflammation, granulation tissue
- Endocarditis and valvular lesions
- Non-bacterial verrucous or Libman-Sacks endocarditis

Neonatal SLE

- Skin lesions and heart block
- Mother/neonate have SSB/LA and SSA/RO antibodies
- Diagnosed in utero

Rheumatic fever

- Delayed autoimmune reaction to Group A, beta-hemolytic streptococcal pharyngitis
- Major criteria: Carditis, migratory polyarthritis, erythema marginatum, subcutaneous nodules, Sydenham chorea
- Minor criteria: Fever, polyarthralgia, elevated acute phase reactants
- *Aschoff nodules*
  - Central fibrinoid necrosis surrounded by inflammatory cells including lymphocytes, plasma cells, and Anitschkow cells
  - Anitschkow cells: Histiocytic cell with ragged borders, vesicular nucleus containing central speculated bar of chromatin
- MacCallum patch in left atrium
- Mitral valve, most commonly involved (mitral stenosis)
- Pericarditis (fibrinous)

Pericardial diseases

PERICARDITIS

- Inflammation of pericardium

Serous effusion

- Viral or non-infectious pericarditis
- Fluid contains proteins, lymphocytes, and fibrinous exudates

Purulent pericarditis

- Caused by pyogenic bacteria (*S. aureus*)
- Direct extension of infection from empyema, pneumonia, mediastinum

- Hematogenous spread from osteomyelitis, pyelonephritis
- Acute illness with fever, chest pain, tachypnea

Tuberculous pericarditis

- Hemorrhagic fluid with caseating granulomas
- Acid-fast *bacilli*

Obliterative or constrictive pericarditis

- Develops in chronic or healed pericarditis

OTHER ANOMALIES

- Pericardial cysts; mesothelial lined and filled with clear fluid
- Congenital aplasia of parietal pericardium; myocardial herniation

Conduction system abnormalities

- Cardiac conduction system composed of SA node, AV node, bundle of HIS, and bundle branches
- Arrhythmias divided into three types

SUPRAVENTRICULAR TACHYCARDIA

- Mostly benign except Wolff-Parkinson-White (WPW) syndrome

WPW syndrome

- Persistent cardiac muscle strands connecting atrial and ventricular muscle (bypassing AV node)
- ECG—short PR interval, broad QRS complex, delta waves

AV CONDUCTION DISORDERS (AV BLOCK)

- Interruption of impulse conduction from atrium to ventricle
- Etiology; congenital heart disease, maternal autoimmune disease with circulating anti-SSA/Ro and anti-SSB/La antibodies
- Pacemaker implantation may be required

VENTRICULAR TACHYCARDIAS

- Long QT syndrome (prolonged QT polarization and slow repolarization)
- Disorders affecting cardiac muscle K^+, Ca^{2+}, NA^+ (channelopathies)
- Catecholaminergic polymorphic ventricular tachycardia
- Risk of sudden death

Pulmonary hypertension

- Mean resting pulmonary artery pressure more than 25 mm Hg
- Pulmonary vasculature includes pre-acinar and intra-acinar arteries
- Pre-acinar pulmonary arteries develop with the pulmonary airways, completing development by 16–17 weeks of intrauterine life
- Intra-acinar arterial development starts in utero but medial muscle development lags behind, completing by 8–10 years of age
- Pulmonary vascular resistance diminished after birth (compared to fetal life); due to release of nitrous oxide/prostacyclin by endothelial cells and dilatation of vessels
- Histological features; medial muscular hypertrophy, intimal fibroplasia, intimal cellular thickening, plexiform lesions, dilation lesion

PERSISTENT PULMONARY HYPERTENSION OF NEWBORN

- Pulmonary vascular resistance fails to drop at birth → right-to-left shunt with cyanosis
- Pulmonary malformation/hypoxia-related maladaptation
- Abnormal muscle thickening in media of peripherally located intra-acinar arteries

CHD WITH LEFT-TO-RIGHT SHUNT

- Increased blood volume and pressure in lungs → smooth muscle hyperplasia and intimal thickening (cellular/fibroid), decreased number of peripheral arteries
- Irreversible if repair is delayed

- Eisenmenger syndrome; pulmonary vascular resistance exceeds systemic vascular resistance, shunt reversal (right → left) with cyanosis

FAMILIAL AND IDIOPATHIC PULMONARY ARTERY HYPERTENSION

- AD
- Mutation in gene *BMRP-2*

LEFT HEART OBSTRUCTIVE DISEASE

- Hypertensive changes in pulmonary arteries/veins

Cardiac tumors

The type of primary cardiac tumor varies with age

RHABDOMYOMA

- First 2 years of life (including fetus and neonates)
- Hamartoma instead of neoplasm
- Solitary or multiple nodules
- Strong association with tuberous sclerosis
- Asymptomatic, arrhythmogenic, or may cause sudden death
- May regress spontaneously
- Fetal diagnosis: Non-immune hydrops, cardiac mass on routine ultrasound, arrhythmias, family history of TS
- Well-circumscribed, yellowish masses, ventricular myocardium, microscopic to larger size
- Composed of large myocardial cells with accumulation of glycogen in cytoplasm (spider cells)

CARDIAC FIBROMA

- Second-most common cardiac tumor of childhood
- Left ventricle or intraventricular septum
- Association with Gorlin syndrome
- Cut surface: Firm, solid, and trabeculated
- Bland spindled cells in collagenized stroma
- Treatment: surgical resection/heart transplant

TERATOMA

- Fetus
- Intrapericardial location, pericardial effusion
- Non-immune hydrops, cardiac tamponade

MYXOMAS

- Adolescents and adults
- Tumor emboli, vascular obstruction, constitutional symptoms
- Sporadic or syndromic
- Associated with *Carney complex* (AD disorder, *PRKAR1A* gene, skin lesions, myxomas, endocrine abnormalities)
- Located in endocardium near fossa ovalis, left atrium
- Gelatinous, frond-like
- Stellate/elongated cells in mucopolysaccharide-rich myxoid matrix
- Immunohistochemistry: Vimentin, calretinin, CD31, CD34, CK (glandular elements)

HISTIOCYTOID CARDIOMYOPATHY

- Infant girls
- Cardiomegaly, arrhythmias, sudden cardiac death
- Small, flat to nodular collections of large pale myocardial cells with foamy cytoplasm, rich in glycogen and lipid
- *EM*: Mitochondria rich
- Stain positively with actin and myosin
- Negative for histiocytic markers

25 The Respiratory Tract

Embryology and development

- Lung development starts at week 3 of embryonic life and involves five stages

EMBRYONAL PERIOD

- 26 days to 6 weeks
- Development of major proximal airways

PSEUDOGLANDULAR PERIOD

- 6–16 weeks
- Development of airways to terminal bronchioles

ACINAR/CANALICULAR PERIOD

- 16–28 weeks
- Acinus development/vascularization

SACCULAR PERIOD

- 28–34 weeks
- Subdivision of saccules by secondary crests
- Division of distal airways into smaller units

ALVEOLAR PERIOD

- 34 weeks and beyond
- Alveoli formed during this period
- At birth, there are about 53 million alveoli
- Alveoli increase to adult number of 300–600 million by 2 years of age
- After 2 years of age, no increase in alveolar number but volume/size of alveoli increase, thus increasing surface area of lung

Congenital and acquired anomalies

NASOPHARYNX

Choanal atresia

- Occlusion of airway between posterior nasal passage and nasopharynx
- Sporadic or syndromal
- CHARGE syndrome (coloboma, heart defects, choanal atresia, retardation, genital defects, ear anomalies)

Cleft lip and/or palate

- Most common malformation of respiratory tract
- Maternal alcohol consumption/cigarette smoking

Laryngocele

- Rare lesion, may contain air or fluid
- If infected = pyolaryngocele

Laryngomalacia

- Maldevelopment of larynx
- Partial laryngeal obstruction, stridor, feeding difficulties
- Pierre Robin, cri-du-chat syndromes

Laryngeal stenosis and atresia

- Supraglottic, glottic, and subglottic developmental webs
- VATER/VACTERL associations
- Pinpoint laryngeal lumen
- Hyperplastic enlarged lungs, rib, markings on surface

Laryngotracheoesophageal cleft

- Failure of tracheoesophageal septum formation
- Familial/VATER association

- Supraglottic interarytenoid cleft, partial cricoid cleft, total cricoid cleft, complete cleft to level of carina

TRACHEA

Tracheal stenosis

- Acquired lesion due to prolonged intubation
- Complete cartilage ring beneath mucosa

Tracheal agenesis

- Rare anomaly, uniformly fatal
- Tracheal agenesis with fused main bronchi and bronchoesophageal fistula

Tracheomalacia

- Soft or collapsing trachea

Tracheobronchomegaly

- Mounier-Kuhn syndrome

Tracheoesophageal fistula (TEF) and esophageal atresia

- Premature infants
- Maternal hydramnios, excessive oral and pharyngeal secretions in neonates
- Choking, cyanosis/coughing at feeding attempts
- Most common type: Esophageal atresia with TEF to distal esophageal segment
- VACTERL association: Vertebral defects, anal atresia, cardiac defects tracheoesophageal fistula, renal defects, and limb anomalies

BRONCHUS

Bronchial atresia/stenosis

- Related to congenital lobar emphysema
- Bronchus shows circumferential/eccentric post-inflammatory fibrosis
- Extrinsic causes of stenosis: Peribronchial masses
- Intrinsic causes of stenosis: Aspiration of meconium or foreign bodies

Bronchomalacia

- Premature infants on prolonged mechanical ventilation
- Small bronchus with islands of immature cartilage in wall

Bronchial isomerism syndromes

- Mirror image lungs (bilateral right or bilateral left lungs)
- Associated with five types of heterotaxy syndromes
- Type I (Ivemark asplenia syndrome-complex): Bilateral right-sidedness, absent spleen, intestinal malrotation, symmetric liver, congenital heart disease, bilateral three-lobed lungs
- Type III (polysplenia syndrome-complex): Bilateral left-sidedness, multiple spleens, intestinal malrotation, symmetric liver, congenital heart disease, bilateral two-lobed lungs

Bronchobiliary and bronchoesophageal fistulae

- Variation of TEF
- Acquired conditions—tuberculosis, Crohn disease

Bronchiectasis

- Congenital/familial conditions
- Infectious disease—Tuberculosis and pertussis

Immotile cilia syndrome

- Also known as Kartagener syndrome
- Situs inversus, otitis, rhinitis, bronchiectasis, male subfertility
- *EM*: Absence of both inner and outer dynein arms, radial spoke defect, compound cilia

Cystic fibrosis

- Mucus stasis in bronchi
- Pseudomonas pneumonia

Williams-Campbell syndrome

- Congenital bronchiectasis
- Deficiency of bronchial cartilage distal to main stem bronchus

Bronchogenic cyst

- Extrapulmonary mass, midline, located in subcutaneous tissue (anywhere from supra sternum to diaphragm)

- No communication with tracheo-bronchial tree/pulmonary parenchyma
- Lined by ciliated pseudostratified columnar/cuboidal epithelium
- Fibrous wall contains mucinous glands and cartilage
- Incidental finding or symptomatic
- Differentiated from esophageal cyst (lined by squamous epithelium, have skeletal muscle), enteric cysts (lined by mucus secreting columnar epithelium, have gastric glands in the wall)

Plastic bronchitis

- Bronchial casts made up of fibrin, mucin, inflammatory cells
- Seen in cardiac and pulmonary diseases

LUNG

Pulmonary agenesis

- Unilateral, compatible with long-term survival
- Associated with VACTERL

Sequestrations

Extralobar

- Masses of pulmonary parenchyma outside visceral pleura, usually inside thorax
- Develop from outpouching of foregut/not connected to tracheobronchial tree
- Present within first 3 months of life
- Dyspnea, cyanosis/feeding difficulties in neonatal period
- CPAM—type 2 associated with sequestration
- Associated anomalies: Bronchogenic cysts, cardiovascular malformations, diaphragmatic hernia
- Well-circumscribed discrete lesion, variable size
- Blood supply by direct branch of thoracic/abdominal aorta (systemic vessels)
- Venous drainage into azygous system
- Back-to-back dilated prominent bronchiole-like structures seen (as in CPAM type 2)
- Prominent lymphatics around broncho-vascular structures
- Rhabdomyomatous dysplasia associated

Intralobar

- Portion of pulmonary parenchyma, within the pleura
- Sequestered from rest of trachea-bronchial tree
- Supplied by systemic artery
- Develops after repeated episodes of pulmonary infection
- Children after 5 years of age, not congenital, not associated with other congenital abnormalities
- Pulmonary parenchyma shows multiple distorted cysts, chronic inflammation, and fibrosis

Hypoplasia

- Incomplete/defective development of lung
- Diminished size due to decreased number/size of alveoli (normal radial alveolar count = 5–6)
- Extrathoracic compression; restriction of space for lung growth (renal agenesis → oligohydramnios → decreased uterine space), enlarged kidneys
- Intrathoracic compression (diaphragmatic hernia, extralobar sequestration, thoracic neuroblastoma)
- Musculoskeletal abnormalities (thanatophoric dwarfism)

Infantile (congenital) lobar emphysema (ILE)

- Overdistension/hyperplasia of pulmonary lobe (due to partial/complete obstruction of bronchus) by extrinsic/intrinsic factors
- Etiology: Bronchial atresia, bronchial stenosis, abnormal origin of bronchus, aspirated meconium, mucus plug, foreign body

Hyperinflated lung

- Classic form: Alveolar ducts/alveoli dilated up to 3–10 times normal size but otherwise unremarkable
- Hyperplastic form: Not overinflated, complex acinar formation, large number of alveoli (↑RAC)

Congenital pulmonary lymphangiectasis

- Rare, fatal disorder, within a few hours of birth

- Fine network of dilated lymphatics beneath pleura, especially at intersection of interlobular septa, increased connective tissue
- Primary disorder/associated with other congenital cardiovascular malformations
- Infants with "total anomalous pulmonary venous return" show enormously dilated lymphatics

Congenital pulmonary airway malformation (CPAM)

- Most frequent cystic lung disease in children
- Hamartomatous lesion
- Classified into five types based on cyst size
- Respiratory distress in newborn
- Type 2 associated with other severe anomalies

CPAM type 0

- Rare/incompatible with life
- Acinar dysplasia

CPAM type 1

- Most common type
- Good prognosis with surgery
- Multiple large cysts surrounded by smaller cysts, compressed normal parenchyma
- Cysts lined by ciliated pseudostratified columnar/cuboidal epithelium
- Mucus-producing cells (potential to produce bronchioloalveolar carcinoma) may be interspersed in between

CPAM type 2

- Medium-size cysts (0.5–2 cm)
- Poor outcome, associated with other anomalies
- Back-to-back bronchiole-like structures lined by cuboidal/columnar cells
- Associated rhabdomyomatous dysplasia
- Similar morphological features seen in extralobar sequestration

CPAM type 3

- Small cysts (0.2 cm) or solid
- Bad prognosis
- Large/bulky mass causes mediastinal shift
- Resembles immature lung, bronchiole-like structures, adenomatoid appearance

CPAM type 4

- Large air-filled cysts at the periphery of lung
- Cyst lined by flattened epithelial cells
- Similar to grade I pleuropulmonary blastoma
- Respiratory distress/pneumothorax (PT)

Congenital alveolar capillary dysplasia

- Progressive hypoxemia in newborn/uniformly fatal
- Lung transplantation necessary
- Associated anomalies: Duodenal atresia, CHD, asplenia
- Failed formation and ingrowth of alveolar capillaries
- Large centrally placed capillaries within alveolar septal wall
- Misalignment of veins: Ectatic veins within bronchovascular bundles

Peripheral cysts of the lung

- Down syndrome, pulmonary infarction/spontaneous PT

Subpleural cysts

- Air-filled, vascular fibrous connective tissue lined by alveolar lining cells, 0.2–1 cm

Hyaline membrane disease (HMD)

- Respiratory distress syndrome (RDS)
- Firm, atelectatic lungs, hyaline (smooth homogenous pink) membranes along terminal/respiratory bronchioles/alveolar ducts
- Premature infants, pulmonary surfactant deficiency
- Surfactant replacement therapy—decreased incidence of HMD

Bronchopulmonary dysplasia

- Also known as chronic lung disease of prematurity
- Premature infants
- Toxic effects of oxygen, mechanical ventilation, poor bronchial drainage

BPD in a child who has not received surfactant therapy

- In bronchi that are fully obstructed (due to necrotic/hyaline membranes): Distal acinus protected from toxic effects of oxygen therapy/mechanical ventilation
- In the bronchi that are fully patent/incompletely obstructed: Distal acini exposed to oxygen toxicity/barotrauma
- Acinar atrophy, pleural fissures, alveolar septal fibrosis

BPD in a child who has received surfactant therapy

- Chronic lung disease very subtle
- The acini increase in size but do not develop much complexity (acinar simplification), thin septa

Congenital surfactant deficiency

- AR disorder
- Rapidly developing respiratory failure immediately after birth
- Lung transplant may be necessary
- Surfactant protein B deficiency most frequent = caused by deficiency of adenosine triphosphate-binding cassette protein (most frequently ABCA3)
- Deficiency of protein A and C less common
- Alveoli filled with eosinophilic granular material admixed with macrophages and desquamated epithelial cells
- Mimics congenital alveolar proteinosis
- Later stages: Alveolar cell hyperplasia, septal fibrosis

Interstitial pulmonary emphysema

- Dissection of air along bronchovascular bundles, intralobular septa and through pleura
- Mechanical ventilation in infants with RDS
- PT, pneumomediastinum, pneumopericardium

Acute

- Less than 7 days
- Air beneath pleura, junction of interlobular septa and pleura

Persistent (PIPE)

- More than 7 days
- Air blebs noted beneath pleura, along interlobular septa
- Cysts are air filled/lined by smooth membrane, compression of pulmonary parenchyma
- Cyst wall made up of fibrous connective tissue, lined by foreign body type giant cells

Aspiration

- In utero/during delivery/during life
- Sudden respiratory distress/chemical pneumonitis (meconium or gastric contents aspiration)
- Post-term infants: Amniotic fluid aspiration fills up alveoli/ducts, by squames
- Aspiration of maternal blood during delivery, milk, and other chemicals and solid objects; symptomatic and dangerous

Meconium aspiration syndrome (MAS)

- Alveoli filled with amorphous debris/neutrophils
- Serious condition, may require ECMO/surfactant lavage

Extracorporeal membrane oxygenation (ECMO)

- Indications: MAS, CHD, ACD, diaphragmatic hernia, severe infections
- Intrapulmonary changes: Alveolar hemorrhage, alveolar cell hyperplasia, interstitial fibrosis, mucinous/squamous cell metaplasia hyperinflation, airway obstruction
- Extrapulmonary changes: Cerebral infarcts, hemorrhages, periventricular leukomalacia

Pulmonary hemorrhage

- Etiology: HMD, BPD, DIC, Goodpasture syndrome, erythroblastosis, congestive heart failure, congenital malformations
- Differentiated from aspirated maternal blood (by identification of fetal erythrocytes)

Pulmonary veno-occlusive disease

- Intrinsic disease of pulmonary veins
- Rare cause of pulmonary hypertension
- Right-sided heart failure

- Prominent pulmonary arteries with Kerley B lines: On x-ray
- Pulmonary veins/venules display eccentric intimal fibrosis/thrombi, arterialized veins
- Medial hypertrophy of arteries
- Poor prognosis, no effective treatment

Pulmonary alveolar microlithiasis

- May cause pulmonary hypertension and respiratory failure
- Miliary pattern on x-ray
- Calcium phosphate micro concretions (bronchoalveolar lavage/lung biopsy)

Pulmonary hemosiderosis

- Indicative of previous hemorrhage/aspiration in lungs

Idiopathic pulmonary hemorrhage

- Hemoptysis, iron deficiency anemia, diffuse parenchymal infiltrates
- Hemosiderin-laden macrophages on BAL

Secondary pulmonary hemorrhage

- Immunologically mediated renal or vascular disease

Infectious diseases

RESPIRATORY SYNCYTIAL VIRUS

- Most common respiratory pathogen of childhood
- Pneumonia, bronchiolitis, bronchitis

ADENOVIRUS

- Severe necrotizing bronchitis, bronchiolitis, and alveolitis
- Intranuclear smudged inclusions basophilic/eosinophilic, bronchiolar/alveolar epithelial cells

LEGIONELLA PNEUMONIA

- Immunocompromised children

EOSINOPHILIC PNEUMONIA

- Acute onset, respiratory distress
- Increased eosinophils in BAL, peripheral blood
- Drugs, parasites, other infectious agents

INTERSTITIAL LUNG DISEASES

- Interstitium includes alveolar walls, interlobular septa, and connective tissue around bronchovascular bundles
- Bilateral, multiple lobes

Chronic lung disease of infancy

- Idiopathic, progressive respiratory insufficiency several days to weeks after birth
- Mild chronic interstitial inflammation, minimal interstitial fibrosis, reactive type 2 pneumocytes
- Possible nutritional deficiencies/postinfectious

Neuroendocrine hyperplasia of infancy

- Tachypnea, hypoxia, failure to thrive
- Stain positive with bombesin, serotonin

Pulmonary interstitial glycogenosis

- Respiratory distress in infant
- Self-limited, resolves
- Interstitium filled with spindled/polygonal cells containing abundant glycogen (PAS positive and diastase labile)

Miscellaneous disorders

SARCOIDOSIS

- Rash, uveitis, and arthritis
- Hypercalcemia, increased angiotensin-converting enzyme levels
- More common in black individuals
- Bilateral hilar lymphadenopathy
- Non-caseating granulomas: Central core of epithelioid cells, multinucleated giant cells, peripheral rim of lymphocytes
- Asteroid bodies/Schaumann bodies in giant cells

- Extrapulmonary organs commonly involved by disease

CYSTIC FIBROSIS

- AR disorder, *CFTR* gene located on chromosome 7, delta F508
- Highly viscous mucoid secretions in lungs, liver, GIT, pancreas
- Mucus plugging and secondary changes in these organs
- Bronchiectasis is common: Massively ectatic bronchi filled with viscid mucus, inflammation
- Secondary infections by *Pseudomonas aeruginosa*, aspergillosis, candidiasis common

ASTHMA

- Spasmodic diffuse airway narrowing
- Increased goblet cells in mucosa/submucosal glands
- Thickening of muscular wall and basement membrane underlying mucosal epithelial cells
- Bronchus infiltrated by lymphocytes, plasma cells, and eosinophils
- Curschmann spirals, creola bodies, Charcot-Leyden crystals in sputum

Diaphragmatic lesions

DIAPHRAGMATIC HERNIA

- Left sided more common
- Herniation of abdominal contents in thoracic cavity
- Hypoplasia of lungs
- Associated anomalies: Trisomy 18 and 21, TEF, CPAM, pulmonary hypoplasia, extralobar sequestration, TOF, ectopia cordis

DIAPHRAGMATIC EVENTRATION

- Thorax markedly reduced in size due to elevation of diaphragm (abdominal contents protruded upward)
- Aplasia/hypoplasia of muscle between diaphragm leaflets
- Diaphragm consists of thin thoracic/abdominal mesothelium with few strands of muscle in between

Pulmonary tumors

- Primary pulmonary tumors rare in children
- Metastatic tumors are common

BENIGN TUMORS

Inflammatory pseudotumor/myofibroblastic tumor

- Circumscribed, interlacing fascicles of spindle-shaped myofibroblasts separated by plasma cells/lymphocytes
- Osteoid focus may be present
- ALK rearrangements in some
- ALK and myofibroblastic markers (SMA, desmin) positive

Chondromatous hamartoma

- Irregular lobules of cartilage, vascularized adipose tissue, fibrous tissue
- May be part of Carney triad (pulmonary chondroma, GIST, extra-adrenal paraganglioma)

Juvenile laryngotracheal papillomatosis

- Larynx/trachea, disseminates to lungs
- Papillomatous nodules of squamoid tumor, koilocytic changes
- HPV6+, HPV11+

Sclerosing hemangioma

- Peripheral solitary tumor composed of surface cells (lining papillae) and round cells (within papillary cores)
- Immunoreactive for TTF1 and EMA

Granular cell myoblastoma

- Cellular tumor, endobronchial in location
- Large uniform cells, abundant granular cytoplasm
- Positive for S100

Sugar tumor

- Also known as PEComa (perivascular epithelioid cell tumor)
- Cells with clear cytoplasm rich in glycogen
- Immunoreactive for HMB45 and Melan-A
- Negative for cytokeratin

MALIGNANT TUMORS

- Most common are metastatic tumors, especially metastatic osteosarcoma

Bronchial carcinoid

- Most common pulmonary malignant tumor in children
- Arises from bronchial neuroendocrine cells
- Cords/nests/trabeculae of uniform cells with round nuclei, finely granular cytoplasm, separated into discrete bundles by delicate vascular septa
- Positive for chromogranin, synaptophysin
- Good prognosis with surgical resection

Bronchial mucoepidermoid carcinoma

- Arises from bronchial minor salivary glands
- Epidermoid/intermediate cells admixed with mucinous cells, arranged in sheets/glands

Adenoid cystic carcinoma

- Arises from bronchial minor salivary glands
- Accumulation of mucin/hyaline material in tumor cell clusters, cribriform pattern

Bronchioloalveolar carcinoma

- Non-invasive peripheral tumor nodule
- Dilated alveoli filled with mucin and clusters of tumor cells
- Alveolar septa lined by columnar epithelial cells, irregular basal nuclei, and apical mucin

Bronchogenic carcinoma

- Adenocarcinoma and undifferentiated carcinoma
- Invasive, poor prognosis
- Primary or second tumors after treatment of Hodgkin lymphoma/Ewing sarcoma

Sarcomas

- Malignant fibrous histiocytoma
- Malignant peripheral nerve sheath tumor (MPNST), leiomyosarcoma, fibrosarcoma

Synovial sarcoma

- Monophasic or biphasic
- Immunoreactive for EMA, CD99, BCL2, CD34, translocation
- t(X;18)

Embryonal/alveolar rhabdomyosarcoma

- Muscle markers desmin+, myogenin+ myoglobin+, MyoD1+

Pleuropulmonary blastoma

- Very young children (under 6 years old)
- Rare embryonic tumor
- Family history of childhood tumors common
- Germline loss of function of *DICER1* mutations in familial pleuropulmonary blastoma syndrome

Type I (cystic)

- Large air-filled cyst resembling type 4—CPAM
- Cyst wall lined by interrupted cuboidal/columnar epithelial cells, overlying fibromuscular stroma
- Dense cambium layer of malignant rhabdomyoblasts (tumor cells beneath epithelial lining)
- Positive for MyoD1, myogenin, myoglobin, and desmin
- Loss of *DICER1* staining in epithelium

Type II (both solid/cystic)

- Cyst lined by cuboidal epithelium
- Solid areas contain blastomatous islands of primitive mesenchymal cells of RMS, chondrosarcoma/undifferentiated sarcomas

Type III (solid)

- Multilobulated mass attached to pleura
- Diffuse hemorrhage and necrosis

- Immature blastemal/mesenchymal components, immature cartilage

Midline poorly differentiated carcinoma

- NUT translocation: t(15;19)(q14;p13.1)
- Very aggressive tumors

Selected pediatric nasopharyngeal tumors

ANGIOFIBROMA

- Nasal obstruction, epistaxis
- Adolescent males; androgen dependent
- Admixture of thin-walled blood vessels in a fibrous background with stellate fibroblasts
- Cells are positive for beta-catenin (nuclear) and CD117 (cytoplasmic)
- Benign neoplasm

NASOPHARYNGEAL CARCINOMA

- Adolescent males, common in southern China
- Malignant neoplasm that metastasizes to unilateral lymph nodes
- Related to Epstein-Barr virus (EBV)
- Neoplastic epithelial cell (nests or singly dispersed) surrounded by a diffuse infiltrate of reactive lymphocytes
- Poor prognosis, radiosensitive

26 Salivary Glands

Anatomy and embryology

- Major salivary glands (submandibular, sublingual, and parotid)
- Minor salivary glands located in submucosa of cheeks, lips, palate
- Development begins between gestational age 5 and 8 weeks
- Derived from ectodermal lining of branchial clefts
- Salivary glands comprised of acinar and ductal structures
- Sublingual glands have mainly mucinous acini
- Parotid and submandibular glands have mainly serous acini

Congenital anomalies

HYPOPLASIA/AGENESIS

- Oculoauriculovertebral syndrome (Goldenhar syndrome)
- Cleft palate associated
- Mandibulofacial dysostosis → xerostomia, periodontal abscess

PALATAL CYSTS

- Inclusion cysts lined by squamous epithelium, keratinized

POLYCYSTIC SALIVARY GLAND DISEASE

- Salivary gland tissue replaced by epithelial cysts of ductal origin
- Lobular architecture retained

HETEROTOPIAS

- Head and neck region
- Acini with/without ducts

BRANCHIAL CLEFT ANOMALIES

- May be located in region of parotid glands

Infections

VIRAL INFECTIONS

- Mumps, cytomegalovirus (CMV), Coxsackie A virus
- Periductal lymphoplasmacytic infiltrate, acinar degeneration, viral inclusions
- HIV lymphadenitis (lymphoepithelial lesions)

GRANULOMATOUS INFECTIONS

- Atypical mycobacterial infections, toxoplasmosis, cat scratch disease

Inflammatory disorders

JUVENILE RECURRENT PAROTITIS

- Cystically dilated intraglandular ducts
- Lymphocytic infiltrate, lymphoid follicles

CHRONIC SIALADENITIS

- Autoimmune in origin (usually)

SIALOLITHIASIS

- Painful swelling of salivary glands while eating

- Ductal foreign bodies, stasis and mucus impaction
- Leads to sialadenitis

MUCOCELE OF SALIVARY GLANDS (RANULA)

- Oral mucus cyst, lower lip common site
- Common lesions, sublingual/submandibular and minor salivary glands

Extravasation type

- Duct disruption, dilated duct wall, absent/attenuated epithelial lining
- Collection of mucus and foamy macrophages
- Periductal fibrosis/granulation tissue
- Simple ranula: Confined to floor of the mouth, blue dome cyst
- Plunging ranula: Cervical extension, extravasation mucocele in which mucus extends up to the level of hyoid bone in neck

Retention type

- Mucus cyst formed due to occluded salivary gland duct orifice

Tumors

INFANTILE HEMANGIOMA

- Intralobular capillary proliferation
- Lobular architecture of gland preserved
- Involution after infancy
- Located in parotid gland mostly

LYMPHATIC MALFORMATION

- Intralobular proliferation of lymphatic channels
- Lobular architecture preserved
- Lesion does not involute over time
- Located in parotid gland mostly

SALIVARY GLAND ANLAGE TUMOR (SGAT)

- Also known as congenital pleomorphic adenoma of nasopharynx
- Newborn infants, respiratory distress, feeding difficulty, bleeding from nose/mouth
- Nests and cords of squamous cells (cytokeratin positive) in a background of stromal nodules (myoepithelial cells, positive for actin)
- Excision is curative

SIALOBLASTOMA

- Infancy
- Parotid and submandibular glands
- Embryonal tumor (low grade)
- Primitive epithelial cell nests surrounded by loose stroma
- Embedded duct-like structures (positive for cytokeratin)
- Spindled myoepithelial cells (S100 and actin positive)
- Local recurrence, no distant metastasis

PLEOMORPHIC ADENOMA (MIXED TUMOR)

- Benign tumor of parotid gland
- Age group: 10–15 years
- Well-circumscribed, partially encapsulated
- Epithelial/myoepithelial cells, fibromyxoid/cartilaginous stroma
- *PLAGI* gene involvement
- Ductal cells positive for cytokeratin (CK), epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA)
- Myoepithelial cells positive for SMA and S100

MUCOEPIDERMOID CARCINOMA

- Most common malignant tumor of salivary glands in children
- Age group: 10–15 years
- Located in parotid gland frequently
- May occur secondary to cranial irradiation
- Epidermoid, mucus-secreting, and intermediate cells (positive for CK stain)
- *MECT1/MAML2* genetic translocations

ACINIC CELL TUMOR

- Malignant neoplasm, solid/cystic
- Predominantly acinar cells (large polygonal cells with basophilic cytoplasm, bland nucleus, DPAS+ granules) forming follicular pattern
- Clear cells, intercalated duct-type cells
- Less common in children

ADENOID CYSTIC CARCINOMA

- Malignant neoplasm
- Tubular, cribriform, and solid architectural pattern
- Basaloid and myoepithelial cells
- Pseudoglandular spaces, true glandular lumina, and perineural invasion
- Myxoid stroma, PAS+ excess basement membrane material
- Less common in children

RHABDOMYOSARCOMA

- May involve salivary gland during childhood

27 Gastrointestinal System

Embryology

- Gastrointestinal tract derived from endoderm germ layer
- Vitelline/omphalomesenteric duct; connection between midgut and yolk sac
- 4 weeks of intrauterine life: Midgut and yolk sac widely connected
- 10 weeks: Connection between lumen of midgut and umbilicus completely obliterated
- 4 weeks: Laryngotracheal diverticulum develops from foregut
- Esophagotracheal septum divides esophagus dorsally from trachea ventrally
- 8 weeks: Rapid elongation of intestines and physiological hernia of the intestines (occurs in umbilical cord)
- Physiological hernia resolves at 12 weeks
- If hernia does not resolve, omphalocele and malrotation
- At 6 weeks, uro-rectal septum divides cloaca into urogenital sinus ventrally and rectum/anus dorsally

Esophagus

CONGENITAL ABNORMALITIES

Inlet patch

- Heterotopic gastric mucosa
- Can be colonized by *Helicobacter pylori*

Duplication

- Separate cylindrical tube adjacent to esophagus (double esophagus)
- Or an esophageal duplication cyst in wall of esophagus with sharing of muscularis propria
- Mucosal lining of stratified squamous/columnar epithelium in both
- Esophageal cyst (two layered muscularis propria in wall)

Enteric cyst

- Lined by gastric/small intestinal mucosa
- Posterior mediastinum, associated with cervical hemivertebra
- If it extends posteriorly into spinal canal = neurenteric cyst

Esophageal atresia and tracheoesophageal fistula

- VATER or VACTERL associations
- Most common type is esophageal atresia with distal tracheoesophageal fistula (<0.5 cm in diameter)
- Coughing/choking during feeding, aspiration pneumonia

Esophageal stenosis

- Caused by webs, membranes, GERD, epidermolysis bullosa

ACQUIRED DISEASES

Gastroesophageal reflux disease (GERD)

- Physiologic GERD during initial months of life; due to immaturity of lower esophageal sphincter/peristalsis
- Persistent GERD; failure to thrive, irritability, regurgitation, gastrointestinal blood loss
- Esophageal mucosa: basal cell hyperplasia, lengthening of papillae, spongiosis, intraepithelial lymphocytes, eosinophils and neutrophils
- Long-term sequelae: Ulcers, bleeding, esophageal strictures, Barrett esophagus
- Treatment with proton pump inhibitors

Barrett esophagus

- Metaplastic condition due to GERD
- Squamous mucosa of esophagus replaced by specialized columnar epithelium with goblet cells (intestinal type)
- Alcian blue (PH 2.5) stains intestinal-type acid mucins with blue color
- Long-term sequelae-dysplasia and adenocarcinoma (very rare)

Eosinophilic esophagitis

- Reaction to ingested or inhaled allergens
- Esophageal mucosa: >15 eosinophils per high-power field, diffuse basal cell hyperplasia, eosinophilic microabscesses
- Findings are of equal intensity in distal and mid-esophagus
- Gastric cardia usually not inflamed (differential from reflux esophagitis)
- Treated with elimination diet, steroids

Infectious esophagitis

- Debilitated, immunosuppressed, premature, or hospitalized children

Herpes simplex esophagitis

- Odynophagia, gingivostomatitis
- Necrotizing esophagitis, neutrophilic infiltrate, ulceration, multinucleated cells
- Squamous cells have intranuclear inclusions (Cowdry type I and II)

Candida esophagitis

- White plaques and ulcerations
- Pseudohyphae, yeast, inflammatory debris, and fibrin

Cytomegalovirus esophagitis

- Part of systemic cytomegalovirus (CMV) infection mostly
- The virus does not infect squamous cells (d/d HSV)

Stomach

CONGENITAL ABNORMALITIES

Hypertrophic pyloric stenosis

- 2–6 weeks of age, white infant boys
- Projectile non-bilious vomiting due to gastric outlet obstruction
- Barium studies; elongated pyloric channel (string sign)
- Hypertrophic, elongated circular muscle layer of muscularis propria in gastric pyloric antrum
- Treated surgically with pyloromyotomy

Gastric duplication

- Cystic mass at greater curvature of antrum
- Gastric-/enteric-type mucosa
- Complications: Bleeding, obstruction, or rupture

Pancreatic heterotopias

- Intramural mass, may be incidental
- Pancreatic acini and ducts identified

ACQUIRED DISEASES

Spontaneous perforation

- Premature, sick neonates
- Ischemic/traumatic in origin
- Abdominal distension and pneumoperitoneum

Gastritis

Hemorrhagic and ischemic gastritis

- Drugs (NSAIDS, corticosteroids, aspirin, alcohol)
- Corrosive chemicals, stress, ischemia
- Mucosal edema and hemorrhage

Helicobacter pylori gastritis

- Mainly antral gastritis
- Small, rod-shaped, curved, Gram-negative bacteria
- Positive for Giemsa, Warthin-Starry, immunoperoxidase stains
- Lymphoid follicles with germinal centers, neutrophilic infiltrate, increased clustering of plasma cells
- Long-term sequelae: Risk of adenocarcinoma and lymphoma of stomach (MALT)

Lymphocytic gastritis

- Increased number of lymphocytes in gastric foveolar or glandular epithelium; >25 lymphocyte/100 epithelial cells
- Celiac disease, *H. pylori* infection

Helicobacter heilmannii gastritis

- Clinical and morphological features mimic *H. pylori*
- Organism larger than *H. pylori* and spiral
- Less serious and less chronic infection than *H. pylori*

Peptic ulcer disease

- Acute (stress) and chronic (*H. pylori*) ulcers
- Chronic ulcers seen in stomach and duodenum
- Associated with antral gastritis and *H. pylori* organisms
- *H. pylori* may cause duodenal ulcers and active duodenitis
- Organisms never identified in duodenum unless there is gastric metaplasia of duodenum

Menetrier disease

- In children, mostly self-limited and caused by CMV infection
- Abdominal pain, weight loss, peripheral edema
- Protein loss from stomach and hypoalbuminemia
- Imaging and endoscopy: Giant gastric folds of corpus, antral sparing
- Elongated and tortuous foveolae, mucus cell hyperplasia, cysts lined by mucus cells, inflammation, CMV inclusions

Eosinophilic gastroenteritis

- Allergies, increased serum IgE levels
- Gastric antrum and proximal small bowel most involved
- Diffuse/patchy eosinophilic inflammatory infiltrate in lamina propria, muscularis mucosae, surface/glandular epithelium, may be transmural
- No ulceration or architectural distortion of glands
- Fleeting symptoms
- Treated with steroids

Crohn disease of stomach

- Focal active gastritis, cryptitis
- Patchy infiltrate of chronic inflammatory cells, granulomas

Granulomatous gastritis

- Differential diagnosis: Crohn disease, chronic granulomatous disease, tuberculosis, fungal infection, sarcoidosis

POLYPS/TUMORS OF STOMACH

Fundic gland polyp

- Associated with intake of proton pump inhibitors for reflux, familial adenomatous polyposis
- Oxyntic mucosa of proximal stomach
- Dilated fundic glands lined by chief and parietal cells, no inflammation, no edema

Hyperplastic polyp

- *H. pylori* infection

Peutz-Jeghers polyps

- Part of generalized tumor syndrome
- Hamartomatous polyps with hyperplasia and splaying of smooth muscle in lamina propria

Miscellaneous

- Gastric teratoma and heterotopic pancreatic tissue (same features as in other sites)

MALIGNANT TUMORS

Gastrointestinal stromal tumors (GISTs)

- Stomach is most common location
- Sporadic or syndromic
- Carney triad; paragangliomas, pulmonary chondromas, and stomach GISTs
- Association with neurofibromatosis
- *KIT* or *PDGFRA* gene mutations are more common in adults
- Originate from interstitial cells of Cajal
- Spindle cell/epithelioid morphology, prominent cytoplasmic vacuolations
- C-kit immunopositivity in most tumors

Miscellaneous

- Malt lymphoma and Burkitt lymphoma (same features as other sites)

Small and large intestine

CONGENITAL ABNORMALITIES

Omphalocele

- Mid-line defect of anterior abdominal wall
- Herniated abdominal contents in ventral membranous sac
- Abdominal musculature, fascia, and skin not formed
- Contents covered by amnion externally and parietal peritoneum internally
- Umbilicus in center of defect
- Associated other congenital anomalies; trisomy 21, Beckwith-Wiedemann syndrome

Gastroschisis

- Paraumbilical abdominal wall defect (right sided)
- No membranous sac
- Herniated abdominal viscera exposed to amniotic fluid
- No associated congenital anomalies

Malrotation

- During period of rapid growth, intestines herniate into umbilical stalk
- Intestines then return to abdominal cavity by 10–11 weeks' gestational age
- Failure of the above sequence to occur in the right manner; spectrum of malrotation anomalies

Volvulus

- Occlusion of mesenteric artery blood flow and infarction of entire midgut
- Ladd = peritoneal fibrous bands causing obstruction of colon

INTESTINAL ATRESIA AND STENOSIS

- Intrauterine vascular accidents/ischemia; resorption/occlusion/scarring of intestinal segment
- Duodenal and jejunoileal atresia more common
- Duodenal atresia associated with Down syndrome, annular pancreas, and malrotation
- Two atretic blind segments of intestine without an intervening cord, wedge-shaped mesenteric defect (most common)
- Atretic segment morphology; granulation tissue, fibrosis, calcification

DUPLICATION CYST

- Tubular/cystic structures adjacent to intestinal tube
- Located anywhere from neck to rectum
- Share muscular wall, intramural (mostly) or may be extramural
- Originate from aberrant diverticula in embryonic life
- Ileal duplication is most common; arises in mesenteric border
- Breathing difficulty, pain, obstruction, bleeding

VITELLINE DUCT ABNORMALITIES

- Persistence of vitelline duct (omphalomesenteric duct) beyond 10 weeks of gestational life
- Leads to cyst, sinus, Meckel diverticulum, or band

Meckel diverticulum

- Most common congenital anomaly of gastrointestinal tract
- Incomplete obliteration of vitelline duct, in mid-ileum
- Antimesenteric border, 1–5 cm long protrusion
- Lined by intestinal epithelium, foci of pancreatic/gastric heterotopia
- Complications: Rectal bleeding, peptic ulceration, lead point of intussusception, intestinal perforation
- Vitelline sinus causes mucoid discharge from umbilicus
- Differentiated from urachal remnants (lined by urothelium) at same site

MECONIUM AND MECONIUM ABNORMALITIES

Meconium

- Dark-green/black mucoid material in distal small bowel/colon of neonates
- Composed of water, mucus, gastrointestinal secretions, bile, vernix caseosa

Meconium ileus

- Obstruction of ileal lumen by thick, inspissated, solid, putty-like meconium
- Associated with cystic fibrosis or congenital anomalies of pancreas/pancreatic ducts
- Ileal lumen and dilated glandular lumina have hypereosinophilic calcified meconium

Meconium peritonitis

- Intestinal perforation in utero → release of meconium into peritoneal space
- Chemical peritonitis, fibrosis, calcification, meconium cyst
- Etiology: Meconium ileus, intestinal obstruction in utero due to atresia, volvulus, congenital bands, vascular insufficiency

Meconium periorchitis

- Intestinal rupture → meconium from the peritoneum migrates to paratesticular region
- In utero patency of inguinal canal to scrotum

Meconium plug

- Less serious condition but similar clinical picture as meconium ileus
- Treated with Gastrografin enema, sporadic condition

CYSTIC FIBROSIS

- White children, AR genetic disease (mutated *CFTR* gene)
- Faulty electrolyte transport across epithelial surfaces → dehydration of luminal contents
- Malabsorption due to exocrine pancreatic insufficiency
- Clinical manifestations: Meconium ileus, meconium peritonitis, small intestinal atresia, stenoses, duplication, volvulus, mesenteric bands, adhesions
- Older children = distal intestinal obstruction syndrome (inspissated fecal material)

HIRSCHSPRUNG DISEASE

- Congenital disorder, more common in white males
- Sporadic/genetic (*RET* genes)/association with Down syndrome
- Delayed passage of meconium, constipation, abdominal distension, enterocolitis

Short segment

- Most frequent, limited to rectum and distal sigmoid colon
- Aganglionic segment very narrow
- Colon proximal to aganglionic segment dilated

Ultra-short segment

- Limited to distal rectum near anal sphincter

Long segment

- Extends proximally up to splenic flexure or transverse colon

Total colonic

- Extends proximally up to cecum

Rectal suction biopsy

- Adequate submucosa, performed 2 cm above dentate line
- Absence of ganglion cells and thick hypertrophic submucosal nerve plexuses

Seromuscular rectal biopsy

- Absence of ganglion cells and hypertrophy of myenteric nerve plexuses

Histochemical stain

- Acetylcholinesterase performed on frozen sections
- Thick, ropy, acetylcholinesterase positive nerve fibers in lamina propria of aganglionic segment of colon

Immunohistochemical stain

- Calretinin performed on formalin-fixed paraffin-embedded tissue

- Absence of calretinin immunoreactive nerve fibers in lamina propria, muscularis mucosae, and submucosa of aganglionic segment of colon

CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

- Impaired/absent peristalsis without mechanical obstruction to intestinal movement
- Classified into neurogenic and myopathic types
- Primary: Disease limited to gastrointestinal tract (congenital-megacystic-microcolon-intestinal hypoperistalsis syndrome)
- Secondary: Due to systemic disease (Duchenne muscular dystrophy, connective tissue disorders)

INTESTINAL NEURONAL DYSPLASIA

- Clinically presents with constipation/bowel obstruction
- Distal colon and rectum involvement
- Giant submucosal ganglia (eight or more ganglion cells)
- Patients improve with conservative measures

Acquired disorders

INTUSSUSCEPTION

- Severe colicky abdominal pain
- Pain relieved by passage of blood/mucus per rectum
- Invagination of one portion of intestine on itself
- Starts usually at ileo-cecal valve, progressive edema, congestion, and gangrene if unrelieved
- Lead points of intussusception: Hyperplastic Peyer patches, lymphoid hyperplasia due to adenovirus infection, Burkitt lymphoma, Meckel diverticulum, duplication cysts, Peutz-Jeghers polyps
- Barium enema: Diagnostic and therapeutic in many cases
- Surgery required if no relief

GASTROINTESTINAL INFECTIONS

- Major cause of morbidity and mortality worldwide

Viral diarrhea

- Non-inflammatory watery diarrhea
- Viruses localize in small intestine and do not invade

Rotavirus *(children younger than 2 years)* ***and Norwalk virus*** *(school-age children)*

- Most prevalent
- Diagnosed by ELISA of stool samples

Enteric adenovirus

- Immunocompromised children
- Viral inclusions in nuclei
- Lymphoid hyperplasia of intestines is the lead point of intussusception

Cytomegalovirus

- Immunocompromised children
- Infect esophagus to colon
- Fulminant hemorrhagic inflammation, ulcerations
- Nuclear inclusions: Endothelial/stroma/glandular cells, but never in squamous cells

Herpes simplex virus

- Immunosuppressed children
- Esophagus; nuclear inclusions (ground glass) mostly in squamous cells, rarely glandular cells

Bacterial diarrhea

Inflammatory diarrhea

- Organism or its toxin invades intestinal mucosa (*Salmonella*, *Shigella*, *Campylobacter jejuni*, *Clostridium difficile*, *Yersinia enterocolitica*, enteroinvasive and enterohemorrhagic *Escherichia coli*)
- Diarrhea, blood/mucus in stools
- Shiga toxin or Shiga-like toxin (enterohemorrhagic strain of *E. coli* O157:H7)
  - Hemolytic uremic syndrome (platelet fibrin thrombi in small blood vessels, microangiopathic hemolytic anemia) in children

  - Thrombotic thrombocytopenic purpura in adults
  - *E. coli* O157:H7 does not ferment sorbitol
  - Detected by characteristic growth on sorbitol-MacConkey agar
- *Clostridium difficile*
  - Pseudomembranous colitis
  - Antibiotic associated (clindamycin)
  - Diagnosis: *C. difficile* toxin in stool by enzyme immunoassay
  - Treated with metronidazole, vancomycin

Non-inflammatory diarrhea

- Vibrio cholerae, enteropathogenic, and enterotoxigenic *E. coli*
- No invasion of intestines by organism or toxin
- Watery diarrhea, no neutrophils or blood in stools

Protozoal infections

Giardia lamblia

- Children with IgA deficiency
- Diarrhea and malabsorption in children
- Duodenal biopsy: Trophozoites on enterocyte surface/mucous coat
- Trophozoites: 16 µ, highlighted by trichrome or CD117 immunostain

Cryptosporidium

- Chronic watery diarrhea in patients with AIDS
- Oocysts: round basophilic structures (3–4 µ) on epithelial cell surface (small/large intestine)
- Visible on hematoxylin and eosin (H&E), Giemsa, and acid-fast stain

Entamoeba histolytica

- Third-world countries
- Invades colonic wall, acute inflammatory reaction, flask-shaped necrotic ulcers, systemic amoebiasis
- Trophozoites resemble histiocytes, pale nucleus, ingested red blood cells in cytoplasm

Fungal diseases

- Aspergillosis, zygomycosis, and candidiasis
- Immunocompromised/debilitated children
- Fungal septicemia

Malabsorption

- Clinical manifestations: Failure of growth, bulky diarrheal stools, vitamin/iron deficiencies, edema, hypoalbuminemia

GASTROENTERITIS AND POSTENTERITIS ENTEROPATHY

- Persistence of malabsorption after infection of gastrointestinal tract
- Mostly self-limited

CELIAC DISEASE

- Gluten-sensitive enteropathy
- Positive anti-tissue transglutaminase test
- More common in children with autoimmune diseases, juvenile-onset diabetes mellitus, dermatitis herpetiformis, Down syndrome, IgA deficiency
- HLA-DQ2 and HLA-DQ8 allele
- Alpha-gliadin within gluten containing food (wheat, barley, rye) injures enterocytes, infiltration by T lymphocytes
- Correlation of histologic findings with panel of serological tests; anti-TTG (most specific), antiendomysial, and antigliadin antibody
- Villous blunting, crypt hyperplasia, increased mitotic figures in crypts, increased intraepithelial lymphocytes in surface epithelium (increase of 30 lymphocytes/100 epithelial cells)
- Increased lamina propria infiltrate of lymphocytes and plasma cells
- CD3 immunostain highlights T lymphocytes in surface epithelium
- Modified Marsh classification (types 0–3)
- Relapse when strict gluten-free dietary restrictions not followed
- Long-term complication: Intestinal lymphoma (T-cell type)

Note: Please refer to the new classification system (Corazza and Villanacci) in the Appendix.

ENTEROPATHY INDUCED BY COW'S MILK PROTEINS

- Bottle-fed infants, allergic to cow's milk protein, soy, or formula protein (casein hydrolysate)
- Vomiting, diarrhea, failure to thrive
- Intestinal biopsy: Patchy, eosinophilic infiltrate (>60 eosinophils/40× field) patchy
- Invade epithelium/muscularis mucosae
- Self-limited, resolves by 1 year of age

INTESTINAL LYMPHANGIECTASIA

- Small intestine biopsy: Dilated lymphatics in lamina propria/superficial submucosa
- Protein losing enteropathy
- Etiology: Extra-intestinal lymphatic malformation or due to lymphatic obstruction

IMMUNODEFICIENCY

- Selective IgA deficiency, common variable immunodeficiency, AIDS
- Villous atrophy, inflammation, absent plasma cells in lamina propria

IPEX

- Immune dysregulation, polyendocrinopathy, enteropathy, X-linkage
- Mutation in *FOXP3* gene
- Duodenal morphology resembles autoimmune enteropathy
- Fatal without stem cell transplantation

Autoimmune enteropathy

- Associated with other autoimmune diseases
- Histology similar to celiac disease
- Serum has antibodies against enterocyte/goblet cell antigens

SHORT BOWEL SYNDROME AND BACTERIAL OVERGROWTH

- Extensive surgical resection of intestine
- Malabsorption due to short segment of remaining intestine (<50 cm in neonates)
- Less transit time and inadequate surface area for absorption
- Bacterial overgrowth
- Treated with intravenous alimentation, small-bowel transplant

ABETALIPOPROTEINEMIA

- Autosomal recessive metabolic disease
- Defective formation and transportation of low-density lipoprotein
- Surface epithelial cells in small bowel mucosa; distended with lipid
- Lipid can be absorbed but not transported out of cells
- Extra-intestinal manifestations: Red cell acanthocytosis, retinitis pigmentosa, neuromuscular degeneration

MICROVILLUS INCLUSION DISEASE

- Severe diarrhea in perinatal life
- Lethal disease without small bowel transplantation
- Small intestine has atrophic mucosa with villous blunting, crypt hypoplasia, no inflammation, and vacuolated surface epithelial cells
- *EM*: Surface enterocytes contain intracytoplasmic inclusions, shortened/absent microvilli
- Inclusions are PAS+ diastase resistant and CD10+

TUFTING ENTEROPATHY

- Disorganization of surface epithelium; crowding, tufting, shedding
- Decreased expression of epithelial cell adhesion molecule

GRAFT-VERSUS-HOST DISEASE (GVHD)

- Intestinal tract, skin, and liver affected by GVHD
- Donor T lymphocytes (when transfused in immunosuppressed host); set up an immune response and destroy epithelial cells of host
- Post-bone marrow/stem cells transplant and posttransfusion of non-irradiated blood
- Profuse watery diarrhea, vomiting, anorexia
- Patchy changes, epithelial cell apoptosis, sparse inflammatory infiltrate
- If untreated, extensive glandular destruction/mucosal denudation

- Mimics morphological changes of chemotherapy, CMV infection, and drug mycophenolate (mofetil)

HENOCH-SCHÖNLEIN PURPURA

- Systemic vasculitis affecting skin, gastrointestinal tract, joints, kidneys
- Leukocytoclastic vasculitis in lamina propria and submucosa
- Abdominal pain and bleeding

COLITIS

Inflammatory bowel disease (IBD)

- Second decade of life
- Intestinal infections should be ruled out; appropriate cultures/stool examination

Ulcerative colitis (UC)

- Chronic inflammatory bowel disease
- Begins in rectum and extends proximally and contiguously
- Diarrhea, rectal bleeding, abdominal pain, anorexia, weight loss
- Toxic megacolon, acute fulminant colitis
- Inflammation limited to mucosa/submucosa
- Basal lymphoplasmacytosis in lamina propria, neutrophilic cryptitis, crypt abscesses, mucosal ulceration, inflammatory pseudopolyps
- Chronic changes: Crypt architectural distortion, crypt shortening, Paneth cell metaplasia
- Long-standing disease complication: Epithelial dysplasia and risk of adenocarcinoma colon
- Extra-intestinal manifestations: Uveitis, large joint arthritis, sclerosing cholangitis in liver, growth failure
- Monitored with periodic biopsies
- Treated with immunosuppressives, total proctocolectomy with sphincter-sparing ileal reservoir (ileal pouch)

Crohn disease

- Classically involves distal ileum and proximal colon
- May occur anywhere from mouth to anus
- Clinical symptoms and signs more insidious than UC; diarrhea, vague abdominal pains, rectal bleeding, growth failure
- Acute and chronic inflammatory cells in lamina propria, neutrophilic cryptitis, crypt abscesses, epithelioid non-caseating granulomas
- Segmental/skip pattern of involvement, transmural inflammation, fissures, fistulas, fibrosis, ileocecal mass, rectal-perineal fistulas
- Less chronic changes compared to UC
- Treatment with immunosuppressives, anti-tumor necrosis factor monoclonal antibody
- Surgery not very effective

Indeterminate colitis

- Temporary designation when impossible to differentiate between Crohn disease or UC (up to a quarter of cases of IBD)
- With disease evolution, more diagnostic distinguishing features may develop

Lymphocytic colitis

- Watery diarrhea, no endoscopic findings
- Associated with autoimmune disease (diabetes mellitus and arthritis)
- Increased T lymphocytes in surface epithelium/lamina propria, surface epithelial damage, no crypt architectural distortion

Collagenous colitis

- Similar morphology/pathogenesis as lymphocytic colitis
- Thickened basement membrane (>10 μ collagenous band) under surface epithelium

Acute self-limited colitis

- Infectious colitis
- Sudden onset of bloody diarrhea, resolves spontaneously after several weeks
- Bacterial infection usually
- No architectural distortion/no basal lymphoplasmacytosis

Pseudomembranous colitis

- Gross/endoscopic; discrete yellow plaques/confluent membranes tightly adherent to mucosa

- Antibiotic (clindamycin)-associated *C. difficile* infection
- Erupting volcano appearance
- Pseudomembrane; desquamated epithelial cells, inflammatory cells, red blood cells, mucus and fibrin
- Diagnosis: *C. difficile* toxin assay

Diversion colitis

- Intestinal segment that is bypassed due to ileostomy/colostomy and left in place
- Chronic inflammation, alteration of bacterial flora in this segment
- Deficiency of short-chain fatty acids in the bypassed segment

Typhlitis (neutropenic enterocolitis)

- Necrotizing enterocolitis limited to cecum
- Children with severe immunosuppression

Neonatal necrotizing enterocolitis

- Severely ill, low birth weight, premature children
- Small and large bowel; coagulative/hemorrhagic necrosis, inflammation
- Superimposed bacterial colonization, pneumatosis intestinalis (gas within bowel wall)
- Terminal ileum, cecum, and ascending colon most involved
- Affected intestinal segments develop fibrosis/stricture
- Etiology: Enteral formula feedings, immature intestinal circulatory regulation

Spontaneous perforation of gastrointestinal tract

- Drug-induced local ischemia
- Defective atretic intestinal segment/lack of muscularis propria in wall

Allergic colitis

- Rectal bleeding in infants
- Allergy to cow's milk protein in artificial formulas/other dietary proteins
- Increased patchy/diffuse infiltrates of eosinophils in lamina propria, epithelium, muscularis mucosae
- Treated with elimination diet

Intestinal neoplasms

- Mostly benign (juvenile and Peutz-Jeghers polyps)
- Malignant (Burkitt lymphoma)

POLYPS

- Hereditary syndromes should be considered
- Higher risk of gastrointestinal/other malignancies

Juvenile polyposis and juvenile polyposis syndrome

- AD disorder, sometimes sporadic
- Multiple hamartomatous gastrointestinal polyps
- Colonic and gastric
- Hyperplasia and cystic dilatation of crypts, edematous and inflamed stroma, surface erosion, granulation tissue
- Increased risk of malignancy of gastrointestinal tract/pancreas

PTEN hamartoma tumor syndrome

- AD disorder
- Mutation of *PTEN* tumor suppressor gene on chromosome 10
- Gastrointestinal polyps resemble juvenile polyps

Cowden syndrome

- Multiple hamartomas involving various organs
- Mucocutaneous lesions, increased risk of malignancy of breast/thyroid/endometrium

Bannayan-Riley-Ruvalcaba syndrome

- Pigmentad penile macules, lipomas, macrocephaly
- Gastrointestinal hamartomas

Peutz-Jeghers polyposis syndrome

- AD disorder
- Mucocutaneous hyperpigmentation, hamartomatous polyps in gastrointestinal tract (small bowel commonly)
- Malignancy in other organs

- Polyp contains disorganized/hyperplastic epithelial glands, central core of arborizing haphazard smooth muscle bundles

Adenomatous polyps

- True neoplasms
- Adenomatous polyposis coli syndrome (most common polyposis, AD disorder)
- Numerous mucosal polyps in colon and increased risk for adenocarcinoma
- May be sporadic or familial (familial adenomatous polyposis)
- Tubular/villous growth pattern, dysplasia (crowded glands, nuclear stratification and hyperchromasia, cribriform epithelial hyperplasia)
- Cytologic dysplasia (elongated, stratified, irregular nuclei, hyperchromasia)
- Gastric fundic gland polyp may be associated
- Congenital hypertrophy of retinal pigment, increase risk of other extra-intestinal malignancies

Turcot syndrome

- Familial
- Adenomatous polyposis and malignancy of central nervous system (glioblastoma or medulloblastoma)

STROMAL TUMORS

Spindle cell tumors

- *Smooth muscle tumors*: EBV positive, immunocompromised children
- *Inflammatory fibroid polyp*: Bland fascicles of spindle-shaped cells, mixed inflammatory infiltrate (eosinophil rich), mutation in *PDGFRA* gene
- *Ganglioneuroma*: Neural immunohistochemical markers

CYSTS

Mesenteric cyst/omental cysts

- Arise from mesentery/omentum
- Benign, no connection to bowel wall

Cystic lymphangioma

- Lined by endothelial cells
- Lymphoid tissue and smooth muscle in wall
- Connected to bowel wall and mesentery

MALIGNANT TUMORS

Lymphoma

Burkitt lymphoma

- Non-Hodgkin lymphoma
- More common in boys
- Arises in submucosal lymphoid tissue, ileocecal region
- Transmural spread, mesenteric lymph nodes involved
- Sheets of lymphoblasts, round/regular noncleaved nuclei, starry-sky pattern
- B-cell immunophenotype
- t(8;14)
- Good prognosis with appropriate surgery/chemotherapy

Posttransplant lymphoproliferative disease

- Develops after solid organ/bone marrow transplant

Langerhans cell histiocytosis

- Mucosal infiltrate, any portion of gastrointestinal tract may be affected
- Histiocytes with grooved nuclei
- Positive for S100 and CD1a

Systemic mastocytosis

- Mutation in *c-Kit* gene
- Dense infiltrate of bland mast cells in lamina propria, increased eosinophils
- Mast cells positive for CD117, Giemsa, toluidine blue

Adenocarcinomas

- Sporadic or syndromic (polyposis coli, juvenile polyposis, Lynch syndrome)
- Associated with ulcerative colitis
- Right-sided colon, poorly differentiated, signet-ring variety

Malignant mesothelioma

- Rare tumor in children
- Association with heavy asbestos exposure
- Peritoneum/pleura

- Plaques/nodules on visceral/parietal peritoneum, ascites
- Mesothelial cells arranged in tubular, papillary, solid architecture, psammoma bodies
- Stain positively for CK5/6, calretinin, WT1
- Negative for CEA

Appendix

NORMAL ANATOMY AND HISTOLOGY

- Gross anatomy and histology resemble intestines

CONGENITAL AND MISCELLANEOUS DISORDERS

- Diverticula in cystic fibrosis
- *Intussusception*: Adenovirus infection, endometriosis, tumor, cystic fibrosis
- Cystic fibrosis, Crohn disease, ulcerative colitis
- *Appendiceal neuroma*: Disorganized proliferation of neural tissue in wall

ACUTE APPENDICITIS

- Common emergent cause of surgery
- In 15% of appendices, no acute inflammation identified after surgery
- Etiology: Obstruction of lumen (fecalith, lymphoid hyperplasia), viral/bacterial infection, local ischemia
- Neutrophilic mucosal infiltrates, focal ulceration
- In severe cases, transmural necrosis, perforation

INTERVAL APPENDECTOMY

- When appendectomy is delayed by 4–8 weeks in patients with perforation/abscess
- In this interval, patients are stabilized/treated conservatively with rest/antibiotics

UNUSUAL INFECTIONS OF APPENDIX

- Measles virus (Warthin-Finkeldey cells/lymphoid hyperplasia)
- Adenovirus (intranuclear inclusions)
- *Enterobius vermicularis* (pinworm)

APPENDICEAL CARCINOID TUMORS

- Location on tip of appendix
- Well-circumscribed, small, yellow nodule
- In submucosa but may invade the wall
- Bland tumor cells, trabecular/insular pattern
- Prognostic features: Depth of invasion, angiolymphatic invasion, size
- Positive staining for synaptophysin, chromogranin, CDX2
- Negative staining for CK7
- Appendectomy with negative margins is curative (if tumor size <2 cm)
- Right hemicolectomy to avoid risk of distant metastasis (if tumor size >2 cm)

Anus

CONGENITAL ABNORMALITIES

- Imperforate anus, atresia of rectum, recto-urethral fistula, persistent cloaca
- *Anorectal anomalies*: Association with VATER, VACTERL, or caudal regression syndrome

ACQUIRED DISEASES

Condyloma acuminata

- Human papillomavirus (HPV 6 and 11)
- May indicate sexual abuse in prepubertal children

Perianal abscess

- *Risk factors*: Leukemia, Crohn disease, immunodeficiency states
- Treated with incision/drainage or surgical resection

Fistulas

High anomalies

- Recto-vaginal and recto-urethral fistulas

28 Liver Biliary System and Gallbladder

Development

- Hepatobiliary system development in first 10 weeks of gestation
- Hepatic diverticulum arises from foregut endoderm
- Diverticulum differentiates cranially into cords of hepatocytes, and caudally into extrahepatic bile ducts/gallbladder
- Right lobe of liver supplied by portal vein
- Left lobe supplied by left umbilical vein
- Liver is dominant site of erythropoiesis from week 12 to third trimester, after which bone marrow takes over

Histology

- Ductal plate in fetal liver formed by collar of epithelial cells at periphery of portal tract and abuts against zone I hepatocytes

CONVENTIONAL HEPATIC LOBULE

- Center—Central vein
- Periphery—Portal tract

NEW (ACINAR) FUNCTIONAL UNIT

- Central portal tract surrounded by concentric zones of hepatocytes (I, II, and III)
- Most peripheral zone (zone III) lying near central vein

Congenital anomalies

- *Agenesis* of right lobe
- Bilaterally symmetrical in *asplenia-polysplenia syndrome*
- Liver is congested, hemorrhagic, and necrotic in *diaphragmatic hernia* and *omphalocele*
- Liver *heterotopia* has same risk of viral hepatitis as orthotopic liver tissue

Liver biopsy triaging

- Core/wedge biopsies triaged to give optimum diagnosis
  - *FFPE*: Histomorphology
  - *Frozen tissue*: (–70° Celsius) molecular/genetic studies and detection of enzymes for metabolic/mitochondrial diseases
  - *Fresh tissue*: Viral and microbiologic cultures, polymerase chain reaction (PCR)
  - *Glutaraldehyde fixed*: EM

Physiologic jaundice

- 15% newborns develop jaundice
- Usually physiological jaundice with unconjugated hyperbilirubinemia (resolves within 2 weeks)
- If direct hyperbilirubinemia (>2 mg/dL); always pathological

Hereditary hyperbilirubinemias

CRIGLER-NAJJAR SYNDROME

- AR
- Unconjugated hyperbilirubinemia
- Deficiency/absence of glucuronyl transferase
- Severe jaundice in type I

GILBERT SYNDROME

- Benign condition with mild clinical symptoms

DUBIN-JOHNSON SYNDROME

- AR
- Conjugated and unconjugated hyperbilirubinemia

- Severe cholestasis
- *ABCC2* gene mutation

ROTOR SYNDROME

- Elevated urinary coproporphyrin

Congenital/acquired cholestatic disorders in newborn/infant

IDIOPATHIC NEONATAL HEPATITIS

- Males > females
- Low birth weight, jaundice first week, good outcome in two thirds of cases
- Mild inflammation, mild fibrosis
- Cholestasis in hepatocytes/canaliculi
- Diagnosis of exclusion

EXTRAHEPATIC BILIARY ATRESIA (EHBA)

- Conjugated hyperbilirubinemia in neonate/young infant
- Sclerotic-inflammatory process resulting in obstruction of part/entire extrahepatic biliary tree
- Most frequent indication for liver transplant in children
- Etiology unknown; hypothesis-viral/toxic/immune/malformative
- Treatment: Biliary drainage (Kasai portoenterostomy) crucial before 60 days of age
- Untreated, cirrhosis develops in <6 months
- Portal expansion with fibrosis and inflammation
- Bile duct/ductular proliferation, bile stasis in bile ducts, bridging fibrosis/cirrhosis
- CBD (common bile duct) shows fibrosis and pinpoint lumina
- Depleted epithelial lining, epithelial nests in duct walls
- Gallbladder may be diminutive/fibrosed

SYNDROMIC BILE DUCT PAUCITY: ALAGILLE SYNDROME

- Autosomal dominant
- Mutation in chromosome 20p12 (*JAG1* gene)
- *NOTCH2* mutations identified in small subset of patients
- Patients have prominent renal manifestations
- Diagnosis made when ratio of bile duct/portal tract is = 0.5 (normal BD/PT ratio = 0.9–2.0)
- Characteristic facial features: Triangular face, prominent forehead, deep-set eyes, hypertelorism
- Cardiac murmur, ocular posterior embryotoxon, and butterfly vertebrae
- Clinical features due to liver disease: Neonatal jaundice in most, persistent jaundice, hepatosplenomegaly, increased serum bilirubin, portal hypertension, hepatic failure
- Paucity of interlobular bile ducts
- Absence of ducts within the portal tracts and presence of proliferating cholangioles at periphery of liver lobules (CK7+ve)
- Paucity of ducts, cholestasis, bile plugs, giant cells, micronodular cirrhosis
- *EM*: Pigment in Golgi bodies, ER, lysosomes
- Liver transplantation in most by 50 years of age
- Remote risk of hepatocellular carcinoma

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC)

- Severe genetic cholestatic abnormalities of earlier life
- Micronodular cirrhosis
- Hepatic lobular disarray, giant cell transformation, canalicular/cytoplasmic cholestasis, central lobular fibrosis

PFIC-1 (ATP8B1): Byler disease

- Amish children
- FIC1 protein (18q21), translocates phospholipids
- Normal or low GGT, elevated bile acids
- Diarrhea, asthma, pancreatitis, hearing impairment

PFIC-II- (ABCB 11)

- Liver failure within first few years of life
- Risk of developing hepatocellular carcinoma

PFIC III-ABCB4/MDR3

- Elevated GGT
- Gene defect identified in some women with intrahepatic cholestasis of pregnancy

BENIGN RECURRENT NON-PROGRESSIVE CHOLESTASIS IN BRIC

- Same locus as PFIC I (18q21)
- Good response to biliary diversion

BILE ACID SYNTHESIS DEFECTS

- Primary: Single enzyme defects
- Secondary: Peroxisomal defects
- Low GGT, cholestasis, abnormal serum bile acids
- Enzyme defects on sterol nucleus (early in life): 3β-Hydroxy δ – *C*27 steroid dehydrogenase, Δ 4-3-oxosteroid 5β-reductase
- Giant cell hepatitis with fibrosis
- Presentation later in life, malabsorption, non-specific hepatitis
- Mass spectrometric analysis of urine bile acids

FAMILIAL CHOLESTASIS: NORTH AMERICAN INDIAN CIRRHOSIS

- High GGT transient neonatal jaundice progressing to biliary cirrhosis
- Fatal in infancy, autosomal recessive
- Maps to 16q22 (CIRHIN-mitochondrial scaffold protein)

Anatomic abnormalities of biliary and hepatic ducts

- Agenesis
- Congenital bronchobiliary fistula (aspiration pneumonia)
- *Ciliated foregut cyst*: Subcapsular, lined by pseudostratified ciliated epithelium, portal hypertension, and abdominal pain

CHOLEDOCHAL CYST OF BILE DUCT

- Clinical triad of pain/jaundice/right upper quadrant mass
- Segmental cystic dilatation of intra-/extrahepatic bile ducts
- Smooth glistening lining of cavity
- Attenuated epithelial lining, dense connective tissue cyst wall, chronic inflammation, no residual smooth muscle
- Bile stasis and hyperbilirubinemia
- Hepatic morphology similar to EHBA

CAROLI DISEASE

- Multiple segmental cystic/saccular dilatations of large intrahepatic bile ducts (continuity with biliary tree)
- Occasional familial cases (no gene identified)
- Associated with ADPKD
- Risk of cholangitis, cirrhosis, cholangiocarcinoma

CONGENITAL HEPATIC FIBROSIS (CHF)

- AR polycystic kidney disease is associated
- Ductal plate abnormality, dilated/concentric arrangement of bile ducts
- Expanded/fibrotic portal region
- Portal hypertension, esophageal varices

Metabolic liver disorders

- Often suspected clinically
- Freezing tissue + EM tissue fixative + tissue for Cu estimation
- Histology indicates a possible metabolic disorder = steatosis, steatohepatitis, storage cells
- Immunohistochemistry, EM = confirm the diagnosis
- Early diagnosis crucial = treatable condition/family counseling/sibling assessment

DISORDERS OF CARBOHYDRATE METABOLISM

Glycogen storage disease

- Metabolic disorders with specific enzyme defects, accumulation of normal/abnormal glycogen within cells
- *Type I (von Gierke disease)*: Hepatocytes distended by glycogen, obliteration of sinusoids, mosaic pattern/glycogenated nuclei

- *Type II (Pompe disease)*: Monoparticulate glycogen within membrane-bound lysosomes
- *Type III (Cori disease)*: Panlobular cytoplasmic distension by glycogen, uniform mosaic pattern
- Type IV (Anderson disease)
  - *EM*: Non-membrane-bound inclusions of fibrillary material, glycogen/tubules
  - Hepatocytes with pale hyaline inclusions surrounded by indistinct halos resembling Lafora bodies
  - Positive for PAS and colloidal iron
  - PAS with diastase = storage material not extracted

Galactosemia

- AR
- Deficiency of galactose –1 phosphate uridyl transferase
- Located on *GALT* gene
- Impaired conversion of galactose into glucose
- Canalicular/hepatocellular cholestasis, pseudo acinar formation, steatosis, bile duct proliferation, fibrosis/cirrhosis
- Similar histology in *tyrosinemia* and *fructosemia*

Tyrosinemia

- Acute fulminant disease in infancy
- Chronic liver disease in childhood
- Histology similar to other metabolic hepatopathies
- If chronic, micronodular cirrhosis
- Long-term risk for HCC
- Liver transplantation recommended soon after diagnosis

Fructosemia

- Deficiency of aldolase B
- Metabolic hepatopathy histology

LYSOSOMAL DISORDERS

Gaucher disease

- Deficiency of glucocerebrosidase
- Massive hepatosplenomegaly, portal hypertension
- Gaucher cells in liver with striated cytoplasm (like wrinkled tissue paper)
- *EM*: Membrane-bound inclusions, twisted tubules in Kupffer cells

Niemann pick disease

- Deficiency of sphingomyelinase
- Finely vacuolated cytoplasm of Kupffer cells/hepatocytes
- *EM*: Myelin figures in Kupffer cells/hepatocytes

Wolman and CESD

- Mutation in gene encoding acid-lipase

Wolman disease

- Generalized accumulation of foam cells, calcification of adrenal glands, fatal in early life
- Steatosis of hepatocytes and Kupffer cells
- *EM*: Cholesterol clefts in cytoplasm

CESD

- Milder disease
- Partial enzyme activity present

Mucopolysaccharidosis

- Deficiency of iduronidase sulfatase
- Hurler, Hunter
- Swollen, clear cytoplasm of hepatocytes and Kupffer cells
- Stored material positive with colloidal iron
- *EM*: Cholesterol clefts and fibrosis

Mucolipidosis (I cell disease, sialidosis, pseudo-Hurler disease)

- Deficiency of acid hydrolases
- Vacuolated hepatocytes and Kupffer cells
- *EM*: Membrane-bound vacuoles with flocculent material

Oligosaccharidosis

- Deficiency of sialidase, mannosidase, fucosidase
- Vacuolated hepatocytes and Kupffer cells
- *EM*: Membrane-bound vacuoles with finely granular material

Metachromatic leukodystrophy

- Deficiency of arylsulfatase-A

- Metachromatic granules in portal macrophages
- *EM*: Lamellar, prismatic inclusions within macrophages, hepatocytes, and Kupffer cells
- Gallbladder has thick mucosa, fine cobblestone/papillary surface
- Papillary fronds lined by columnar epithelial cells, amphophilic cytoplasm
- *EM*: Lysosomal inclusions with closely packed herringbone appearance

Farber (lipogranulomatosis)

- Deficiency of acid ceramidase
- Lipo granulomatous infiltrates
- *EM*: Curvilinear, banana-shaped lysosomal inclusions

Gangliosidosis

- Deficiency of β-Galactosidase
- GM1 and GM2 types
- Tay-Sachs disease (GM2) = hexosaminidase A deficiency
- Sandhoff disease (GM2) = hexosaminidase A and B deficiency
- Zebra bodies; concentric membrane-bound lysosomal inclusions

Fabry disease

- Endothelial cells affected
- *EM*: Membrane-bound lysosomal inclusions with lamellar/concentric patterns

BILE ACID METABOLISM DISORDERS

- AR, progressive disorders
- Neonatal hepatitis in younger children and chronic hepatitis in older children
- Treatment is bile acid substitution

PEROXISOMAL DISORDERS

Zellweger syndrome
(cerebrohepatorenal syndrome)

- AR disorder
- Multiple congenital anomalies, craniofacial abnormalities, psychomotor defects, renal cortical cysts, liver abnormalities
- Mutation of genes involved in peroxisome biosynthesis
- Absence of peroxisomes in hepatic/renal tubular cells

IRON STORAGE DISEASE

- AR disorder
- Excessive iron deposits in liver due to increased body iron

Primary (hemochromatosis)

- Gene mutations (*HFE* gene on chromosome 6)
- Disordered regulation of iron absorption by intestines
- Cirrhosis of liver, diabetes (iron deposition in pancreas), congestive cardiomyopathy (iron deposition in myocardium), hypermelanosis of skin
- High risk of HCC, prevented by early treatment (phlebotomy)
- Iron deposited in hepatocytes, biliary cells, and Kupffer cells

Secondary overload (hemosiderosis)

- Transfusion induced (children with hemoglobin disorders)
- Iron initially deposited in Kupffer cells only

Neonatal iron storage disease

- Massive iron storage in liver and other organs
- Iron deposited in parenchymal and Kupffer cells
- Metabolic error, high recurrence rate in subsequent pregnancies
- Iron deposits in minor salivary glands = oral mucosa biopsy for diagnosis

WILSON DISEASE

- Gene (*ATP7B*) encodes ATPase-dependent copper transporter
- Localized to chromosome 13q-14.3
- Failure of Cu biliary excretion and incorporation into ceruloplasmin
- Serum ceruloplasmin decreases, serum Cu variable

- Increase in 24-hour urinary Cu excretion
- Liver Cu markedly increased; 250 µg/gm dry weight
- Kayser-Fleisher ring in eye (slit lamp)
- D-penicillamine = good prognosis if started early
- Hepatocytes with ballooning, decreased cytoplasmic eosinophilia, glycogenated nuclei, apoptotic bodies, finely granular cytoplasm, hepatocyte necrosis/ultimately cirrhosis
- Rhodamine/orcein biochemical stains highlight copper in periportal hepatocytes
- *EM*: Lysosomal copper deposits in hepatocytes

FATTY ACIDS OXIDATION DEFECTS

Carnitine deficiency

- Recurrent episodes of Reye-syndrome-like illness and similar hepatic histology

Acyl-CoA-dehydrogenase deficiency

- Glutaric aciduria, acidosis, non-ketotic hypoglycemia, multiple congenital malformations, panlobular steatosis, and portal fibrosis

PORPHYRIAS

- Disorders of porphyrin and heme biosynthesis
- Steatosis, iron deposition, fibrosis
- Long-term risk for HCC

UREA CYCLE DISORDERS

- Hyperammonemia
- Deficiency of ornithine transcarbamylase (Xp21.1), citrullinemia
- Non-specific morphological changes

Hepatic steatosis and steatohepatitis

- Associated with several metabolic/nutritional disorders
- Childhood obesity and type II diabetes; non-alcoholic fatty liver disease (NAFLD).
- Macro-vesicular and micro-vesicular steatosis, hepatocyte ballooning, inflammation in portal tracts/lobules, glycogenated nuclei, fibrosis/cirrhosis

Note: Refer to the Appendix for scoring system.

Reye syndrome

- Acute childhood disease with acute encephalopathy, hepatic fatty degeneration, progressive coma/death
- Mitochondrial injury in liver, brain, muscle leading to abnormal lipid metabolism
- Microvesicular steatosis, panacinar
- No hepatocellular necrosis or fibrosis
- Attributed to salicylate use in febrile children
- Changes partially reversible in children who recover

Alpha-1-Antitrypsin deficiency

- AR disease
- Mutation in protease inhibitor (Pi) gene → neutrophil elastase not neutralized
- Mutant form of A1AT not released from hepatocytes and continues to accumulate
- Hepatocyte injury and liver disease
- Most common genetic cause of neonatal liver disease
- Normal genotype is PiMM, heterozygous PiMZ, homozygous PiZZ
- Manifested as emphysema in lungs
- *EM*: Liver, abnormal protein accumulated in RER
- Eosinophilic globules (DPAS+) in zone I hepatocytes
- Biliary features mimic biliary atresia, bile-duct hypoplasia, hepatitis/non-specific

Cystic fibrosis

- Mutation in *CFTR* gene
- Increased bile viscosity (low water and sodium) → decreased bile flow → bile duct obstruction and damage

- Distinctive bile duct lesion (focal biliary cirrhosis-foci of fibrosis, bile duct proliferation, intraluminal inspissated eosinophilic secretions)
- Metabolic hepatopathy (cholestasis, steatosis, cirrhosis)
- Biliary tree may show microgallbladder, cholelithiasis, distal common duct stenosis

Viral hepatitis

HEPATITIS A

- RNA virus
- Fecal-oral route transmission
- No chronic carrier status and no chronic hepatitis

HEPATITIS B

- DNA virus
- Perinatal and parenteral transmission
- Acute and chronic hepatitis
- HBs Ag (cytoplasmic pattern reactivity)
- HBc Ag (nuclear pattern reactivity)
- Surface and core antigens demonstrated on immunohistochemistry and indicate chronicity
- HBe Ag—carrier state
- Chronic hepatitis risk factor for cirrhosis/HCC

HEPATITIS C

- RNA virus
- Chronic hepatitis: Risk factor for cirrhosis and HCC
- Portal chronic inflammation, germinal center formation
- Microsteatosis, lobular inflammation, and fibrosis

HEPATITIS D

- RNA virus, Delta agent
- Co-infection with Hep B virus—massive hepatic necrosis and chronic disease

HEPATITIS E

- RNA virus
- Fecal oral transmission
- Mild self-limiting disease

Chronic hepatitis

- Multiple etiology: HBV, HCV, drug toxicity, autoimmune hepatitis, other viral infections, idiopathic conditions
- Chronic necroinflammatory diseases affecting hepatocytes rather than biliary structures
- Lobular inflammation predominant in acute hepatitis
- Portal/periportal inflammation dominant in chronic hepatitis
- Grade determines degree of inflammatory activity and stage depicts degree of fibrosis
  - **Note:** See Appendix for classification scheme

Fulminant hepatic failure

- Etiology: Viral infections (HBV, HCV, HSV, CMV), drugs (acetaminophen), inborn errors of metabolism, pregnancy induced, malignancy
- Hepatic failure, altered mental status, coagulopathy
- Necrosis and loss of zones of hepatocytes

Primary sclerosing cholangitis

- Associated with ulcerative colitis, Langerhans cell histiocytosis, and immunodeficiencies
- Diffuse biliary cirrhosis and bile staining
- Elevated serum alkaline phosphatase, bilirubin, p-ANCA, IgM
- Severe chronic portal inflammation, bile duct proliferation, interface hepatitis, portal fibrosis and concentric onion-skin fibrosis around the bile ducts
- Long-term complication of PSC and UC: Adenocarcinoma of bile duct/colon

Autoimmune hepatitis

- Co-existing other autoimmune disorders/family history of autoimmune diseases
- Serum antinuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), anti-LKM1 are increased
- Plasma cells in inflammatory infiltrate, interface hepatitis, pseudo-acinar (rosette) pattern of hepatocytes and increased fibrosis
- AIH and PSC co-existent = autoimmune sclerosing cholangitis overlap syndrome

Abscesses

- Complication of chronic granulomatous disease
- Central area of suppurative necrosis surrounded by macrophages
- Pigmented lipid laden macrophages in portal tracts and sinusoids
- Amoebic liver abscess in endemic areas (*Entamoeba histolytica*)
- Other causes: Bacterial infection, umbilical catheterization in neonates, post-portoenterostomy procedure for EHBA

Parasitic diseases

PROTOZOAL INFECTIONS

- Toxoplasmosis (congenital or transmitted through house cats)
- Malaria by *Plasmodium falciparum* (hemozoin pigment within Kupffer cells)
- Kala azar (leishmaniasis—Leishman-Donovan bodies)
- Amoebic hepatitis by *Entamoeba histolytica* (anchovy-sauce-like material in amoebic abscess, trophozoites PAS+)

HELMINTHIC INFECTIONS

- *Schistosoma japonicum* (migration of ova through portal vein)
- Clonorchis sinensis
- *Fasciola hepatica* (liver flukes)
- Echinococcus granulosus; hydatid cyst = outer thick laminated wall and inner germinal layer with brood capsules from scolices, hydatid sand in cyst fluid
- Toxocara canis = visceral larva migrans

Granulomatous hepatitis

- Tuberculosis and sarcoidosis

Vascular disorders

CAVERNOUS TRANSFORMATION OF PORTAL VEIN

- Common cause of non-cirrhotic portal hypertension in children
- Obstruction of portal vein by thrombus
- Cavernous transformation due to recanalization

BUDD-CHIARI SYNDROME

- Young women (pregnancy/contraceptive use)
- Obstruction to hepatic vein (central vein)
- Ascites and hepatomegaly
- Centrilobular congestion, ischemia, hepatocyte degeneration (zone III)
- Less-affected hepatocytes near portal tract
- May progress to cirrhosis

VASO-OCCLUSIVE DISEASE

- Pyrrolizidine alkaloids in Senecio tea, cytotoxic agents in chemotherapy, irradiation
- Partial/complete obliteration of central vein, peri-central vein fibrosis
- Morphological features resemble allograft rejection

PELIOSIS HEPATIS

- Liver infection by *Bartonella henselae* in HIV-infected children
- Pools of erythrocytes in liver lobules (no zonal distribution)
- Organism detected by Warthin-Starry stain and PCR

GOLDENHAR SYNDROME

- Oculoauriculovertebral dysplasia with absence of portal vein

Total parenteral nutrition–related injury

- Hepatobiliary injury caused with parenteral feedings
- Incidence inversely correlated with gestational age and birth weight
- Non-specific features; diagnosis of exclusion
- Degree of liver injury correlates with duration of TPN
- Potentiating factors: Loss of protection from gut lymphoid tissue, sepsis, lack of essential nutrients, and hepatotoxicity of some parenteral nutrients (amino acids and lipids)
- Portal tract expansion by fibrous tissue, bile duct proliferation, and cholestasis
- Pseudo-acinar pattern of hepatocytes, cytoplasmic cholestasis, apoptosis
- Improvement in features after cessation of TPN and starting enteral feedings
- Persistent features in resilient cases

Cirrhosis

- End result of hepatocellular necrosis caused by various injuries
- Fibrosis, abnormal regenerative nodules
- *Alper disease*: Mitochondrial disorder, neuronal degeneration and liver cirrhosis
- Fetal alcohol syndrome, cardiac cirrhosis (due to congenital heart disease), metabolic abnormalities, biliary obstruction, infections
- *Grossly*: Micronodule (<3 mm), macronodule (>3 mm)

PRENEOPLASTIC LESIONS

- *Large cell dysplasia* = enlarged cells and nuclei, hyperchromasia, prominent nucleoli, multinucleation
- *Macroregenerative nodule (nodule within a nodule)* = adenomatous hyperplasia, (intermediate lesion)
- *Small cell dysplasia* = atypical adenomatous hyperplasia → may progress to HCC

Hepatic tumors

FOCAL NODULAR HYPERPLASIA

- Hyperperfusion of localized parenchyma by vascular abnormality
- Well-circumscribed lesion, central scar, parenchyma divided into smaller nodules by bands of fibrous tissue
- Fibrous tissue edges contain scattered small ducts, small to large vessels, and inflammatory cells

NODULAR REGENERATIVE HYPERPLASIA

- Mass of variable-sized nodules in liver
- Nodules (<3 mm) composed of hyperplastic regenerative hepatocytes, minimal perisinusoidal fibrosis
- Hyperproliferative response to obstructive portal venopathy

HEPATOCELLULAR ADENOMA

- Oral contraceptive use, teenage girls
- Poorly circumscribed light yellow-tan mass, smaller satellite nodules
- Trabeculae of uniform hepatocytes, some surrounding canaliculi
- No portal areas, no bile ducts present
- Hemorrhagic/infracted foci in tumor parenchyma
- Proliferating cell labeling index (PCNA) low in hepatic adenomas compared to HCC and hepatoblastomas

MESENCHYMAL HAMARTOMA

- Second-most common benign hepatic tumor of children (under 2 years of age)
- Associated placental mesenchymal abnormalities

- Cut surface; multiple variably sized cysts lined by smooth surface, yellow gelatinous fluid in lumen
- Admixture of mesenchyme, bile ducts, hepatocyte cords, and variable-sized cysts
- Mesenchyme has stellate cells, extramedullary hematopoiesis
- Bile duct/hepatocytes = CK+, mesenchyme = vimentin+
- Translocation t(11; 19)
- Association with undifferentiated sarcoma

INFANTILE HEMANGIOENDOTHELIOMA

- Most common benign tumor of liver in infants and children (under 1 year of age)
- Congestive heart failure, hepatomegaly, anemia
- Clinical course intermediate between hemangioma and angiosarcoma
- Cut surface; multiple blood-filled nodules
- Vascular channels lined by endothelial cells, positive for *CD31*, *CD34*, and *GLUT1*
- Supporting fibrous stroma has bile ducts
- Cavernous vascular change at margin of lesion
- Hemorrhagic infarction
- Treated by ligation/embolization of hepatic artery/tumor resection

TERATOMA

- Large irregular mass containing solid and cystic components derived from various germ cell layers
- Morphologically, tissue of various somatic lines including endoderm, ectoderm, and mesoderm

HEPATOBLASTOMA

- Malignant neoplasm
- Usually found up to 5 years of age
- Association with Beckwith and Wiedemann (BWS) and familial adenomatous polyposis (FAP)
- Anemia, thrombocytosis, high AFP
- Deregulation of APC/β-catenin pathway, mutation in APC gene (FAP-associated hepatoblastoma)
- Mutation in β-catenin gene (sporadic hepatoblastoma)
- Positive for AFP, HCG, Hep-Par1, polyclonal CEA, nuclear β-catenin, GPC3
- *Stage* 1: Complete resolution. *Stage* 2: Microscopic residual tumor. *Stage* 3: Gross residual tumor. S*tage* 4: Metastatic disease
- Treatment includes pre-operative chemotherapy followed by surgery

Epithelial type

Fetal pattern

- Uniform cells resembling normal small hepatocytes
- EMH seen in all patterns of hepatoblastoma
- Best prognosis

Embryonal pattern

- Sheets of irregular angulated cells, increased nucleo/cytoplasmic ratio, nuclear hyperchromasia, and indistinct cell outlines

Macrotrabecular pattern

- Solid sheets and trabeculae of hepatocytes more than 10 cell thick, necrosis

Small cell undifferentiated pattern

- Small, round blue cells
- Worst prognosis

Mixed epithelial and mesenchymal type

- Epithelial elements admixed with cells resembling fibroblastic/myofibroblastic tissue

Without teratoid features

- Epithelial cells, fibrous tissue, and osteoid-like material

With teratoid features

- Stratified squamous epithelium, melanin pigment, mucinous epithelium, cartilage, bone, striated muscle

HEPATOCELLULAR CARCINOMA

- More common in children older than 10 years
- Underlying liver dysfunction; viral hepatitis (HBV and HCV), alpha-1-antitrypsin deficiency, hereditary tyrosinemia, or cirrhosis
- Abdominal mass, pain, elevated serum AFP
- Poor prognosis (worse than hepatoblastoma)
- Broad trabeculae (2–10 layer thick) of poor to moderately differentiated hepatocytes
- Pseudoglandular cell appearance with central necrosis
- Giant tumor cells, atypical mitoses, hepatocellular cholestasis, and nuclear anisocytosis
- Positive for Hep-Par1, GPC 3, nuclear β-catenin

FIBROLAMELLAR VARIANT OF HCC

- More common in young children than adults
- Not associated with cirrhosis/viral hepatitis/no elevation of AFP
- Broad bands of plump collagen, aggregates of large hepatocytes
- Hepatocytes have prominent eosinophilic, finely granular cytoplasm and large nucleoli
- In children, fibrolamellar—HCC biologically similar to classic HCC and has same prognosis

UNDIFFERENTIATED EMBRYONAL SARCOMA

- Mesenchymal origin, peak age 6–10 years
- May be associated with Li-Fraumeni syndrome
- Serum AFP and bilirubin not elevated
- Poor prognosis
- Spindle/stellate cells in myxoid stroma, bizarre tumor giant cells (with large and multiple nuclei)
- Cytoplasm shows smooth eosinophilic globules
- Structural alteration of chromosome 19 (as in mesenchymal hamartoma)
- Positive for vimentin, pancytokeratin, and bcl2

CALCIFYING NESTED STROMAL EPITHELIAL TUMOR

- Rounded nests of epithelial and spindle cells, background of myofibroblastic/desmoplastic stroma
- Variable psammomatous calcification/ossification
- Tumor cells coexpress cytokeratin/vimentin, nuclear staining for WT-1
- Long-term prognosis good

EMBRYONAL RHABDOMYOSARCOMA OF BILIARY TRACT

- Obstructive jaundice
- Botryoid gelatinous mass
- Occlusion of lumen of right/left/common bile duct
- Cambium layer of rhabdomyoblasts between bile duct epithelium and wall below
- Cells are round/spindly/straplike, scant cytoplasm, mitotically active
- Positive for desmin, myogenin, MyoD1

ANGIOSARCOMA

- Mean age of presentation 4 years
- No association with environmental pathogens or syndromes
- Nodules of spindle cells, hemorrhage
- Bizarre endothelial cells fill sinusoids compressing/destroying hepatic trabeculae
- Positive for vascular marker stains

GALLBLADDER

- Agenesis, duplication, septation
- In EHBA reduced to a fibrous cord
- Pigmented cholelithiasis = hemolytic anemias (congenital spherocytosis, thalassemia, spherocytosis)
- Cholesterol cholelithiasis = obese adolescents
- Neoplasia rare, embryonal rhabdomyosarcoma

29 The Pancreas

Embryology and anatomy

- Ventral foregut gives rise to two pancreatic buds at 4 weeks of gestation
- Dorsal bud: Forms the body, tail, and superior portion of head of pancreas
- Ventral bud: Forms the uncinate process and inferior portion of head of pancreas
- Two ducts: Duct of Wirsung (drains most of pancreas and joins common bile duct proximal to ampulla of Vater) and duct of Santorini (accessory duct)

Congenital anomalies and malformations

AGENESIS AND HYPOPLASIA

- Very rare
- Growth retardation/early death, malabsorption
- Islet cell agenesis: Severe growth retardation, diabetes mellitus (maternal insulin does not cross placenta)
- *Shwachman-Diamond syndrome*: Fatty replacement of pancreatic acinar tissue with preserved islets; pancreatic insufficiency, bone marrow dysplasia, metaphyseal dysplasia

ANNULAR PANCREAS

- Band of pancreatic tissue surrounding second part of duodenum
- Association with trisomy 21
- Other intestinal malformations may be associated
- Polyhydramnios in fetus
- Bile-stained vomiting in infant (constriction is below ampulla)
- "Double-bubble" sign on radiographs

ECTOPIC PANCREAS

- Located in wall of stomach, duodenum, or Meckel diverticulum
- Incidental finding, peptic ulceration, hemorrhage, obstruction, or intussusception
- Morphologic features: Normal pancreas or proliferation of ducts only (*adenomyoma*)

PANCREATIC HYPERPLASIA

- Beckwith-Wiedemann syndrome; predominance of endocrine tissue in pancreas, sparse acinar tissue
- Congenital leukemia/extramedullary hematopoiesis

PANCREAS DIVISUM

- Dominant dorsal duct syndrome; the bulk of pancreatic tissue drains through dorsal duct (Santorini) into minor papilla
- May manifest as pancreatitis

CYSTS

- Von Hippel-Lindau syndrome, infantile polycystic disease of kidney/liver, Meckel-Gruber syndrome, trisomy 13
- Splenosis (spleen fusion) in pancreatic tail in trisomy 13

CYSTIC FIBROSIS

- AR
- *CFTR* gene mutation (δ F508) on chromosome 7
- Thick tenacious eosinophilic secretions blocking exocrine acini/ducts and small airways
- Ductular dilatation and cyst formation, acinar destruction, fibrosis

- Inspissated eosinophilic secretions also seen in dehydration, sepsis, heart failure, uremia

PEARSON SYNDROME

- Sideroblastic anemia, exocrine pancreatic insufficiency, neutropenia
- Acinar atrophy with fibrosis (no lipomatosis)

SHWACHMAN-DIAMOND SYNDROME

- Autosomal recessive disorder
- Acini diminished/absent and pancreatic tissue replaced by adipocytes
- Ducts and endocrine tissue preserved
- No fibrosis/scarring
- Pancreatic insufficiency, normal sweat test

NEONATAL HEMOCHROMATOSIS

- Massive acinar iron deposition, fibrosis
- Islets are spared

PANCREATITIS

- *Etiology*: Infections (congenital syphilis, rubella, mumps, adenovirus, cytomegalovirus), pancreas divisum
- *Acute pancreatitis*: Traumatic pancreatitis with fat necrosis, saponification, acute inflammation
- *CMV pancreatitis*: Inclusions in ductal, exocrine, and endocrine cells
- *Chronic pancreatitis*: Obstructive pancreatitis with fibrosis, duct ectasia, acinar atrophy, abundance of endocrine islets
- *IPEX*: Chronic pancreatitis

Pancreatic tumors

EXOCRINE TUMORS

Pancreatoblastoma

- Most frequent pancreatic tumor of childhood
- Associated with Beckwith-Wiedemann syndrome
- Abnormalities of APC/β catenin pathway
- Epithelial neoplasm with multiple lines of differentiation
- Lobulated tumor separated by stroma
- Solid sheets, small acini, may contain heterologous bone and cartilage
- Squamoid corpuscles are the hallmark
- Positive for CEA, CA19-9, beta-catenin
- Good response to surgical resection/chemotherapy

Solid pseudopapillary neoplasm

- Adolescent and young females
- Good post-surgery survival
- Mutations in beta-catenin
- Solid growth, pseudo papillae, eosinophilic globules in cells
- Positive staining with CD56+, CD10+, nuclear beta-catenin, progesterone
- Negative staining with cytokeratin

Acinar cell carcinoma

- Positive for enzymes: lipase, trypsin, chymotrypsin
- Negative for chromogranin and synaptophysin

Ductal cell adenocarcinoma

- Malignant neoplasm
- Atypical duct-like structures surrounded by fibrous stroma
- Metastasizes to distant organs

ENDOCRINE NEOPLASMS

Insulinoma

- Associated with *MEN1* or solitary
- Persistent hypoglycemia, stupor, confusion, and high serum insulin levels
- Neuroendocrine neoplasm of beta-cells of the islets
- Associated with nesidioblastosis
- Malignant insulinoma is rare in children
- Benign tumor mostly <2 cm
- Nests and cords of tumor cells, no intermixed acinar tissue, thin fibrous capsule
- Positive stains are insulin, chromogranin, CK19
- Prognosis depends on tumor size, cellularity, and cytologic atypia

Anomalies of endocrine pancreas

ISLET HYPERTROPHY

- When more than 10% of islets are over 200 mm in diameter (infants under 2 months)
- Islet cell hyperplasia/hypertrophy seen in infants of diabetic mothers

INFANTS OF DIABETIC MOTHER

- Maternal hyperglycemia and anti-insulin antibodies
- Maternal insulin and glucagon do not normally cross placenta
- Glucose and antibodies to insulin normally cross placenta
- Other associated anomalies: Cardiac, lumbosacral agenesis, macrosomia
- Islet hypertrophy and hyperplasia
- Expansion of β-cell mass and pleomorphism of β-cell nuclei
- Eosinophilic insulitis and peri-insular fibrosis
- Obese infants, neonatal hypoglycemia, macrosomia and tendency to develop diabetes mellitus in life

DIABETES MELLITUS (DM)

Type I (insulin-dependent DM, juvenile-onset)

- Autoimmune with anti-islet-cell antibodies
- Insulitis

Type II (adult type)

- Obesity
- Genetic predisposition
- High prevalence in some ethnic groups

Neonatal DM

- Most cases are transient/mild
- Sometimes, insulin requiring hyperglycemia within first 3 months of life
- Pancreatic hypoplasia/aplasia
- Wolcott-Rallison syndrome

Maturity onset diabetes of the young (MODY)

- Autosomal dominant inheritance
- Early onset DM (before age 25 years)
- Genetic defects in pancreatic β-cell transcription factors

HYPERINSULINISM

Congenital hyperinsulinemia (CHI) with B-cell ATP-sensitive potassium channel abnormalities

- Recessive inactivating mutations of *ABCC8* and *KCNJ11* (most frequent CHI)
- Nesidioblastosis: Histologic finding in hyperinsulinemia (obsolete terminology)
- Nesidioblastosis (direct transformation of ductal epithelial cells into islet tissue), includes hypertrophic islets with atypical β-cells, ductoinsular complexes
- Diffuse or focal morphologic patterns

Diffuse hyperinsulinemia

- Autosomal recessive
- Homozygous *ABCC8* and *KCNJ11* gene mutations located on chromosome 11p
- Hypoglycemia at birth
- Intraoperative frozen section biopsies (from head, body, and tail); islet cell nucleomegaly/bizarre nuclei with pseudoinclusions
- Total pancreatectomy indicated for treatment
- Bad prognosis

Focal hyperinsulinemia

- Paternally inherited mutations of genes *ABCC8* and *KCNJ11*
- Loss of maternal alleles of chromosome 11p15, and tumor suppressor genes
- Intraoperative frozen section usually shows normal islet cell nuclei
- Islet cell adenomatous/adenoma lesions; localized increase in islet tissue with nucleomegaly and nuclear pleomorphism
- Chromogranin A positive
- No nuclear changes in islets away from the adenomatous lesion
- Resect the focal lesion only; no need for total pancreatectomy
- Better prognosis than diffuse

PANCREATIC ISLETS IN SHOCK

- Fetal asphyxia
- Partial/full coagulative necrosis of islets

Malformation syndromes

BECKWITH-WIEDEMANN SYNDROME

- Congenital overgrowth syndrome
- Dysregulation of imprinted growth regulatory genes clustered at 11p15
- Macrosomia, macroglossia, omphalocele, visceromegaly, hemihyperplasia, tumors
- Hyperinsulinemia-associated hypoglycemia
- Pancreas contain islet-like aggregates of endocrine cells (chromogranin A positive)
- Exocrine acini are poorly developed

PERLMAN SYNDROME

- Islet cell hyperplasia
- Nephroblastomatosis, hamartomas, fetal gigantism

WOLCOTT-RALLISON SYNDROME

- Neonatal insulin-dependent DM
- Epiphyseal dysplasia

LEPRECHAUNISM

- Islet cell hyperplasia
- Hirsutism, enlarged genitalia, decreased muscle tissue

30 Bone Marrow

- Marrow constitutes 3%–6% of total body weight
- Site of origin of peripheral blood, macrophages, mast cells, lymphocytes, NK cells, and osteoclasts

Development

- Earliest site of hematopoiesis in embryo is yolk sac
- At 10–12 weeks, liver and spleen take over
- At 4–5 months, bone marrow is main site of hematopoiesis
- Hematopoiesis changes from axial skeleton (in newborns) to flat bones of central skeleton by 12–16 years of age
- As age advances, marrow is replaced by fat

Bone marrow structure

- Composed of capillary-venous sinuses, extracellular matrix, hematopoietic stem cells, progenitor cells, adventitial reticular cells (add connective tissue elements)
- Marrow cellularity (fat/hematopoietic ratio) = 100% – Age (approximately)
- Immature and mitotically active cells located in paratrabecular/perivascular zones

Stem cells

- Hematopoietic stem cells have capability of sustained self-renewal
- Multilineage differentiation potential
- Stain positively for CD34, c-kit
- Stain negatively for CD38

Progenitor cells

- Progressed stem cells with lineage commitment
- Positive for CD34, c-kit, and CD38
- Proliferation/lineage maturation stimulated by colony-stimulating factors/interleukins
- Inhibited by tumor necrosis factor

Hematopoietic lineages

GRANULOPOIESIS

- Various stages of granulocyte maturation include myeloblast → promyelocyte → myelocyte → metamyelocyte → band neutrophil → segmented neutrophil
- Maturation involves progressive nuclear segmentation, decrease in nuclear-cytoplasmic ratio, acquisition of primary/secondary cytoplasmic granules
- Regulatory factors in granulopoiesis; GM-CSF (granulocyte macrophage-colony-stimulating factor), G-CSF, and IL-3
- Occurs in paratrabecular/perivascular zones
- Highlighted by myeloperoxidase stain

ERYTHROPOIESIS

- Basophilic normoblast → polychromatophilic normoblast → orthochromatic normoblast → reticulocyte → mature erythrocyte
- Maturation involves progressive nuclear condensation and finally nuclear extrusion with formation of erythrocyte
- Cytoplasm changes from basophilic to completely hemoglobinized

- Regulated by erythropoietin (EPO) and other general growth factors
- Erythropoiesis occurs in small colonies (erythroblast islands), randomly distributed throughout the bone marrow
- Highlighted by Glycophorin A stain

MEGAKARYOCYTOPOIESIS

- Megakaryocyte is largest nucleated cell in bone marrow (50–150 μ)
- Differentiation by endomitosis; increasing nuclear lobulation without cell division
- Regulated by thrombopoietin
- Megakaryoblast → basophilic megakaryocyte → granular megakaryocyte → platelet producing megakaryocyte
- With progressive maturation, increase in cell size, increased lobulation, and acquisition of purple-pink cytoplasmic granules
- Localized at parasinusoidal foci in bone marrow
- Pseudopods release proplatelets into vascular space

MONOPOIESIS AND DENDRITIC CELL DEVELOPMENT

- Monocyte is the largest leukocyte (12–20 μ)
- Maturation regulated by M-CSF
- Monoblast → promonocyte → mature monocyte
- Monocytes circulate in blood → migrate to solid organs → convert into macrophages/immune accessory cells

LYMPHOPOIESIS

- Lymphocytes derived from same stem cells as other hematopoietic elements
- Interleukins involved in proliferation/differentiation of both B cells and T cells
- B-cell development takes place in bone marrow
- T-cell precursors migrate from bone marrow to thymus for maturation/differentiation
- Earliest B cells express TdT, surface CD34, CD79a, HLA-DR, CD10
- More mature B cells express cytoplasmic mu heavy chain and later surface immunoglobulin, CD20
- T-cell antigen profile; cytoplasmic and later surface CD3 expression
- Terminal maturation of T cells involves acquisition of either surface helper antigen (CD4) or suppressor antigen (CD8)

NATURAL KILLER CELLS

- Large granular lymphocytes
- Resemble cytotoxic/suppressor T cells (both express adhesion molecules CD56, CD57, and CD16)
- Differ from cytotoxic/suppressor T cells in being negative for CD3 and CD8 expression

Normal hematopoietic parameters

- Bone marrow cellularity evaluated on biopsy sections/imprint
- Cellularity decreases with age

Hematopoietic profile of neonate

- In normal term infants, hematocrit, MCV, red cell count, and white cell count are higher than normal at any age
- Peripheral blood shows physiologic circulation of red cell precursors (up to 3–4 days of life)
- Physiologic anemia of infancy due to reversal of relative hypoxia in utero

Examination of bone marrow in children

- In young infants = tibia is preferred site of bone marrow aspiration
- In older children = posterior iliac crest
- *Culture*: Workup of infection
- *Immunohistochemistry*: Determines lineage of hematopoietic and metastatic disorders
- *Immunophenotyping (by flow cytometry)*: Determines immunophenotype of

malignant hematopoietic disorders (leukemias and lymphomas) and benign cells (hematogones)
- *Cytogenetics*: Yields diagnostic and prognostic information in malignancies
- *FISH*: Determines specific cytogenetic abnormality and detects minimal residual disease
- *Molecular analysis*: Determines B and T cell clonality and gene rearrangements/aberrations

Constitutional hematopoietic disorders

- Heterogeneous group of diseases involving individual lineage defects of erythrocytes, megakaryocytes, and histiocytes
- Usually associated with abnormalities in other organ systems

APLASTIC ANEMIA IN CHILDREN

- Constitutional or acquired
- Initial presentation with trilineage hyperplasia eventually leading to trilineage hypoplasia and bone marrow failure
- Fanconi anemia (FA) is most common genetic aplastic anemia = constitutional DNA repair defect in *FA* gene
- Secondary causes: Radiation, drugs, viruses, immunological

BENIGN ERYTHROID DISORDERS IN CHILDREN

- Non-neoplastic erythroid disorders are called pure red cell aplasia
- Congenital or acquired anemias
- *Neonatal physiologic polycythemia*: Due to intrauterine hypoxia
- Three primary causes of red cell aplasia: Diamond-Blackfan anemia, transient erythroblastopenia of childhood, and Parvovirus infection (acquired disorder and shows intranuclear viral inclusions)
- In all types of red cell aplasias, marrow shows diminished maturing erythroid cells

CONGENITAL DYSERYTHROPOIETIC ANEMIA (CDA)

- Group of rare hereditary disorders characterized by dyserythropoiesis/marked ineffective erythropoiesis
- Three major types (types I, II, and III) and several minor subgroups have been identified
- Beneficial role of splenectomy in CDA type II
- Efficacy of interferon-α in type I
- Type II is most common

Type	Gene
CDA type I	*CDAN1*
CDA type II	*SEC23B*
CDA type III	*CDAN3*

Constitutional disorders affecting granulocytes

CHRONIC GRANULOMATOUS DISEASE

- X-linked or AR
- Abscess and granulomas
- Defective microbial killing by phagocytic cells
- Most common in gastrointestinal tract and lungs

LEUKOCYTE ADHESION DEFECT

- AR
- Lack of neutrophils at site of infection
- Peripheral neutrophilia and myeloid hyperplasia of bone marrow
- Delayed wound healing, delayed attachment of umbilical cord, recurrent infection

CHEDIAK-HIGASHI SYNDROME

- AR
- Functionally defective neutrophils, giant cytoplasmic granules
- Recurrent pyogenic infections, partial oculocutaneous albinism

CYCLIC NEUTROPENIA

- AD or sporadic
- Cyclic hematopoiesis with periods of neutropenia lasting from 9–21 days followed by neutrophilia
- Absence of granulocyte precursors in neutropenic phase
- Increased infections correspond to neutropenic cycle

KOSTMANN SYNDROME

- AR/sporadic
- Severe neutropenia with sustained myeloid aplasia in bone marrow
- Recurrent bacterial infections
- Risk for myelodysplasia, acute myeloid leukemia (AML)

Inherited immunodeficiency disorders

- Lymphocytes (evenly dispersed), constitute up to 40% of nucleated cells in bone marrow/peripheral blood
- Lymphocytic aggregates: Suggest autoimmune disorders/inflammation

HEMATOGONES

- Benign lymphocytes in marrow of young children
- Round/regular nuclei, fine condensed chromatin, inconspicuous nucleoli, high nuclear-cytoplasmic ratio
- Increased in hematological disorders and in marrow recovering after suppression
- Dispersed in marrow with clustering
- Immunoprofile ranges from immature B cells to mature polyclonal B cells

SPECIFIC INHERITED IMMUNODEFICIENCY DISORDERS

Antibody deficiency

Common variable immunodeficiency

- B-cell deficiency, no plasma cells, recurrent gastrointestinal and sino-pulmonary infections

X-linked (Bruton) agammaglobulinemia

- Mutation in tyrosine kinase gene, hypoplastic lymphoid organs, recurrent infections

Selective IgA deficiency

- Common, mild symptoms. In gastrointestinal tract; villus blunting and follicular hyperplasia, celiac disease, infections

Hyper IgM syndrome

- Atrophic germinal centers, abundant plasma cells, recurrent infections

T-cell deficiency

Subacute combined immunodeficiency (SCID)

- Disorders of T cells and B cells, severe systemic infections

Ataxia-telangiectasia

- Chromosome 11q22–23 gene defect, loss of Purkinje cells in cerebellum, hypoplastic lymphoid tissue, recurrent infections, ataxia, and telangiectasia

Wiskott-Aldrich

- X-linked recessive, lymphoid depletion, thrombocytopenia, petechiae, bleeding, eczema

Platelet and megakaryocytic disorders

NEONATAL THROMBOCYTOPENIA

Transient thrombocytopenia

- Seen in 4% of newborns
- Idiopathic, distressed newborns
- Spontaneous remission

DOWN SYNDROME

- Giant platelets, thrombocytopenia, circulating megakaryocytes

TAR SYNDROME

- Mutation in *RBM8A* gene
- Decreased bone marrow megakaryocytes, thrombocytopenia, absent radii

OTHER CAUSES

- Maternal drug therapy
- Maternal illness
- Maternal alloimmunization against fetal antigens
- Fetal chromosomal disorders, infections

Neoplastic disorders of bone marrow

COMMON IMMUNOPHENOTYPES OF HEMATOPOIETIC CELLS

T cells: CD2, CD3, CD5, CD7, either CD4 or CD8

B cells: CD79a, CD19, CD20, CD22, HLA-DR, sIg

NK cells: CD16, CD56, CD57

Monocytes: CD11b, CD11c, CD13, CD33, CD68, CD163

Megakaryocytes: CD41, CD61

Erythrocytes: GLUT 1, glycophorin A, glycophorin B, CD71 (precursors through reticulocytes)

Plasma cells: CD38, CD138

MYELOPROLIFERATIVE DISORDERS IN DOWN SYNDROME

Transient myeloproliferative disorder

- Neonates with DS
- Leukocytosis with increased circulating heterogeneous blasts (erythroblasts and megakaryoblasts)
- *GATA1* mutation involved
- Spontaneously resolve in 1–2 months
- Many patients develop acute megakaryoblastic leukemia

Acute leukemias

- Higher incidence in children with DS
- Severe bone marrow failure and hepatosplenomegaly
- In children younger than 3 years, acute megakaryoblastic leukemia + erythroid blasts
- *GATA1* mutation involved
- In children older than 3 years, acute lymphoblastic leukemia

CONGENITAL ACUTE LEUKEMIAS

- Presenting at birth up to 1 month of age
- Poor prognosis, central nervous system (CNS) involvement
- Mostly myeloid with monoblastic component
- Marked leukocytosis, extramedullary disease, skin lesions, hepatosplenomegaly
- If lymphoid, 11q23 translocation (*MLL* gene)
- Immunoprofile: CD10-ve, CD15+ve, B-cell precursor phenotype with myeloid antigen coexpression
- Acute megakaryoblastic leukemia; associated with t(1;22) (severe pancytopenia, bone marrow/extramedullary tumor infiltrates are very fibrotic)

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

- Children <15 years of age, boys, DS or with translocation 11q23
- Fever, bleeding, hepatosplenomegaly, leukocytosis, mediastinal mass, CNS involvement
- Derived from B or T precursor cells, morphologically indistinguishable
- Most acute lymphoblastic leukemias are derived from B lymphocytes
- *FAB classification*: L1 (blasts with high nuclear/cytoplasm ratio), L2 (blasts with moderate to abundant cytoplasm), and L3 (blasts with deeply basophilic and vacuolated cytoplasm)

Biologic basis of classification

- Chromosomal abnormalities noted in most cases of ALL

ALL (numerical abnormalities)

- Hyperdiploid (25%–40%): Favorable response to antimetabolite therapy
- Hypodiploid (2%–8%): Poor prognosis

ALL (structural abnormalities)

- t(12;21) TEL/AML1
  - Good prognosis, most common
- t(9;22) BCR/ABL
  - Poor response to therapy (Ph chromosome positive)

- t(1;19) E2A/PBX1
  - Neonates and infants, high risk disease at presentation, poor response to therapy
- t(11q23) MLL
  - High risk disease at presentation, poor treatment outcome, therapy related/congenital leukemias
- t(8;14) (q24;q32)
  - MYC dysregulation, B-ALL with L3 (Burkitt) morphology, mature B-cell phenotype
- t(5;14)
  - Aggressive clinical course, tissue eosinophilia, organomegaly, older children

ACUTE MYELOGENOUS LEUKEMIA (AML)

- Most congenital leukemias are myeloid
- Overall incidence of AML lower in children compared to adults
- Association with constitutional genetic disorders, environmental/occupational exposures (chemicals, radiation), smoking, acquired bone marrow diseases, therapeutic agents

AML staining profile

- *Myeloblast*: Sudan Black B+, MPO+. Immunophenotype: HLA-DR+, CD13+, CD33+, CD34+, MPO+
- *Promyelocyte*: Sudan Black B+, MPO+. Immunophenotype: CD13+, CD33+, MPO+
- *Monoblast*: NSE+. Immunophenotype: CD13+, CD33+, CD4+, HLA-DR+
- *Promonocyte*: NSE+. Immunophenotype: CD13+, CD33+, CD4+, CD14+, HLA-DR+
- *Erythroblast*: PAS+. Immunophenotype: Glycophorin A+, CD71+, HbA+
- *Megakaryoblast*: PAS+. Immunophenotype: CD41+, CD61+, HLA-DR+, factor VIII

Biologic basis of classification

AML numerical abnormalities

- –5, –7, –X, –Y, del(7q)—found in 30%–40% of children with AML
- Linked to adverse outcomes

AML structural abnormalities

- t(8;21) AML1/ETO
  - Favorable prognosis
  - May present with extramedullary disease
  - Blasts with long slender Auer rods/abnormal granules
- t(15;17) PML/RARA
  - Acute promyelocytic leukemia (M3)
  - Favorable prognosis
  - Abnormal promyelocytes, multiple Auer rods, coarse cytoplasmic granules
  - Pancytopenia, marked thrombocytopenia/coagulopathy
  - *Microgranular variant*: Leukocytosis, hypogranular promyelocytes, marked nuclear folding
  - Stain intensely with myeloperoxidase and Sudan Black B
  - Good prognosis with treatment (all-trans retinoic acid therapy)
- Inv16 CBF beta/MYH11
  - Acute myelomonocytic leukemia (M4)
  - Favorable prognosis
  - May present with myeloid sarcoma
  - Abnormal eosinophils, large eosinophilic/basophilic granules, decreased lobulation
- 11q23 MLL (multiple partner gene)
  - Congenital myeloid leukemias, monoblastic, t(4;11)
  - Therapy-related monoblastic/monocytic leukemias (following topoisomerase II inhibitor therapy)
  - Poor outcome overall
- AML with monosomy 7
  - Poor overall prognosis
  - Pre-existing myelodysplastic syndrome, monosomy 7 or CMML
  - Dyserythropoiesis, abnormal granular myelocytes, nuclear/cytoplasmic dyssynchrony

Requirements for assigning more than one lineage to a single blast population (mixed phenotypic acute leukemias)

Myeloid lineage

- Myeloperoxidase (flow cytometry, IHC, or cytochemistry)
  or

- Monocytic differentiation (at least two of these should be positive: NSE, CD11c, CD14, CD64, lysozyme)

T lineage

- Cytoplasmic CD3 (flow cytometry, IHC)
  or
- Surface CD3

B lineage

- Strong CD19 with at least one of these strongly expressed (CD79a, cytoplasmic CD22, CD10)
  or
- Weak CD19 with at least two of these strongly expressed (CD79a, cytoplasmic CD22, CD10)

Chronic myelodysplastic/ myeloproliferative disorders in children

- Leukocytosis, neutrophilia, monocytosis
- Left shift to blasts, multilineage dyspoiesis
- Anemia and thrombocytopenia
- Skin lesions and hepatosplenomegaly

JUVENILE MYELOMONOCYTIC LEUKEMIA

- Monosomy 7/del(7q)
- No PH+ chromosome (d/d CML)
- Similar features as monosomy 7 syndrome
- Increased hemoglobin F, mutations in *RAS/NF1* gene
- Leukocytosis, monocytosis, left shift, dysplasia
- <20% blasts + promonocytes in bone marrow
- Poor overall prognosis

CONVENTIONAL CML

- Philadelphia chromosome positive, t(9;22)

Neoplastic histiocytic disorders in bone marrow

MONOCYTIC/MYELOMONOCYTIC LEUKEMIAS

- Described earlier

LANGERHANS CELL HISTIOCYTOSIS

- Minimal to extensive involvement of bone marrow
- Characteristic folded nucleus of lesional cells, delicate chromatin, abundant cytoplasm, admixture of eosinophils, neutrophils, and multinucleated cells in background
- CD1a and S100 positive

HISTIOCYTIC SARCOMA/ MALIGNANT HISTIOCYTOSIS

- Very large cells with marked atypia
- Express myeloid/monocytic antigens, NSE
- Mass lesion with less than 25% malignant cells in bone marrow

Metastatic disorders in bone marrow

- Common tumors: Neuroblastoma, primitive neuroectodermal tumor (PNET), rhabdomyosarcoma, synovial sarcoma, and lymphoma
- Metastatic tumors display cell cohesion
- Diagnosis aided by immunohistochemistry

Bone marrow transplantation

- Therapeutic option for untreatable acute leukemias, lymphomas, and solid tumors
- Autogenic and allogenic (HLA-matched donors) bone marrow transplants

ALLOGENIC TRANSPLANT

- Performed in diseases involving clonal stem cells
- Prior ablation by intensive chemotherapy/ body irradiation required (to eradicate immunogenic cells and tumor cells in marrow)

AUTOGENIC TRANSPLANT

- Collections of bone marrow or stem cells from the patient
- Transplanted marrow should be free from tumor cells
- No prior ablation required

- No serious risks of transplantation (graft-versus-host disease, myelodysplasia, post-transplant lymphoproliferative disease, secondary malignancies, solid tumors graft rejection)

Morphology of posttransplant bone marrow

Immediate (1–7 days posttransplant)

- Marrow fibrosis, serous atrophy, edema, increased stromal cells

After 7 days

- Engraftment begins
- Colonies of erythrocytes, leukocytes, and megakaryocytes formed

At 21 days

- Bone marrow cellularity increased to about 50%
- Graft failure occurs if there is failure of transplanted cells to engraft by day 28

Hemophagocytic lymphohistiocytosis (HLH)

- Uncommon hematologic disorder clinically manifesting as fever, hepatosplenomegaly, lymphadenopathy, jaundice, rash
- Excessive activation of T lymphocytes and macrophages
- Pathologic findings: Histiocytosis, hemophagocytosis, pancytopenia
- Laboratory findings: Increased ferritin levels, abnormal liver function tests
- Primary HLH (familial HLH) is autosomal recessive
- Familial HLH mostly caused by mutation in genes: *PRF1* and *UNC13D*
- Secondary HLH (acquired HLH) occurs after strong immunologic activation (systemic infection, immunodeficiency, or underlying malignancy
- Sometimes secondary may be self-limited

31 Lymph Nodes, Spleen, and Thymus

Lymph nodes

NORMAL STRUCTURE AND FUNCTION

- Normal lymph node less than 1 cm in size
- Enlarged when immunogenic lymph drains into it
- Composed of four zones: Follicles (B lymphocytes), mantle zone (B lymphocytes), paracortex (macrophages, T lymphocytes, dendritic cells), and sinuses (macrophages and antigen-presenting cells)
- Lymph node biopsy recommended if size >2 cm, abnormal chest x-ray, no signs/symptoms of recent inflammation/infection

TRIAGE OF LYMPH NODE BIOPSY/ASPIRATE

- Touch preps/smears immediately after lymph node biopsy/aspirate
- If hematological malignancy, perform flow cytometry, cytogenetics/fluorescence in situ hybridization (FISH) analysis, histology and immunohistochemistry
- If reactive/Hodgkin lymphoma/metastatic malignancy; cultures, cytogenetic analysis, histology, and immunohistochemistry

Cytogenetic studies

- Viable fresh tissue used for cultures to prepare metaphase spread
- Karyotypic abnormalities (diagnostic for certain malignancies) may predict prognosis
- FISH: Rapid turn-around time, performed on fixed tissue, formalin-fixed paraffin-embedded tissue, touch prep, cytospin prep

REACTIVE LYMPHADENOPATHY

- Follicular hyperplasia/interfollicular hyperplasia
- Immunoblastic, granulomatous, or histiocytic

Follicular hyperplasias

Non-specific germinal center hyperplasia

- Round/irregular germinal centers
- Germinal center composed of B lymphocytes, tingible body macrophages, apoptotic cells
- Follicles mainly in cortex but if severe, may involve paracortex and medulla

HIV-related adenopathy

- Generalized lymphadenopathy
- Florid follicular hyperplasia, large/serpentine germinal centers
- Follicular lysis, follicular depletion

Progressively transformed germinal centers

- Adolescent/young males
- Cervical/inguinal lymphadenopathy
- Florid follicular hyperplasia
- Disrupted follicles infiltrated by small mantle zone lymphocytes
- Absence of variant Reed-Sternberg cells (d/d from Hodgkin lymphoma)

Toxoplasmosis

- Cervical lymph nodes
- Florid follicular hyperplasia
- Aggregates of epithelioid histiocytes encroaching follicular centers
- Hyperplasia of parasinusoidal monocytoid B cells

Castleman disease/angiofollicular hyperplasia

- Hyaline vascular variant (HV-CD)
  - Cervical/mediastinal lymph nodes

  - Small/uniform follicles (involuted germinal centers) evenly dispersed throughout cortex and medulla (bag of marbles)
  - Onion skin mantle zones, multiple germinal centers
  - Radially penetrating hyalinized high endothelial venules passing through the germinal centers into the paracortex (lollypops)
  - Dense aggregates of follicular dendritic cells highlighted by CD21 and CD23 stains
  - Plasma cells are monotypic (lambda positive)
- Plasma cell variant (PV-CD)
  - Uncommon in children
  - Systemic disorder, fever, weight loss, hypergammaglobulinemia
  - Follicular hyperplasia, interfollicular plasmacytosis
  - HIV-infected patients; PV-CD associated with HHV-8 infection

Interfollicular/para-cortical reactions—immunoblastic

Epstein-Barr virus (EBV) infection (infectious mononucleosis)

- Acute illness, self-limited
- Preserved architecture, moth-eaten/compressed follicles
- Expansion of paracortex by immunoblasts, plasma cells, plasmacytoid lymphocytes, histiocytes
- Increased number of high endothelial venules
- B and T immunoblasts highlighted by CD20 and CD3 stains, respectively
- Polytypic pattern of light chain expression
- Markers of EBV infection positive (latent membrane protein [LMP] and EBER)

Non-EBV viral adenopathy

- Para-cortical hyperplasia, necrosis
- Viral inclusions
- Serology diagnostic (CMV, HSV)

Hypersensitivity reactions

- Dilantin or various vaccines (small pox, measles, tetanus)
- Distorted architecture, expansion of paracortex (by immunoblasts, lymphocytes, plasma cells, and eosinophils)

Juvenile-onset rheumatoid arthritis

- Still disease
- Follicular hyperplasia, interfollicular plasma cells, intrasinusoidal neutrophils

Systemic lupus erythematosus

- Peripheral/generalized lymphadenopathy
- Follicular hyperplasia, patchy para-cortical necrosis
- Necrotic foci show eosinophilic debris, apoptotic cells, and scant neutrophils/plasma cells
- Hematoxylin bodies (5–15 μ blue oblong)
- Vascular encrustations (Azzopardi effect)

Histiocytic necrotizing lymphadenitis

- Also known as Kikuchi-Fujimoto disease
- Initially diagnosed in Japan but worldwide now
- Follicular hyperplasia, para-cortical zonal karyorrhexis
- Scant neutrophilic response
- Paracortex contains small lymphocytes, immunoblasts, apoptotic debris, plasmacytoid monocytes, high endothelial venules
- Mostly CD8+ T lymphocytes
- May present with hemophagocytic syndrome

Autoimmune lymphoproliferative syndrome

- Lymphadenopathy secondary to Fas or Fas ligand-mediated apoptosis
- First 2 years of life
- Bulky generalized lymphadenopathy, hepatosplenomegaly
- Immunoblasts and T lymphocytes in interfollicular region are CD3+
- Double-negative T cells
- Gene sequencing confirms diagnosis

Kawasaki disease

- Also known as mucocutaneous lymph node syndrome
- Endemic in Japan
- 3–4 year old children

- Patchy para-cortical necrosis, phlebitis, and fibrin microthrombi
- Acute necrotizing arteritis in perinodal tissue

Granulomatous lymphadenitis

Cat scratch disease

- *Bartonella henselae* (small intracellular gram-negative rods)
- Serpiginous/stellate neutrophil-rich micro-abscesses in lymph nodes
- Warthin-Starry stain highlights pleomorphic rods and cocci
- Polymerase chain reaction (PCR) for diagnostic confirmation
- Similar histology of lymph nodes seen in Yersinia, tularemia, lymphogranuloma venereum (LGV), *Mycobacterium avium-intracellulare* (MAI)

Mycobacterial infections

- Tubercular granulomatous lymphadenitis with caseous necrosis
- Non-tubercular atypical mycobacterial infection (MAI, *Mycobacterium scrofulaceum*)
- Follicular hyperplasia, well-formed epithelioid granulomas, microabscesses
- Organisms demonstrated by acid-fast stain, auramine orange (fluorescence microscopy), MPT64 Ag (immunochromatographic test), and immunohistochemistry
- PCR confirms diagnosis

Chronic granulomatous disease

- Defective component of NADPH-oxidase pathway
- Lymph nodes and other tissues infiltrated by granulomas and neutrophil-rich abscesses
- Superimposed infections by *Staphylococcus aureus*, Gram-negative bacilli, and *Aspergillus*
- Diagnostic tests: Nitroblue tetrazolium reduction, chemiluminescence, flow-cytometry, molecular testing
- Differential diagnosis with sarcoidosis

Histiocytic lymphadenitis

Interfollicular processes with histiocytic proliferation

- Lymph nodes draining inflammatory/malignant processes of skin, bowel, lungs
- Subcapsular/paratrabecular sinuses filled with histiocytes (CD68+ve, S100–ve, CD1a–ve)
- Compressed follicles with diminutive germinal centers

Sinus histiocytosis with massive lymphadenopathy

- Also known as Rosai-Dorfman disease
- Compressed/diminutive germinal centers and paracortex
- Sinuses expanded and filled with mixed infiltrate of lymphocytes, plasma cells, histiocytes, xanthoma cells, and Rosai-Dorfman histiocytes
- *Emperipolesis*: Rosai-Dorfman histiocytes show engulfed lymphocytes in cytoplasm
- Immunophenotye of Rosai-Dorfman cells: CD68+, S100+, CD21–, and CD1a–

Foreign body sinusoidal histiocytic reactions

- Benign condition
- Seen in lymph nodes located close to joint prosthesis, contrast media, primary metabolic diseases
- Lymph nodes draining tumor/ulcerated areas
- Sinuses distended by foamy macrophages with vacuoles, histiocytes, multinucleated giant cells

Dermatopathic lymphadenitis

- Eczema or chronic exanthematous disorder
- Enlarged axillary/inguinal lymph nodes
- Follicular hyperplasia and expansion of sinuses by histiocytes (with melanin/hemosiderin pigment), Langerhans cells, eosinophils
- Paracortex is pale pink/mottled due to collections of histiocytes/Langerhans cells

Hemophagocytic lymphohistiocytosis (HLH)

- Specific clinical, laboratory, and histopathologic criteria required for diagnosis
- Small follicles and paracortex
- Sinuses distended with histiocytes (many with phagocytosis)

- Histiocytes have bland nuclei, abundant eosinophilic cytoplasm (engulfed red blood cells/fragments of red blood cells)
- Erythrophagocytosis more common than leukophagocytosis
- Immunophenotype: CD68+, S100–, CD1a–, and CD207–

Langerhans cell histiocytosis

- Systemic multiorgan disease
- Sinuses expanded by Langerhans cells, non-Langerhans histiocytes, dendritic cells, lymphocytes, eosinophils
- Immunophenotype of Langerhans cells; CD1a+, S100+, CD207+ (Langerin) CD68–
- *EM*: Birbeck granules (tennis racket shaped)

MALIGNANT LYMPHADENOPATHY

Non-Hodgkin lymphoma

- Nodal malignancies are mostly of lymphoid lineage
- Four most common pediatric lymphomas are precursor B-cell or T-cell lymphoblastic lymphoma, anaplastic large cell lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma

Precursor B lymphoblastic lymphoma

- Nodal architecture effaced by diffuse proliferation of small/intermediate lymphoblasts
- Infiltration in capsular collagen, perinodal fat
- Fine/speckled chromatin, indistinct nucleoli, scant cytoplasm, high mitotic activity
- Immunophenotype: CD45 (dim to negative), TdT+, CD10+, CD19+, CD20–, sIg–
- Differential diagnosis with other small blue cell tumors
- B-cell lymphoblastic lymphoma comprises 15% of lymphoblastic lymphomas
- T-cell lymphoblastic lymphoma comprises 85% of lymphoblastic lymphomas (commonly involves mediastinum)

Diffuse large B-cell lymphoma

- Patients have congenital/acquired immune deficiency
- Steadily enlarging peripheral lymphadenopathy or extra-nodal disease
- Diffuse growth pattern, abundant cytoplasm
- Neoplastic lymphocytes mimic reactive immunoblasts or may be frankly anaplastic multilobate cells
- Immunophenotype: pan B-cell markers (CD19+, CD20+, CD79a+), BCL6+(many), sIg+

Burkitt lymphoma

- Lymph node architecture distorted by diffuse proliferation of intermediate-size lymphocytes
- Round/oval nuclei, prominent nucleoli, amphophilic abundant vacuolated cytoplasm, necrosis, high mitotic activity
- Starry sky appearance (macrophages with cellular debris)
- >95% MIB-1/Ki-67 positivity
- Immunophenotype: mature B cell, sIg+, CD19+, CD20+, CD10+, BCL6+, TdT–ve, BCL2–ve
- FISH: t(8;14) = C-MYC
- Endemic
  - Africa, children
  - Strong association with EBV
  - Affects body parts involved with active growth/hormonally responsive (jaw, breast, ovaries, testes)
- Sporadic
  - Affects children and adults
  - Less commonly associated with EBV
  - Viscera (intestines) involved
- Immunodeficiency related
  - Congenital immunodeficiency, HIV infection, posttransplant
  - Visceral involvement (intestines)

T-Lymphoblastic lymphoma

- Adolescent and young adults
- Comprise about 85% of lymphoblastic lymphomas
- Mediastinal involvement (compress heart/great vessels, pleural/pericardial effusion)
- Limited bone marrow disease (<25%)
- Neoplastic lymphocytes have similar morphology to B-lymphoblastic lymphoma
- Immunophenotype; immature T-cell (CD45 dim/negative, TdT+, cytoplasmic CD3+, surface CD3–, CD2+, CD7+, HLA-DR–, CD10 (positive in 25%)

Peripheral T-cell lymphoma

- Angioimmunoblastic lymphomas
- Lymph node architecture effaced; heterogeneous lymphoid population (small/intermediate/large), scattered infiltrate of eosinophils and plasma cells
- Neoplastic T-lymphoid cells have irregular nuclei
- Prominent thick-walled blood vessels
- Immunophenotype; CD45+, CD3+, CD45Ro+, CD4+, TdT–, CD8–

Anaplastic large cell-lymphoma

- All ages affected
- Cervical lymphadenopathy, skin, bones, soft tissue
- Neoplastic cells are large, bizarre lobulated wreath-like nuclei, conspicuous nucleoli, abundant eosinophilic cytoplasm
- Immunophenotype: CD30+ (membranous and Golgi positive), ALK-1+, EMA+, CD45+, EBER–
- FISH: t(2;5) = *ALK* gene

Follicular lymphoma

- Rare in children
- CD10+, BCL-6+
- BCL2–ve (unlike adults)

Hodgkin lymphoma

- Nodal tumor of B-cell lineage
- Lymph nodes contain neoplastic Reed-Sternberg (RS) cells (appropriate phenotype) and bland population of background inflammatory cells
- *Lymphocyte predominant Hodgkin lymphoma*
- *Classic Hodgkin lymphoma* (nodular scleroses, mixed cellularity, lymphocyte rich, and lymphocyte depleted)
- RS cells may be classic type (20–40 μ, multilobed nucleus, large nucleoli, abundant eosinophilic cytoplasm), mononuclear type, or lacunar type (nodular scleroses)
- Immunophenotype: CD45–, CD30+, CD15±, CD20±, EBER + (50% cases)

Nodular scleroses

- More common in girls
- Cervical, mediastinal, supraclavicular lymphadenopathy
- Lymph nodes contain broad bands of fibrosis
- Background mixed cellularity of lymphocytes, neutrophils, eosinophils, histiocytes
- RS cells mostly mononuclear, lacunar type

Mixed cellularity

- All age groups
- Neck and mediastinum
- Mixed cellular infiltrate and classic RS cell
- Differential diagnosis with T-cell rich B-cell lymphoma and peripheral T-cell lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma

- Males, fourth decade
- Asymptomatic lymphadenopathy
- Lymph nodes contain nodules of small B lymphocytes, scattered lymphocytic and histiocytic (L&H) RS cell variants
- Collarette of T cells around L&H cells
- L&H cells are multinucleated (popcorn cells)
- Immunophenotype: B-cell phenotype = CD45+, CD20+, OCT-2+ve, BOB.1+ve, CD15–, CD30–, collarette of T cells around L&H cells (CD57+)

Tumors of monocyte/macrophage lineage

- Chloroma/granulocytic sarcoma (in association with AML)
- Lymphadenopathy or visceral/soft-tissue mass
- Lymph node architecture effaced by neoplastic proliferation of intermediate-size cells
- Myeloblasts have round/oval nuclei, fine chromatin, moderate cytoplasm
- Cells positive for CD45, myeloperoxidase, Leder stain (chloroacetate esterase)

Spleen

EMBRYOLOGY

- Develops from mesenchyme located in dorsal mesogastrium

NORMAL STRUCTURE AND FUNCTION

- Major site of blood filtration, antigen-antibody reactions, protects against encapsulated bacteria

Red pulp

- Constitutes major splenic volume
- Site of removal of diseased red cells/platelets/antibody-coated red cells

White pulp

- Gray-white dots in red pulp
- Composed of masses of B/T lymphocytes

COMMON CAUSES OF SPLENECTOMY

- Hereditary spherocytosis, hemolytic anemias, trauma, ITP, hypersplenism

CONGENITAL ANOMALIES

Asplenia

- More common in boys
- Associated cardiac anomalies, poor prognosis (due to associated defects)
- *Findings in peripheral blood*; Howell-Jolly bodies, Pappenheimer bodies, dysmorphic/nucleated red blood cells

Polysplenia

- More common in girls
- Small splenic masses in right quadrant
- Poor prognosis

Accessory spleen

- Solitary usually
- Located in splenic hilum
- Should be removed at time of therapeutic splenectomy (to prevent recurrence of primary disease)

Fusion

- Spleen fused with left testis

Hamartoma

- Uncommon benign tumor, red pulp
- Associated with tuberous sclerosis

Cysts

- Hydatid cysts uncommon in United States
- True cysts (lined by epithelium)
- Pseudocysts (unlined, trauma related)

DISEASES OF RED PULP

Congestion

- Chronic passive congestion in portal hypertension/right-sided heart failure
- Splenic sinuses distended with red cells

Thrombocytopenia

- Refractory thrombocytopenia treated with splenectomy
- Etiology: Drug induced, virus induced, autoimmune, immunodeficiency related, ITP
- Numerous reactive lymphoid follicles
- Red pulp shows myeloid hyperplasia, foamy histiocytes (containing platelet debris)

Hereditary hemolytic anemias

- Disorders include hereditary spherocytosis, elliptocytosis, hemoglobinopathies (thalassemias, sickle-cell anemia)
- Subtotal splenectomy (preserving lower pole) recommended; cures hemolysis, retains spleen function
- Sickle cell anemia (after 10 years of age); spontaneous autosplenectomy (small and fibrotic spleen, multicolored deposits of minerals/hemosiderin = Gamma-Gandy bodies)
- Hereditary hemolytic anemias; splenic congestion, extra-medullary hematopoiesis

Infection

- Acute splenitis; bloodborne bacteria (neutrophilic and plasma cell infiltrate)
- Granulomatous inflammation; fungal, mycobacterial infections
- Vascular peliosis; *Bartonella henselae* in spleen/liver
- EBV-related infectious mononucleosis; red/white pulp infiltrated by polymorphous T and B immunoblasts (CD30 + , CD15–, and CD45–), they should be differentiated from RS cells

DISORDERS OF WHITE PULP

Inborn errors of metabolism

Gaucher disease type I

- Chronic non-neuronopathic type

- Macrophages contain glucosylceramide-laden lysosomes; accumulate in bone marrow/spleen
- Splenic sinuses expanded by clusters/sheets of large macrophages (Gaucher cells)
- Nuclei are bland, round/oval, cytoplasm abundant, wrinkled tissue-paper type
- PAS and iron stains positive
- Leukocytes have diminished/absent lysosomal β-glucocerebrosidase activity
- Pseudo-Gaucher cells in the spleen; seen in CML

Niemann-Pick disease

- Type A (infantile): Severe neurodegenerative disease of infancy
- Accumulation of storage macrophages with sphingomyelin in spleen/other organs
- Niemann-Pick cells have vacuolated cytoplasm (staining blue-green with Giemsa stain)
- Cells positive with PAS and lipid stains but negative with iron stain

Tay-Sachs disease

- Deficiency of hexosaminidase A
- European Jews
- Splenic macrophages have vacuolated cytoplasm
- Stain positive for lipids

Mucopolysaccharidosis

- Macrophage, endothelial cells, and intimal smooth muscle cells involved
- Positive for PAS stain and negative for lipids

Chediak-Higashi syndrome

- Mutation in *LYST* gene
- Formation of abnormal lymphohistiocytic cells with giant abnormal granules
- Oculocutaneous albinism, bleeding abnormalities, bacterial infections, neurologic symptoms

Langerhans cell histiocytosis

- Red pulp infiltrated by neoplastic cells (multisystemic LCH)

Virus-associated hemophagocytic syndrome

- Red pulp contains erythrophagocytic histiocytes

LEUKEMIA AND MYELOPROLIFERATIVE DISORDERS

- Splenomegaly most marked in myeloproliferative disorders; chronic myelogenous leukemia and juvenile myelomonocytic leukemia
- Sheets of immature and maturing myeloid cells in the red pulp

VASCULAR TUMORS

- Non-hematopoietic proliferations in spleen
- Hemangiomas, lymphangiomas
- Peliosis: Dilated blood filled spaces (diffusely dispersed throughout spleen) lacking endothelial lining
- Littoral cell angiomas: Benign vascular tumors, sinusoidal spaces lined by tall endothelial cells (endothelial/histiocytic markers expressed)

OTHER NON-HEMATOPOIETIC TUMORS

- Inflammatory myofibroblastic tumors (positive for SMA, MSA, and cytokeratin)
- Metastatic tumors to spleen are rare

FOLLICULAR HYPERPLASIA

- Uncommon
- Associated with autoimmune diseases

NON-HODGKIN LYMPHOMA

- Rare involvement of spleen

HODGKIN LYMPHOMA

- Fibrotic, well-circumscribed gray-tan masses, in white pulp
- Epithelioid granulomas may be seen

Thymus

- Lymphoepithelial organ located in anterior mediastinum
- Important role in normal T-cell development and cell-mediated immunity

EMBRYOLOGY

- Develops from fourth pharyngeal pouch and inferior aspect of third pharyngeal pouch
- Thymocyte differentiation begins at ninth week of gestation
- Organization into cortex and medulla begins at 12th week of gestation

ANATOMY AND HISTOLOGY

- Thymus continues to grow from birth to puberty
- After puberty it progressively involutes to old age
- Two lobes forming Y-shaped structure
- Contains subspecialized epithelial cells, T lymphocytes, mixed population of monocytes, plasma cells, eosinophils, and mature B lymphocytes
- Cortical lymphocytes express markers of immature T cells
- Medullary thymocytes express markers of mature peripheral T cells
- Epithelial cells in cortex and medulla provide stroma/framework for developing thymocytes
- Hassall corpuscles located in medulla; concentric whorls of keratinized epithelial cells with cystic degeneration

CONGENITAL ANOMALIES

Thymic atrophy

- Normal aging (replacement of lymphoid tissue by adipocytes)
- Acquired hypoplasia: Irradiation, cytotoxic drugs, stress, malnourishment (cortex infiltrated by macrophages, starry sky appearance)

Thymic hypoplasia/complete agenesis

- Primary immunodeficiencies and AIDS

DiGeorge anomaly

- Also known as velocardiofacial syndrome
- Failure of normal development of third and fourth branchial arches
- Hypoplasia/aplasia of thymus, hypoplasia of parathyroid glands/hypocalcemia, truncus arteriosus, dysmorphic facies, micrognathia
- Deletion of chromosome 22q11.2

Severe combined immunodeficiency

- Infants from an early age prone to life-threatening viral/fungal infections
- Depletion of all lymphoid tissue in body, including thymus
- Thymic epithelial tissue becomes prominent

THYMIC TUMORS/TUMOR-LIKE CONDITIONS

- Cysts, thymolipomas, thymic hyperplasia, and thymic tumors

Thymic hyperplasia

- Associated with autoimmune diseases such as myasthenia gravis
- Diagnosis of hypertrophy: Thymus must weigh >100 g

Thymic neoplasms

Thymoma

- Anterior mediastinal tumors
- Very rare in children
- Neoplasms of thymic epithelial cells (positive for cytokeratin and EMA)
- Reactive non-neoplastic lymphoid cells (immature T lymphocytes positive for TdT, CD1, CD2, coexpress CD4 and CD8)
- Myasthenia gravis/other autoimmune disorders develop in children with thymoma
- World Health Organization classification:
  - Type A thymoma (spindle cell)
  - Type AB thymoma (mixed cell)
  - Type B1 thymoma (lymphocyte-predominant thymoma)
  - Type B2 thymoma (mixed lymphoepithelial thymoma)
  - Type B3 thymoma (epithelial predominant thymoma)
  - Type C thymoma (thymic carcinoma)—cells have cytological features of epithelial malignancy

Non-Hodgkin lymphomas

- Low-/intermediate-grade lymphomas, rare in children
- Most of lymphomas in children are Burkitt and lymphoblastic lymphomas
- 80% of non-Hodgkin lymphomas in children are T-cell type
- Most of the mediastinal lymphoblastic lymphomas are T-cell lymphomas (arise in thymic remnants)

Lymphoblastic lymphoma

- Anterior mediastinal mass, cough, chest pain, dysphagia, dyspnea, superior vena cava syndrome
- 80%–90% of tumors are T-cell type and express TdT, CD1a, CD2, CD3 (cytoplasmic), CD7, CD43
- Coexpress CD4 and CD8 or may express neither CD4 nor CD8
- B-lymphoblastic lymphomas express CD10, TdT, CD19, and no expression of surface immunoglobulin
- Lymphoblastic lymphoma where lymphoblasts comprise >25% of bone marrow are classified as acute lymphoblastic leukemia

Large-cell lymphoma

- Young women, symptomatology similar to lymphoblastic lymphoma in mediastinum
- Mature B cell (CD19 and CD20 positive)
- IHC differentiates the neoplasm from seminomas (PLAP+ and LCA–), thymic carcinoma (keratin+ and LCA–), ALCL (AlK+, EMA+, and CD30+), syncytial variant of nodular sclerosis Hodgkin lymphoma (RS cells positive for CD15 and CD30)

Hodgkin lymphoma

- In mediastinum, common type is nodular sclerosis
- Dense bands of collagen in lymph nodes/thymus

32 Selected Topics in Pediatric Blood-Banking and Coagulation

Pediatric blood transfusion

- For most children transfusion should be considered with 15%–20% blood loss
- 10–15 mL/kg red blood cells (RBCs) will raise the hemoglobin by 2–3 g/dL
- Transfuse over 1–2 hours but transfusion must be completed in less than 4 hours
- In the blood administration set, RBC transfusion filter is 170–260 μ
- To remove platelets, leukocytes, and fibrin, 20–40 μ microaggregate filter is used

LEUKOREDUCED RBCs

- Must have less than 5×10^6 leukocytes/unit while retaining 85% of the RBCs
- Prestorage, laboratory, or bedside filtration
- Pre-storage leukoreduction is better as no cytokines released and hence decreased frequency of febrile transfusion reactions
- Leukoreduction helps in reduction of cytomegalovirus (CMV) transmission, reduction of human leukocyte antigen (HLA) alloimmunization, and reduction of febrile transfusion reactions

BLOOD ADDITIVES

- Nutrients and buffer that preserve the red cells and extend shelf life to 42 days
- With age RBCs lose potassium and 2,3-DPG (diphosphoglycerate)
- Some hospitals use units ≤7–14 days old in neonates for massive transfusions, cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO), or exchange transfusion

IRRADIATION

- 25 GY irradiation minimum is needed to prevent graft-versus-host disease
- Expiration life shortens to less than 28 days after irradiation

WASHED RBCs

- Standard wash procedure removes 98% of plasma
- Expiration life of unit is reduced to 24 hours after washing
- Used in an infant who requires large volume transfusion; hyperkalemia-induced arrhythmias avoided
- Prevention of severe allergic reactions/anaphylaxis in IgA-deficient patients

PLATELET TRANSFUSION

Platelet pheresis (PP)

- Also known as apheresis platelets or single donor platelets
- One donor from an apheresis procedure provides at least 3×10^{11} platelets (constitutes one dose for a large child or an adult)

Random donor platelets

- At least 5.5×10^{10} platelets (three to six units constitute one dose)

Platelets

- Shelf life is 5 days
- Room temperature = 20–24°C
- Gentle agitation for gas diffusion
- After pooling or otherwise entering, unit must be used within 4 hours

Indications

- Thrombocytopenia, congenital, or acquired qualitative platelet dysfunction
- Normal platelet count in neonate is same as that of older children/adults

- 50 K platelet count is considered hemostatic unless the patient has other underlying diseases
- In sick premature infant, platelet transfusion recommended if platelet count is 100 K/µL (due to risk of bleeding)
- In stable premature infant, platelet transfusion recommended if platelet count is <50 K/µL

Contraindications of platelet transfusion

- ITP, TTP/HUS, HIT (heparin-induced thrombocytopenia)

General recommendations

- Plasma of the donor should be ABO compatible with red cells of the recipient
- Platelets contain small amount of RBCs so Rh–ve platelet transfusions should be given to Rh–ve recipient
- RhIG: If Rh incompatible platelets transfused in an emergency, then one full dose of RhIG can protect the transfusion recipient for up to 15 mL of D-positive red cells
- 5–10 mL/kg of single donor platelets or PP component should increase platelet count by 50 K

Neonatal alloimmune thrombocytopenic purpura

- Severe congenital thrombocytopenia
- Usually due to maternal anti-PL^{A1}
- Treated with washed maternal platelets (lack the offending antigen and antibody)

PLASMA COMPONENTS

Fresh frozen plasma (FFP)

- Stored at –180°C for up to 1 year
- 1 unit of FFP contains 1 unit of coagulation factor activity, 200–250 mL volume
- WBCs non-functional (no cryoprotectant)
- Leukoreduction and irradiation are unnecessary
- It is frozen within 8 hours and preserves labile factors V and VIII

Uses of FFP

- Acutely bleeding patient
- Invasive procedure planned in a patient with documented coagulation factor deficiency
- Patients with liver disease
- PT >1.5 times normal
- Reversal of warfarin, treatment of DIC, replacement fluid for TTP, HUS

Contraindications for FFP

- Do not give for volume expansion/nutritional support
- Colloids or protein containing solutions better for volume expansion/nutritional support, as no risk of viral transmission

Cryosupernatant

- Cryo poor plasma used in patients who are refractory to initial treatment with FFP
- Lacks large molecular weight Von Willebrand multimers
- Prepared by removing cryoprecipitate from FFP

Cryoprecipitate

- Prepared by thawing 1 unit of FFP at 1–6°C and removing the supernatant
- Contains fibrinogen, factor VIII C, factor VIII VWF, factor XIII
- Small volume (10–15 mL) allows more rapid replacement of coagulation factors than a single unit of FFP (200 mL)
- Reduced risk of volume overload
- Not the "product of choice" for treating hemophilia, despite high levels of factor VIII
- Recombinant or virus-inactivated products remain the first-line therapy for hemophilia
- Not the "product of choice" for treating Von Willebrand disease
- Pharmacologic agents (DDAVP) or virus-inactivated concentrates (Humate P) are primary therapies for VW disease

HEMOLYTIC DISEASE OF THE NEWBORN (HDN)

- Most severe HDN is with anti-D
- Anemia, indirect hyperbilirubinemia/jaundice

- Positive DAT, erythroblastosis fetalis (increase in nRBCs in circulation in response to increased destruction)
- Hydrops fetalis (most severe HDN, often fatal in utero, extra-medullary hematopoiesis in the liver)

Abo HDN

- Most common type of HDN
- Mild or undiagnosed usually
- The antibodies are of IgM type, large in size, and thus cannot cross the placenta
- Group O moms, Group A or B babies
- No intervention necessary unless very severe

Rh HDN

- Most severe HDN
- Anti-D antibodies are of IgG type and can cross the placenta
- Not manifested in first pregnancy (unless mother has prior history of transfusion)
- D–ve moms, D+ve babies
- *Prevention*: RhIG—commercially prepared anti-D (RhoGam)

Lab testing

- Infant D+ve, DAT strongly +ve
- Antibody screen = anti-D, indirect bilirubin elevated
- Increased change in amniotic fluid optical density at 450 nm (Liley graph)

RhoGam

- Prevents D antigen recognition in vulnerable moms
- *Obstetric indications* → D–ve female at 28 weeks' gestation, D–ve female within 72 hours of D+ve infant's birth, D–ve female with pregnancy complications or invasive procedures (e.g., amniocentesis)
- *Dosage*: One full dose vial (30 µgm) per 30 mL of D+ve whole blood
- Kleihauer-Betke test—quantitative test (acid-resistant HbF; fetal RBCs stain brightly)
- KB% × 5/3 = number of vials required to be injected

EXCHANGE TRANSFUSION

- Exchange transfusion indicated for HDN, hyperleukocytosis, or sickle cell anemia
- Purpose of exchange transfusion will determine recommended hematocrit and amount of fresh frozen plasma to be used in reconstituted unit
- Compatability testing: Mother's serum may be used for crossmatch

CONGENITAL HEMOGLOBINOPATHIES

Thalassemia

- Transfusion improves oxygen-carrying capacity of blood
- To suppress endogenous erythropoiesis that causes bony abnormalities
- Transfuse every 3–4 weeks at a dose to maintain pre-transfusion Hb of 9.5–10.5 g/dL and posttransfusion Hb of 13–13.5 g/dL
- Chronic transfusion can cause iron overload

ABO SELECTION OF BLOOD COMPONENTS

When transfusing whole blood/packed RBCs

RECIPIENT \ DONOR	A	B	AB	O
A	✓			✓
B		✓		✓
AB	✓	✓	✓	✓
O				✓

When transfusing plasma

RECIPIENT \ DONOR	A	B	AB	O
A	✓		✓	
B		✓	✓	
AB			✓	
O	✓	✓	✓	✓

SELECTION OF RBCs (IMMUNOLOGICAL CONSIDERATIONS)

- Everyone can receive "O" RBCs. Most receive group-specific RBCs
- D-positive individuals can receive D-positive or D-negative RBCs

- D-negative individuals should receive D-negative RBCs

NEONATES

- Contain maternal immunoglobulin
- Transfusion must be compatible with infant's blood group and maternal blood group
- For simplicity, many transfusion services transfuse group O to all neonates
- Antibody screen must be done prior to neonatal transfusion either using neonate's serum or mother's serum

Selected Topics in Coagulation Disorders

- Coagulation system is divided into five components: Vascular endothelium, circulating platelets, coagulation factors, coagulation inhibitors, and fibrinolysis

Vascular endothelium

- *When intact*
  - Vascular endothelium prevents coagulation by secreting platelet inhibitors such as prostacyclin PGI2 and nitric oxide, thus preventing platelet adhesion
  - It also secretes fibrinolytic proteins such as tissue plasminogen activator tPA and plasminogen activator inhibitor PAI
- *When damaged*
  - Vascular endothelium promotes thrombogenesis; platelet adhesion stimulated by subendothelial collagen and von Willebrand factor (vWF)
  - Tissue factor activates the extrinsic coagulation cascade
  - Factors V and VIII are released triggering thrombosis

Platelets

- Help in thrombosis by platelet adhesion (GP Ib), activation, and aggregation (IIb/IIIa)
- Platelets cross-link to each other thus stabilizing the fibrin clot

Coagulation proteins

- Extrinsic (factor VII and tissue factor), intrinsic (contact activation, XII, XI, IX, and VIII), and the common pathway (X, V, prothrombin, thrombin, fibrinogen, fibrin, stable clot)
- End result is cleavage of fibrinogen and formation of fibrin clot
- Thrombin is the gatekeeper of the entire clotting cascade

Coagulation inhibitors

- Antithrombin III and heparin cofactor II (both members of SERPIN family) inhibit the fact or Xa/thrombin pathway
- Activated protein C/S prevent thrombogenesis by blocking factor Va and factor VIIIa in the clotting cascade
- Tissue factor pathway inhibition is done by two serine protease inhibitors TFPI-1 and TFPI-2

Fibrinolysis

- Process by which a thrombus/clot is removed from intravascular/extravascular site
- The proteolytic enzyme that aides in this process is plasmin (produced from plasminogen)

HEMORRHAGIC DISEASE OF THE NEWBORN

- Coagulation factors II, VII, IX, and X are produced in the liver and are dependent on vitamin K
- After birth, the levels of these factors normally fall very rapidly
- Unless vitamin K (1 mg intramuscularly) is administered prophylactically to all newborns, there may be risk of hemorrhage
- Risk factors for vitamin K deficiency are antibiotic treatment, exclusive breastfeeding, conjugated hyperbilirubinemia

THROMBOPHILIA IN NEONATES AND CHILDREN

- Genetic factors: Factor V Leiden, prothrombin mutation, protein S and C deficiency, antithrombin deficiency
- Common sites of thrombosis in neonates: Renal veins, vena cava, central lines, catheter sites

- Multiple genetic factors greatly increase the risk of thromboembolism
- Initial workup in the affected patients should include AT III levels, protein C activity, free and total protein S antigen/activity, factor V Leiden, prothrombin G20210A, MTHFR T677T, fasting homocysteine level
- If the mother has a history of lupus; perform circulating lupus anticoagulant and anticardiolipin antibodies

MATERNAL THROMBOPHILIA AND EFFECTS ON PREGNANT MOTHER/FETUS

- Pregnancy is normally a thrombophilic state due to various factors (overall risk of venous thromboembolism in pregnancy is 1:1000)
- An underlying genetic thrombophilia further enhances the prothrombotic features of pregnancy
- The high thrombotic risk is caused by antithrombin III (AT III) deficiency, homozygous factor V Leiden, and the combined defect (factor V Leiden + prothrombin G20210A)
- Uteroplacental circulation is compromised causing fetal growth retardation, fetal death, placental abruption, pre-eclampsia
- Placenta shows multiple infarcts and fibrinoid necrosis of fetal vessels

INHERITED FACTOR DEFICIENCIES

- *Factor VIII deficiency (hemophilia A)*
  - Most common bleeding disorder, X-linked recessive trait, disease manifested if factor VIII levels between 5% and 50%
  - Markedly prolonged aPTT, normal PT, and normal BT
  - Reduced factor VIII:C and normal vWF:Ag and ristocetin cofactor
- *Factor IX deficiency (hemophilia B, Christmas disease)*
  - Clinically indistinguishable from hemophilia A
- *Von Willebrand disease*
  - vWF is a large multimeric glycoprotein synthesized in megakaryocytes and vascular endothelial cells, stored in Weibel-Palade bodies in endothelial cells and alpha granules of platelets
  - Inherited as AD trait
  - Prolonged BT, abnormal PFA-100 result. reduced vWF Ag, decreased ristocetin cofactor, decreased vWF multimers
- *Factor XIII deficiency*
  - Clinically presents as delayed umbilical cord separation, bleeding from umbilical stump, and hemorrhage at circumcision site
  - Screening test: Abnormal clot solubility in 5M urea
- *Antithrombin, protein C, and protein S deficiencies*
- *Activated protein C resistance (Factor V Leiden)*
  - Most common cause of thrombophilia
  - Single point mutation—Arginine 506 replaced by glutamine
  - Bimodal peaks: Neonates and children 11–18 years old
- Prothrombin gene *20210A* mutation
  - Glutamine to arginine mutation at prothrombin gene at position 20210A

DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC)

- Life-threatening microvascular thrombotic condition caused by a variety of insults
- Laboratory screening: Prolonged aPTT, PT, elevated D-dimer and decreased fibrinogen, plasma factors, and platelets

THROMBOTIC MICROANGIOPATHIES

Thrombotic thrombocytopenic purpura (TTP)

- Combination of profound thrombocytopenia, hemolytic anemia, and schistocytosis
- Presence or absence of fever, neurologic symptoms, and renal failure
- Primary and acquired TTP is caused by deficiency of ADAMTS13, a plasma metalloprotease that cleaves von Willebrand factor. May also be secondarily caused by drugs, infectious colitis
- Platelet-rich thrombi noted in heart, pancreas, kidney, adrenal gland, brain, and other organs

Hemolytic uremic syndrome (HUS)

- Hemolytic anemia, acute kidney failure, and thrombocytopenia
- Fibrin/red cell rich thrombi seen mostly confined to kidney

Stec-HUS

- Most common in children
- Proceeded by a prodrome of diarrhea
- Typical HUS caused by Shiga toxin-producing *Escherichia coli* (STEC-HUS)
- *E. coli* O157:H7 accounts for 60% of cases

Atypical HUS

- Less common and heterogeneous
- No prodrome of diarrhea
- Could be caused due to dysregulation of alternative complement pathway

Note

- TTP and HUS are pathologically distinct entities, although they are clinically indistinguishable sometimes
- Differentiation of TTP from HUS in pediatrics is critical
- A life-saving treatment (plasma exchange therapy) is available for TTP, but only supportive therapy/renal dialysis for HUS

33 Transplant Pathology

- Immunosuppressive regimens are the standard of care after organ transplant
- Acute cellular rejection more common than antibody-mediated rejection
- Chronic rejection is fibrosing process; more common in lung transplant
- PTLD (posttransplant lymphoproliferative disease); seen in transplanted organ and extranodal sites
- Alloantigens (foreign) elicit immune response and cause graft rejection
- Alloantigens responsible for rejection; encoded by major histocompatibility complex (MHC)
- Three histopathological types of rejection: Hyperacute, acute, and chronic

Cellular rejection

HYPERACUTE ALLOGRAFT REJECTION

- Thrombotic occlusion of graft vasculature
- Begins within minutes/hours after blood vessel anastomosis
- Preformed antibodies in recipient bind to donor endothelial cells eliciting immune response
- Complement activation → leads to endothelial cell destruction and thrombosis

ACUTE ALLOGRAFT REJECTION

- Encountered in solid organ transplant
- Influx of infiltrating lymphocytes (mainly T lymphocytes); mediate direct killing, macrophage activation, and tissue damage

CHRONIC ALLOGRAFT REJECTION

- Fibrosis and vascular damage, due to repeated episodes of acute rejection
- Both cell-mediated and humoral mechanisms contribute

ALLOGRAFT TOLERANCE

- Donor-derived leukocytes participate in allograft tolerance
- Microchimeras (individuals composed of two or more genetically distinct type of cells) tolerate their allografts better (patients who have received solid organ allograft and partial bone marrow transplant tolerate their allograft better)
- Patients receiving liver allograft do better (large number of leukocytes from the allografted liver migrate to recipient's bone marrow and persist)

Transplant pathology of intestine

- Indication of transplantation: Necrotizing enterocolitis, volvulus, gastroschisis, massive resections, Hirschsprung disease
- Patients who suffer TPN-associated liver disease (portal hypertension and cirrhosis) usually undergo combined intestinal and liver transplant and do well
- Size matching of graft is important factor in pediatric population due to smaller abdominal cavity

PRESERVATION INJURY AND HYPERACUTE REJECTION

- Negligible preservation injury due to villous circulation
- Hyperacute rejection caused by preformed donor-specific antibodies
- Damage to endothelium, fibrin thrombi, and congestion within lamina propria

ACUTE REJECTION

- Commonly observed (50%)
- Occurs within 100 days of transplant
- Non-specific gastrointestinal (GI) symptoms: Fever, nausea, abdominal distension
- Diminished peristalsis, mucosal ulceration
- Mild rejection: Crypt apoptosis (more than 6 apoptotic figures per 10 crypts), lamina propria inflammation (perivascular infiltrate of lymphocytes), and crypt architectural distortion
- Moderate to severe rejection: Enhanced morphological features, villous flattening, mucosal ulceration, and features mimicking pseudomembranous colitis

CHRONIC REJECTION

- Uncommon
- Months after transplantation
- Patients with acute rejection prone to chronic rejection
- Chronic ischemia (due to arterial obstruction); destruction of crypts, villi and lamina propria fibrosis

COMPLICATIONS OF TRANSPLANTATION

Infection

- Common: Bacterial, fungal, and viral (cytomegalovirus [CMV], adenovirus, Epstein-Barr virus [EBV])
- In severely immunocompromised patients, inflammation is mild

Posttransplant lymphoproliferative disorder (PTLD)

- Complication of EBV infection seen after intestinal transplant (common)
- In situ hybridization for EBV early antigen (EBER)
- Polymorphic or monomorphic in origin

Graft-versus-host disease

- Most common in intestines, skin, and liver tissue
- Develops after bone marrow transplant or after transfusion of non-irradiated blood in immunocompromised host
- Donor leukocytes recognize recipient tissue as foreign and attempt to reject them

Acute GVHD

- Profuse watery diarrhea
- Upper GI tract shows lymphocytic infiltration of crypts, apoptosis/vacuolization/karyorrhexis of crypt epithelial cells
- Progresses to neutrophilic infiltration, mucosal ulceration, crypt abscess, villous atrophy
- Immunosuppressive drug for solid organ transplant; *Mycophenolate mofetil* mimics similar histologic features in intestine
- Esophagus: Vacuolization and inflammation of basal cell layer progressing to mucosal desquamation and ulceration

Chronic GVHD

- Small intestine spared
- Esophagus shows scleroderma-like changes and loss of motility

Transplant pathology of liver

- Most common indication; extrahepatic biliary atresia (EHBA)
- Split liver transplant = right trisegment transplanted into adult host and the left lateral lobe transplanted into pediatric host

PRESERVATION (HARVESTING) INJURY

- Originates from donor and tissue procurement factors
- Results in poor allograft function during postoperative period
- Donor risk factors for poor graft function = macrovesicular steatosis (susceptible to ischemic changes), fibrosis, chronic liver disease, donor age
- Injury appears 1–2 posttransplant day
- Poor bile production and elevation of AST and ALT
- Centrilobular pallor and cholestasis

HEPATIC ARTERY THROMBOSIS

- May occur early or late
- Early: Severe graft dysfunction and higher mortality rate
- Late: Coagulative necrosis of centrilobular hepatocytes/bile duct necrosis

BILIARY COMPLICATIONS

- Increased alkaline phosphatase and GGT
- Biliary obstruction, biliary cirrhosis, and biliary vascular fistula

HYPERACUTE (HUMORAL) REJECTION

- Preformed cytotoxic antibodies against ABO blood group antigens or class I and II MHC antigens

ACUTE REJECTION

- Fever, decreased bile flow, and elevated liver enzymes
- Three diagnostic criteria for rejection: Portal inflammation, subendothelial inflammation, and bile duct damage
- Mild rejection = portal inflammation is mild
- Moderate rejection = most portal tracts involved by inflammation
- Severe rejection = spillover into hepatic parenchyma, hepatocyte necrosis (periportal and perivenular)
- Rejection activity index (RAI) is usually mentioned in pathologic report

Note: Refer to the Appendix for Rejection activity index (RAI).

CHRONIC REJECTION

- Rare in frequency
- Generally non-reversible
- Risk factors: Primary diagnosis of autoimmune liver disease, several episodes of acute rejection, non-white race
- Bile duct atrophy, foam cell arteriopathy, bile duct loss

DE NOVO AND RECURRENT AUTOIMMUNE HEPATITIS (AIH)

- Patients transplanted with primary diagnosis of AIH; develop recurrence of disease within a few years of transplant
- Some patients after liver transplant may develop de novo AIH, without prior history of disease
- Criteria: Autoantibodies, lymphoplasmacytic portal inflammation, interface and lobular activity, serological evidence of liver injury, hypergammaglobulinemia
- No evidence of viral hepatitis, drug-induced hepatitis, or rejection

POSTTRANSPLANT OPPORTUNISTIC INFECTION

- Viral infections common (CMV, EBV, HSV, adenovirus)
- EBV infection can lead to PTLD = confirm with EBER

LIVER CHANGES POST-BONE MARROW TRANSPLANTATION

- *GVHD*: Portal inflammation and bile duct injury in acute phase; duct damage and loss in chronic phase
- *Chemotherapy/irradiation*: Veno-occlusive disease (detected with reticulin stain)
- *Infections:* Opportunistic organisms due to immunosuppression

Transplant pathology of pancreas

- Transplant performed in type I diabetes mellitus or in conjunction with kidney allograft due to end-stage kidney disease in diabetes mellitus
- Histopathologic evaluation of pancreatic graft rarely performed
- *Acute rejection*: Divided into several grades depending on intensity of septal, acinar, ductal, and vascular inflammation
- *Chronic rejection*: Shows extensive fibrosis and vascular stenosis

Renal transplant pathology

- Causes of graft failure: Chronic rejection, vascular thrombosis, recurrence of original disease, acute rejection
- Optimal biopsy should have at least 10 glomeruli and 2 arteries

HYPERACUTE AND ACCELERATED ACUTE REJECTION AND DELAYED GRAFT FUNCTION

- Preformed antidonor antibodies and acute tubular necrosis
- *Hyperacute rejection*: Immediately/within days of transplantation leading to graft swelling, tenderness, and anuria
- *Accelerated acute rejection*: C4d immunostaining along peritubular capillaries present
- *Delayed graft function*: Donor factors, peritransplant ischemic injury, drug toxicity

ACUTE REJECTION

- Now diminished drastically in children (due to medical advances)
- *Based on Banff classification*

Type IA

- Mononuclear cell interstitial infiltrates (T lymphocytes) involving more than 25% of parenchyma
- Type IA = tubulitis with at least two foci showing 5–10 intraepithelial mononuclear cells in a tubular cross section (non-atrophic tubules)
- Type IB = severe tubulitis with >10 intraepithelial mononuclear cells in a tubular cross section (non-atrophic tubules)

Type II

In addition to the morphological features of type I A above:

- Intimal arteritis showing lymphocytic infiltration beneath the endothelium of arteries
- Type IIA = mild/moderate endarteritis (in at least one arterial cross section)
- Type IIB = severe intimal arteritis with at least 25% reduction in arterial lumen (in at least one arterial cross section)

Type III

In addition to the morphological features of type I above:

- Transmural arteritis showing fibrinoid mural necrosis with lymphocytic inflammation

Note: For further details on Banff classification refer to the Appendix.

ANTIBODY-MEDIATED REJECTION (AMR)

- Diffuse linear staining for C4d along peritubular capillaries
- C4d-positive cases have higher serum creatinine levels
- Reduced long-term graft survival

CHRONIC ALLOGRAFT NEPHROPATHY

- Graded by extent of tubular atrophy and interstitial fibrosis
- Antibody-mediated rejection = double contours along glomerular capillary walls on silver stains
- Fibrous intimal thickening in arteries
- Diffuse C4d staining along peritubular capillaries

VASCULAR THROMBOSIS

- Important cause of graft failure
- Negative for C4d staining along peritubular capillaries
- Risk factors: Pretransplant peritoneal dialysis, cadaveric kidney from donor less than 6 years old, recipient less than 2 years old, prior transplantation

RECURRENT DISEASE

- Recurrence of original disease in transplanted kidney contributes to allograft dysfunction
- Common diseases include FSGS (most common), MPGN type I, MPGN type II

IMMUNOSUPPRESSIVE DRUG TOXICITY

- Calcineurin inhibitors (*cyclosporine and tacrolimus*) have most significant renal toxicity

- Chronic toxicity; PAS positive subadventitial mural hyaline nodules in wall of arterioles

POLYOMAVIRUS TYPE BK (BKV) INFECTION

- Reduced long-term graft function
- Recipient seronegativity for BKV is risk factor
- Large basophilic inclusion bearing cells in tubular epithelial cells; stain with antibody to SV-40 large T antigen
- Inclusion-bearing cells (decoy cells), identified in urine

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

- 1% of renal transplant recipients (uncommon)
- Interstitial infiltrate is dense, composed of monomorphic/polymorphic range of lymphoid cells (mainly B lymphocytes), without neutrophils or eosinophils
- No tubulitis or endarteritis
- Confirmed by EBER

Heart transplant pathology

- First year of life is most common for heart transplant
- Indications: Congenital cardiac malformations (mostly post-surgery), dilated cardiomyopathy, re-transplantation after rejection

REJECTION

- Gold standard for surveillance of acute cellular rejection = endomyocardial biopsy
- T-cell-mediated response directed against cardiac allograft
- Increased B lymphocytes, natural killer (NK) cells, neutrophils, and eosinophils seen
- Old grading system of ISHLT transplant rejection, devised in 1990
- New system devised in 2005 and 2013 = simpler and reproducible:
  - No rejection: *grade 0R*
  - Mild low grade rejection (interstitial and/or focal perivascular cellular infiltrate with up to one focus of myocyte damage): *grade IR*
  - Moderate intermediate grade rejection (two or more foci of cellular infiltrate with myocyte damage): *grade 2R*
  - Severe high-grade rejection (diffuse cellular infiltrate with multifocal myocyte damage. Associated edema, hemorrhage, vasculitis): *grade 3R*

ANTIBODY-MEDIATED REJECTION (AMR)

- Antidonor-reactive antibodies, activation of complement system leading to graft damage
- AMR does not respond to immunosuppressives
- Risk factors for AMR: Previous transplantation, blood transfusion, use of ventilator assist devices
- Decreased survival of patient
- Capillary endothelial changes including swelling, congestion, macrophages (CD68 positive) and neutrophils in capillaries, fibrin deposition in vessels
- C4d immunostaining of capillaries
- IF: Deposition of IgG, IgM, IgA, C3d, C4d, and C1q in capillaries

Chronic rejection

- Epicardial and endocardial coronary arteries affected
- Intimal fibrosis, lesion resembles atherosclerosis

INFECTION

- Bacterial and opportunistic reactions in lungs, GI tract, skin, and nervous system
- Toxoplasmosis and CMV
- PTLD is EBV driven, involves extra-cardiac sites (polyclonal lymphoplasmacytoid or monoclonal)

OTHER COMPLICATIONS

- Hypertension, renal dysfunction, hyperlipidemia

OTHER BIOPSY FINDINGS

Quilty lesion

- Lesion not related to graft rejection, unknown cause, no effect on prognosis
- Endocardial lymphocytic lesion composed of B and T lymphocytes
- Infiltrate may extend into underlying myometrium

Adipose tissue

- Accumulates in transplanted hearts over time

Site of previous biopsy

- Granulation tissue, fibrin, and mild inflammation

Calcification and fibrosis

- Due to previous biopsy, old infarct, drug induced

Lung transplant pathology

- Indications (in children): Cystic fibrosis and primary pulmonary artery hypertension (PPAH)
- Indications (in neonates): Heritable surfactant deficiency and alveolar capillary dysplasia
- Methods of evaluation of allograft dysfunction: Transbronchial biopsy, endobronchial biopsy, BAL with culture

VASCULAR COMPLICATIONS

- Thrombosis of arterial/venous vessels
- Later thrombus is organized with stenosis, fibrosis, and foreign body giant cell reaction

AIRWAY ANASTOMOTIC COMPLICATIONS

- Polypoid granulation tissue, ischemic changes, coagulative necrosis, superimposed bacterial/fungal infections
- Ultimately airway fibrosis and stenosis

HYPERACUTE REJECTION

- Not reported in children

ACUTE REJECTION

- Cell-mediated reaction; host mononuclear cells infiltrate the graft
- Cellular targets are endothelial and epithelial cells in graft
- Between 2 and 9 months posttransplant
- Cellular infiltrate; lymphocytes admixed with scattered eosinophils, neutrophils, and plasma cells
- Infiltrate begins in perivascular region and extends into airways/lung parenchyma
- Mimics infection (do lung cultures to differentiate) or bronchial-associated lymphoid tissue (BALT)

CHRONIC REJECTION

- Manifested as bronchiolitis obliterans (BO)
- May occur 1 year after transplant
- Bronchiolitis obliterans syndrome (BOS) is graded from 1 to 3 depending upon degree of loss of lung function
- Concentric/eccentric submucosal fibrosis, total/partial obstruction of lumen
- In BO there is dense mature collagen seen in small airways (BOOP has loose fibromyxoid plugs)

INFECTIONS

- Post-lung transplant patients very susceptible to infection throughout their lives because they are on immunosuppressive drugs
- Bacterial infections (mostly in the first month of transplant), viral (CMV, adenovirus), fungal (*Candida, Aspergillus*)

PULMONARY COMPLICATIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

- Graft versus host disease, idiopathic pneumonia syndrome

Posttransplant lymphoproliferative disorder

- Lymphoid hyperplasia/neoplasia occurring in organ/bone marrow transplant patients
- Heavy immunosuppression and EBV infection are predisposing factors
- Lymphoid tissue, organ allograft, or extranodal sites
- B lymphocytes (most common), T lymphocytes, or NK cells
- Hyperplastic, atypical lymphoid lesions, lymphomas (non-Hodgkin)
- Arise from recipient cells (solid organ transplant) or donor cells (bone marrow transplant)
- May be polymorphic (P-PTLD) or monomorphic (M-PTLD)
- PTLD is more frequent after solid organ transplant (most after lung/intestinal and least after renal) and less frequent after bone marrow transplant

34 Appendix

Tissue triaging

- Pathologist is a medical professional who diagnoses lesions/diseases in the body
- Helps determine the disease's prognosis, treatment, and pathogenesis
- Participates actively in various research activities
- Provides further insight into biology of diseases

TUMOR TISSUE

- Frozen tissue with cryopreservative: intraoperative diagnosis
- Cytologic scrape/squash imprints, touch preps: Intraoperative diagnosis (ideal for hematological malignancies)
- Formalin-fixed tissue: Routine histopathology, immunohistochemistry, tissue microarray, in situ hybridization (ISH), fluorescence in situ hybridization (FISH), reverse transcriptase-polymerase chain reaction (RT-PCR)
- Glutaraldehyde-fixed tissue: Electron microscopy (EM)
- Fresh tissue in tissue culture medium: Cytogenetics and tissue culture
- Frozen tissue without cryopreservative: Molecular studies
- Fresh tissue: Flow cytometry analysis for DNA ploidy and cell surface markers
- Fresh tissue: Biochemical analysis for tumor-specific markers

INFLAMED AND INFECTIOUS TISSUE

Fresh tissue for microbiologic studies

- Bacterial cultures (aerobic and anaerobic)
- Fungal cultures
- Viral cultures
- RT-PCR for rapid diagnosis of viruses that cannot be cultured
- Acid-fast *Bacillus* culture and RT-PCR
- Molecular microbiologic studies (frozen tissue without cryo-preservative can also be used)

Electron microscopy

- Aim of sample preparation for electron microscope is good structural preservation of cells and tissue so that the cell organelles can be easily recognized

MATERIALS/METHODS/EQUIPMENT

- Transmission electron microscope
- Ultramicrotome: Equipped with a glass or diamond knife for cutting very thin sections
- Glutaraldehyde: Fixative to preserve the proteins better
- Osmium tetroxide: Fixative to preserve the lipids better
- Embedding media: Plastic (epoxy-resin) for easier cutting
- Diamond knife: Extremely sharp cutting edge made up of diamond, thickness range for cutting is between 30 and 150 nm
- 80 nm thick sections with an area of about 1–2 mm^2
- Incubated in heavy metals like lead citrate and uranyl acetate—For double contrast staining
- Tissue mounted on fine mesh copper grid screen (instead of glass slide)

Corazza and Villanacci (new classification system for celiac disease)

- Grade A: Non-atrophic with normal crypt and villous architecture and increased IELs (>25 IELs per 100 enterocytes)

- Grade B1: Atrophic with villous to crypt ratio of <3:1, but villi are still detectable and IELs are increased (>25 IELs per 100 enterocytes)
- Grade B2: Atrophic and flat, villi are not detectable and IELs are increased (>25 lymphocytes per 100 enterocytes)

Non-alcoholic fatty liver disease (NAFLD) activity score and fibrosis (stage)

- *NAFLD activity score*: Sum of
  - Steatosis: 0 (↓5%), 1 (5%–33%), 2 (33%–66%), 3(↑66%)
  - Lobular inflammation: 0, 1 (<2 foci), 2 (2–4 foci), 3 (>4 foci)
  - Ballooning: 0, 1 (few), 2(many)
  - Total: 0–8
- *Fibrosis/staging*: 0–4

Simple scoring system of chronic hepatitis (modified Scheuer)

- Includes five grades and five stages

GRADE (ACTIVITY)

Portal/periportal inflammation

- Absent portal/periportal inflammation = 0
- Portal inflammation only = 1
- Mild piecemeal necrosis = 2
- Moderate piecemeal necrosis = 3
- Severe piecemeal necrosis = 4

Lobular activity

- None = 0
- Inflammation but no hepatocellular necrosis = 1
- Focal necrosis or apoptosis = 2
- Severe focal cell necrosis = 3
- Bridging confluent necrosis = 4

STAGE

- No fibrosis = 0
- Fibrosis confined to the portal tracts = 1
- Periportal or portal-portal septa but intact vascular relationships = 2
- Fibrosis with distorted architecture but no obvious cirrhosis = 3
- Probable or definite cirrhosis = 4

Rejection activity index (RAI) (*after liver transplantation*)

PORTAL INFLAMMATION

- Lymphocytic inflammation in minority of triads = 0
- Mixed inflammation in most but not all triads = 1
- Extensive mixed inflammation in all triads with periportal spillage = 3

BILE DUCT INFLAMMATION/DAMAGE

- Minority of ducts cuffed by inflammatory cells, mild epithelial reactive changes = 1
- Majority of ducts cuffed by inflammatory cells, moderate epithelial degenerative changes = 2
- All the ducts with marked inflammation, degenerative changes, focal luminal disruption = 3

VENOUS ENDOTHELIAL INFLAMMATION

- Sub-endothelial lymphocytic infiltration involving some of the hepatic/portal veins = 1
- Sub-endothelial lymphocytic infiltration involving most of the hepatic/portal veins = 2
- As in sub-endothelial lymphocytic infiltration involving most of the hepatic/portal veins, with moderate to severe perivenular inflammation and perivenular hepatocyte necrosis = 3

Banff classification renal allograft pathology (2007)

1. *Normal*
2. *Antibody-mediated rejection*: C4d deposition, acute antibody mediated, chronic active antibody mediated
3. *Borderline changes*: "Suspicious" for acute T-cell-mediated rejection

4. *T-cell-mediated rejection*

Acute T-cell-mediated rejection:

- Type IA: Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
- Type IB: Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
- Type IIA: Cases with mild to moderate intimal arteritis (v1)
- Type IIB: Cases with severe intimal arteritis comprising >25% of luminal area (v2)
- Type III: Cases with "transmural" arteritis or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

Chronic active T-cell-mediated rejection

- "Chronic allograft arteriopathy" (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

5. *Interstitial fibrosis and tubular atrophy*: No evidence of any specific etiology

- Grade I: Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
- Grade II: Moderate interstitial fibrosis and tubular atrophy (26%–50% of cortical area)
- Grade III: Severe interstitial fibrosis and tubular atrophy/loss (>50% of cortical area)

6. *Other*: Changes not considered to be due to rejection

Quantitative criteria for mononuclear cell interstitial inflammation

- ti0: No or trivial interstitial inflammation (<10% of parenchyma)
- ti1: 10%–25% of parenchyma inflamed
- ti2: 26%–50% of parenchyma inflamed
- ti3: >50% of parenchyma inflamed

National Wilms tumor study staging definitions (Children's Oncology Group)

- *Stage 1*: Tumor confined to kidney parenchyma and completely resected. Renal capsule intact and not penetrated by tumor. No involvement of vessels of renal sinuses. No biopsy before surgery
- *Stage 2*: Tumor extends beyond renal parenchyma but is completely resected. Resection margin uninvolved by the tumor. Tumor penetration of the renal capsule into vessels of the renal sinus including renal vein. No biopsy before surgery
- *Stage 3*: Residual non-hematogenous tumor confined to abdomen. Tumor in abdominal nodes, tumor spillage involving parenchyma, peripheral implants, tumor involvement of resection margins. Includes the cases in which a biopsy of the tumor was done before surgery
- *Stage 4*: Hematogenous metastasis or nodal deposits outside abdomen
- *Stage 5*: Bilateral renal tumor (substage should be for each side)

Flow cytometry

- Components; laser light source, series of prisms and filters for emitted light, computer driven including analytical system software
- Forward angle light scatter (FALS) relates to cell size (light collected along axis of laser beam)
- Side scatter (SS) relates to internal cellular characteristics such as nuclear complexity or cytoplasmic granularity (light collected at 90 degree angle to beam axis)
- Scatter plot data/histogram data
- Gating strategy (select cells for analysis)
- Pure antibodies directed to different surface and cytoplasmic antigens utilized in different combinations to assign cell lineage, detect aberrant antigenic profiles and detect clonality
- Antibodies are conjugated to different fluorochromes which emit light at different wavelength
- Several antibodies linked to different dyes utilized to stain cells of interest and study antigens associated with cells of interest fluorochromes
- CD45 antigen density versus side scatter utilized for initial gating strategy, then cells

of interest evaluated with a panel of monoclonal antibodies to identify neoplastic cells
- Characterize antigenic profile of cells of interest to diagnose disease process, useful for detection of recurrent/residual neoplastic cell populations including minimal residual disease

Miscellaneous genetic mutations

- Beckwith-Wiedemann syndrome: *CDKN1C/NSDI*
- Carney complex: *PRKAR1A*
- Cowden: *PTEN*
- Familial adenomatous polyposis coli: *APC*
- Medullary thyroid Ca: *RET*
- Hyperparathyroidism jaw tumor: *HRPT2*
- Li-Fraumeni: *TP53*
- McCune-Albright: *GNAS*
- Men1: *MEN-1*
- Men2: *RET*
- Nf1: *NF-1*
- Von Hippel: *VHL*

Cytogenetic and Molecular Abnormalities in Selected Diseases

Diseases	Cytogenetics	FISH
Acute lymphoblastic leukemia	t(9;22)(q34;q11.2)	BCR-ABL
Acute lymphoblastic leukemia	t(1;19)(q23;p13.3)	E2A-PBX1
Acute lymphoblastic leukemia (biphenotypic or bilineal)	t(4;11)(q21;q23)	AF4-MLL
Acute lymphoblastic leukemia	t(12;21)(p13;q22)	TEL-AML1
Acute lymphoblastic leukemia	t(9;11)(q21;23)	AF9-MLL
Acute myelogenous leukemia		Trib2
Acute myeloid leukemia	t(9;11)(p13.1;q23)	MLL
Acute myeloid leukemia (biphenotypic or bilineal)	t(4;11)(q21;q23)	AF4-MLL
Acute myeloid leukemia (M2)	t(8;21)(q22;q22)	AML1-ETO
Acute myeloid leukemia (M3)	t(15;17)(q22;q12)	PML-RARA
Acute myeloid leukemia (M4E0)	t(16;16)(p13;q22), Inv(16)(p13;q22)	CBFB-MYH11
Acute myeloid leukemia (M7 in Down syndrome)	+ 21	
Acute myeloid leukemia (M7 with germ cell tumor)	i(12p)	
Alveolar rhabdomyosarcoma	t(1;13)(p36;q14)	PAX7-FKHR
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	PAX3-FKHR
Alveolar soft part sarcoma	t(X;17)(p11;q25)	ASPL-TFE3
Anaplastic large cell lymphoma	t(2;5)(p23;q35)	NPM-ALK
Aneurysmal bone cyst	t(16;17)(q22;p13)	CDH11-USP6
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	FUS-ATF1
Breast carcinoma, secretory	t(12;15)(q13;q25)	ETV6-NTRK3
Burkitt lymphoma	t(8;14)(q24.1;q32)	C-MYC
Chondromyxoid fibroma	t(6;9)(q25;q22)	
Chronic myelogenous leukemia	t(9;22)(q34;q11)	BCR-ABL1
Clear cell sarcoma of the kidney (CCSK)	t(10;17)(q22;p13)	
Clear cell sarcoma of soft-tissue/malignant melanoma of soft parts	t(12;22)(q13;q12)	EWS-ATF1
Congenital mesoblastic nephroma	t(12;15)(p13;q26)	ETV6-NTRK3

Continued

Cytogenetic and Molecular Abnormalities in Selected Diseases (*Continued*)

Diseases	Cytogenetics	FISH
Dermatofibrosarcoma protruberans	t(17;22)(q22;q13)	COL1A1-PDGFB
Desmoplastic small round blue cell tumor	t(11;22)(p13;q12)	EWS-WT1
Ewing sarcoma/ primitive neuroectodermal tumor (PNET)	t(11;22)(q24;q12)	EWS-FLI-1
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	EWSR1-NR4A3
Fibrosarcoma, infantile	t(12;15)(p13;q26)	ETV6-NTRK3
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11)	FUS-BBF2H7(CREB-3)
Myxoid liposarcoma	t(12;22)(q13;q12)	EWS-CHOP
Neuroblastoma	del(1p36), del(11q)	
Midline carcinoma with NUT rearrangement	t(15;19)(q15;p13)	BRD4-NUT
Subcutaneous lipoma	t(3;12)(q28;q14)	HMGIC/LPP
Synovial sarcoma	t(x;18)(p11;q11)	SYT-SSX1
Therapy associated acute myeloid leukemia/ myelodysplastic syndrome	del(5)9q31-q32)	
Wilms tumor	11p13	WT1

Section C

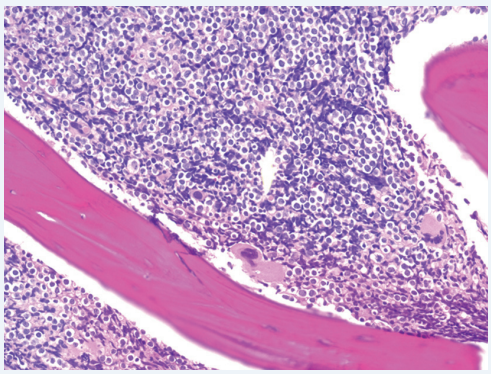
Self-Assessment

35 Quiz

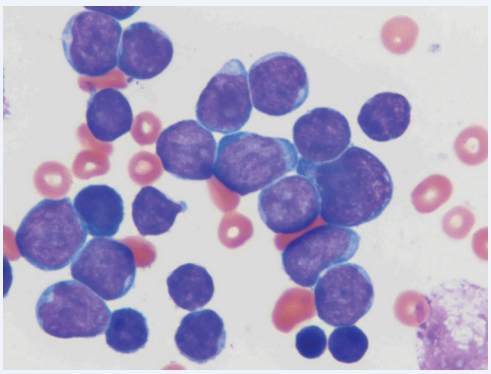
CASE 1

History

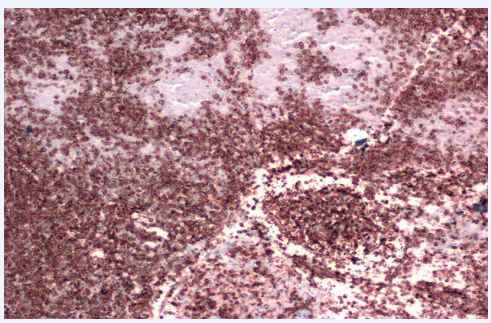
Two-year-old boy presented with generalized bone pains and hepatosplenomegaly. Bone marrow biopsy/aspirate



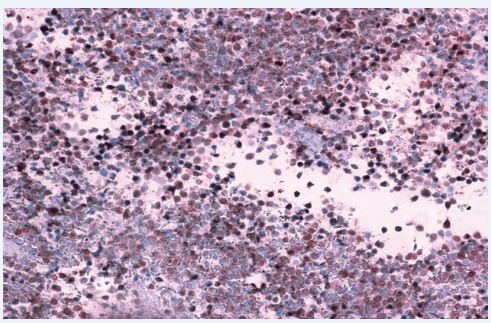
H&E



Giemsa



CD79a



TdT

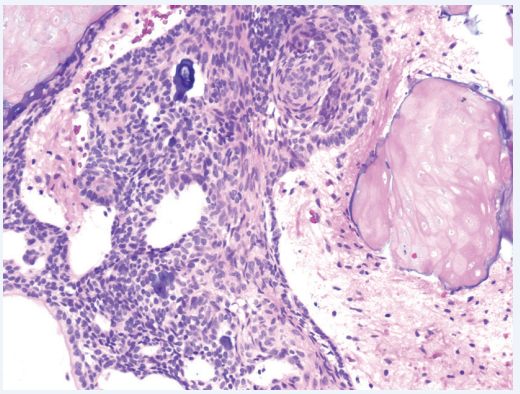
Diagnosis

B-cell acute lymphoblastic leukemia

CASE 2

History

Five-year-old boy with mass in the sellar region near third ventricle. Tumor biopsy



H&E

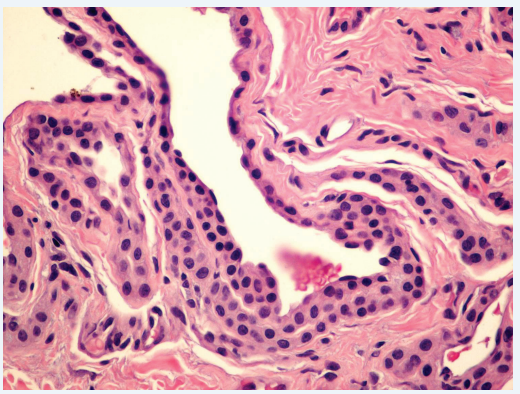
Diagnosis

Adamantinomatous craniopharyngioma

CASE 3

History

Four-year-old girl presented with a painful 1 cm subungual mass on her left index finger



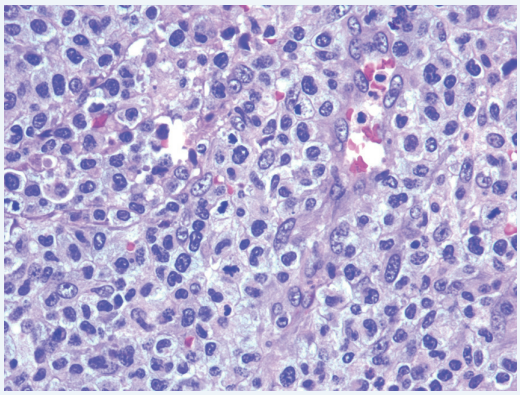
Diagnosis

Glomus tumor

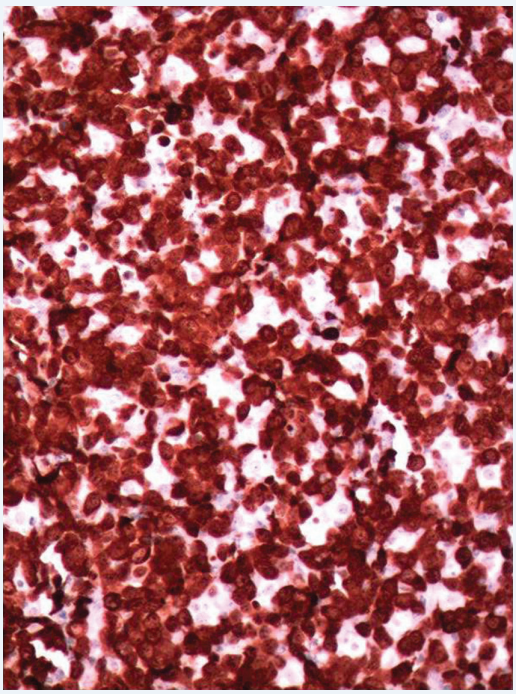
CASE 4

History

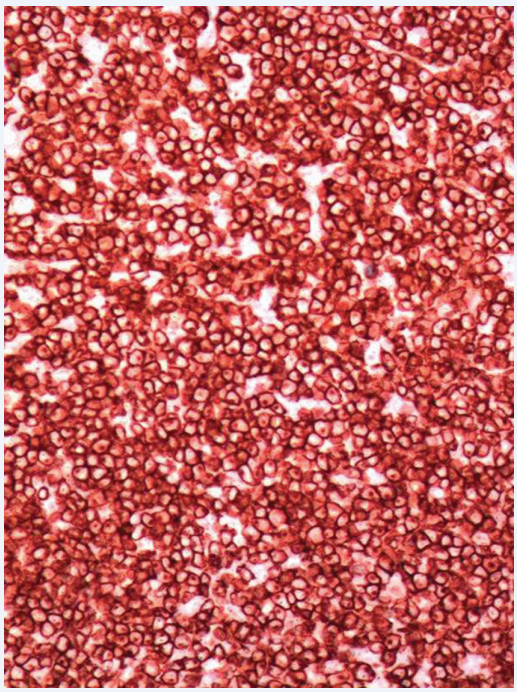
Eight-year-old boy with peripheral lymphadenopathy and very high fever. Cervical lymph node biopsy showed tumor cells to be positive for CD30 and AlK-1



H&E



ALK1



CD30

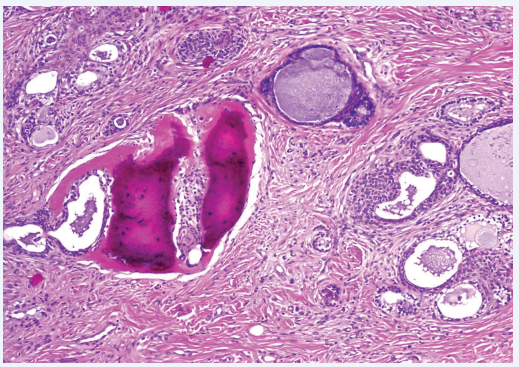
Diagnosis

Anaplastic large cell lymphoma

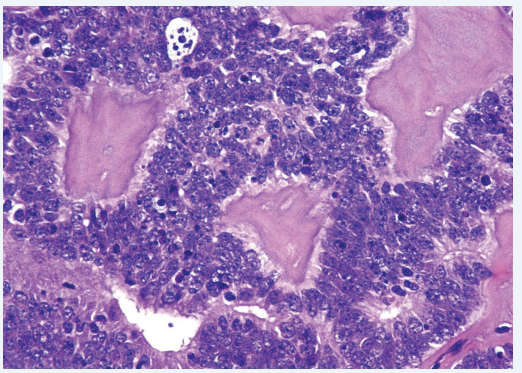
CASE 5

History

Ten-month-old infant with a large retroperitoneal mass



H&E



H&E

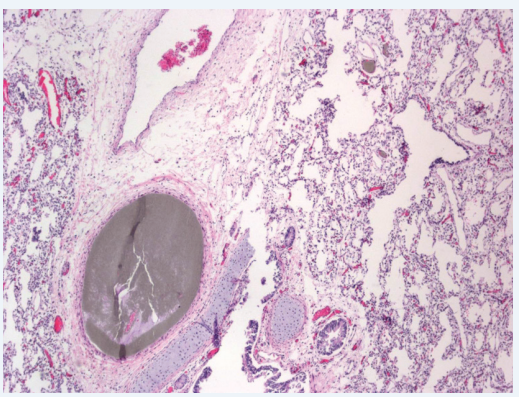
Diagnosis

Teratoma (mature and immature components present)

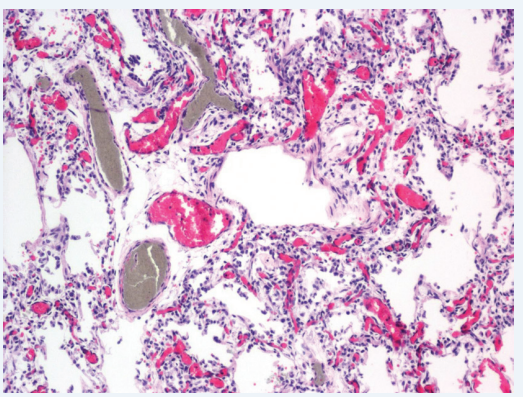
CASE 6

History

Newborn girl with severe respiratory distress and pulmonary hypertension. Lung biopsy



H&E



H&E

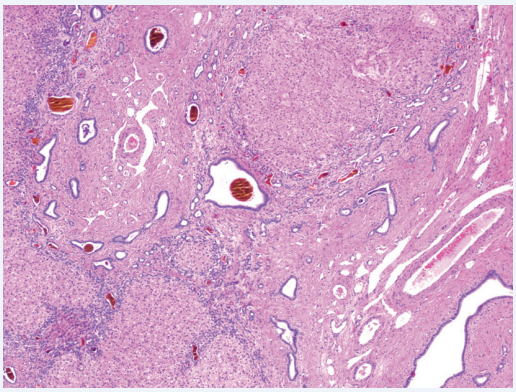
Diagnosis

Alveolar capillary dysplasia with misaligned veins

CASE 7

History

Twelve-year-old boy with hematemesis and melena. He has a past history of ARPKD. Liver biopsy



H&E

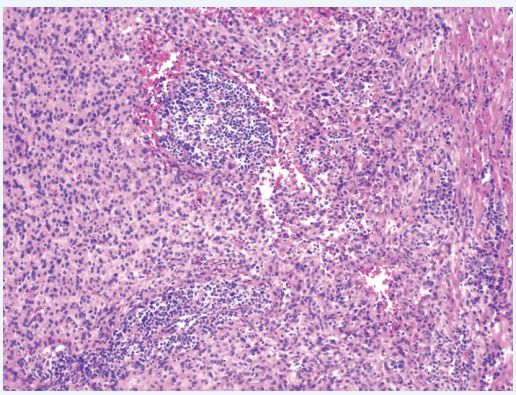
Diagnosis

Congenital hepatic fibrosis

CASE 8

History

Teenager with malaise, fever, and mass in popliteal fossa. Tumor biopsy was done. Tumor cells are positive for Calponin, CD68, and EMA



H&E

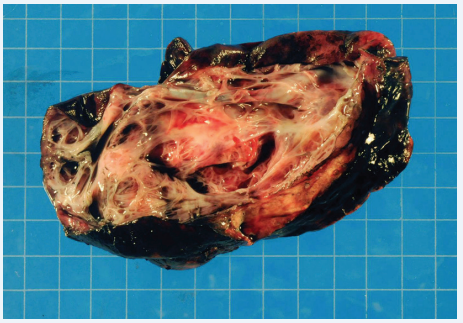
Diagnosis

Angiomatoid fibrous histiocytoma

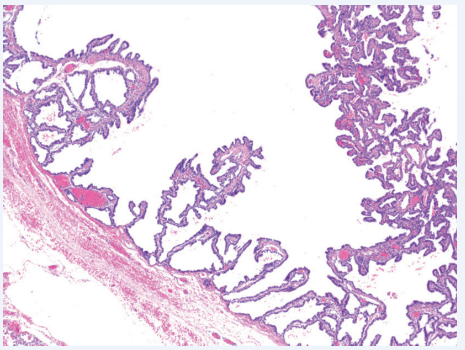
CASE 9

History

Neonate with progressive respiratory distress; chest radiograph shows a multicystic mass. The mass was resected



GROSS



H&E

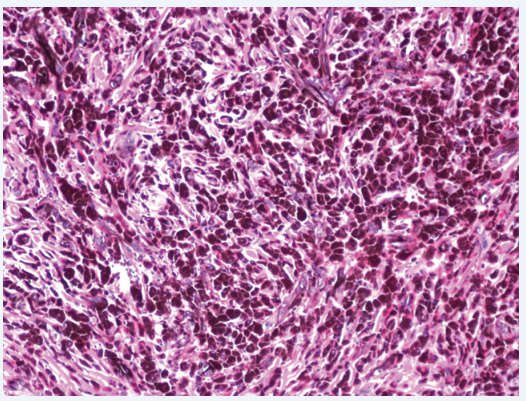
Diagnosis

Congenital pulmonary airway malformation (type I)

CASE 10

History

Smooth surfaced 1 cm dark brown, dome-shaped lesion on scalp of a 9-year-old boy. Skin biopsy. Lesional cells are positive for HMB45



H&E

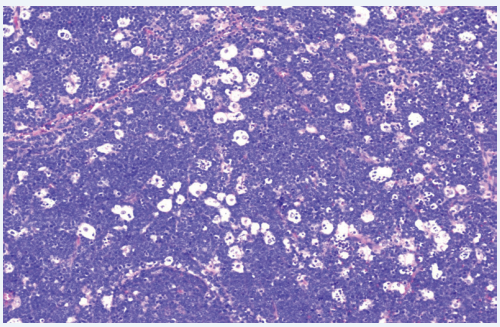
Diagnosis

Blue nevus

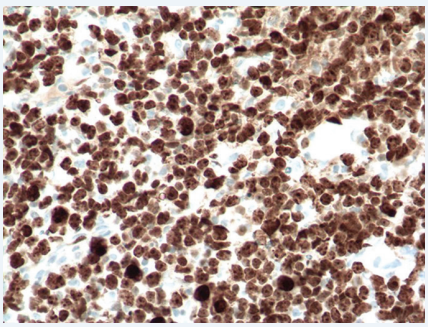
CASE 11

History

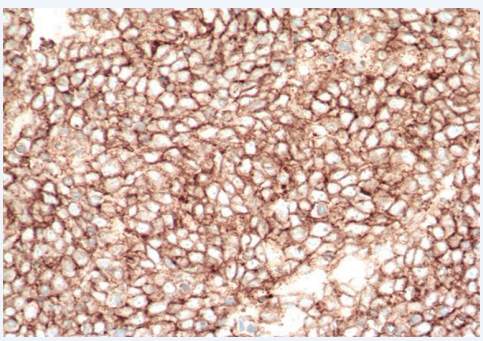
Eight-year-old African boy with a mass in ileocecal region. Tumor biopsy



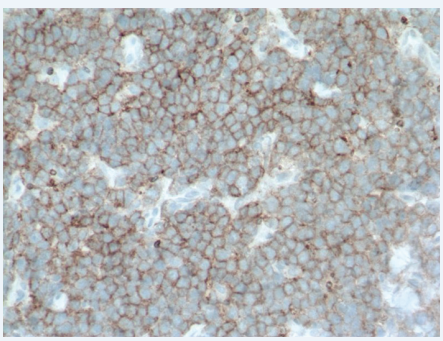
H&E



Ki67



CD10



CD20

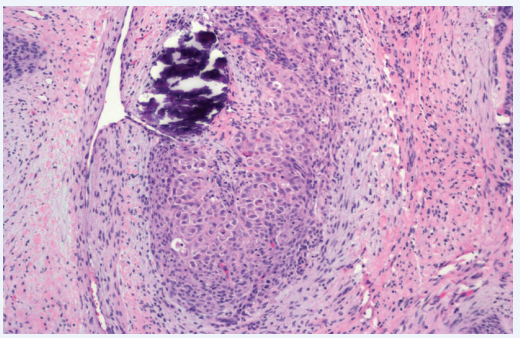
Diagnosis

Burkitt lymphoma

CASE 12

History

Ten-year-old boy with Cushing syndrome and hepatic mass. Liver tumor biopsy



H&E

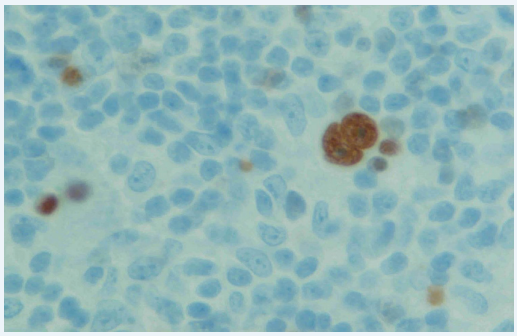
Diagnosis

Calcifying nested stromal-epithelial tumor of liver

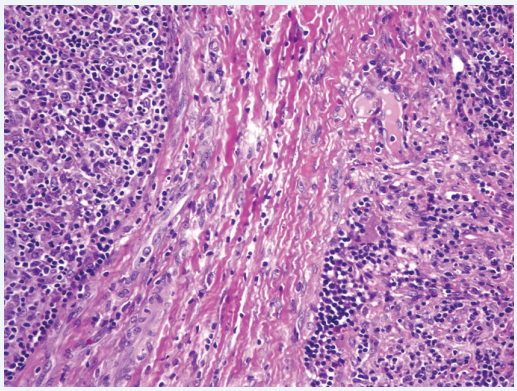
CASE 13

History

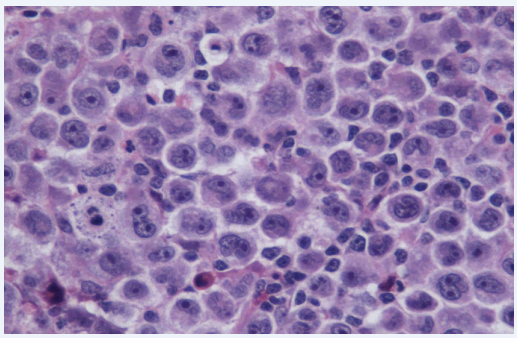
Sixteen-year-old girl with cervical lymphadenopathy. The neoplastic cells are positive for CD15 and MUM1



MUM1



H&E



H&E

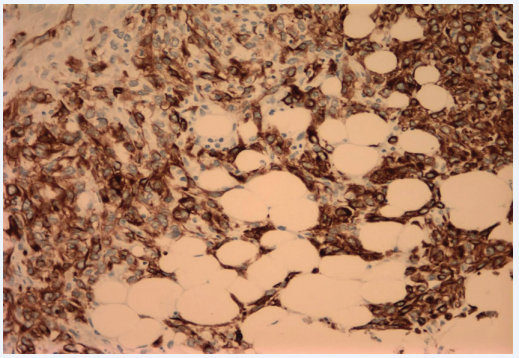
Diagnosis

Hodgkin lymphoma nodular sclerosis type

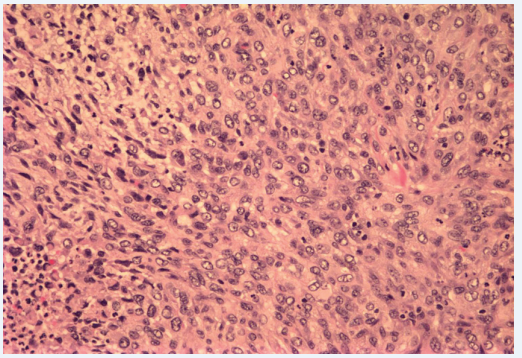
CASE 14

History

Eighteen-year-old boy with a firm to hard palpable mass in the soft tissue of hand. The lesional cells are positive for AE1/AE3. Tumor biopsy



AE1/AE3



H&E

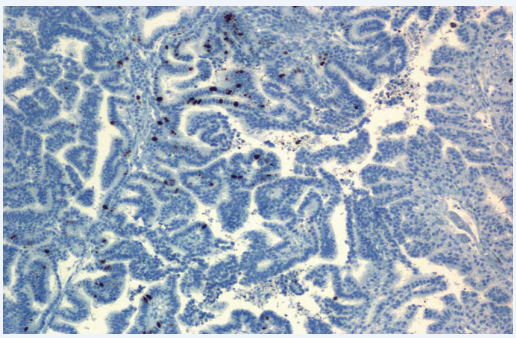
Diagnosis

Epithelioid sarcoma

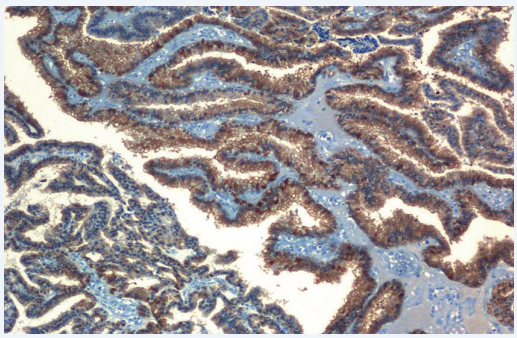
CASE 15

History

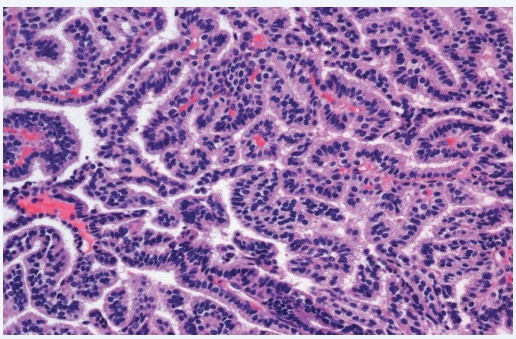
Eleven-year-old boy presented with long-standing history of hydrocephalus. On imaging a mass was seen in right lateral ventricle of brain. Tumor cells are positive with S100 and focally with GFAP



MIB1



S100



H&E

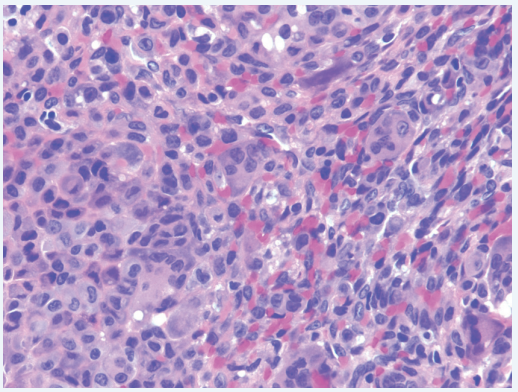
Diagnosis

Choroid plexus papilloma

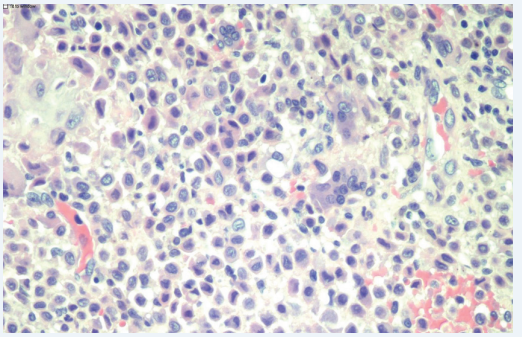
CASE 16

History

Nine-year-old boy with pain and swelling in the knee. Tumor cells are positive with S100 and vimentin. Tumor biopsy



H&E



H&E

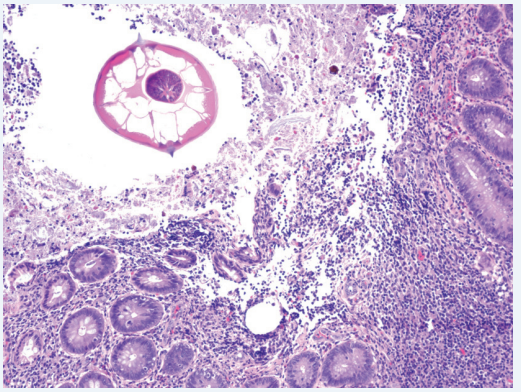
Diagnosis

Chondroblastoma

CASE 17

History

Four-year-old girl from Haiti who underwent appendectomy for mild features of appendicitis. Appendectomy specimen



H&E

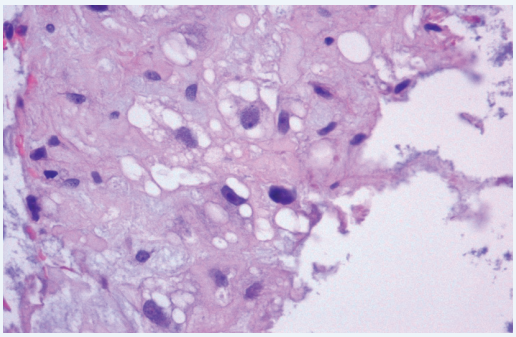
Diagnosis

Enterobius vermicularis

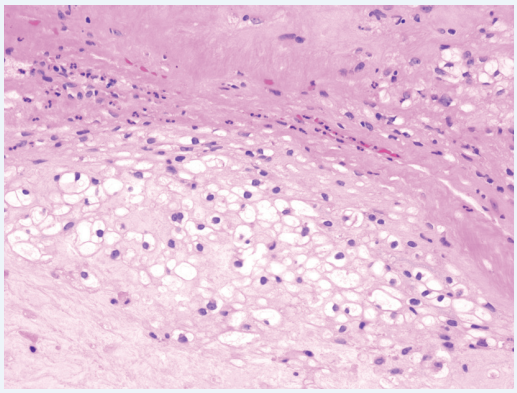
CASE 18

History

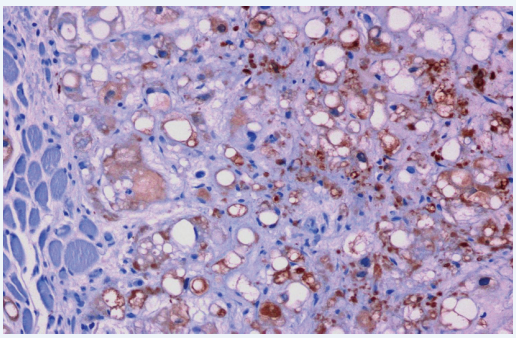
Fifteen-month-old boy presented with a slow-growing mass in sacrum. Tumor biopsy



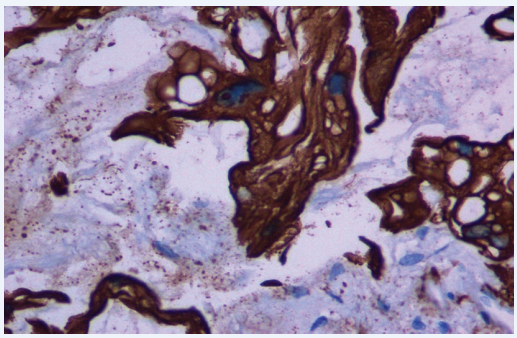
H&E



H&E



S100



AE1/AE3

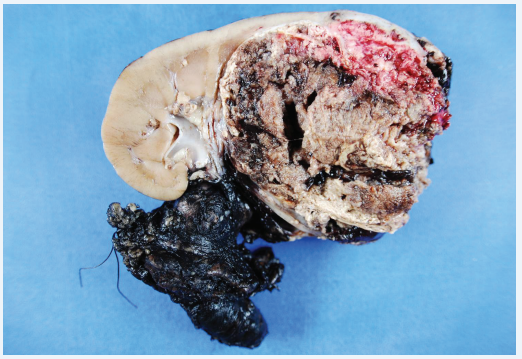
Diagnosis

Chordoma

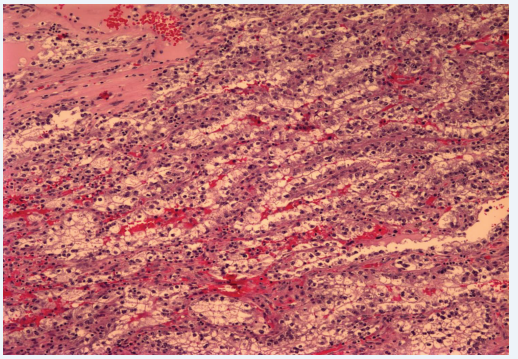
CASE 19

History

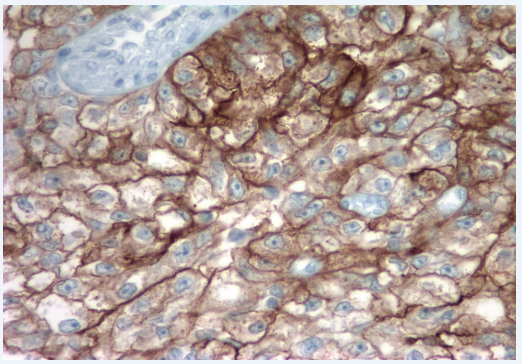
Three-year-old girl presented with kidney mass that showed nuclear expression of TFE3 immunostain and had Xp11.2 translocation



Gross



H&E



CD10

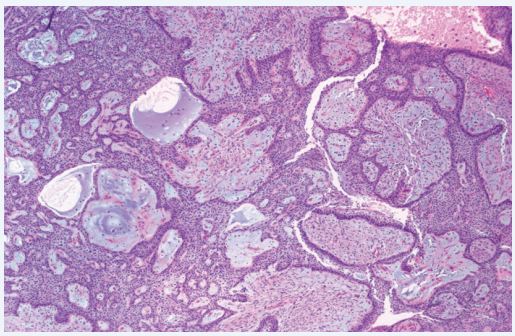
Diagnosis

Xp11.2 translocation renal cell carcinoma

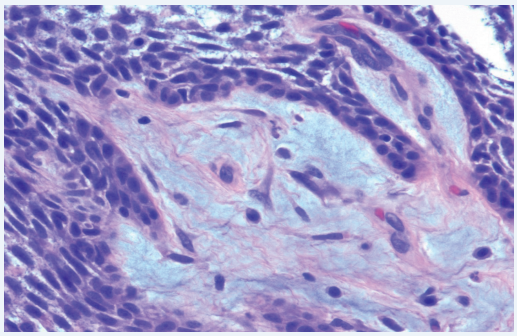
CASE 20

History

Two-year-old girl with painless swelling and deformity in maxilla. Imaging showed a soap bubble appearance. Neoplastic cells are positive for CK5. Tumor biopsy



H&E



H&E

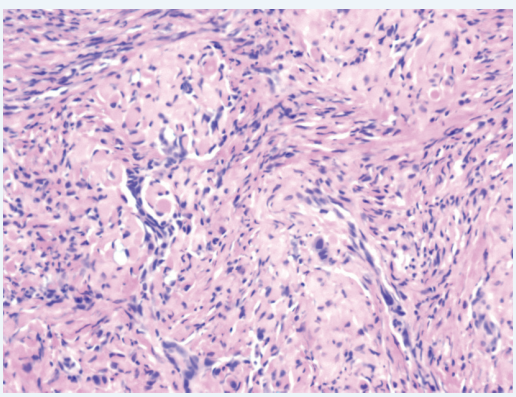
Diagnosis

Ameloblastoma

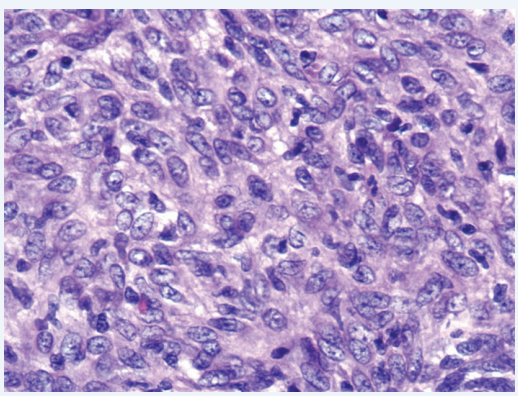
CASE 21

History

Premature infant with recurrent large right shoulder mass. Tumor was positive for t(12;15) *ETV6-NTRK3* gene rearrangement. Neoplastic cells are positive for vimentin



H&E



H&E

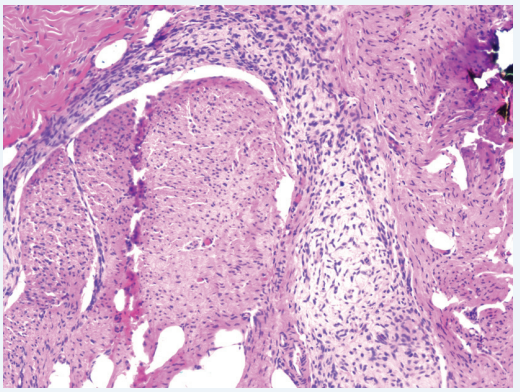
Diagnosis

Congenital infantile fibrosarcoma

CASE 22

History

One-year-old with mass in right axilla. Lesional cells are positive for vimentin and actin. Tumor biopsy



H&E

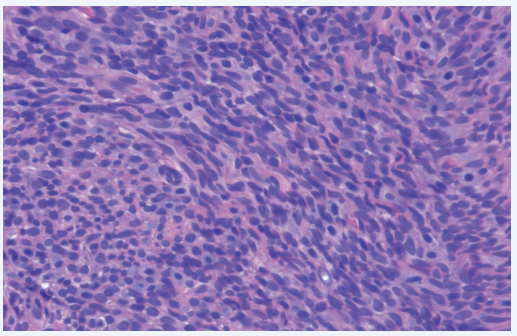
Diagnosis

Fibrous hamartoma of infancy

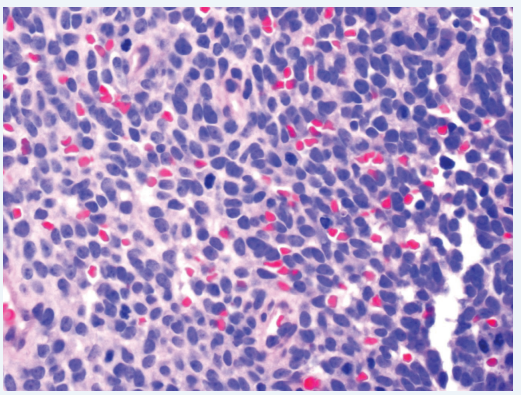
CASE 23

History

Long-standing deep-seated mass in ankle of a 12 year old. Tumor cells are positive for EMA and vimentin



H&E



H&E

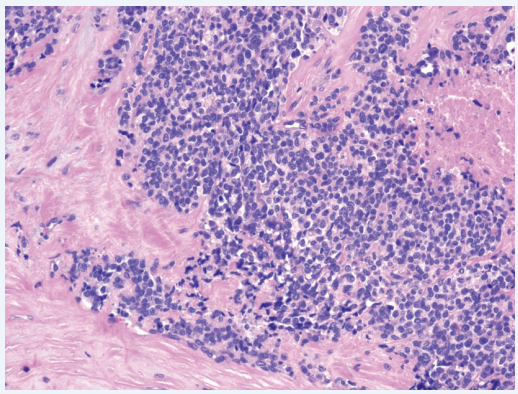
Diagnosis

Synovial sarcoma

CASE 24

History

Fourteen-year-old boy with intra-abdominal mass. Tumor cells are positive for WT-1. Molecular studies show t(11;22), *WT1-EWS* gene rearrangement



H&E

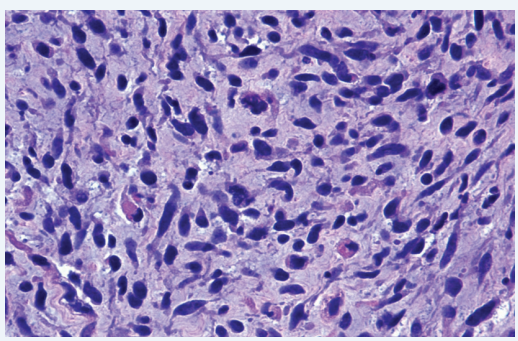
Diagnosis

Desmoplastic small round cell tumor

CASE 25

History

Three-year-old boy with a mass in the paratesticular region. Neoplastic cells are diffusely positive for desmin and show weak patchy positivity for myogenin. Tumor biopsy



H&E

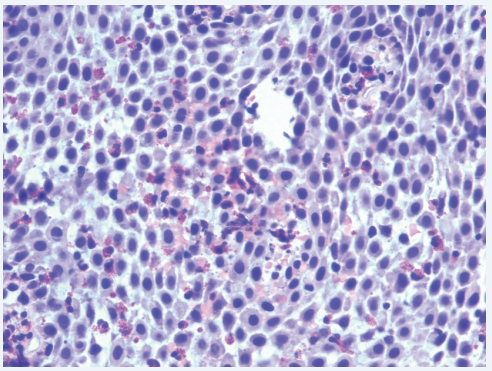
Diagnosis

Embryonal rhabdomyosarcoma

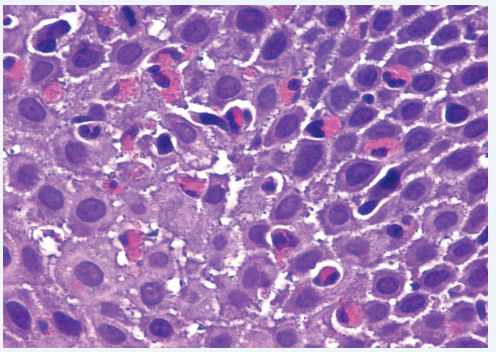
CASE 26

History

Two-and-a-half-year-old girl with wheezing and failure to thrive. Biopsy from proximal esophageal mucosa



H&E



H&E

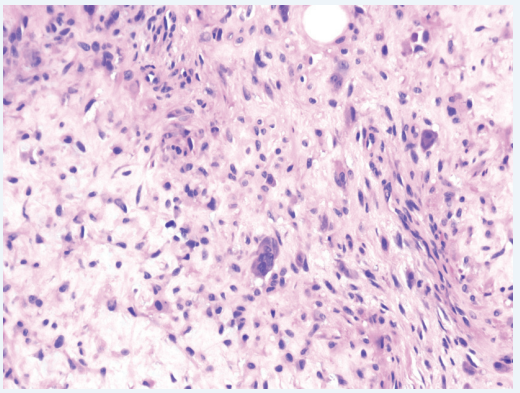
Diagnosis

Eosinophilic esophagitis

CASE 27

History

Fifteen-year-old with a lytic well-circumscribed mass in metaphysis of right tibia. Tumor biopsy



H&E

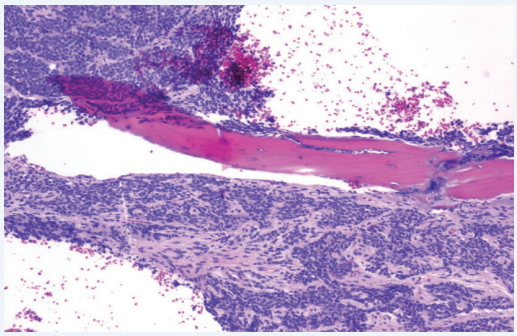
Diagnosis

Chondromyxoid fibroma

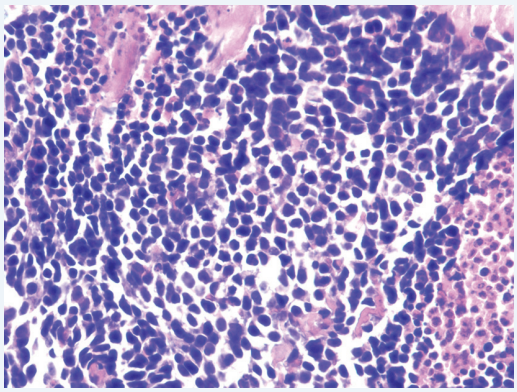
CASE 28

History

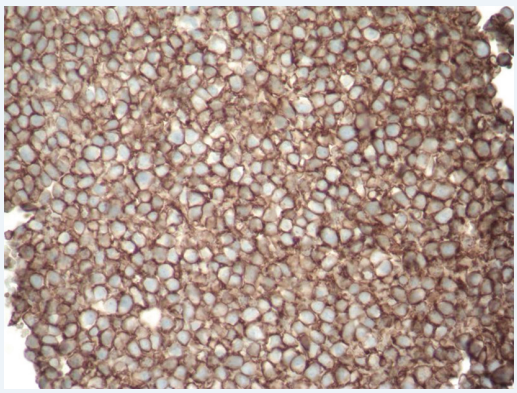
Ten-year-old boy with pain, fever, and weight loss. Lytic destructive lesion of femur on imaging. Tumor biopsy



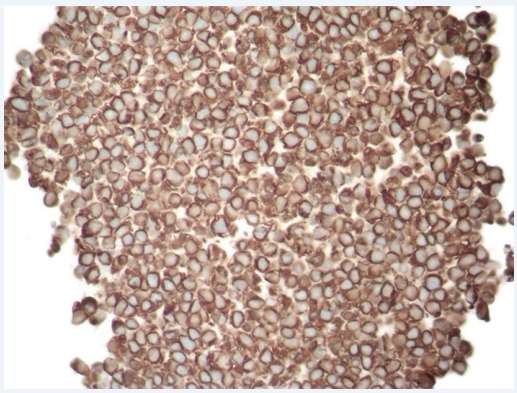
H&E



H&E



CD99



VIMENTIN

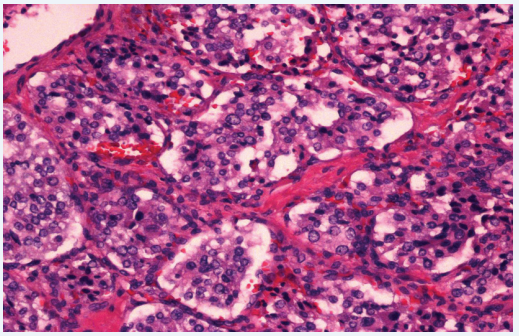
Diagnosis

Ewing sarcoma

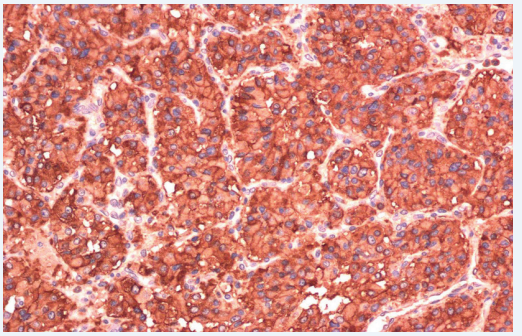
CASE 29

History

Eighteen-year-old girl with MEN2a syndrome and recurrent tumor in front of lumbar vertebra. Tumor biopsy



H&E



CHROMOGRANIN

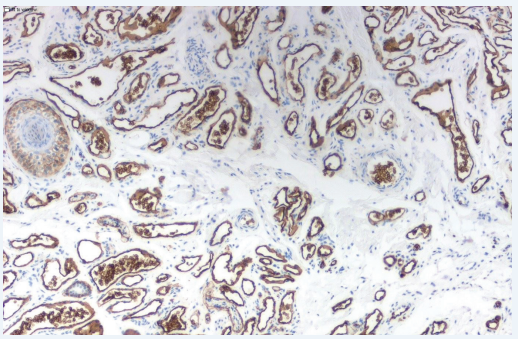
Diagnosis

Extra-adrenal paraganglioma

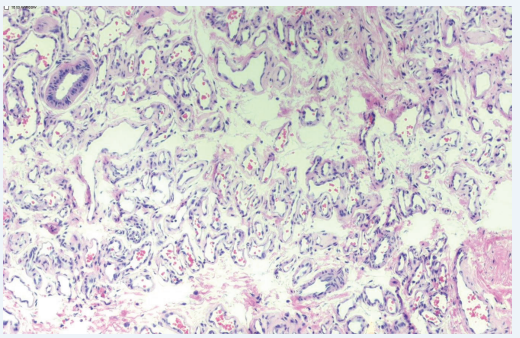
CASE 30

History

Six-month-old boy with a large pink papule on neck. The neoplastic cells are positive for CD31 and GLUT-1. Biopsy from the lesion



GLUT1



H&E

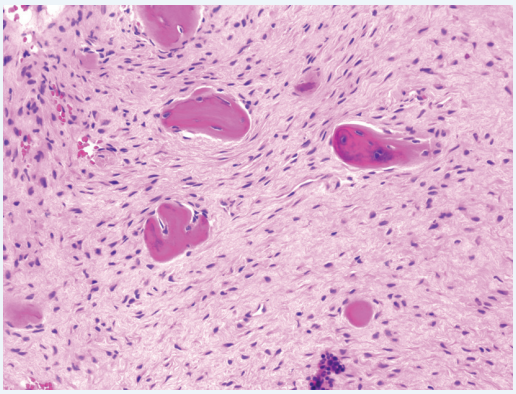
Diagnosis

Juvenile hemangioma

CASE 31

History

Seven-year-old girl with spontaneous fracture of the orbital bone. Bone biopsy



H&E

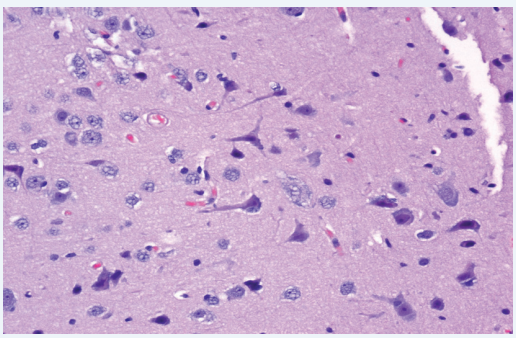
Diagnosis

Fibrous dysplasia

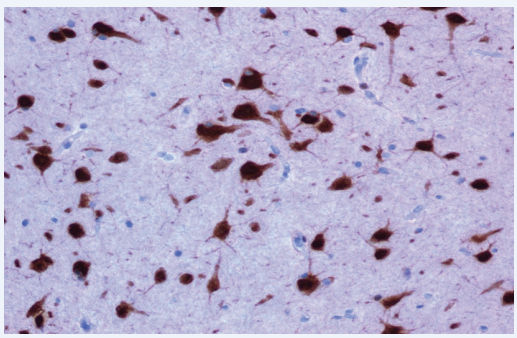
CASE 32

History

Eight-year-old boy with progressive cognitive impairment and seizures. Imaging did not show any mass lesion. Biopsy from frontal lobe of brain



H&E



NEU-N

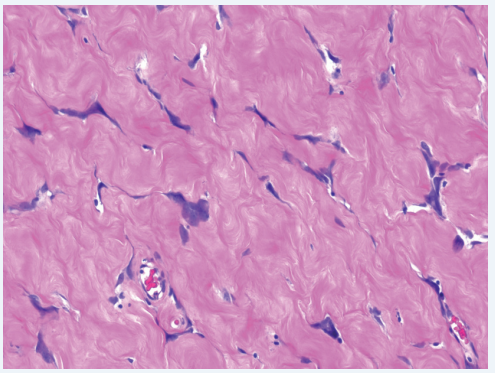
Diagnosis

Focal cortical dysplasia type IIA

CASE 33

History

Five-year-old boy with painless subcutaneous mass in trunk. Tumor cells are positive for vimentin and CD34, and negative for S100. Tumor biopsy



H&E

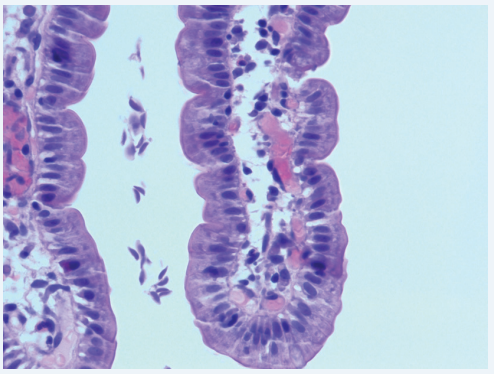
Diagnosis

Giant cell fibroblastoma

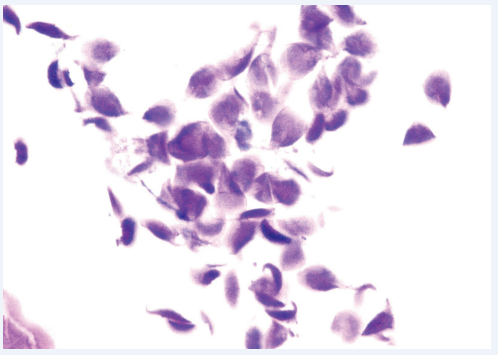
CASE 34

History

Six-year-old boy with chronic diarrhea and malabsorption after he returned from a camping trip. Duodenal biopsy



H&E



H&E

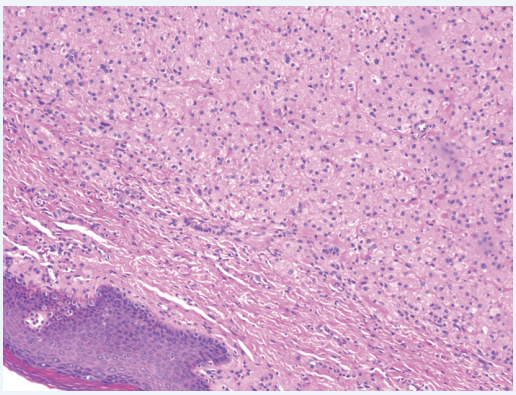
Diagnosis

Giardia lamblia

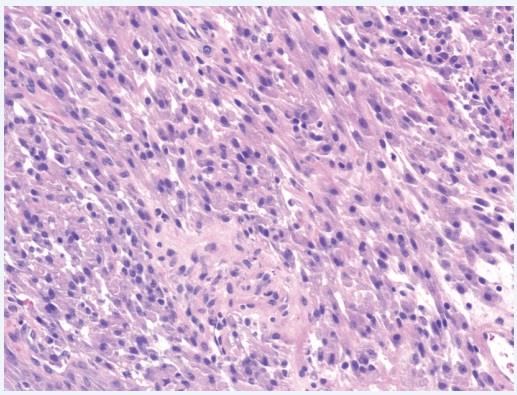
CASE 35

History

Eleven-year-old boy with lesion in perianal skin. Cells are S-100 and PAS positive. Tumor biopsy



H&E



H&E

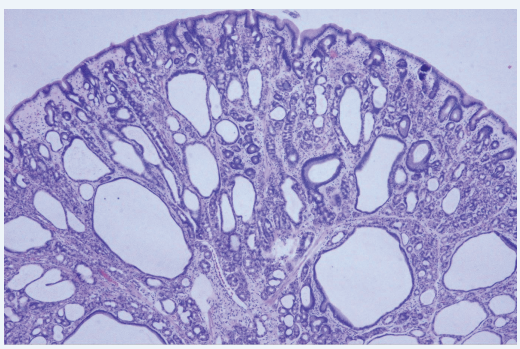
Diagnosis

Granular cell tumor

CASE 36

History

Fourteen-year-old girl was on proton pump inhibitors for hyperacidity. Endoscopy of the gastric fundus showed an incidental 5 mm mucosal nodule



H&E

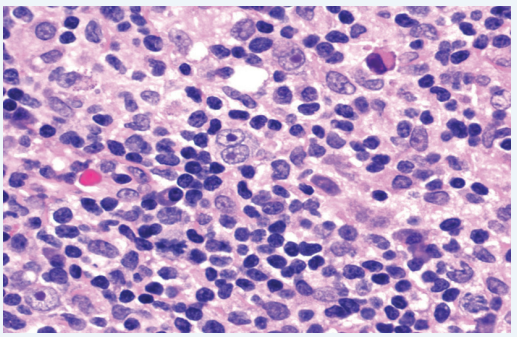
Diagnosis

Fundic gland polyp

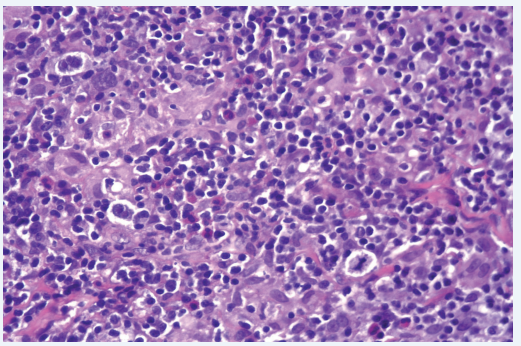
CASE 37

History

Sixteen-year-old boy with fever, night sweats, and enlarged mediastinal lymph nodes. Tumor cells are positive for CD15, CD30, and EBV. Lymph node biopsy



H&E



H&E

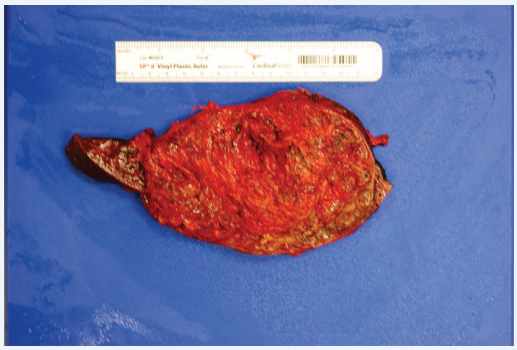
Diagnosis

Hodgkin lymphoma—mixed cellularity

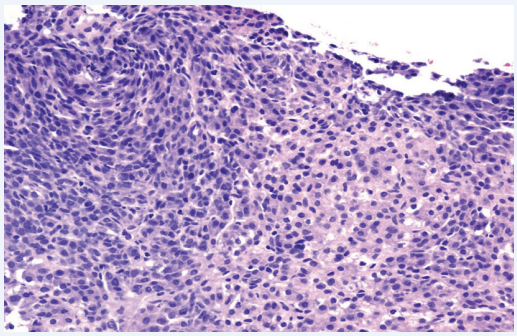
CASE 38

History

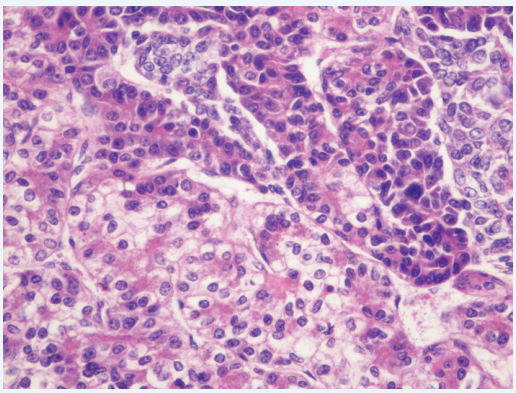
Six-month-old boy with Beckwith-Wiedemann syndrome and abdominal mass. Liver mass was resected. Nuclear beta-catenin positivity was noted



GROSS



H&E



H&E

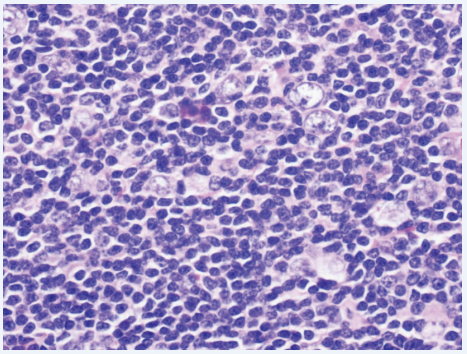
Diagnosis

Hepatoblastoma epithelial type (fetal and embryonal)

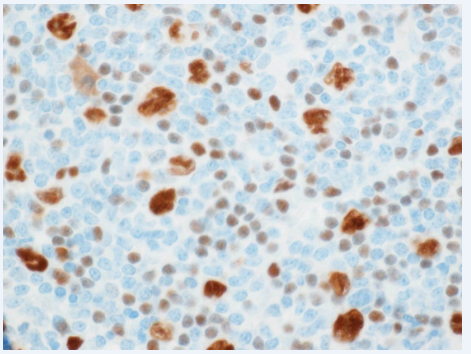
CASE 39

History

Enlarged mediastinal lymph nodes in a 13-year-old girl. Neoplastic cells are positive for OCT-2, CD20, BOB1, and CD45. Lymph node biopsy



H&E



OCT-2

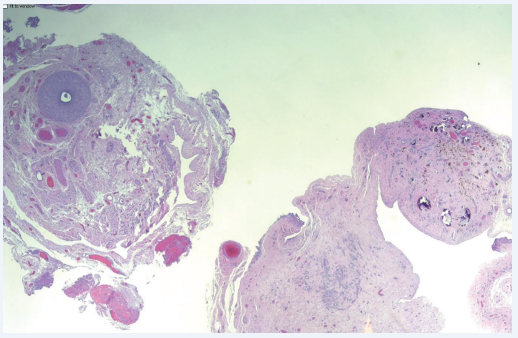
Diagnosis

Hodgkin lymphoma—nodular lymphocyte predominant

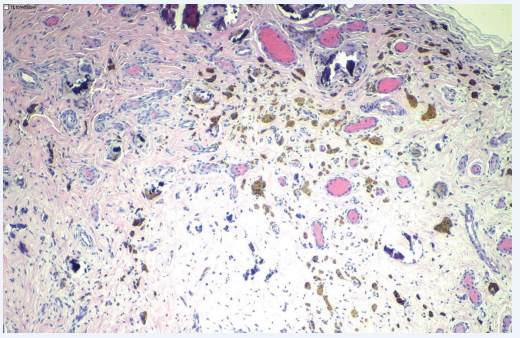
CASE 40

History

Six-year-old boy with ambiguous genitalia and history of right testicular cryptorchidism. Biopsy is from a 1 cm right inguinal mass



H&E



H&E

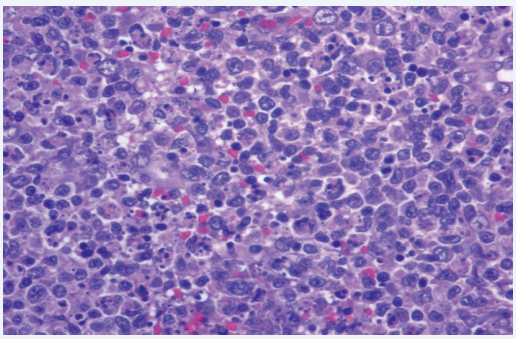
Diagnosis

Testicular regression syndrome

CASE 41

History

Seventeen-year-old girl with fever, cervical lymphadenopathy, and negative infectious workup. Flow cytometry findings were not suggestive of lymphoma. Lymph node biopsy



H&E

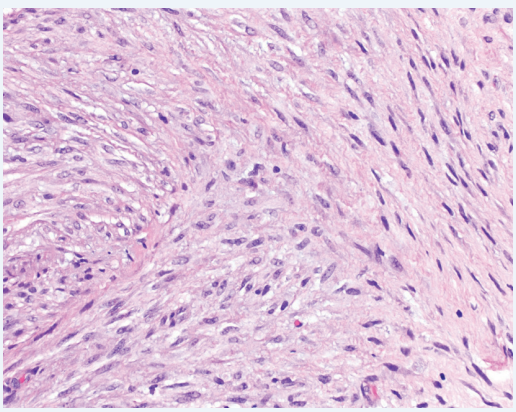
Diagnosis

Kikuchi lymphadenitis

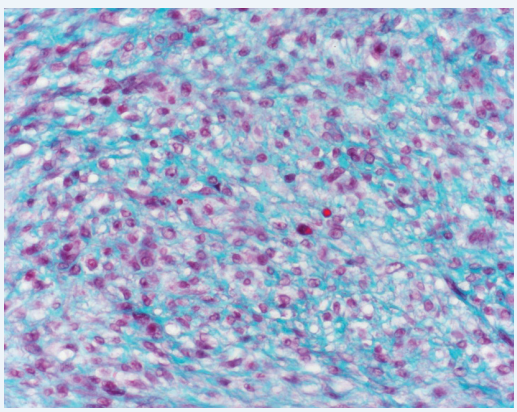
CASE 42

History

A 1 cm nodular mass on the dorsum of index finger in a 6-month-old infant. Biopsy from the mass



H&E



TRICHROME

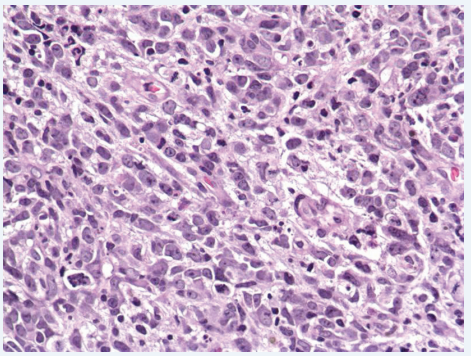
Diagnosis

Inclusion body fibromatosis

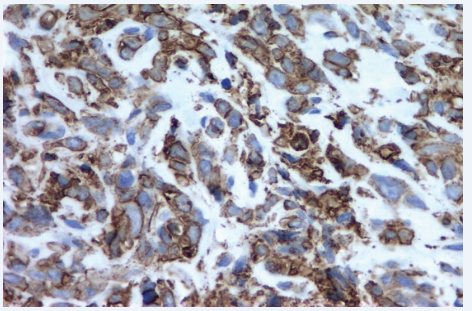
CASE 43

History

Orbital mass in a 2-year-old girl with a history of unknown malignancy. Neoplastic cells are positive for myeloperoxidase and CD68. Biopsy from the orbit



H&E



CD34

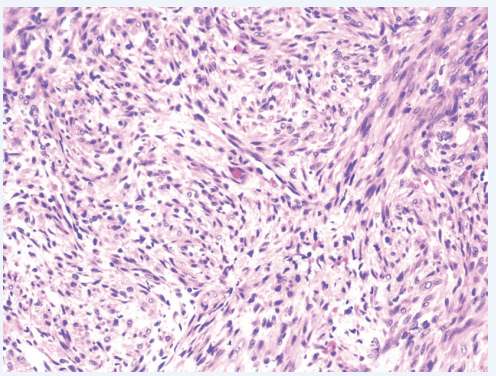
Diagnosis

Extramedullary myeloid sarcoma

CASE 44

History

Seven-month-old girl with a raised hard violaceous mass 6 cm × 6 cm, on left side of face. Biopsy from mass showed spindle-shaped cells positive for smooth muscle actin and vimentin stain



H&E

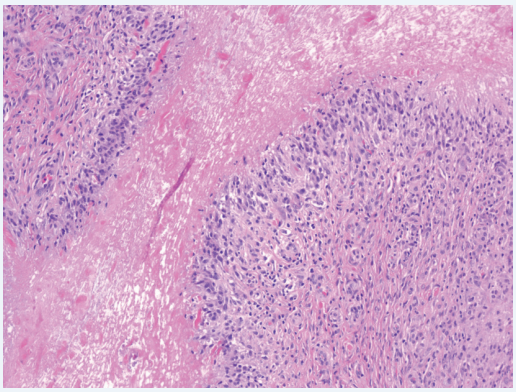
Diagnosis

Myofibroma/myofibromatosis

CASE 45

History

Fifteen-year-old boy with an erythematous, scaling and pruritic 2 cm mass on dorsum of hand. Biopsy from the mass



H&E

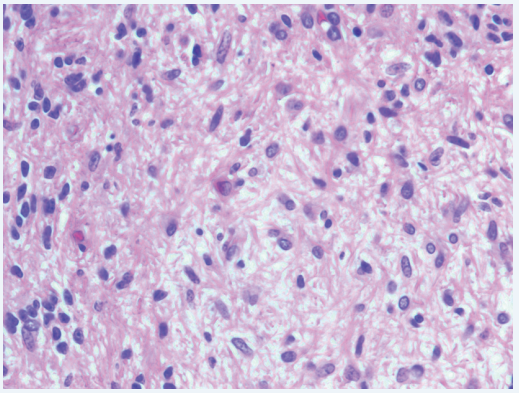
Diagnosis

Granuloma annulare

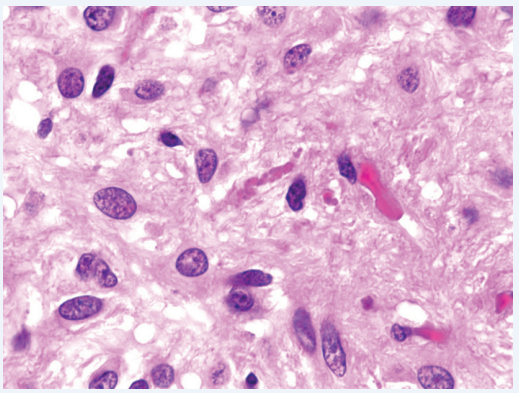
CASE 46

History

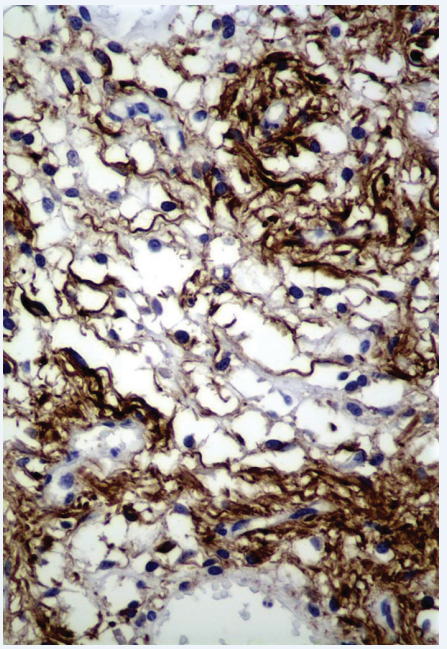
Seven-year-old girl with a well-circumscribed, slow-growing cerebellar mass. On imaging the mass was contrast enhancing and cystic in appearance. Brain tumor biopsy



H&E



H&E



GFAP

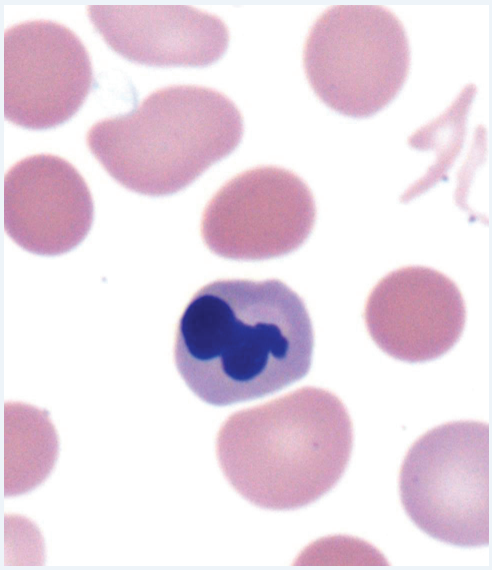
Diagnosis

Pilocytic astrocytoma

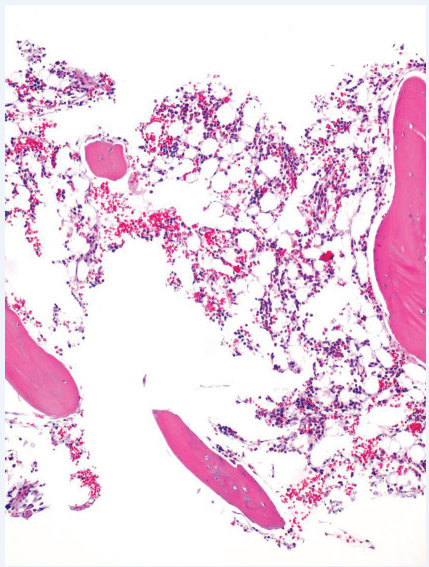
CASE 47

History

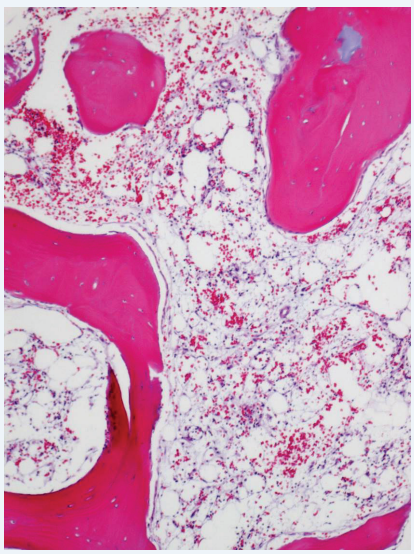
Six-year-old boy with anemia, bleeding, and recurrent infections. Cytogenetic studies showed monosomy 7. Bone marrow biopsy/aspirate



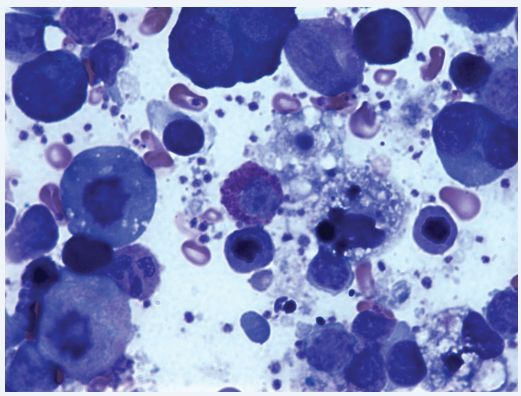
GIEMSA



H&E



H&E



Giemsa

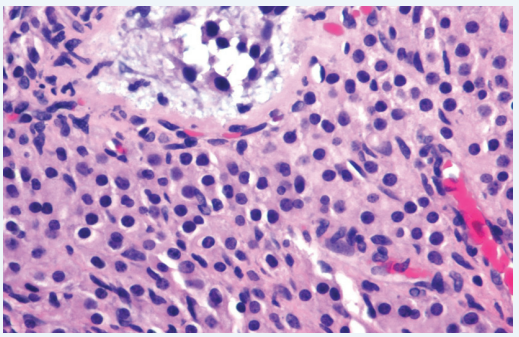
Diagnosis

Aplastic anemia with myelodysplasia

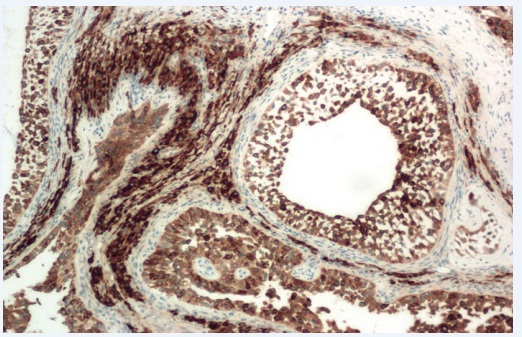
CASE 48

History

Nine-year-old girl with precocious puberty. Biopsy from ovarian tumor



H&E



INHIBIN

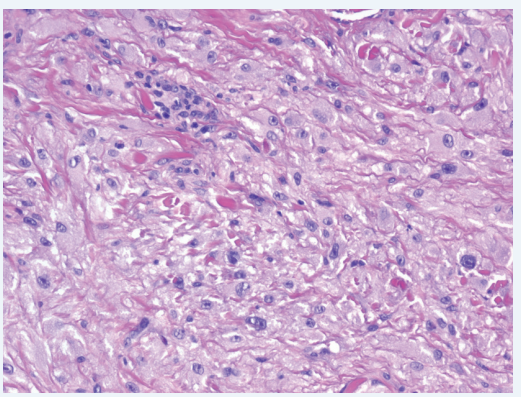
Diagnosis

Juvenile granulosa cell tumor

CASE 49

History

One-year-old girl with circumscribed yellow papular mass on dorsum of tongue. Biopsy from the mass showed lesional cells to be positive for CD68 and negative for S100



H&E

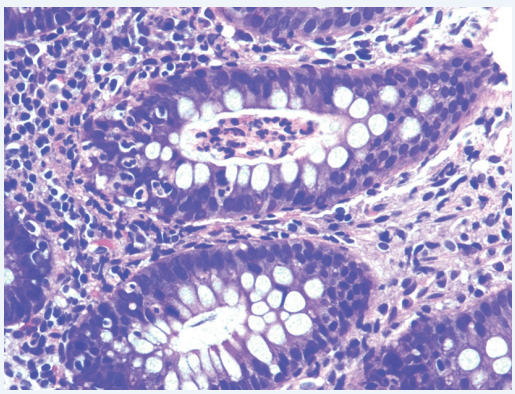
Diagnosis

Juvenile xanthogranuloma

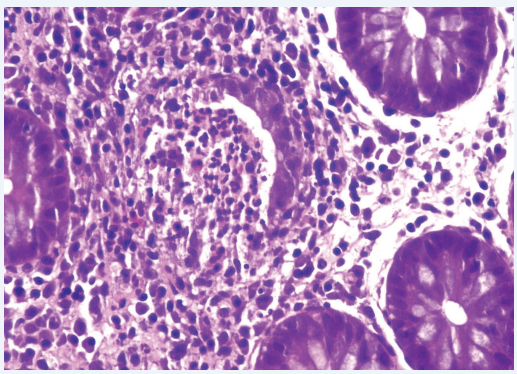
CASE 50

History

Sixteen-year-old girl with abdominal pain, diarrhea, and bloody stools. Biopsy from cecum



H&E



H&E

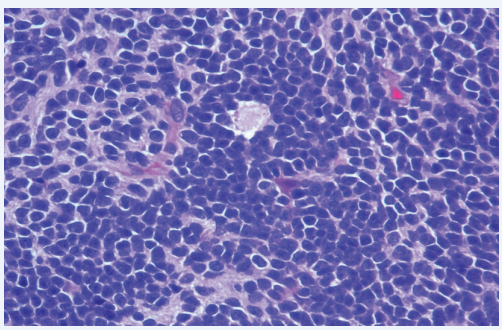
Diagnosis

Inflammatory bowel disease—Crohn colitis

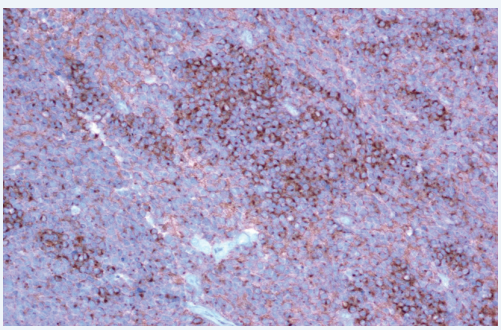
CASE 51

History

Five-year-old girl with headaches and rapidly enlarging posterior fossa mass. MIB-1 was very high. Brain tumor biopsy



H&E



SYNAPTOPHYSIN

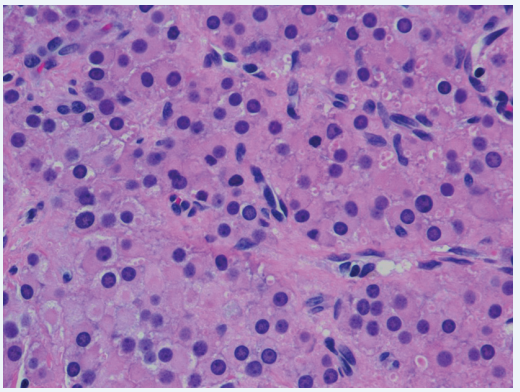
Diagnosis

Medulloblastoma

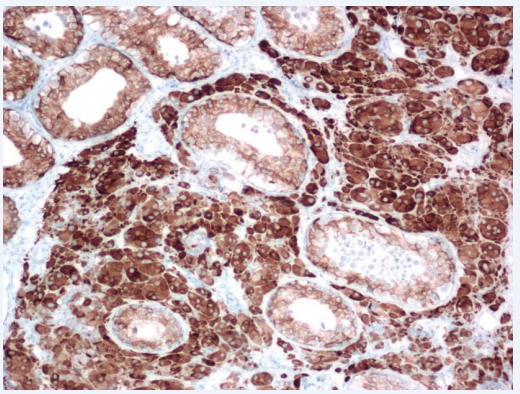
CASE 52

History

Eight-year-old boy with virilization, precocious puberty, and testicular mass. Testicular biopsy



H&E



Inhibin

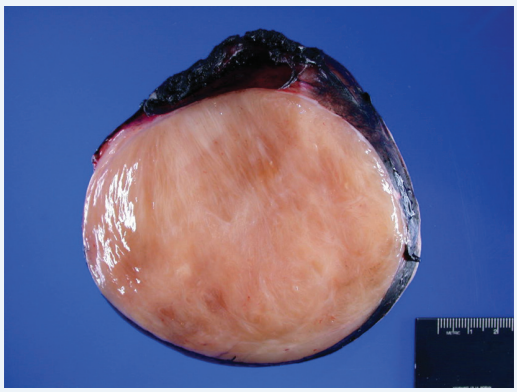
Diagnosis

Leydig cell tumor

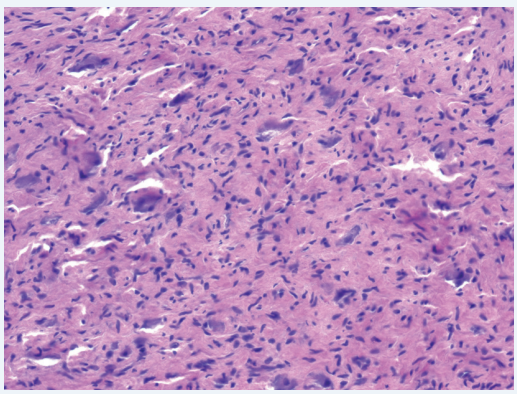
CASE 53

History

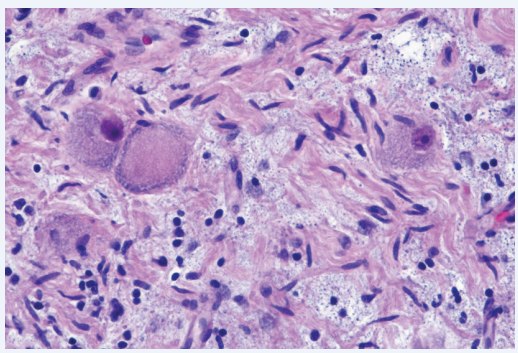
Eight-year-old boy with posterior mediastinal mass. Mass was resected and it showed a gray-white solid homogenous cut surface



GROSS



H&E



H&E

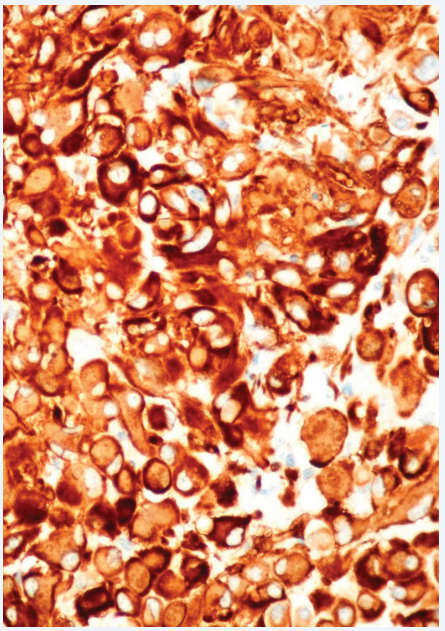
Diagnosis

Mature ganglioneuroma

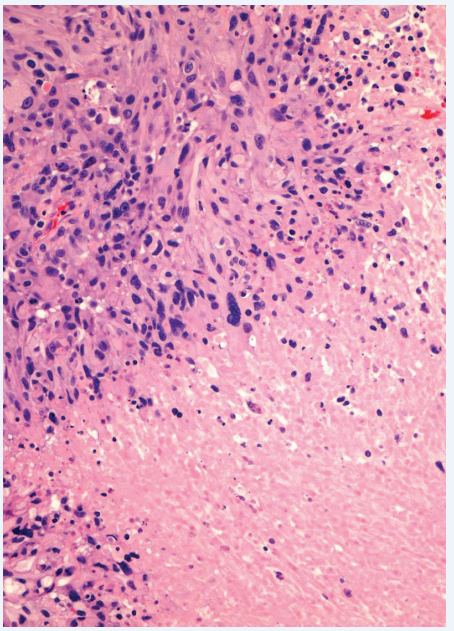
CASE 54

History

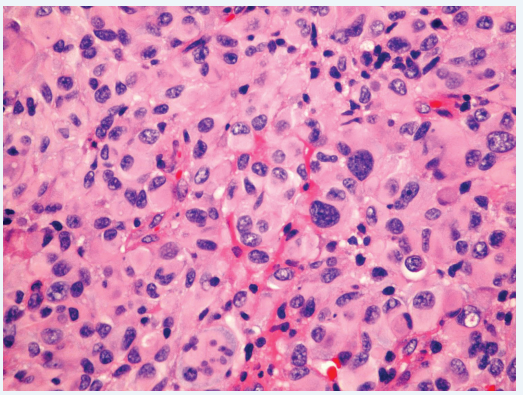
Seven-year-old boy with a solitary, rapidly enlarging supratenticular brain mass. On imaging, the mass was ring-enhancing



GFAP



H&E



H&E

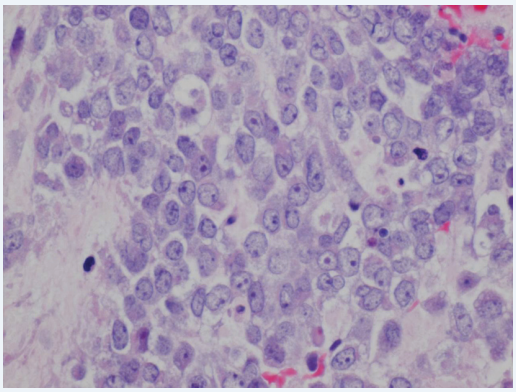
Diagnosis

Glioblastoma multiforme

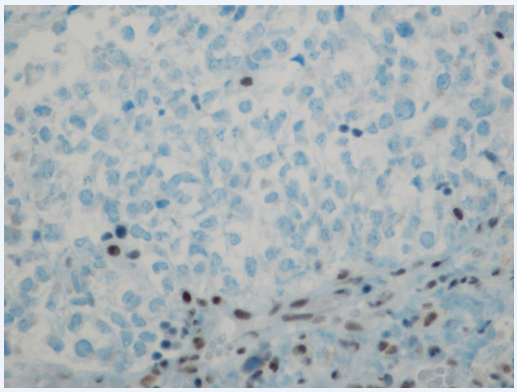
CASE 55

History

Seventeen-month-old boy with rapidly growing mass in posterior fossa. Tumor cells are INI-1 negative but positive for EMA, SMA, and GFAP. Biopsy from the brain tumor



H&E



INI-1

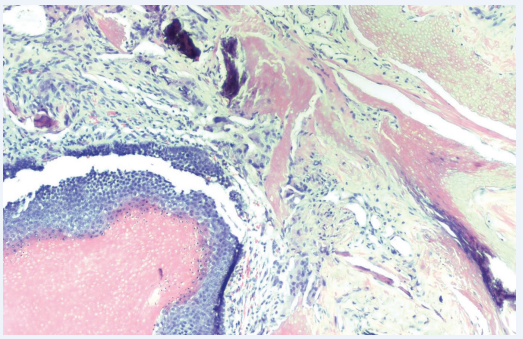
Diagnosis

Atypical teratoid rhabdoid tumor

CASE 56

History

Three-year-old girl with a firm to bony hard mass on left cheek. Cut surface of the mass was chalky white



H&E

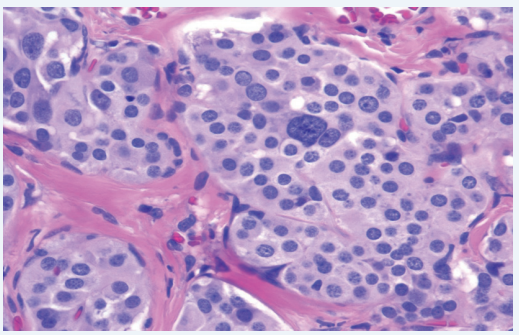
Diagnosis

Pilomatrixoma

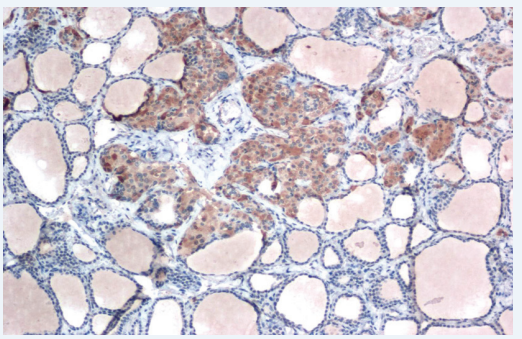
CASE 57

History

Teenage boy with MEN2a and increased serum calcitonin. Cells are positive for calcitonin and congo-red staining is identified. Biopsy from thyroid gland



H&E



CALCITONIN

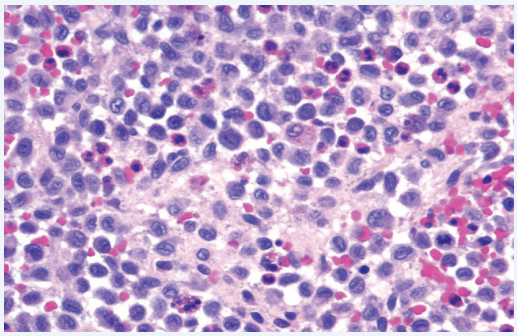
Diagnosis

Medullary carcinoma thyroid gland

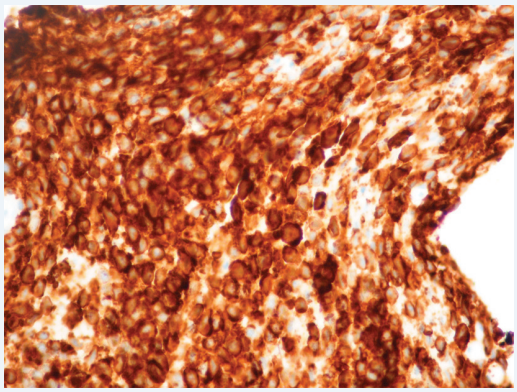
CASE 58

History

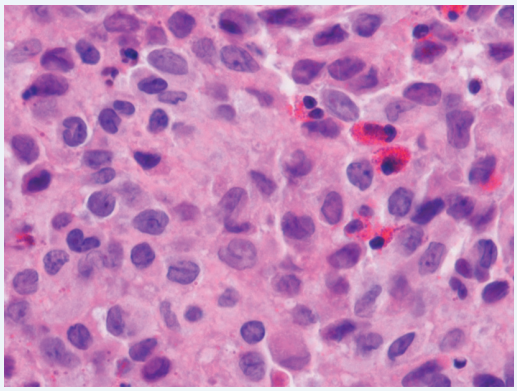
Five-year-old boy with a tender, palpable lytic mass in the skull. Biopsy from the skull mass



H&E



CD1a



H&E

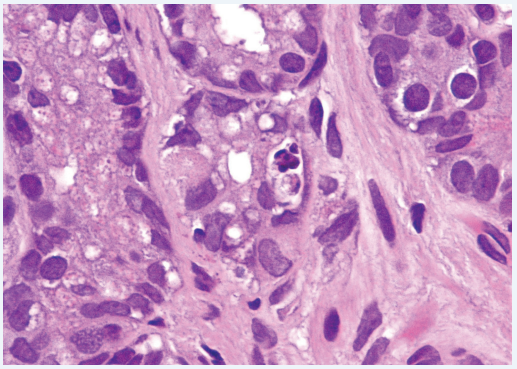
Diagnosis

Langerhans cell histiocytosis

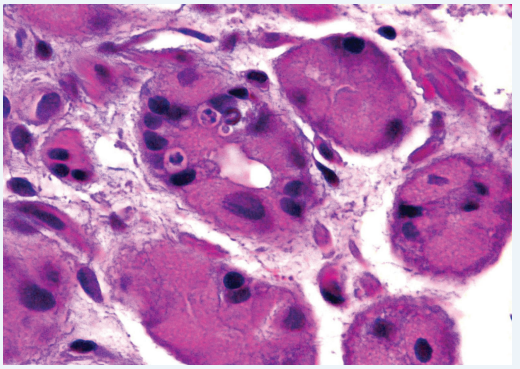
CASE 59

History

Twelve-year-old boy who developed severe diarrhea after allogenic bone marrow transplant



H&E



H&E

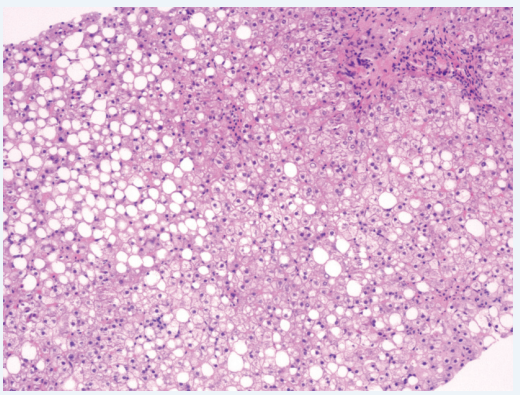
Diagnosis

Graft versus host disease—stomach

CASE 60

History

Markedly obese 14-year-old boy with impaired liver function tests. Liver biopsy



H&E

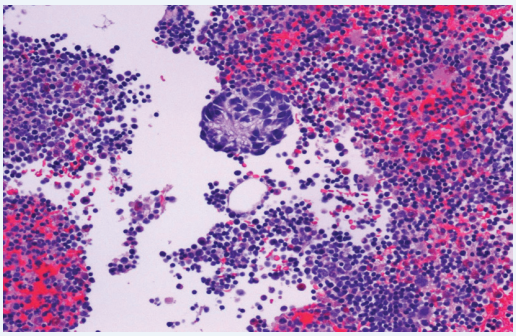
Diagnosis

Non-alcoholic fatty liver disease (NAFLD)

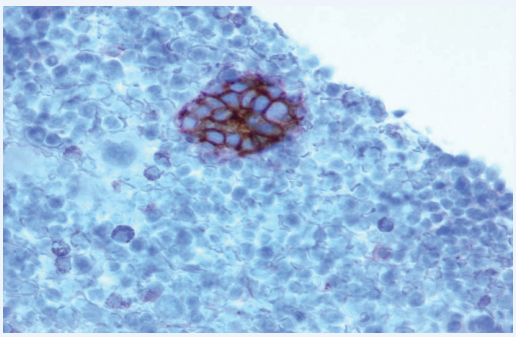
CASE 61

History

Bone marrow biopsy in a 1-year-old infant who has a large mediastinal mass. The neoplastic cells are positive for CD56, tyrosine hydroxylase and PGP9.5



H&E



CD56

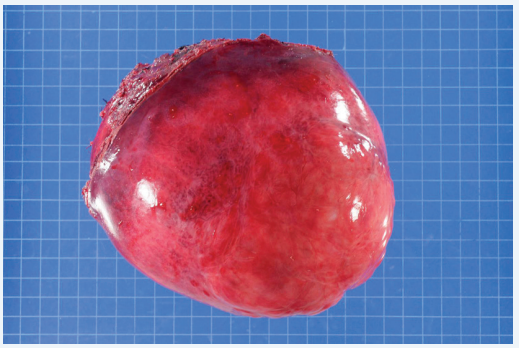
Diagnosis

Metastatic neuroblastoma bone marrow

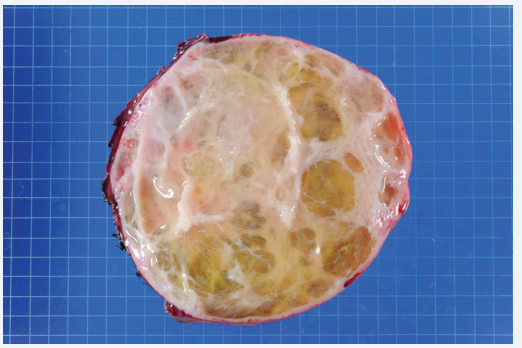
CASE 62

History

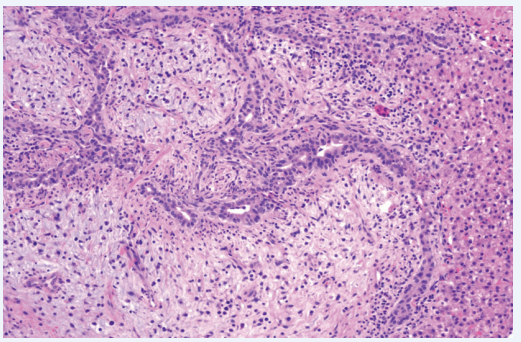
Eleven-month-old boy with a large liver mass. The mass was well circumscribed and had a solid-cystic cut surface



GROSS EXTERNAL SURFACE



GROSS: CUT SURFACE



H&E

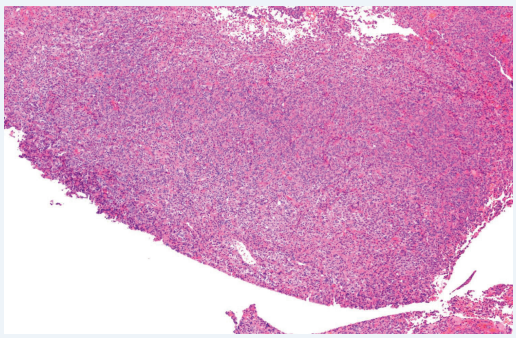
Diagnosis

Mesenchymal hamartoma liver

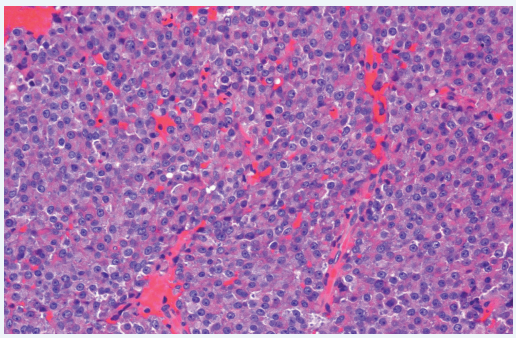
CASE 63

History

Slow-growing sellar mass in a 13-year-old girl who presented with history of headaches and galactorrhea. Tumor cells are positive for chromogranin



H&E



H&E

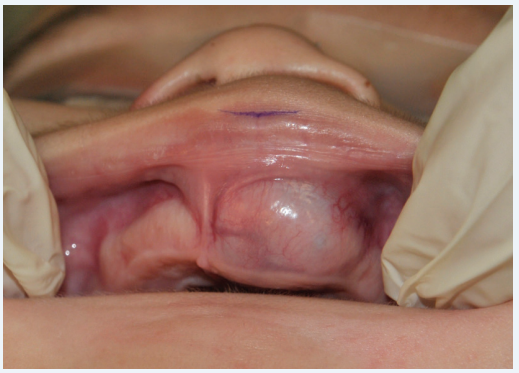
Diagnosis

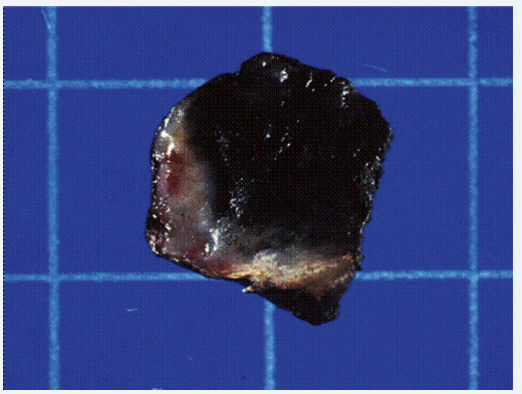
Pituitary adenoma

CASE 64

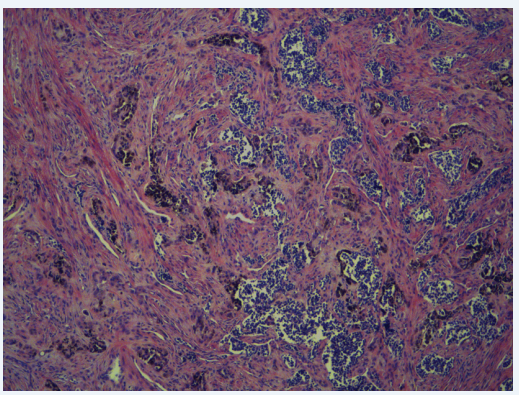
History

Osteolytic mass lesion in maxilla of newborn infant. Mass was brown-black in color and solid in appearance. Tumor cells are positive for HMB45, CK, and NSE





GROSS



H&E

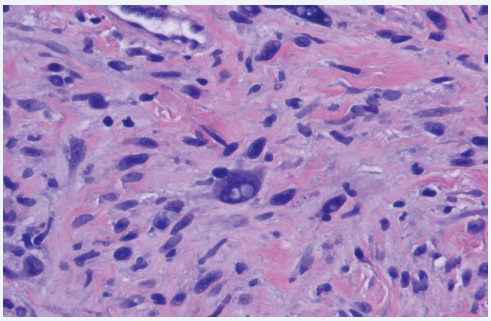
Diagnosis

Melanotic neuroectodermal tumor of infancy

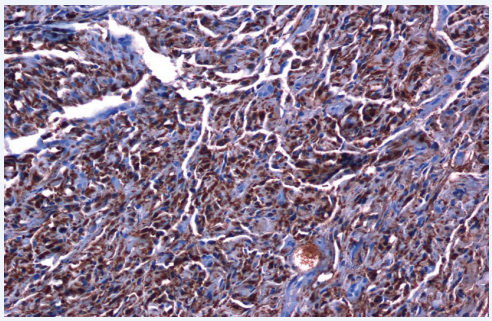
CASE 65

History

Recurrent mass in gluteal region in a 12-year-old boy with NF1. Tumor biopsy



H&E



S100

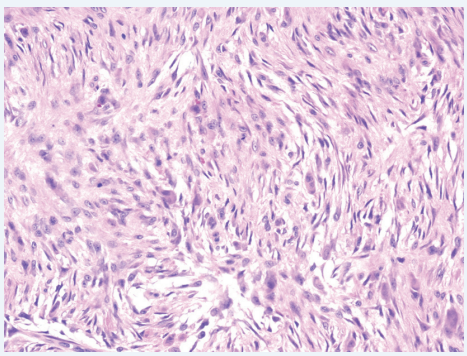
Diagnosis

Malignant peripheral nerve sheath tumor

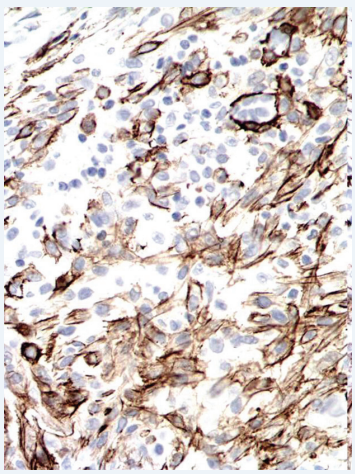
CASE 66

History

Eleven-year-old boy with a rapidly enlarging 3 cm nodular painful mass in forearm. Biopsy from the mass



H&E



SMA

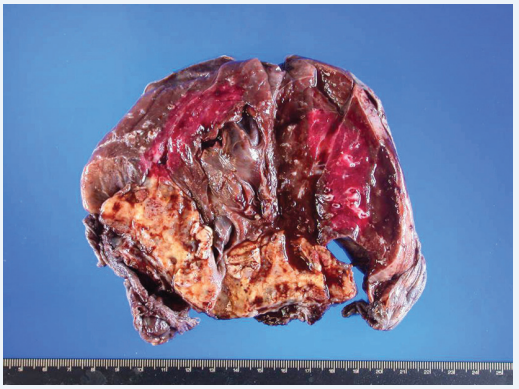
Diagnosis

Nodular fasciitis

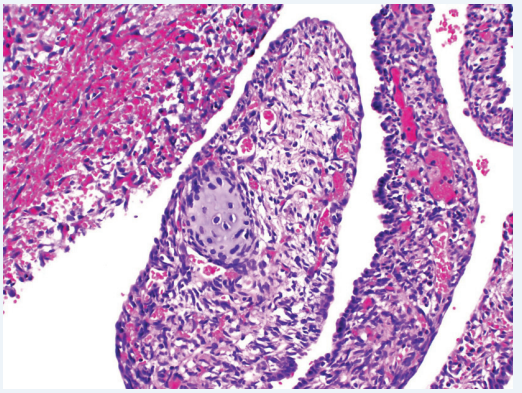
CASE 67

History

Four-month-old girl with shortness of breath and lung mass. The mass was solid-cystic and hemorrhagic in appearance. Right lung lobectomy was done



GROSS



H&E

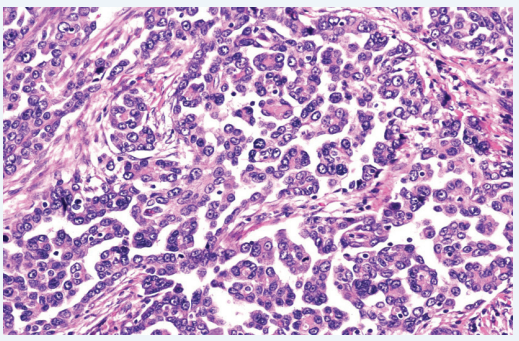
Diagnosis

Pleuropulmonary blastoma

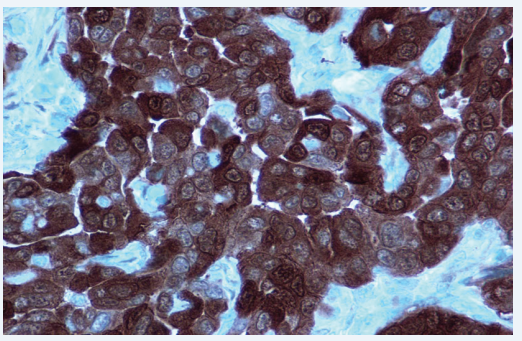
CASE 68

History

Peritoneal mass in 18-year-old boy with prior history of radiotherapy. Tumor cells are positive for CK5/6, WT-1, and calretinin. Biopsy from the mass



H&E



CALRETININ

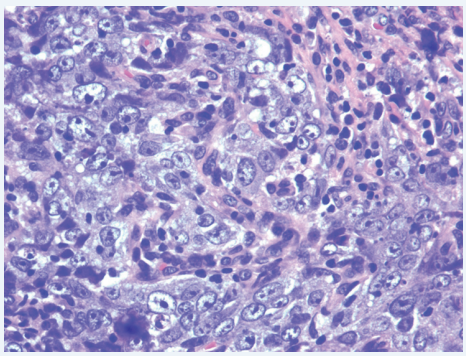
Diagnosis

Mesothelioma

CASE 69

History

Fourteen-year-old African boy with a metastatic tumor in left cervical lymph node. The tumor cells were positive for cytokeratin and Epstein-Barr virus. Lymph node biopsy



H&E

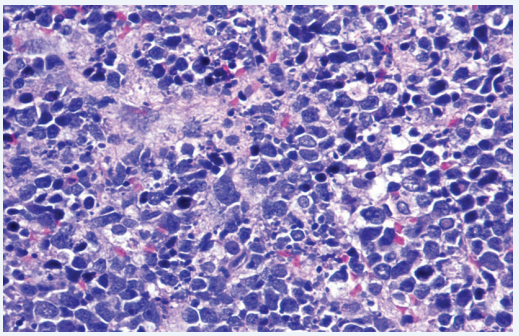
Diagnosis

Nasopharyngeal carcinoma

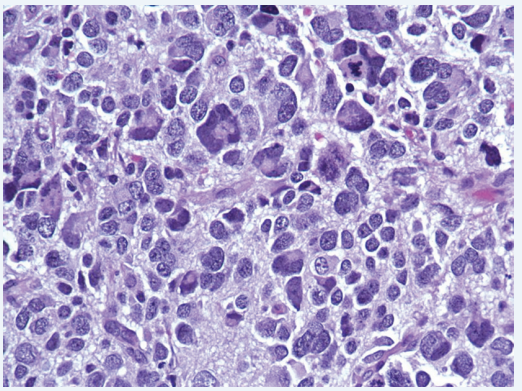
CASE 70

History

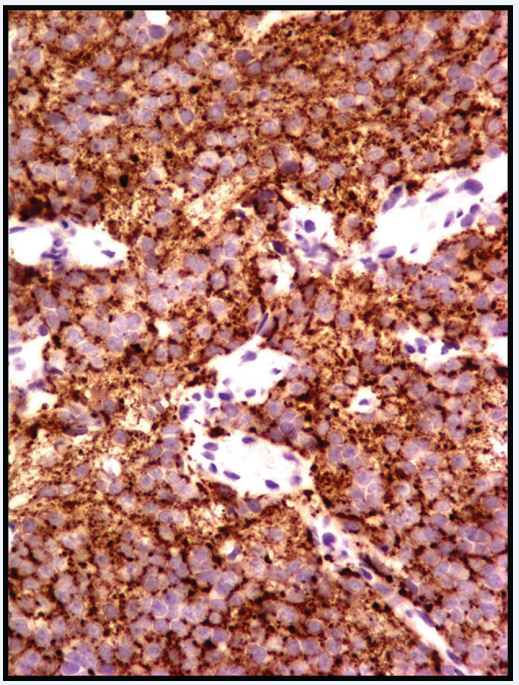
Twenty-month-old boy with a large abdominal mass, fever, and weight loss. The lesion was positive for chromogranin, tyrosine hydroxylase and negative for CD99. Biopsy from the adrenal gland mass



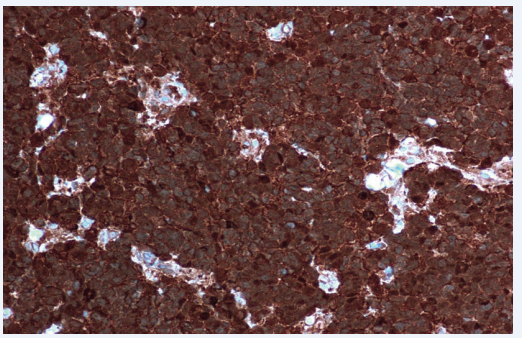
H&E



H&E



SYNAPTOPHYSIN



PGP 9.5

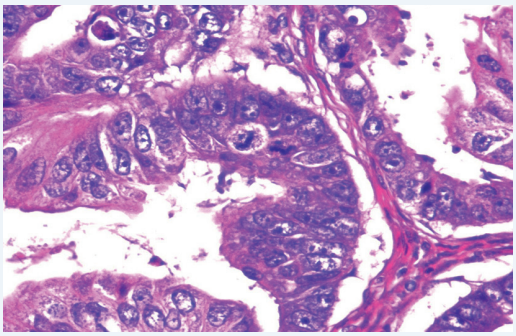
Diagnosis

Poorly differentiated neuroblastoma

CASE 71

History

Fifteen-year-old girl with a large solid-cystic mucinous mass of right ovary. Neoplastic cells are positive for CEA and CA125. Biopsy from ovarian tumor



H&E

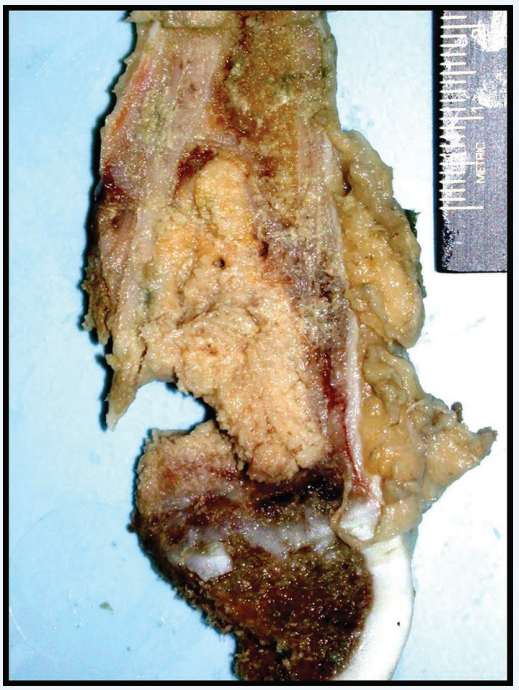
Diagnosis

Malignant mucinous cystadenocarcinoma of ovary

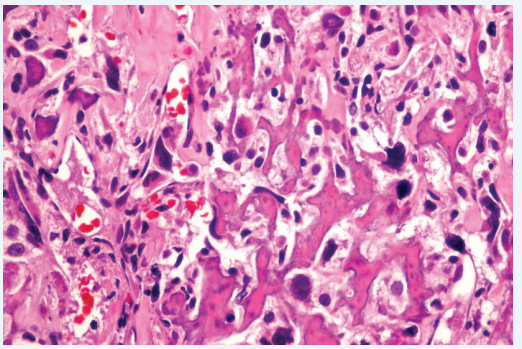
CASE 72

History

Fourteen-year-old boy with a lytic mass in the distal femur. Bone was resected and showed a necrotic tumor mass



GROSS



H&E

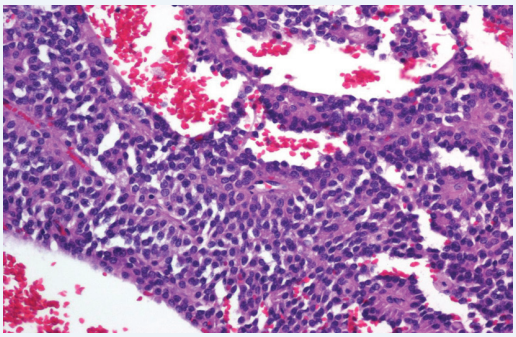
Diagnosis

Osteosarcoma

CASE 73

History

Nineteen-year-old girl with a multinodular mass in her pancreas. Grossly, the tumor was partly necrotic and cystic. Tumor cells are positive for vimentin, CD10, and progesterone. Tumor biopsy



H&E

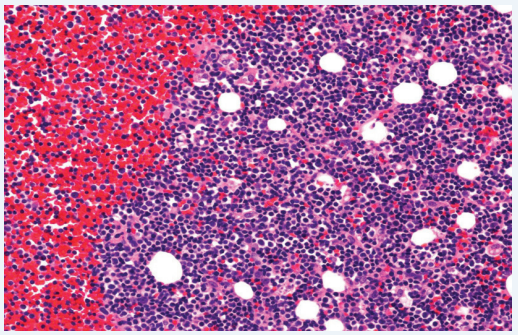
Diagnosis

Solid pseudopapillary neoplasm of pancreas

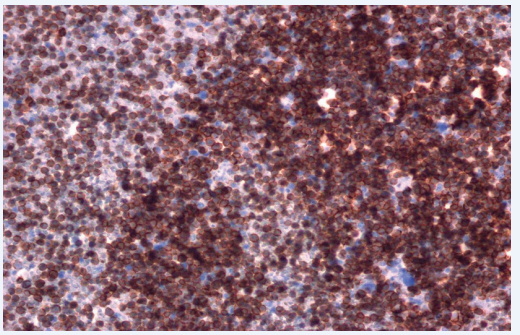
CASE 74

History

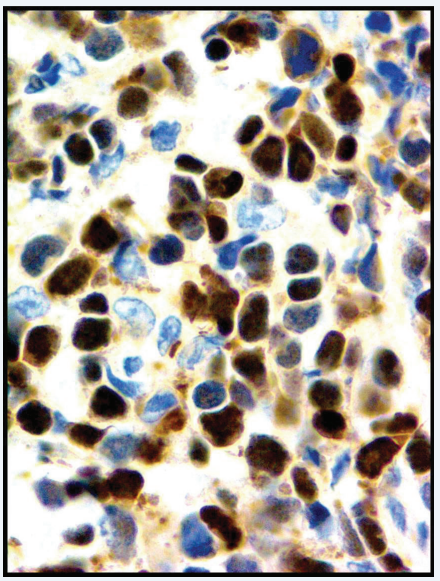
Six-year-old boy with weight loss, fever, bleeding, and anemia. Bone marrow biopsy



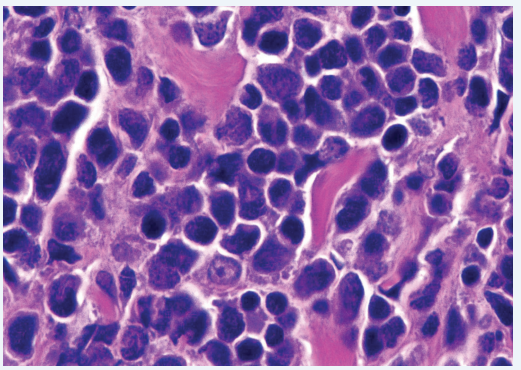
H&E



CD3



TDT



H&E

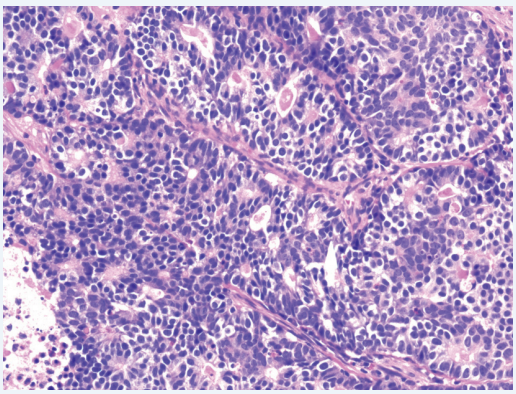
Diagnosis

T-cell acute lymphoblastic leukemia

CASE 75

History

Two-year-old girl with mass in the pancreas. Tumor cells are positive for cytokeratin and beta-catenin, and negative for NSE. Pancreatic mass biopsy



H&E

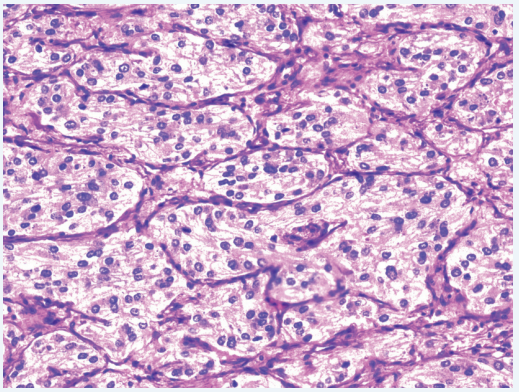
Diagnosis

Pancreatoblastoma

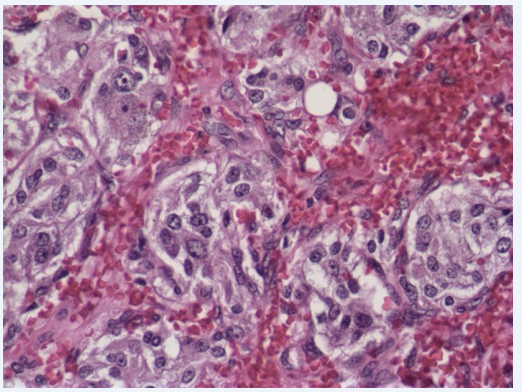
CASE 76

History

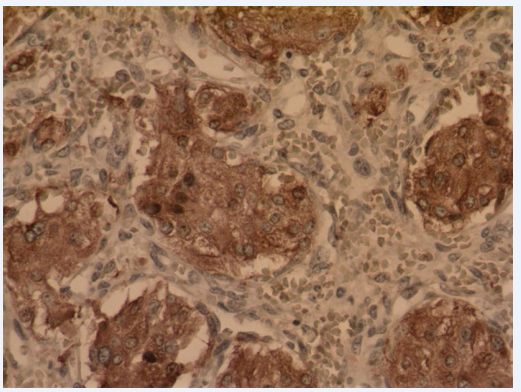
Ten-year-old boy with headaches, tachycardia, and an abdominal mass. Adrenal gland biopsy



H&E



H&E



CHROMOGRANIN

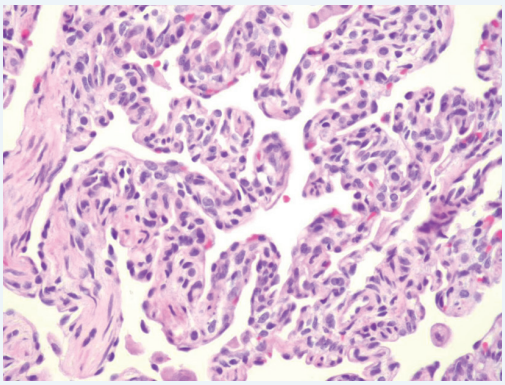
Diagnosis

Pheochromocytoma adrenal medulla

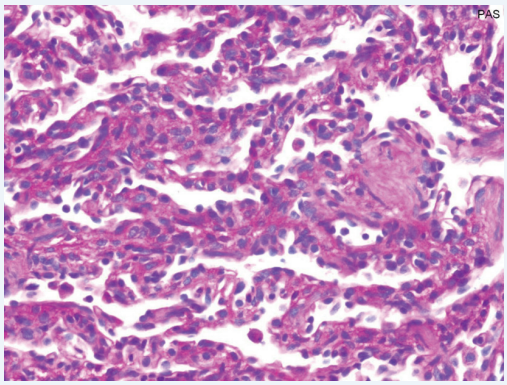
CASE 77

History

Lung biopsy from a 1-month-old infant who has severe respiratory distress and needs oxygen supplementation



H&E



PAS

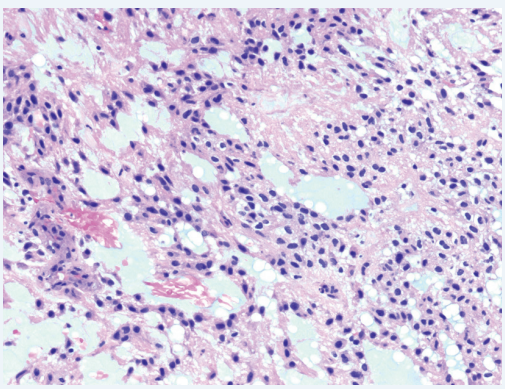
Diagnosis

Pulmonary interstitial glycogenosis

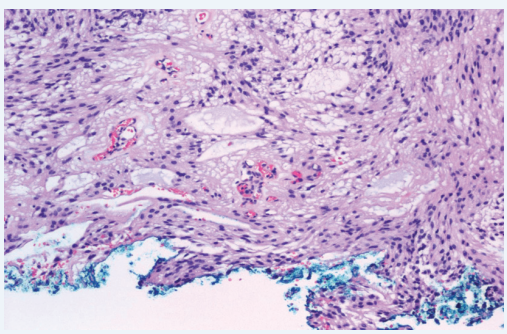
CASE 78

History

Twelve-year-old girl with a sharply circumscribed, enhancing lesion in the filum terminale of the spinal cord. GFAP was positive and CK was negative in tumor cells. Tumor biopsy



H&E



H&E

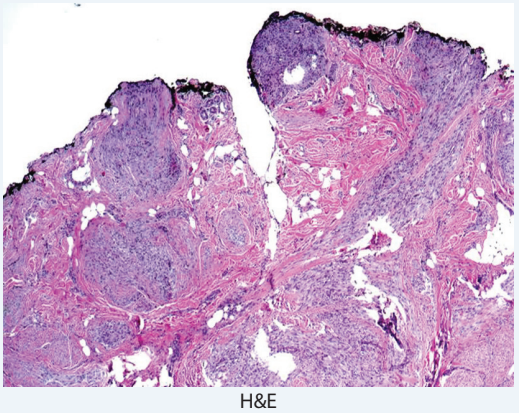
Diagnosis

Myxopapillary ependymoma

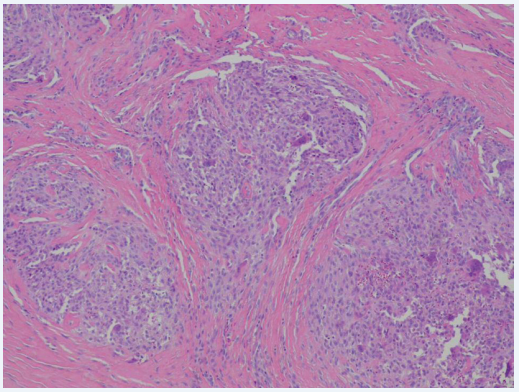
CASE 79

History

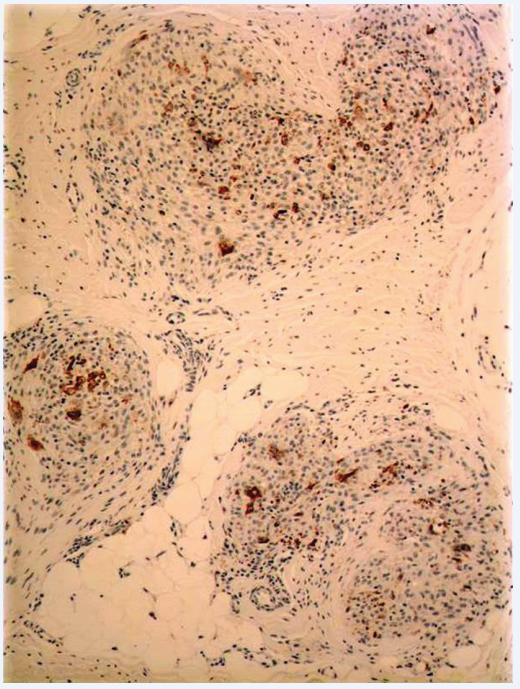
Twelve-year-old girl with multinodular poorly circumscribed subcutaneous mass on the foot. Biopsy from the mass



H&E



H&E



CD68

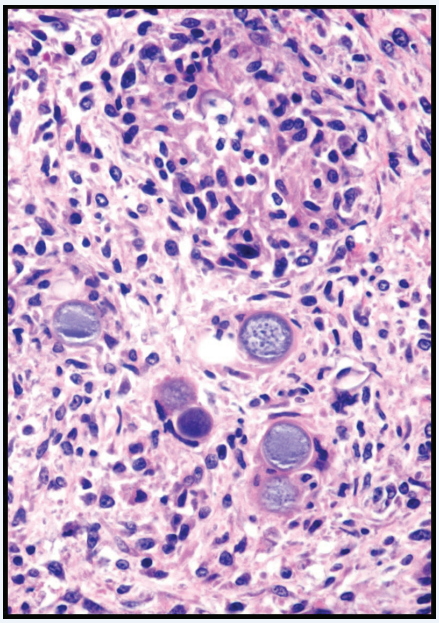
Diagnosis

Plexiform fibrohistiocytic tumor

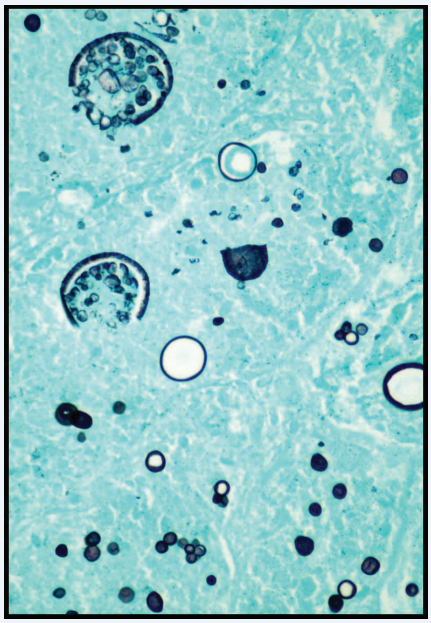
CASE 80

History

Five-year-old HIV positive immunosuppressed boy who is a resident of Arizona and presented with a granulomatous lesion in left lung



H&E



GMS

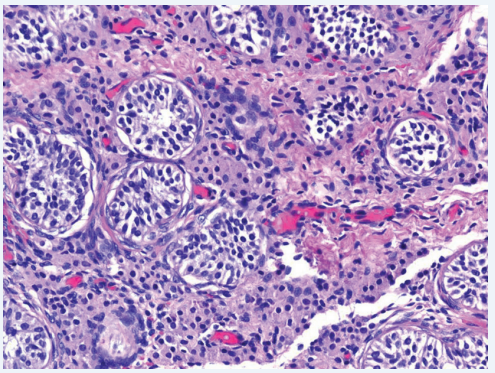
Diagnosis

Coccidioides immites infection lung

CASE 81

History

Fourteen-year-old girl with primary amenorrhea and pelvic pain. Neoplastic cells are positive for inhibin and calretinin. Ovarian tumor biopsy



H&E

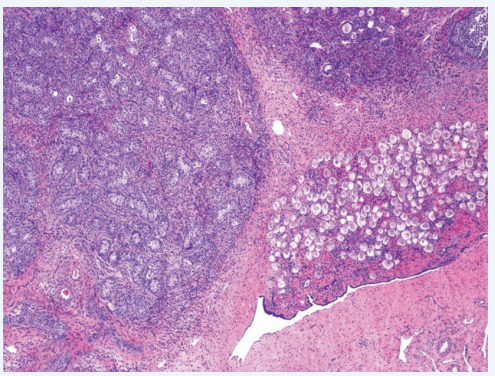
Diagnosis

Sertoli-Leydig cell tumor ovary

CASE 82

History

A 1.5-year-old girl with a 1 cm nodular mass in the right inguinal region. Biopsy is from the tissue labeled as "right gonad"



H&E

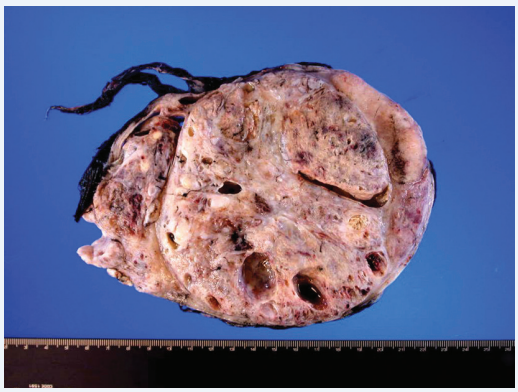
Diagnosis

Ovotestis

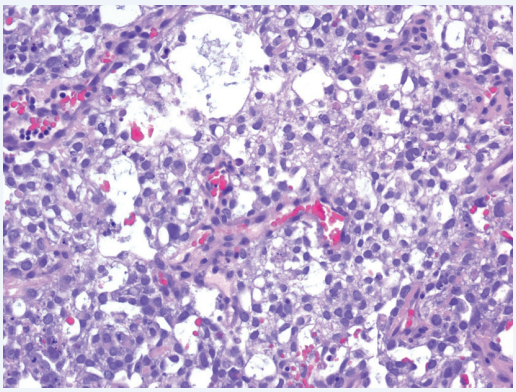
CASE 83

History

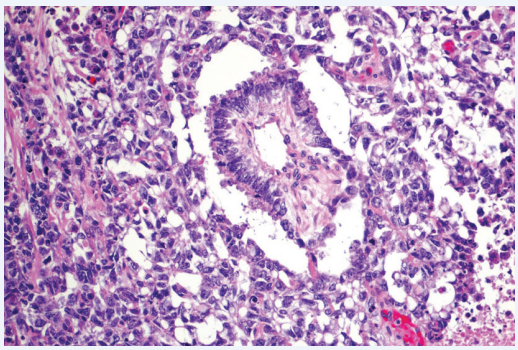
Five-year-old girl with abdominal pain and rapidly growing abdominal mass. Serum AFP levels were high. Ovarian mass was resected, and it showed a variegated solid-cystic cut surface with zones of necrosis



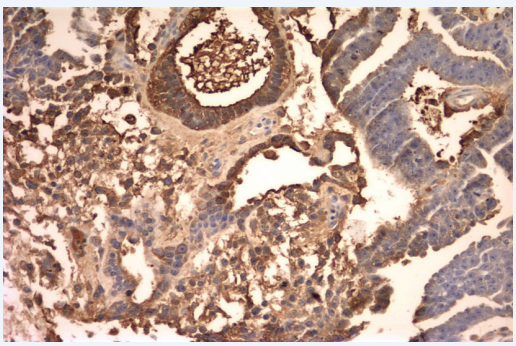
GROSS



H&E



H&E



ALPHA-FETOPROTEIN (AFP)

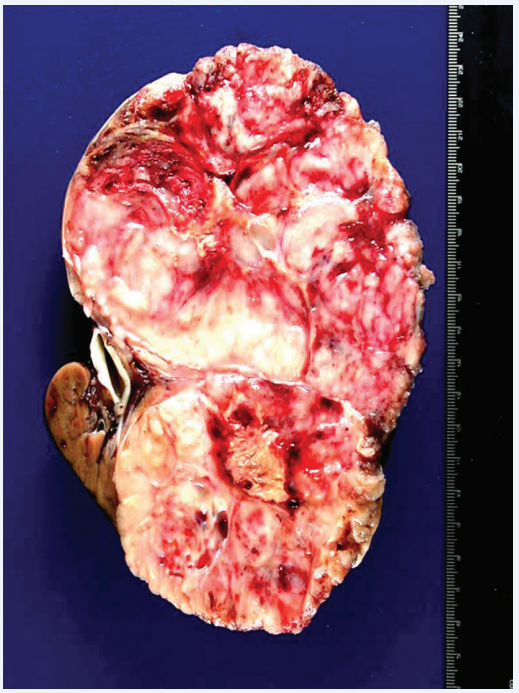
Diagnosis

Yolk sac tumor

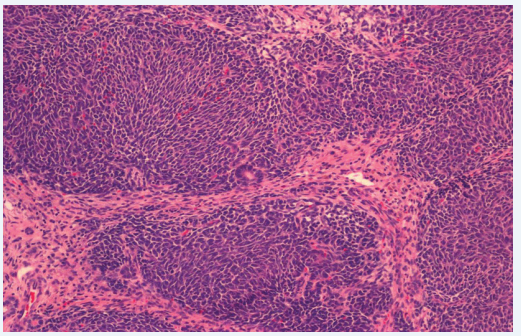
CASE 84

History

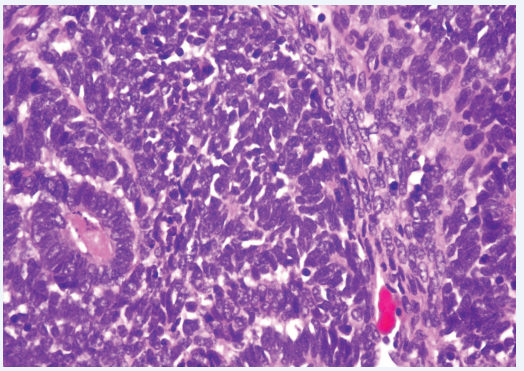
Four-year-old girl with a large abdominal mass. The right kidney was resected, and it showed a large solid yellow-colored mass replacing the entire kidney



GROSS



H&E



H&E

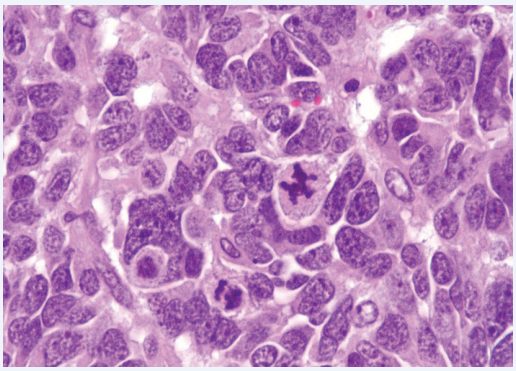
Diagnosis

Wilms tumor (favorable histology)

CASE 85

History

Three-year-old girl with enlarged right kidney. She has a past history of known Wilms tumor of left kidney. Section is from the right kidney tumor



H&E

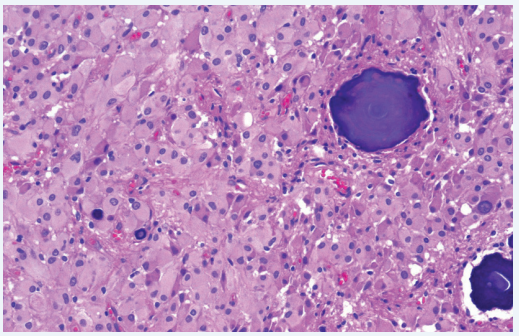
Diagnosis

Wilms tumor with diffuse anaplasia (unfavorable histology)

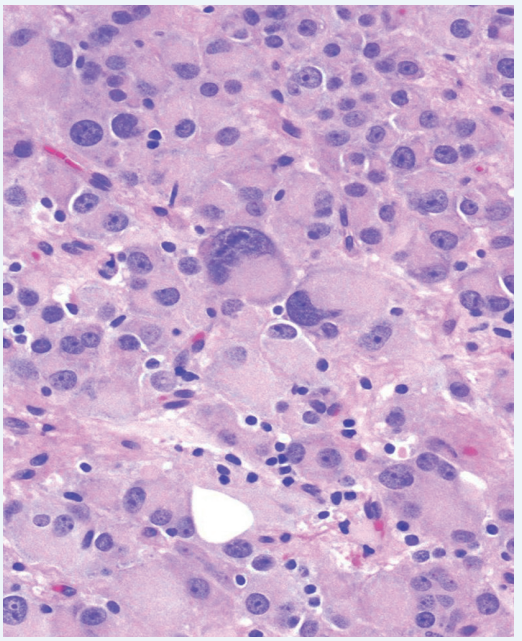
CASE 86

History

Six-year-old boy with a history of tuberous sclerosis presented with a mass in the third ventricle of the brain. Brain tumor biopsy



H&E



H&E

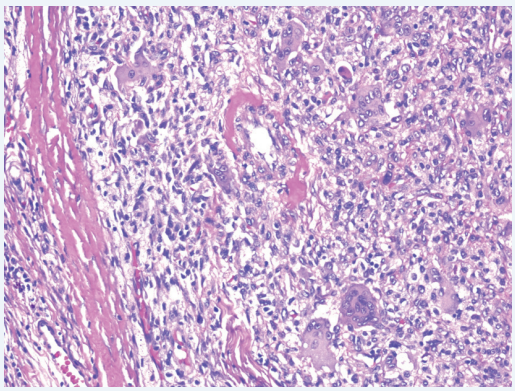
Diagnosis

Subependymal giant cell astrocytoma

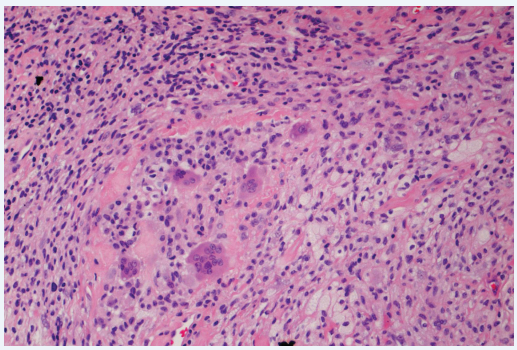
CASE 87

History

Fourteen-year-old boy with a mass in right popliteal fossa. Biopsy is from the mass



H&E



H&E

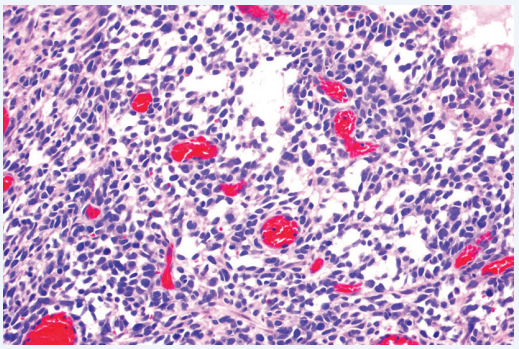
Diagnosis

Giant cell tumor of tendon sheath

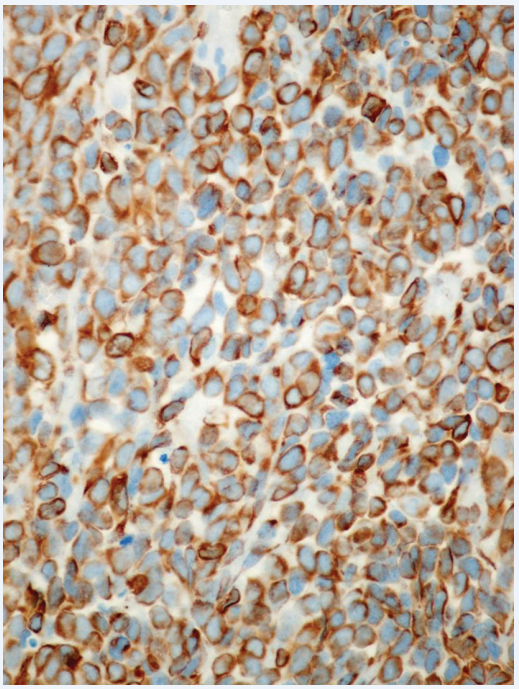
CASE 88

History

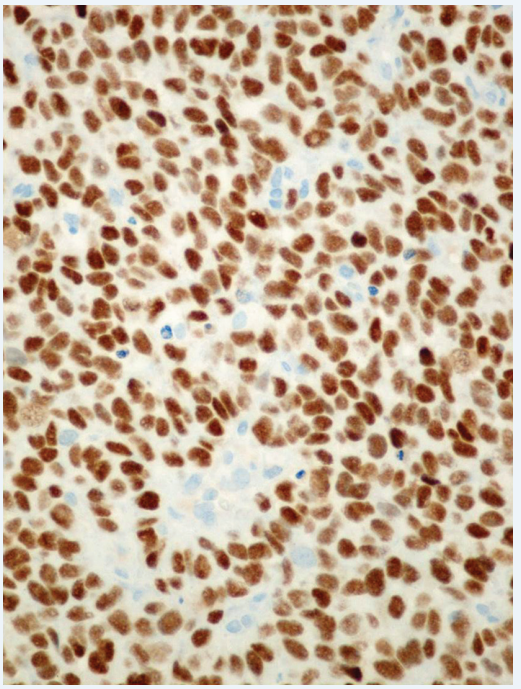
Seven-year-old girl with an enlarging soft-tissue mass in the heel of left foot. FISH studies show *PAX3-FOXO1* gene rearrangements. Biopsy is from the mass



H&E



DESMIN



MYOGENIN

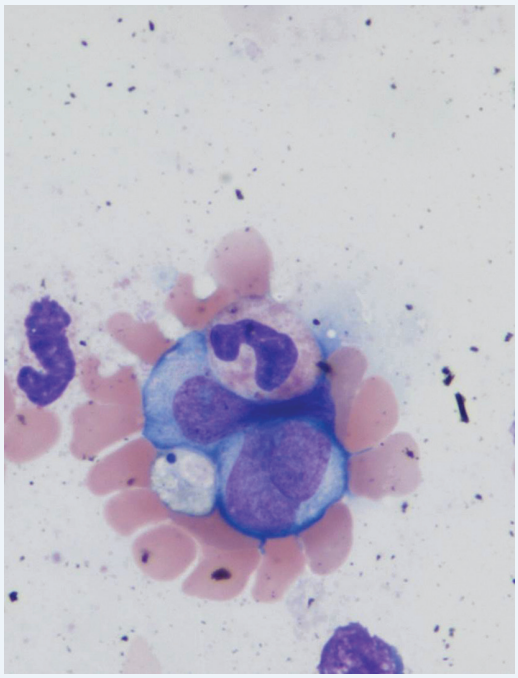
Diagnosis

Alveolar rhabdomyosarcoma

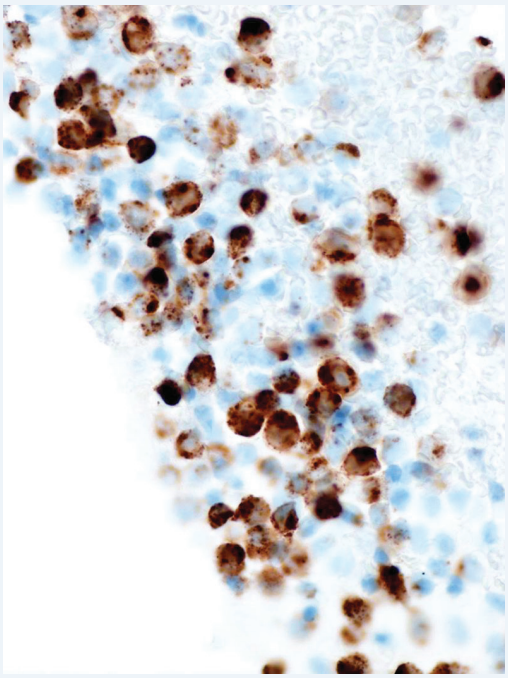
CASE 89

History

Six-year-old girl with generalized weakness, weight loss, and fever for 1 week. Bone marrow biopsy/aspirate was performed. Flow cytometry confirmed expression of cD11b, CD11c, CD13, CD33, HLA-DR, myeloperoxidase, and CD163



GIEMSA



MYELOPEROXIDASE (MPO)

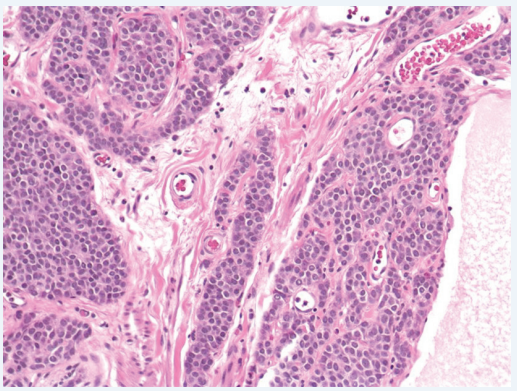
Diagnosis

Acute myeloid leukemia—bone marrow

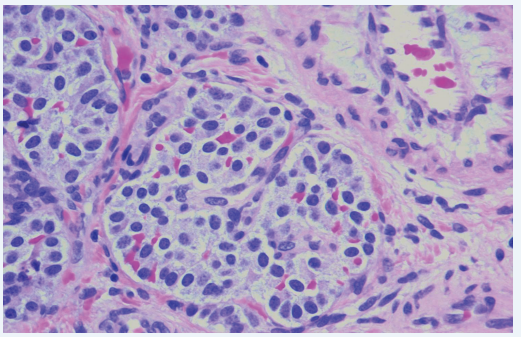
CASE 90

History

Eight-year-old boy who underwent appendectomy for appendicitis. At the time of surgery an incidental 1 cm yellow circumscribed mass was found on tip of the appendix. Tumor cells express chromogranin and are negative for CEA



H&E



H&E

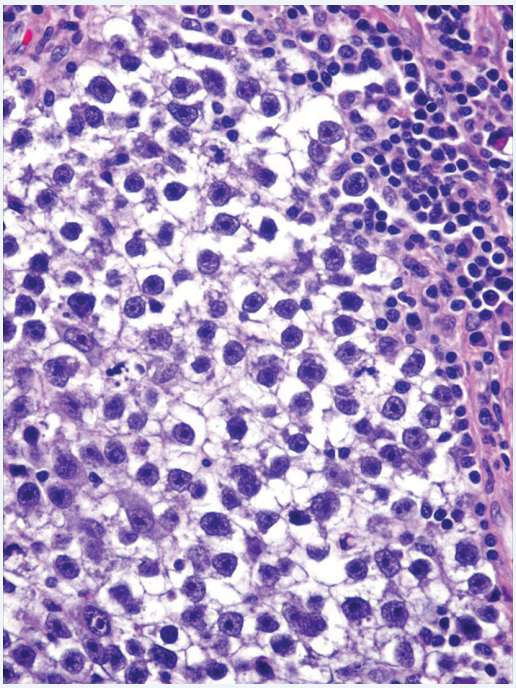
Diagnosis

Carcinoid tumor—appendix

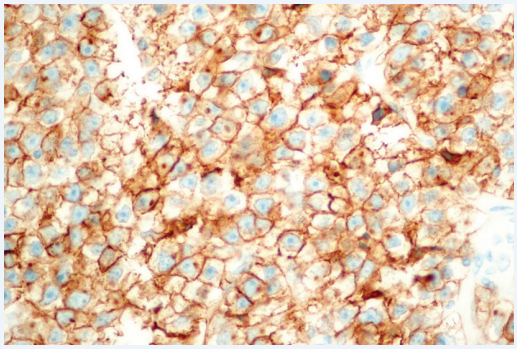
CASE 91

History

Five-year-old boy with a painful testicular enlargement. Testicular tumor biopsy was performed and tumor cells were seen to express CD117, OCT4, and PLAP



H&E



PLACENTAL ALKALINE PHOSPHATASE (PLAP)

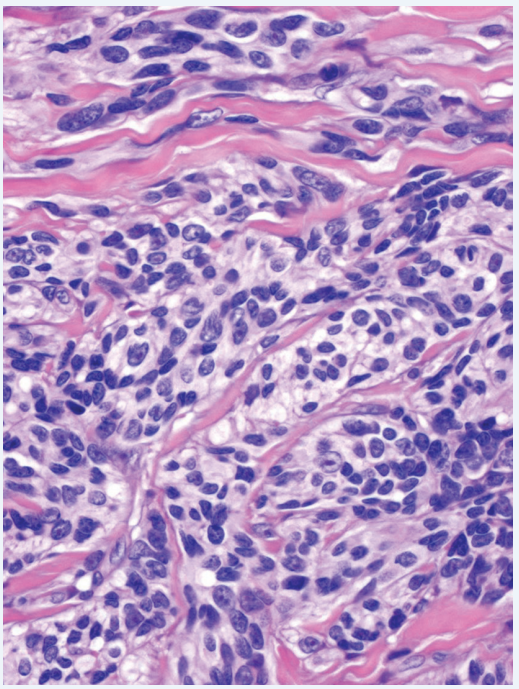
Diagnosis

Seminoma

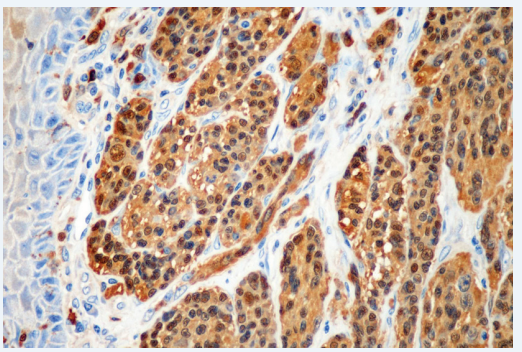
CASE 92

History

Twelve-year-old boy with a deep soft-tissue mass in thigh. Tumor biopsy



H&E



HMB-45

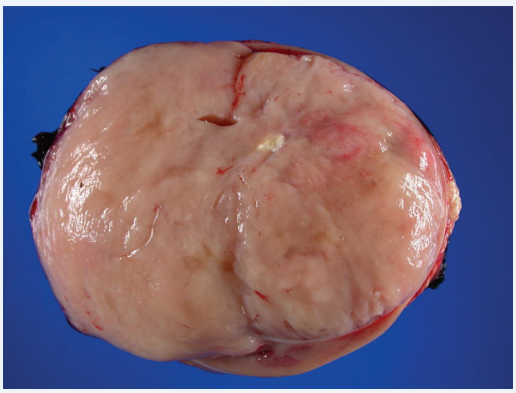
Diagnosis

Malignant melanoma of soft parts

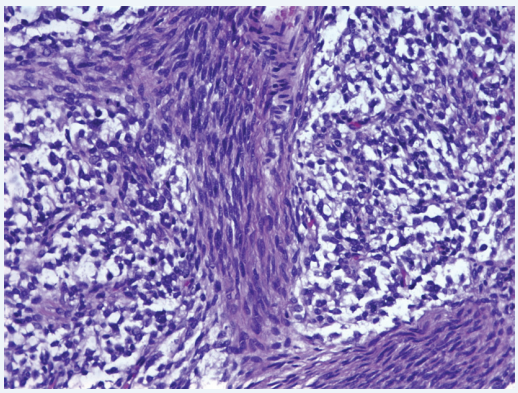
CASE 93

History

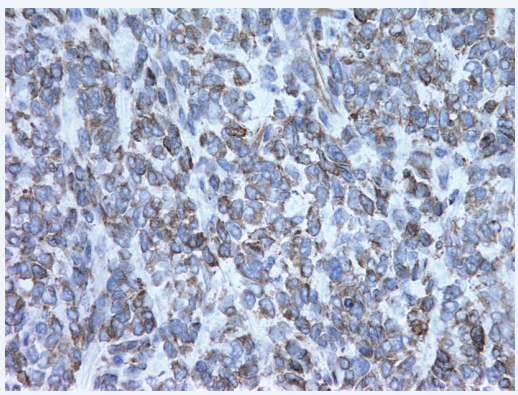
Eight-year-old boy with large mass in left kidney. The kidney was resected, and it showed a large gray-white solid tumorous mass. The tumor had also metastasized to the pelvic bone



GROSS: CUT SURFACE



H&E



BCL2

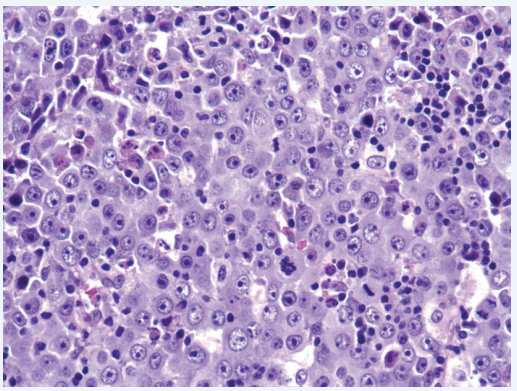
Diagnosis

Clear cell sarcoma of kidney

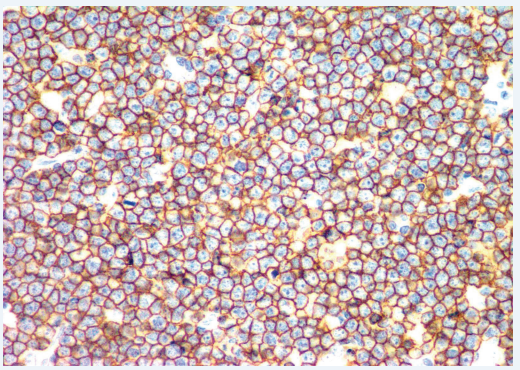
CASE 94

History

Cervical lymph node biopsy from a 14-year-old boy with anemia and weight loss. Lesional cells expressed CD19, CD20 and light chain restriction. The cells did not express CD10 or TdT



H&E



CD20

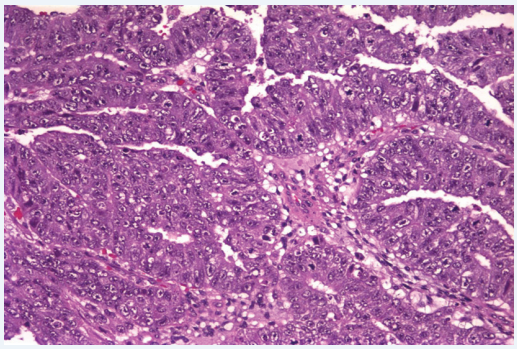
Diagnosis

Diffuse large B-cell lymphoma

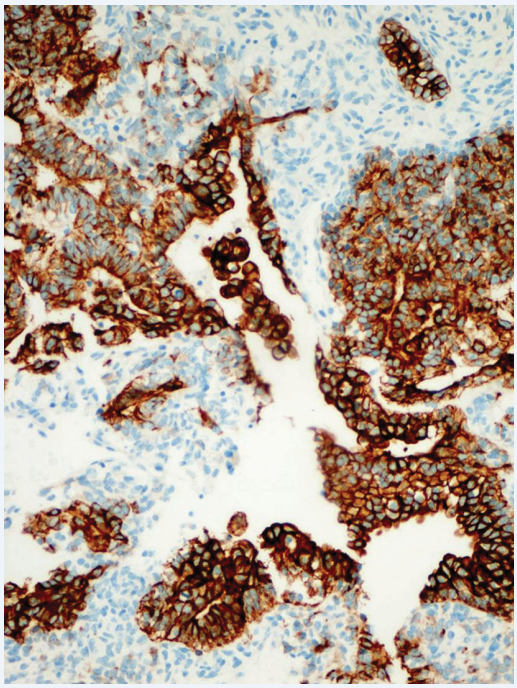
CASE 95

History

Testicular resection for tumorous mass in a 8-year-old boy. Tumor cells expressed CK, CD30, and OCT4 but not EMA



H&E



CYTOKERATIN (CK)

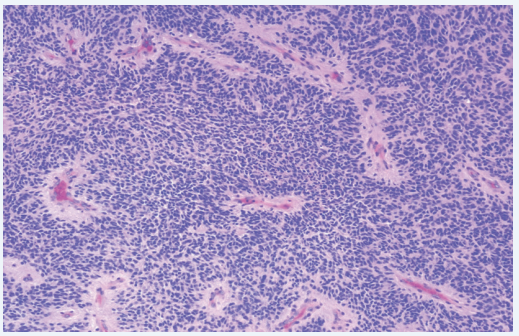
Diagnosis

Embryonal carcinoma of testis

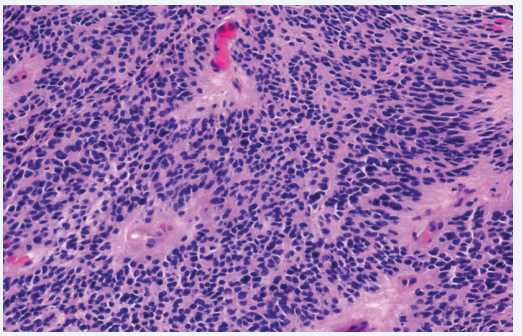
CASE 96

History

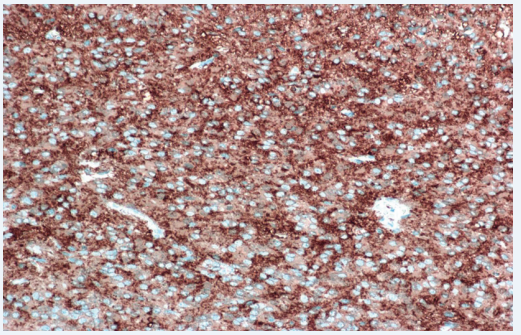
Large tumor in the posterior fossa of the brain in a 5-year-old girl presenting with headaches. Tumor cells expressed GFAP and EMA



H&E



H&E



GFAP

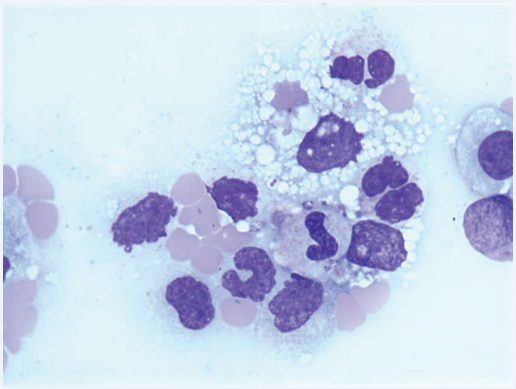
Diagnosis

Ependymoma

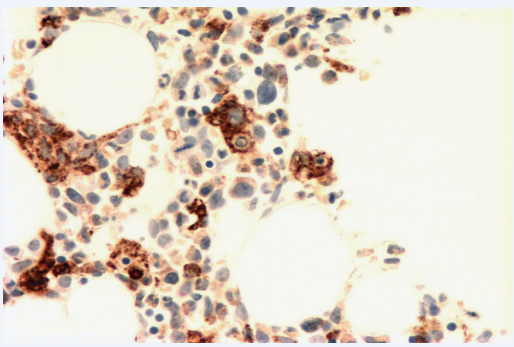
CASE 97

History

Bone marrow biopsy/aspirate in a 5-year-old boy who presented with fever, increased serum ferritin, abnormal liver function tests, and weakness



GIEMSA



CD68

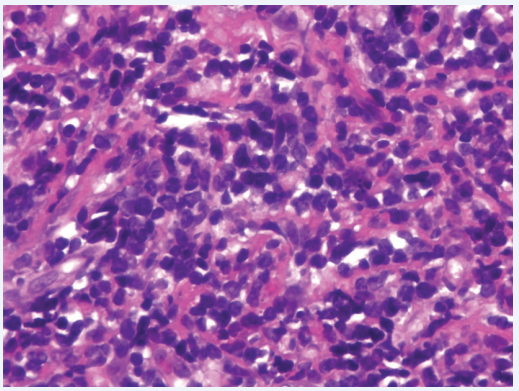
Diagnosis

Hemophagocytic lymphohistiocytosis

CASE 98

History

Twelve-year-old boy who presented with a large mediastinal mass, dyspnea, and superior vena cava syndrome. Biopsy from the mass



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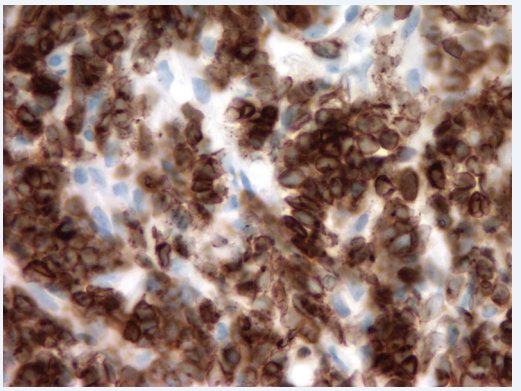
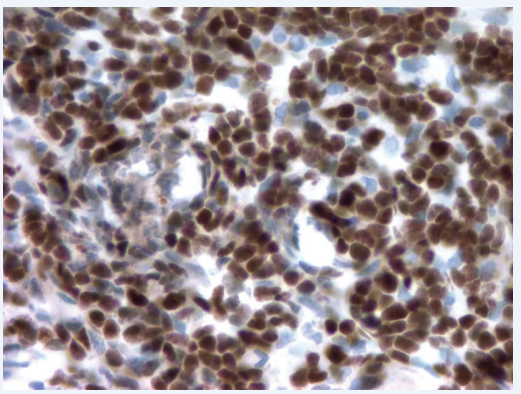


CD3



TDT

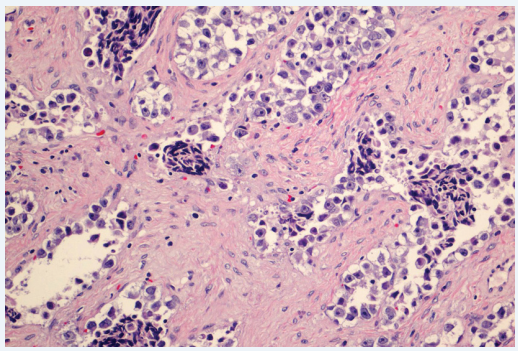
Diagnosis

T-cell lymphoblastic lymphoma of mediastinum

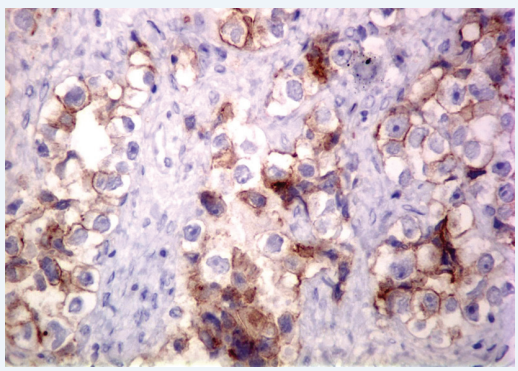
CASE 99

History

Ten-year-old girl presented with a large mass in the wall of small bowel. Tumor cells are positive for *c-Kit*, vimentin, and CD34



H&E



CD117

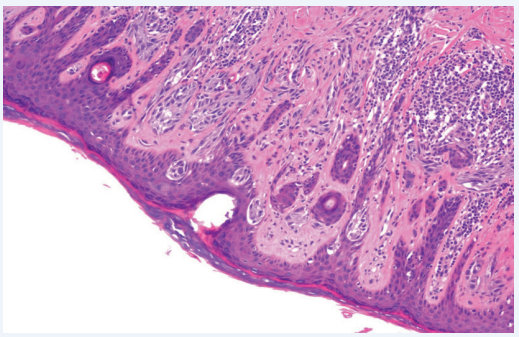
Diagnosis

Gastrointestinal stromal tumor (epithelioid variant)

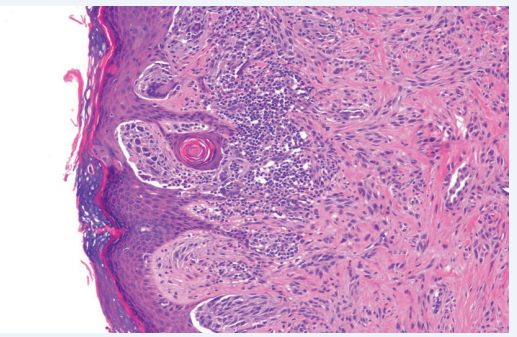
CASE 100

History

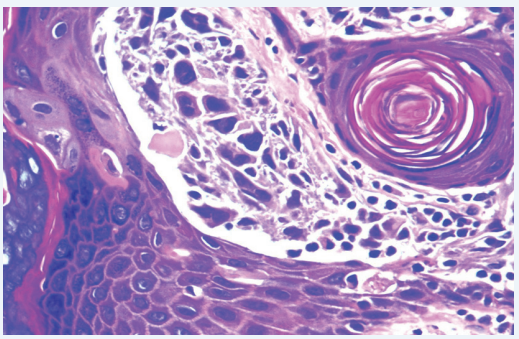
Eight-year-old boy with a tan-colored papular mass (1 cm) on the cheek



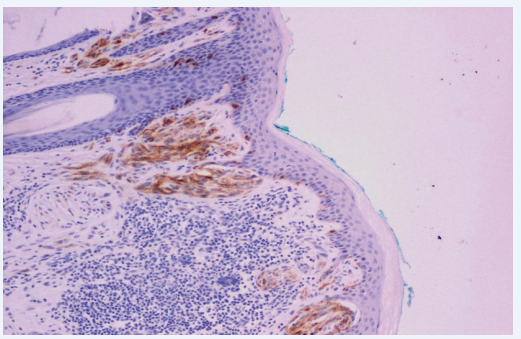
H&E



H&E



H&E



HMB45

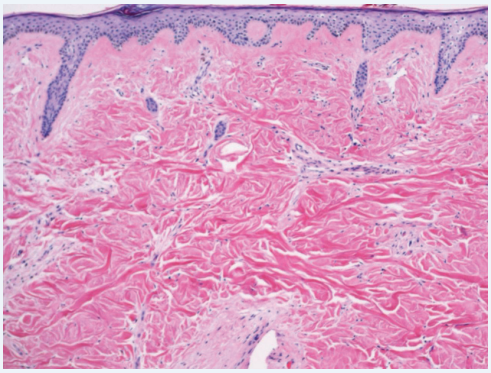
Diagnosis

Spitz nevus (spindle and epithelioid cell nevus)

CASE 101

History

Nine-year-old girl with history of autoimmune disorders now presented with atrophic, hypopigmented patchy skin lesion on the genitalia



H&E

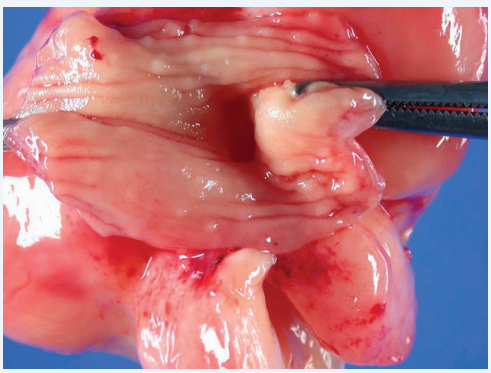
Diagnosis

Scleroderma (morphea)

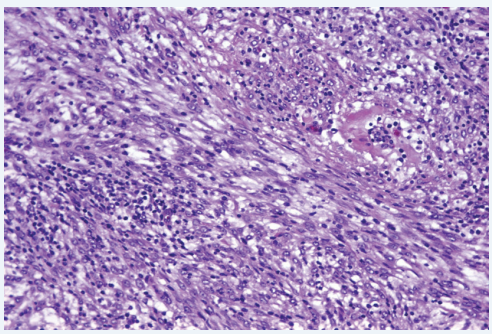
CASE 102

History

Seven-year-old boy with tumor of urinary bladder. The resected mass showed spindle cells that were positive for smooth muscle actin stain and AlK1. Several lymphocytes and plasma cells were admixed



GROSS



H&E

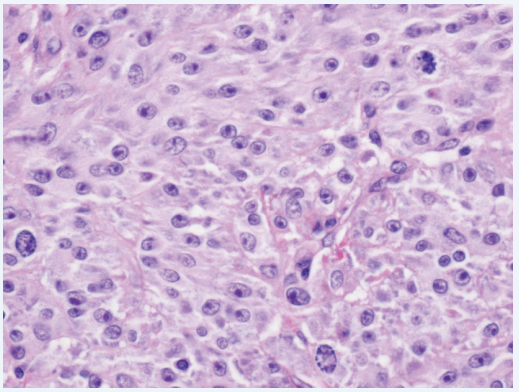
Diagnosis

Inflammatory myofibroblastic tumor

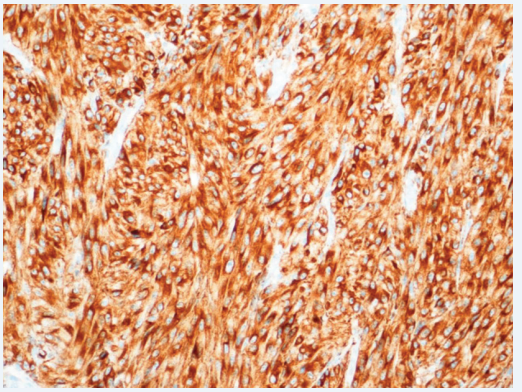
CASE 103

History

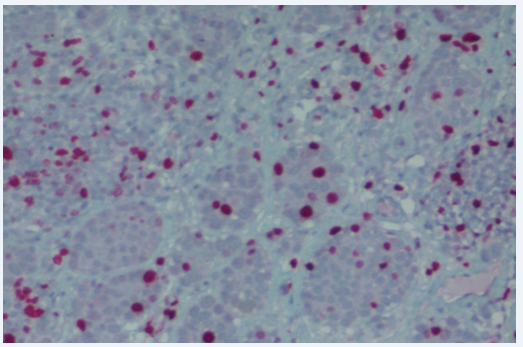
Seven-year-old girl with a sudden enlargement in size of a skin lesion on forearm. The lesion is painful, irregular in shape, and 1.8 cm in size



H&E



HMB-45



Ki-67

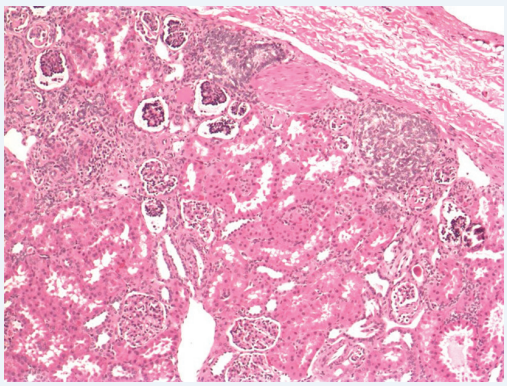
Diagnosis

Spitzoid malignant melanoma

CASE 104

History

Biopsy from the right kidney of a 2-year-old boy who had the left kidney resected for a tumorous mass 1 year ago



H&E

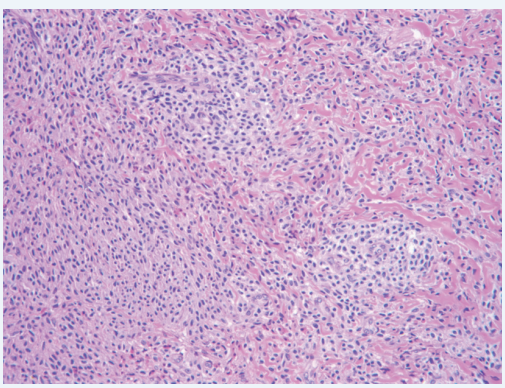
Diagnosis

Perilobar nephrogenic rests

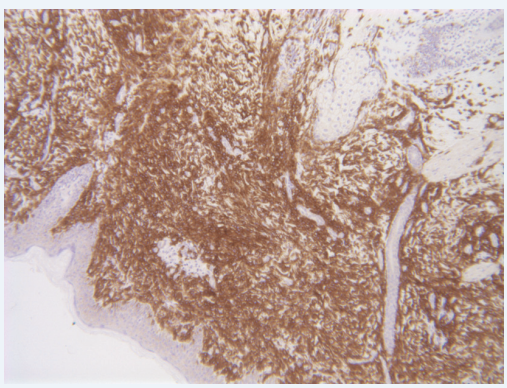
CASE 105

History

Five-year-old boy with erythematous macules and telangiectasia in the legs. Lesional cells are positive for CD117 and toluidine blue



H&E



CD117

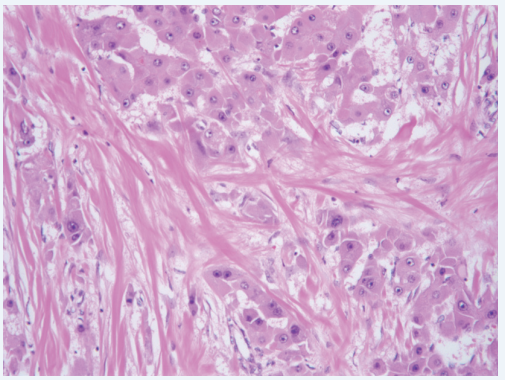
Diagnosis

Cutaneous mastocytosis

CASE 106

History

Fifteen-year-old boy with a large abdominal mass. Tumor cells express HepPar and Ck7. Liver biopsy



H&E

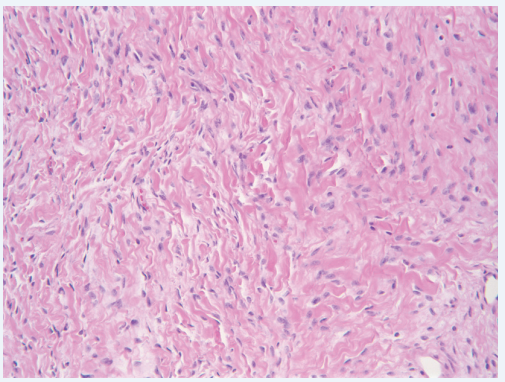
Diagnosis

Hepatocellular carcinoma—fibrolamellar variant

CASE 107

History

Seven-year-old boy with a cardiac mass that resulted in fatal ventricular arrhythmia. Tumor cells were positive for vimentin



H&E

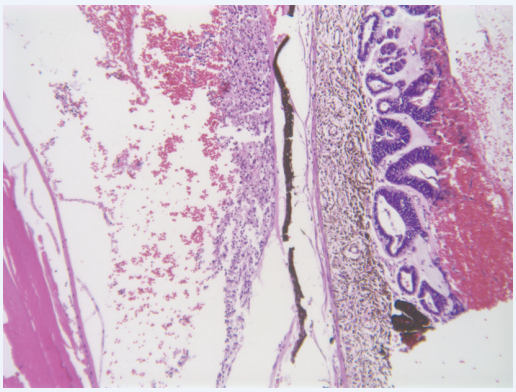
Diagnosis

Fibroma of heart

CASE 108

History

Eight-year-old girl with a tumorous mass arising in the ciliary body of the eye



H&E

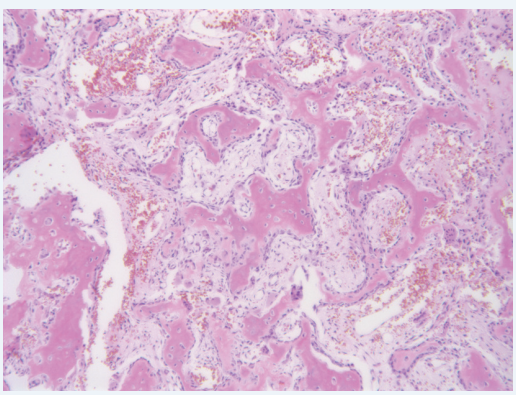
Diagnosis

Medulloepithelioma

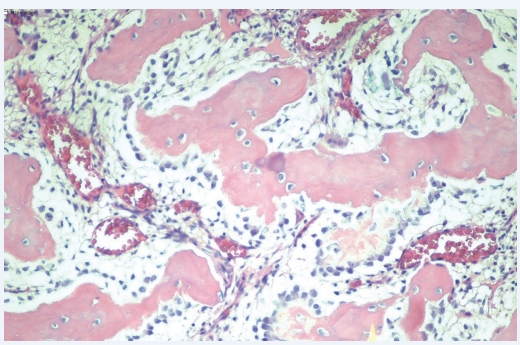
CASE 109

History

Eleven-year-old girl with a 3 cm painful mass in base of the skull. On imaging, the mass was well demarcated and had a central nidus



H&E



H&E

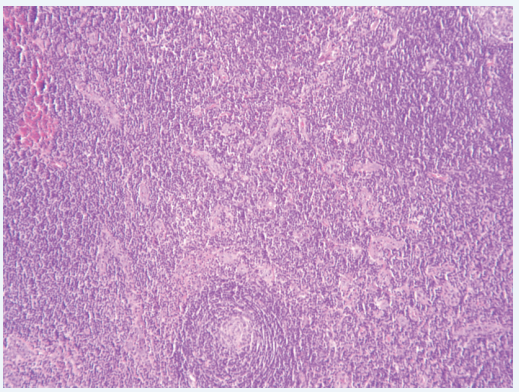
Diagnosis

Osteoblastoma

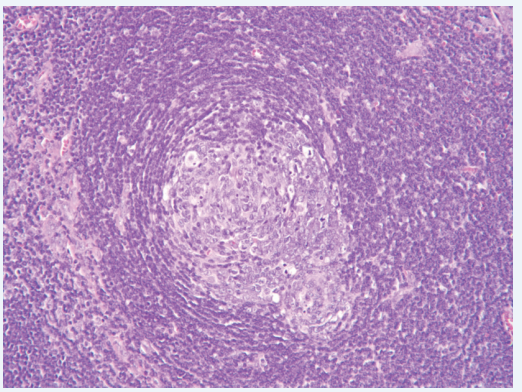
CASE 110

History

Sixteen-year-old girl with supraclavicular lymphadenopathy



H&E



H&E

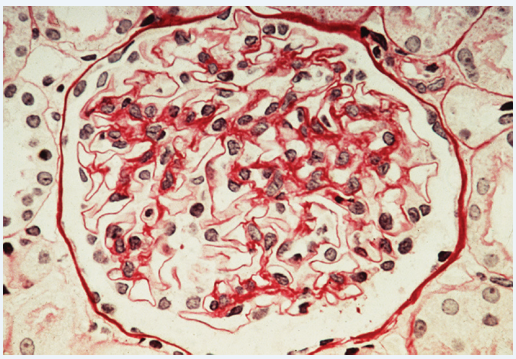
Diagnosis

Castleman disease—hyaline vascular variant

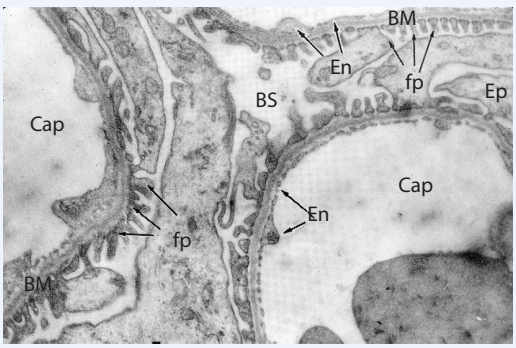
CASE 111

History

Twelve-year-old girl who died in a motor vehicle accident. Kidney biopsy



H&E



EM

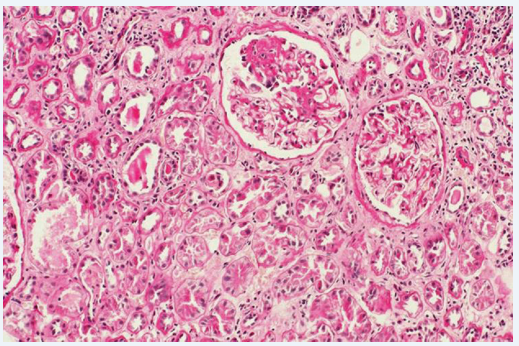
Diagnosis

Normal glomerulus

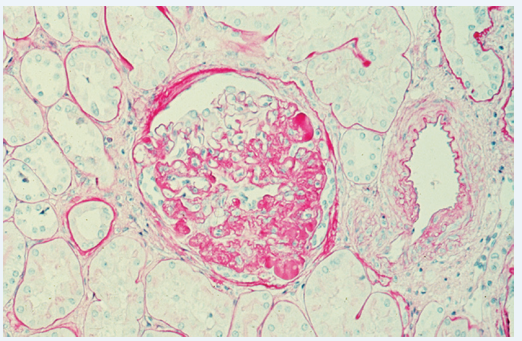
CASE 112

History

Five-year-old African American boy who presented with proteinuria, hematuria, hypertension, and edema. Electron microscopy (EM) showed extensive foot process effacement with epithelial cell vacuolization and often separation of the epithelial cells from underlying glomerular basement membrane



H&E



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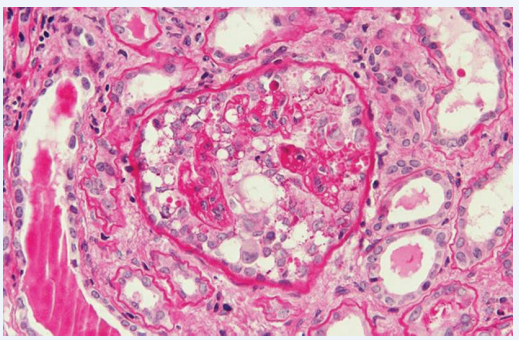
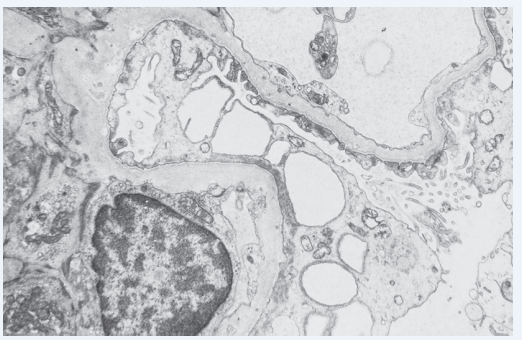
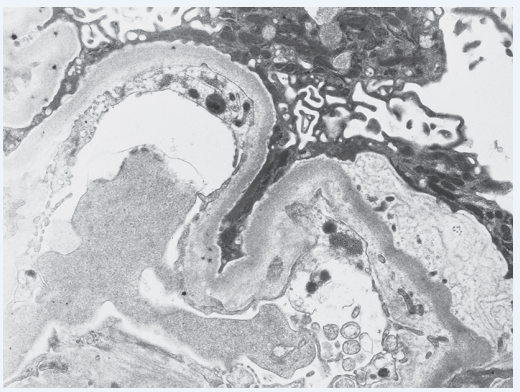


H&E



EM



EM

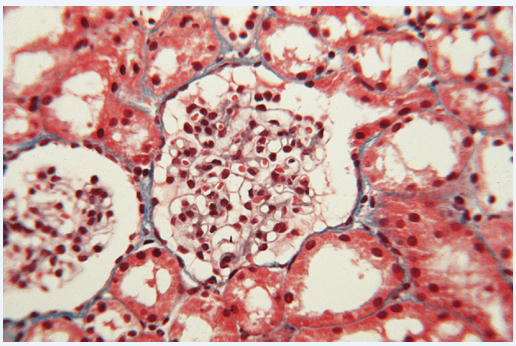
Diagnosis

Focal segmental glomerulosclerosis

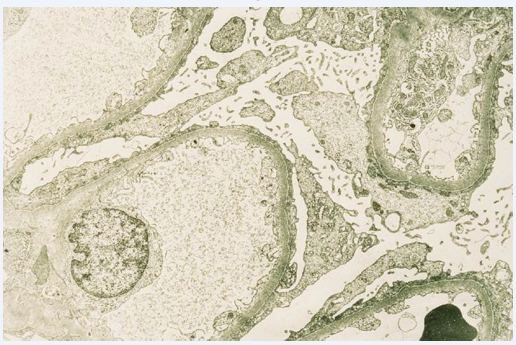
CASE 113

History

Eleven-year-old girl with severe edema, heavy albuminuria, hypoalbuminemia, elevated serum cholesterol but no hematuria or hypertension. EM shows diffuse effacement of the foot processes. There are no electron-dense deposits



H&E



EM

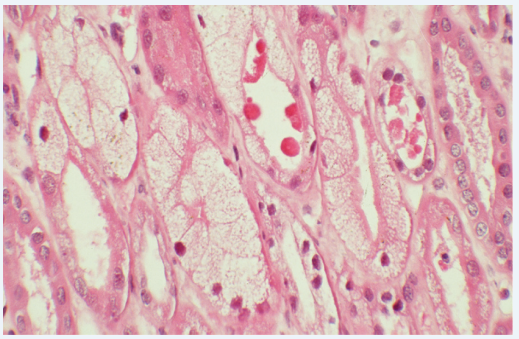
Diagnosis

Minimal change glomerulopathy

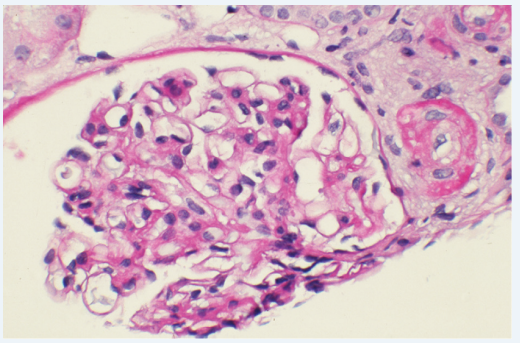
CASE 114

History

Eight-year-old girl who was a recipient of allogenic renal transplant for end-stage kidney failure. She was given anti-rejection therapy to prevent acute cellular rejection



H&E



H&E

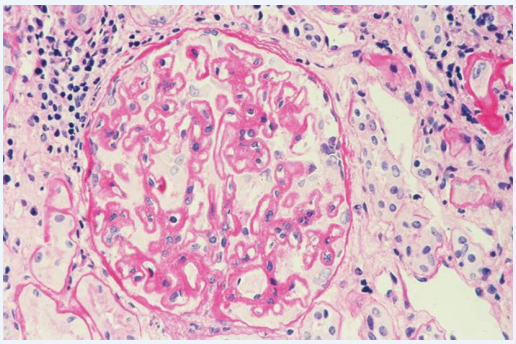
Diagnosis

Cyclosporine/tacrolimus related nephrotoxicity

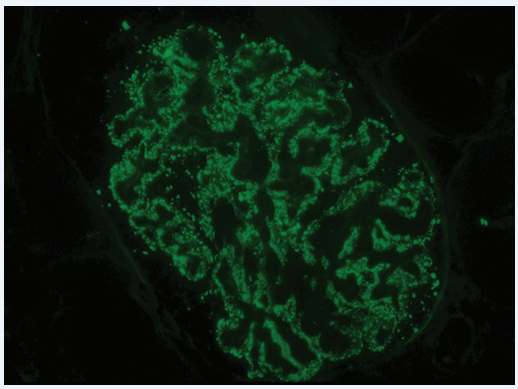
CASE 115

History

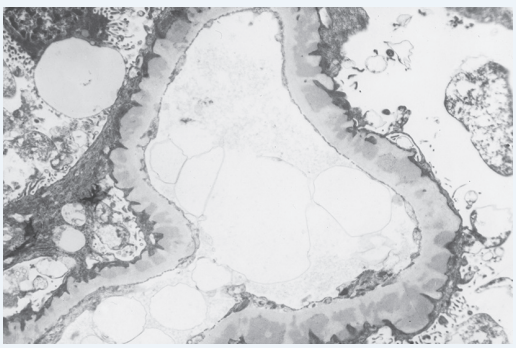
Insidious onset of nephrotic syndrome in a 15-year-old girl with hepatitis B-associated chronic hepatitis. IF shows confluent granular deposits of IgG and C3 along glomerular capillary loops. EM shows subepithelial electron dense deposits and fusion of epithelial foot processes



H&E



IF



EM

Diagnosis

Membranous glomerulonephritis

Index

B

C

M

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