Cancer Grading Manual

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Preface

The grading and staging of tumors are routinely performed during the work-up of most patients who have cancer. Whereas the staging of tumors relies on a wealth of clinical, intraoperative, or radiologic data, tumor grading remains in the domain of pathologists—hence, the idea to compile a book for our colleagues in diagnostic surgical pathology and their residents.

Like most surgical pathologists, we grade and stage tumors every day, and the assigned values are included in the final pathology reports. During the sign-out, we use the *AJCC Cancer Staging Handbook* or *TNM Atlas: Illustrated Guide to the TNM Classification of Malignant Tumors*. As strange as it might sound, although many textbooks contain instructions on how to grade tumors, there is no concise, "ready-to-use," practice-oriented manual on the microscopic grading of tumors. Confronted with the perceived need for such a book (and especially encouraged by our residents), we undertook the task of extracting the pertinent facts from books, monographs, and seminal papers and presenting them in a concise form. Since pathology is a visual discipline, the publisher allowed us to liberally use color microphotographs whenever needed to make a point, and thus produce an illustrated manual that could be applied in the daily practice of surgical pathology without the need to resort to other books. We thank the publisher for this support. From now on, our residents will no longer need to ask us which book they should use for grading tumors. We hope that other practicing surgical pathologists will find the book useful as well, and keep it as a companion to their favorite tumor staging manual.

In preparing this book, we have consulted a number of leading textbooks of surgical pathology, monographs prepared by the experts of the World Health Organization, and tumor atlases published by the Armed Forces Institute of Pathology. Readers interested in these sources, as well the recent comprehensive, seminal articles, will find them listed as references at the end of each chapter. While there is nothing new in this compilation, it is the first to present these data in such a condensed form, illustrated with so many color images.

We have concentrated on tumors that are common, and thus have omitted some of the less common neoplasms and some of the neoplastic diseases that are in the domain of subspecialties of pathology (most notably hematology). We have not included the grading of some common inflammatory non-neoplastic diseases, such as chronic hepatitis or lupus nephritis. We hope that readers will not mind, but if you feel that some omissions are unpardonable, we would love to hear from you. Comments and suggestions for improvements, updates, or revisions are welcome.

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History and General Aspects of Tumor Grading

Ivan Damjanov

Malignity only differs in degree.

—Rudolph Virchow, 1860

History of Tumor Grading

The relationship between tumor morphology and the clinical behavior of tumors has been known for more than a century, and the study of such clinicopathologic correlations could be traced to the teachings of Rudolf Virchow and the scientific beginnings of microscopic pathology. From the historical point of view, however, the first attempts to correlate the microscopic features of tumors with their biology and clinical behavior traditionally are attributed to von Hansemann (1–3). In the 1890s, this German pathologist published his observations on anaplasia and abnormal mitotic figures and first suggested that the biologic and clinical behavior of tumors could be predicted from their microscopic characteristics. His pioneering publications on tumor cell atypia, anaplasia, and asymmetrical mitoses were summarized in a 1897 book, which was so popular that it reappeared 5 years later in a second edition (Figure 1-1). This book, based on meticulous microscopic study of tumors, contains drawings illustrating the author's views of cancer (Figure 1-2). The clarity of these illustrations is fascinating even today.

In the 1920s, Broders published his experience with the grading of squamous cell carcinoma of the lip and skin and correlated the histologic grade with the outcome of the neoplastic disease (Figure 1-3) (4–6). Broders declared that all malignant tumors could be divided into 4 groups, depending on the extent of tumor cell differentiation. He used a 4-tiered system and classified tumors into those that contain 25%, 50%, 75%, or 100% incompletely differentiated cells. His ideas were subsequently adopted by many others and applied to tumors in other organ systems.

Greenhough was the first to propose the idea of histologic grading for breast cancers in 1925 (7). He assigned a grade to tumors based on the overall evaluation of 8 histologic features. Using a 3-tiered grading system, these authors showed a clear association between tumor grade and a 5-year "cure" in their clinicopathologic study. It is fair to say that current breast tumor grading systems stem from his original ideas and work from the early 20th century.

The concepts and conclusions drawn from these early studies were used and modified repeatedly during the following years (8–10). Some of the early students of grading combined it with staging, and their eponymous systems, such as the Dukes system for classifying colonic cancer (8), survived up to modern times. For breast cancer alone, more than 10 grading methods and their modifications have been proposed; by the late 1990s, over 40 histologic grading systems for prostatic carcinoma had been proposed (11).

Despite a plethora of longitudinal retrospective and prospective studies showing the usefulness of microscopic grading, the idea of routine tumor grading did not gain much popularity among clinicians and pathologists until the 1970s. This was partly due to the complexity and subjectivity of some grading systems, and partly to the limitation of treatment options corresponding to different grades of tumor. However, as the treatment options multiplied, the need for better stratification of patients became imperative. Carriaga and Henson (12) found that the overall frequency of grading increased over the 15-year period of 1973–1987 by 18% for all sites combined: 65% of all cancers were graded in 1983–1987, compared with 47% in 1973–1977.

Today, there is an overwhelming consensus that in many instances tumor grading has not only a prognostic and predictive value, but might also have a significant impact on choosing optimal treatment. Admittedly, the grading systems for some tumors are less than perfect, but for others grading has become an absolute must and

Die

mikroskopische Diagnose

der

bösartigen Geschwülste

von

Professor Dr. **David von Hansemann.**

Zweite Auflage.

Mit 106 Figuren im Text.

Berlin 1902.

Verlag von August Hirschwald.

N.W. Unter den Linden 68.

FIGURE 1-1. Front page of the second edition of von Hansemann's textbook.

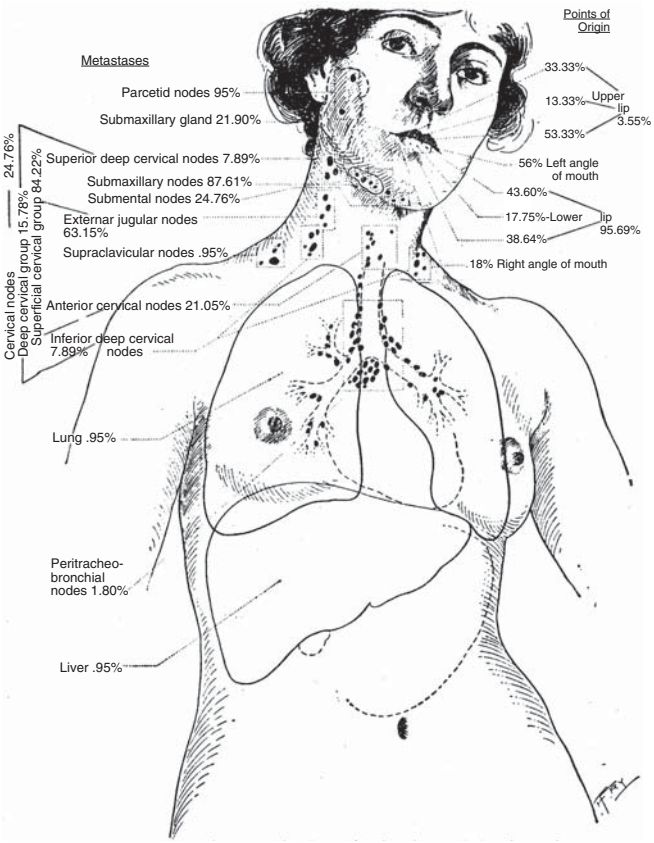

FIGURE 1-3. Broders's seminal paper on the grading of tumors, (*JAMA,* 1920;656–664).

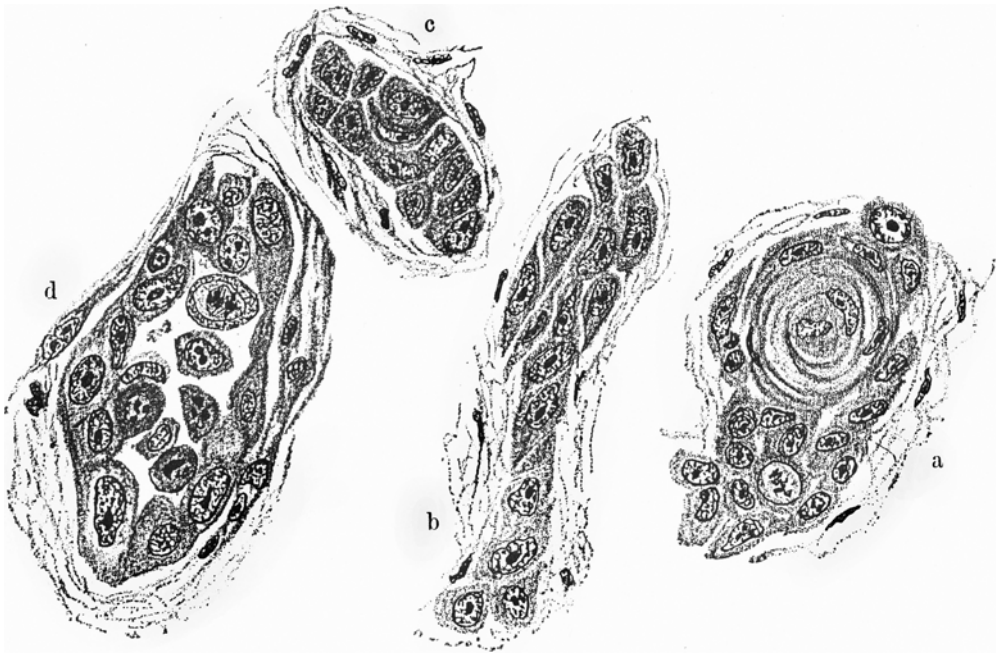

FIGURE 1-2. Artist's drawing of squamous carcinoma cells. From von Hanseman D, Die mikroskopische Diagnose der bösartigen Geschwülste. 2nd edition. Berlin: A. Hirschwald; , 1902.

the tumor grade is routinely included in the pathology reports. The old grading schemes are constantly being refined, and there is hope that the standard microscopic grading of tumors could be considerably improved by the introduction of new methods of immunohistochemistry, image analysis, molecular biology, and other technological innovations.

General Principles of Tumor Grading

The main principle of tumor grading, originating from Broders' earlier work, is to evaluate the percentage of tumor that is differentiated. The grading method uses standard light microscopic interpretation of hematoxylin and eosin (H&E) stained tissue sections. Some earlier grading systems required grading of up to 15 histologic features, which included growth pattern, cell morphology, and tumor stromal response (13). However, such elaborate systems were found to be cumbersome, unreliable, and not always reproducible. A good grading scheme should be simple, easy to perform, reliable and reproducible, and should be able to stand the test of time (14).

In general, the grading process includes assessment of both the architectural and cytologic features of the tumor. Some systems, however, focus on 1 histologic feature. For example, grading of prostatic adenocarcinoma is based entirely on the architecture feature, and grading of renal cell carcinoma is based entirely on the nuclear feature. The most poorly differentiated part of the tumor determines the final tumor grade, with the exception of the Gleason grading system for prostatic adenocarcinoma, in which the 2 most prevalent patterns are used for grading. It is worth noting that even well-established systems, such as the Gleason grading of prostate carcinoma, are still being modified; the need for identifying a tertiary pattern has been expressed, and the reporting of cancer grades was found to vary even among urologic pathologists (15,16).

So far, all grading systems are designed for the primary untreated tumor. Attempts have been made to apply the same grading scheme for metastatic foci and residual tumors after radiation and/or chemotherapy. At present, however, there is no general consensus on this issue.

Ancillary Methods in Tumor Grading

Nearly all the systems for grading malignant tumors are based on morphologic evaluation of tumor sections under the microscope. Several improvements of the time-honored microscopic approach have been recommended, but few of these have been adopted in routine surgical pathology practice. The most notable exception is the immunohistochemical staining with the antibody MIB-1 (Ki-67), recognizing cell proliferation. This immunohistochemical technique has been proposed as an objective supplement of several tumor-grading systems, including the grading of breast carcinoma, brain astrocytoma, and lymphoma (17,18). With advanced understanding of diseases and the development of new technology, prognostic biomarkers and genetic information may be incorporated in tumor grading in the future.

The prognostic and predictive value of microscopic tumor grading can be enhanced by using other immunohistochemical methods (17–21). For example, in breast carcinoma immunohistochemical data with antibodies to estrogen receptor, bcl-2, and Her2/neu have predictive value in both univariate and multivariate analysis, and are useful for predicting the patient's response to specific therapy (18). In most instances, however, there is no consensus on the value of these ancillary methods. For instance, the International Consensus Panel on cytology and bladder tumor markers could not agree on the value of multiple markers in predicting tumor recurrence, progression, metastasis, or response to therapy (19). This panel evaluated various prognostic indicators classified into 6 groups:

- Microsatellite-associated markers
- Proto-oncogenes/oncogenes
- Tumor suppressor genes
- Cell cycle regulators
- Angiogenesis-related factors
- Extracellular matrix adhesion molecules

The panel concluded that certain markers, such as Ki-67 and p53, appear to be promising in predicting recurrence and progression of bladder cancer, but the data are still incomplete. The panel decided that no consensus could be reached until major prospective studies are performed and recommended identifying definitive criteria for test positivity, performing studies of clearly defined patient populations, standardization of techniques for evaluating the markers, and clearly specified clinical endpoints with good statistical documentation.

The use of ancillary methods has been especially championed by neuropathologists, who have adopted several techniques to estimate the proliferative potential of brain tumors. As summarized in a recent review article by Quinones-Hinojosa et al (21), in addition to immunohistochemical staining with antibody Ki-67 (MIB-1) such measurements can include bromodeoxyuridine labeling index (BrdU LI), flow cytometry (FCM), and staining for the proliferating cell nuclear antigen (PCNA), and argyrophilic nucleolar organizing regions (AgNOR). At present, MIB-1 and AgNOR are the simplest and most reliable of these techniques. Radiographic studies such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and most recently magnetic resonance spectroscopy (MRS) used as

follow-up measures have the potential to provide an assessment of tumor proliferation without the need for invasive measures.

Clinical Value of Tumor Grading

Data obtained by tumor grading are usually combined with those obtained by tumor staging and other clinical techniques, and are then evaluated by multivariate analysis. In most studies of this kind, it has been shown that tumor grade contributes to the multivariate prognosis, but in some it was found that grading alone could be a valid prognosticator, even in an univariate analysis. Henson (9) published a study in 1988 on the relation between tumor grade and patient outcome. More than 500,000 cases from 15 anatomic sites with up to a 9-year follow-up were reviewed. The results showed that, stage by stage, the grade further subdivided the overall survival rates for each site into distinct subsets that were significantly different. Carriaga and Henson (12) later performed a similar study and demonstrated that the histologic grade is a strong predictor of outcome that refines the prognostic information provided by the stage of disease. There are numerous other studies showing that microscopic tumor grading has independent prognostic value (14–17).

Due to the availability of different treatment options, tumor grading has an additional clinical value as guidance for therapy choice. While surgical resection may suffice for a low-grade tumor, additional radiation and/or chemotherapy may be necessary for high-grade tumors. By combining grading with staging and clinical data, one may construct nomograms that may predict the outcome of the treatment, disease-free survival, or cure rate. This is the case for many epithelial tumors, brain tumors, and sarcomas of bones and soft tissues, but many tumors still do not lend themselves to grading (22,23). Nevertheless, most tumors can be stratified microscopically, and if the grade assigned to them is combined with other clinical data, it may serve as a powerful predictor of clinical outcome of neoplastic disease, as well as for choosing the appropriate therapy for many cancer patients.

Perspective

Tumor grading has been an integral part of the pathologic examination of biopsies and surgically resected tumors for close to 100 years. During that period, numerous studies have been performed on the value of grading, and modifications of various systems have been proposed and tested. Thus, tumor grading could be considered a work in progress, and additional efforts to improve the existing schemes are obviously necessary. This will require prospective studies, improvement of the intra- and interobserver variability, statistical evaluation of reproducibility, and correlation with the endpoint treatment outcome results (14).

Current systems for grading tumors are far from perfect or ideal. Nevertheless, the general consensus of pathologists, surgeons, and clinical oncologists is that the tumor grade deserves to be a part of the routine pathology report for most tumors and should be performed by diagnostic pathologists as meticulously as the situation requires.

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2
Tumors of the Mouth, Pharynx, Nose, and Paranasal Sinuses

Ossama Tawfik and Asraa Namiq

Introduction

Tumors of the mouth, pharynx, nose, and paranasal sinuses are commonly encountered in general surgical pathology practice. Some, such as squamous cell carcinoma, resemble homonymous tumors in other parts of the body, whereas others, such as olfactory neuroblastomas, are unique to this anatomic region. This chapter limits the discussion to the tumors that are most often graded by surgical pathologists.

Squamous Cell Carcinoma and Related Lesions of the Mouth

Squamous cell carcinoma is the most common cancer of the mouth. It affects men more often than women, and has the highest incidence in the fourth to sixth decades of life.

Squamous cell carcinoma of the mouth, like all other squamous cell carcinomas, may be preceded by intraepithelial changes that can be graded as mild, moderate, and severe. Invasive carcinoma is graded as well-differentiated, moderately differentiated, and poorly differentiated carcinoma.

Benign and Intraepithelial Malignant Pre-invasive Squamous Cell Lesions

Epithelial lesions of the mouth usually present as leukoplakia or erythroplakia, i.e., as white or reddish plaques. Pathologically, these lesions are classified as either benign keratosis or dysplasia (1–3).

- **Keratosis.** This benign reactive lesion is typically related to an identifiable irritant (e.g., ill-fitted dentures or tobacco abuse). Microscopically, the lesions appear as thickened squamous epithelium showing surface orthokeratosis and/or parakeratosis. Although keratosis may show signs of mild reactive epithelial dysplasia, in most instances it has a low association with cancer.
- **Squamous dysplasia.** This intraepithelial neoplasia may progress to invasive cancer. It shows strong association with tobacco smoking. Grading of head and neck squamous dysplasia is similar to the grading of similar intraepithelial lesions in other sites, such as the uterine cervix, and includes mild, moderate, and severe dysplasia. The term carcinoma in situ is usually avoided, and the high-grade lesions are included in the severe dysplasia category (Table 2-1).

Oral Squamous Cell Carcinoma

Although the grading of oral squamous cell carcinoma is subjective, most pathologists use it (4). The most widely used system includes 3 categories (Table 2-2), as follows:

- **Grade 1, well-differentiated squamous cell carcinoma.** This tumor is composed of squamous cells forming large nests, often containing prominent foci of keratin pearl formation (Figure 2-1A).
- **Grade 2, moderately differentiated squamous cell carcinoma.** This tumor contains squamous cells forming smaller nests. The cells show considerable pleomorphism, but less prominent squamous differentiation than that seen in well-differentiated squamous cell carcinomas (Figure 2-1B). There is moderate mitotic activity.
- **Grade 3, poorly differentiated squamous cell carcinoma.** This tumor has sheets of anaplastic cells, showing considerable pleomorphism. Cells also form small nests and strands invading into the stroma. Mitoses are prominent. Tumor borders are usually ragged (Figure 2-1C).

Variants of Squamous Cell Carcinoma

Several variants of squamous cell carcinoma (3–6) include:

Table 2-1. Histologic criteria for the grading of oral squamous dysplasia.

Features	Mild	Moderate	Severe
Nuclear crowding	Basal	Lower half	Upper third
Nuclear irregularity	+	++	+++
Chromatin	Almost normal	Peripheral condensation with central clearing	Irregular clumping alternating with clearing
Mitoses (location)	Basal	Lower half	Anywhere including the upper third
Dyskeratotic cells	Absent	Absent	Present at random

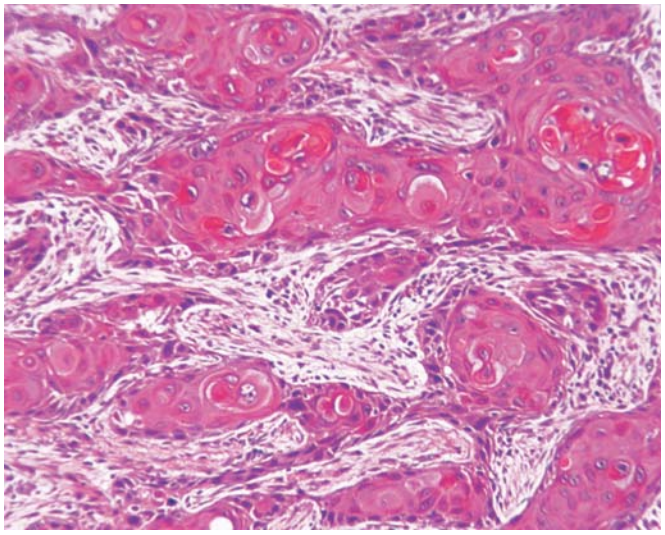
- **Verrucous carcinoma (Ackerman's tumor).** This is an overtly papillary, wart-like, heavily keratinized,well-differentiated squamous cell carcinoma. It does not metastasize, provided that a conventional squamous cell carcinoma component is not present.
- **Spindle cell carcinoma** (also known as spindle cell squamous cell carcinoma, sarcomatoid carcinoma, carcinosarcoma, collision tumor). Clinically, this often presents as a polypoid exophytic lesion of the tongue, lips, or other parts of the buccal mucosa.The tumor is composed of a prominent spindle cell component associated with an overtly squamous component in variable proportions (Figure 2-2). It is not uncommon to see osteoid, cartilaginous, or myxoid areas in the spindle cell component.
- **Papillary (exophytic) squamous cell carcinoma.** This is usually a well-differentiated or moderately well-differentiated tumor.
- **Basaloid squamous cell carcinoma.** This is a high-grade, aggressive, poorly differentiated carcinoma (Figure 2-3).
- **Adenoid squamous cell carcinoma.** This tumor occurs on the lips. It is composed of well-differentiated keratotic cells that show a tendency for acantholysis, which accounts for the pseudoglandular appearance of the tumor. It is usually a well-differentiated or moderately well-differentiated tumor.
- **Lymphoepithelioma-like carcinoma**. This is a high-grade, poorly differentiated tumor, similar to nasopharyngeal carcinomas in appearance.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma that most often affects persons in the fourth to sixth decades of life (7). It affects men more frequently

Table 2-2. Histologic criteria for grading oral squamous cell carcinoma of the head and neck.

Features	Well-differentiated	Moderately differentiated	Poorly differentiated
Tumor borders	Round or ragged	Round or ragged	Ragged and overtly invasive
Size of tumor nests	Variable	Variable	Variable, but often small and even composed of a few cells; isolated single cells
Keratinization of cells and intercellular bridges	Prominent	Almost always present, but less prominent	Minimal or absent
Keratin pearls	Common	Less common	Rare
Mitoses	Infrequent	More frequent	Frequent and atypical
Angiolymphatic invasion	Rare	May be seen	Common



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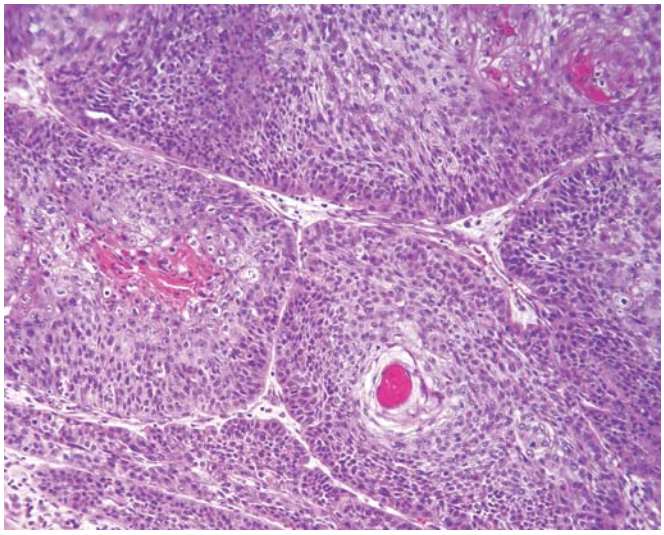

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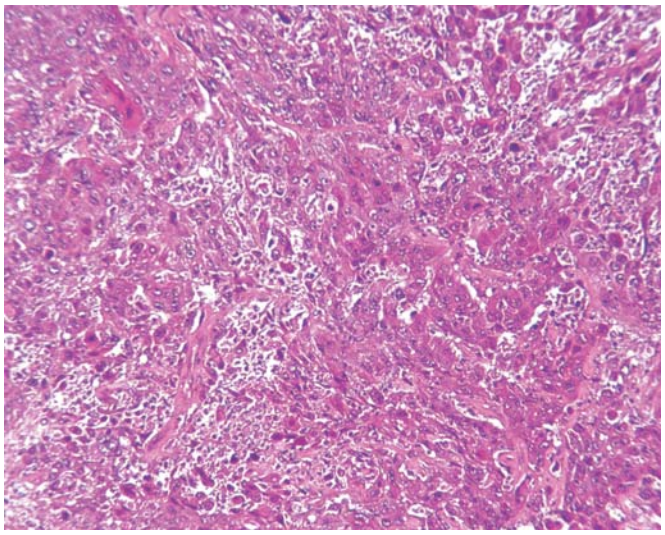


C

FIGURE 2-1. Squamous cell carcinoma. A. A well-differentiated squamous cell carcinoma, characterized by cohesive growth pattern and prominent keratinization of squamous cells. B. A moderately differentiated squamous cell carcinoma, consisting of undifferentiated squamous cells showing focal keratinization in the center of tumor nests. C. A poorly differentiated squamous cell carcinoma, characterized by a disorderly invasive growth of squamous cells. Tumor cells have hyperchromatic, pleomorphic nuclei, and although they have an eosinophilic cytoplasm, only occasional keratin pearls are found.

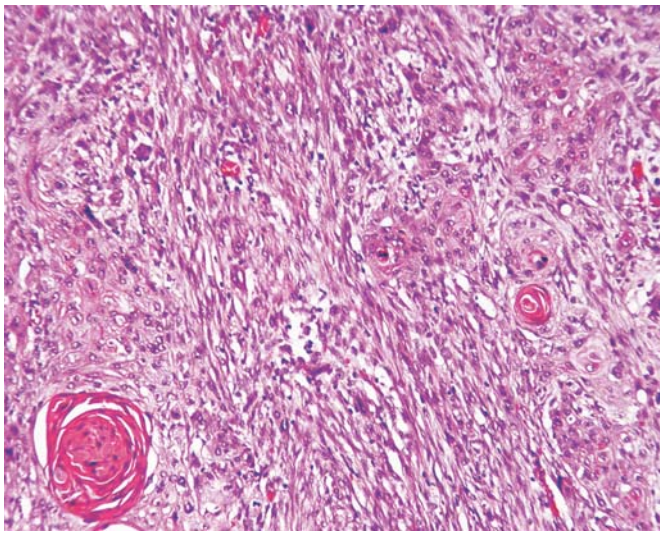


FIGURE 2-2. Spindle cell squamous carcinoma. The tumor is composed of elongated neoplastic cells intermixed with stromal cells. Occasional keratin pearls may be seen, like the one in the lower left corner.

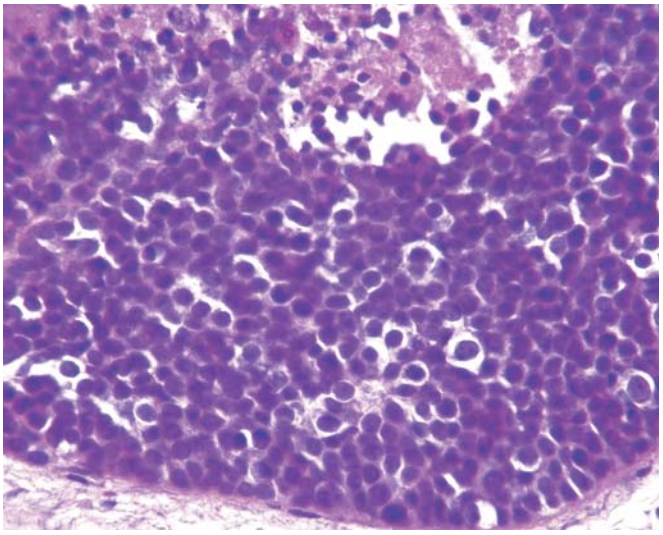
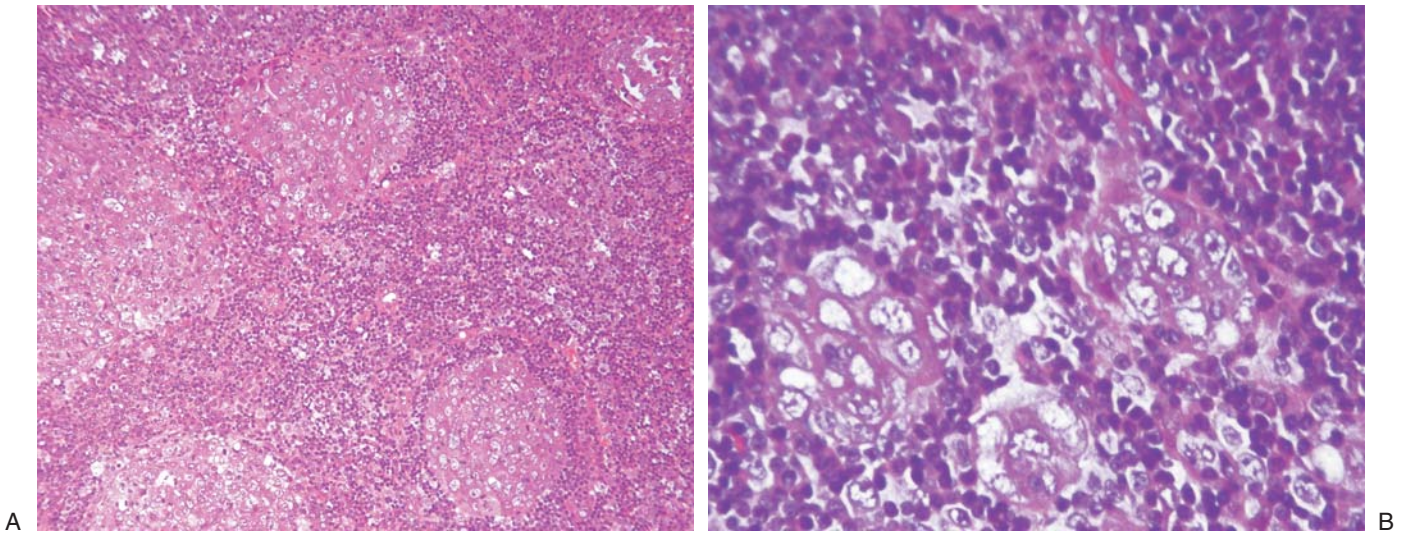


FIGURE 2-3. Basaloid squamous cell carcinoma. The tumor is composed of nests of bluish basaloid cells. Prominent foci of necrosis are seen in the center of these nests.



A B

FIGURE 2-4. Nasopharyngeal carcinoma. A. The tumor is composed of sheets of neoplastic cells surrounded by lymphoid tissues. B. At higher magnification, the cohesive tumor cells show vesicular nuclei surrounded by eosinophilic cytoplasm.

than women. In the United States, it accounts for 0.25% of cancers; in China, however, it accounts for about 18% of all cancer cases, and this may be related to infections with the Epstein-Barr virus in that part of the world. The tumor is closely related to the nasopharyngeal lymphoid tissue and may remain asymptomatic for prolonged periods. In some instances, it initially presents with metastases.

According to the World Health Organization classification, 2 main histologic variants of NPC are recognized: keratinizing and nonkeratinizing. The nonkeratinizing is further classified into differentiated and undifferentiated NPC. The most important features of these 3 variants are summarized as follows:

- **Keratinizing, conventional squamous cell carcinoma**. This tumor accounts for 25% of the cases of this type of carcinoma. They are not responsive to radiotherapy. Microscopically, they are graded as well-differentiated, moderately differentiated, or poorly differentiated squamous cell carcinomas.
- **Nonkeratinizing, differentiated carcinoma**. This is the least common form of NPC, accounting for about 12% of the cases. It shows strong association with Epstein-Barr virus and variable response to radiotherapy. Its growth patter is reminiscent of that for bladder cancer, and it is usually poorly differentiated.
- **Nonkeratinizing, undifferentiated carcinoma**. This is the most common form of NPC, accounting for 60% of the cases. It shows strong association with Epstein-Barr virus, and it is radiosensitive. It may show 2 growth patterns: syncytial (the so-called Regaud type), or a discohesive, individual cell invasive growth pattern (the so-called "Schmincke type") (Figure 2-4).

Overlapping histologic features are not uncommon, and accordingly tumors may show features of more than 1 variant. In those cases, the NPC is classified according to its dominant component.

Sinonasal Carcinoma

Sinonasal carcinoma is a rare tumor accounting for less than 1% of all cancer deaths in the United States. Generally, it is located in the vestibule of the nose or lateral sides of the nose. Of the sinuses, most often the ethmoid sinus is involved. Sinonasal carcinomas occur in several microscopic forms (8–10), including:

- **Squamous cell carcinoma**. This is the most common form of sinonasal carcinoma. Poorly differentiated tumors predominate.
- **Transitional cell carcinoma**. This is a heterogeneous group of neoplasms, and their degree of differentiation varies. Tumors that develop within schneiderian papillomas usually have an excellent prognosis. These must be distinguished from high-grade transitional cell carcinoma that superficially resembles sinonasal papillomas, but actually tends to be aggressive and have a poor prognosis.

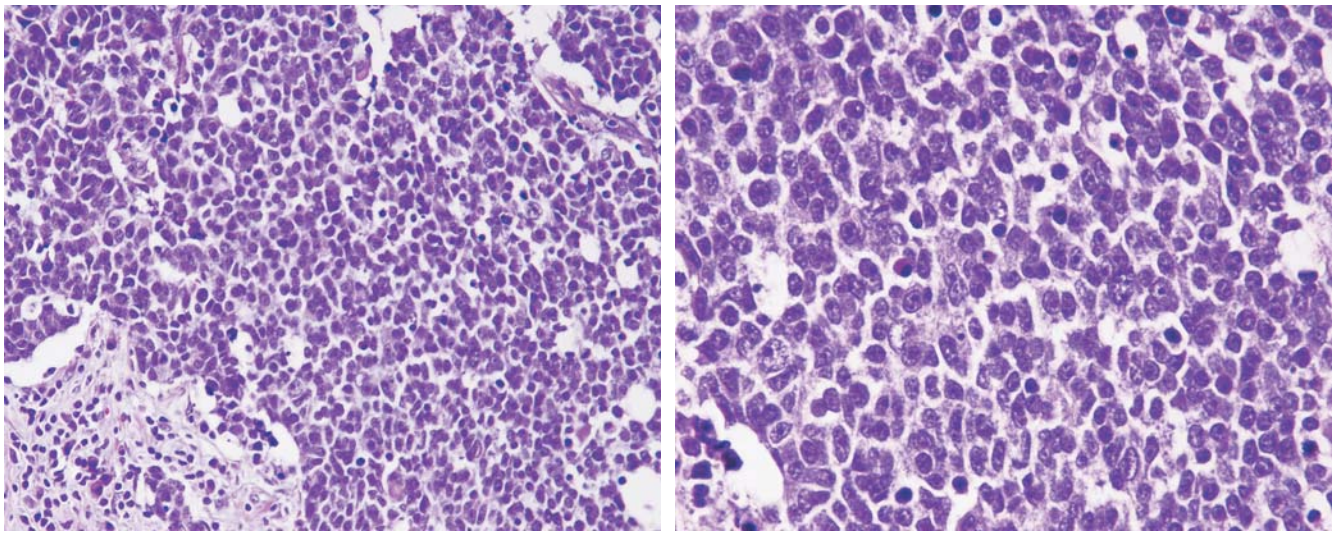


FIGURE 2-5. Sinonasal undifferentiated carcinoma. A. The tumor nests are composed of small blue cells arranged without any distinct pattern. B. Higher magnification shows that the cells have scant cytoplasm and hyperchromatic nuclei.

- **Adenocarcinoma**. This tumor of the sinonasal area occurs in several forms and may be low or high grade. With some exceptions, as a rule papillary adenocarcinomas lined by cuboidal cells are usually are low-grade tumors, whereas tumors resembling mucus-secreting colonic adenocarcinomas are high-grade tumors (8,9).
- **Sinonasal undifferentiated carcinoma.** This is a highly malignant epithelial neoplasm of the nasal cavity and paranasal sinuses. As its name suggests, the tumors show no microscopic evidence of squamous or glandular differentiation. Nevertheless, immunohistochemistry shows that the cells are epithelial, and some show signs of neuroendocrine differentiation (10). The tumor cells belong to the category of "small blue cells" and are arranged solid sheets, nests, and trabeculae. (Figure 2-5). The cells are anaplastic, with round to oval nuclei, and a high nuclear to cytoplasmic ratio. There is high mitotic activity, and areas of necrosis are prominent. Vascular and perineural invasion are common.

Neuroendocrine Tumors

Neuroendocrine tumors of the upper aerodigestive tract can be divided into 2 large groups (11), as follows:

- **Group I neuroendocrine tumors**. This group includes carcinoid, atypical carcinoid, and small cell carcinoma. In accordance with the prevailing trend, Mills (11) recommends that group I tumors be called, in analogy with the lung tumors, as well-differentiated, moderately differentiated, and poorly differentiated neuroendocrine carcinoma. The latter category should be further subdivided into small cell and large cell variants. The classification and grading of these tumors is discussed in greater detail in Chapter 5.
- **Group II neuroendocrine tumors**. This group includes neuroblastomas and peripheral neuroectodermal tumors.

Olfactory Neuroblastoma

Olfactory neuroblastoma, also known as esthesioneuroblastoma, is a malignant neoplasm of the sinonasal tract arising from the neuroepithelial cells of the olfactory nasal epithelium or the olfactory placode (11). It is most often located in the upper nasal cavity, ethmoid, and paranasal sinuses, and presents as a large polypoid mass. It can occur in any age group.

Microscopically, it consists of small round to oval cells, with eosinophilic cytoplasm and indistinct cell borders. The cells have vesicular nuclei with fine chromatin, and mild to moderate atypia (Figure 2-6). Between the cells, the stroma is fibrillar. The mitotic count is low. Some tumors contain Homer-Wright and Flexner-Wintersteiner rosettes, but ganglion cells are not seen. Immunohistochemistry is valuable for the diagnosis, since the tumors are positive for chromogranin, synaptophysin, and neurofilaments. Some cells at the periphery of nests are typically positive for S-100 protein.The most widely used system of grading, proposed by Hyams, is presented in a somewhat modified form in Table 2-3.

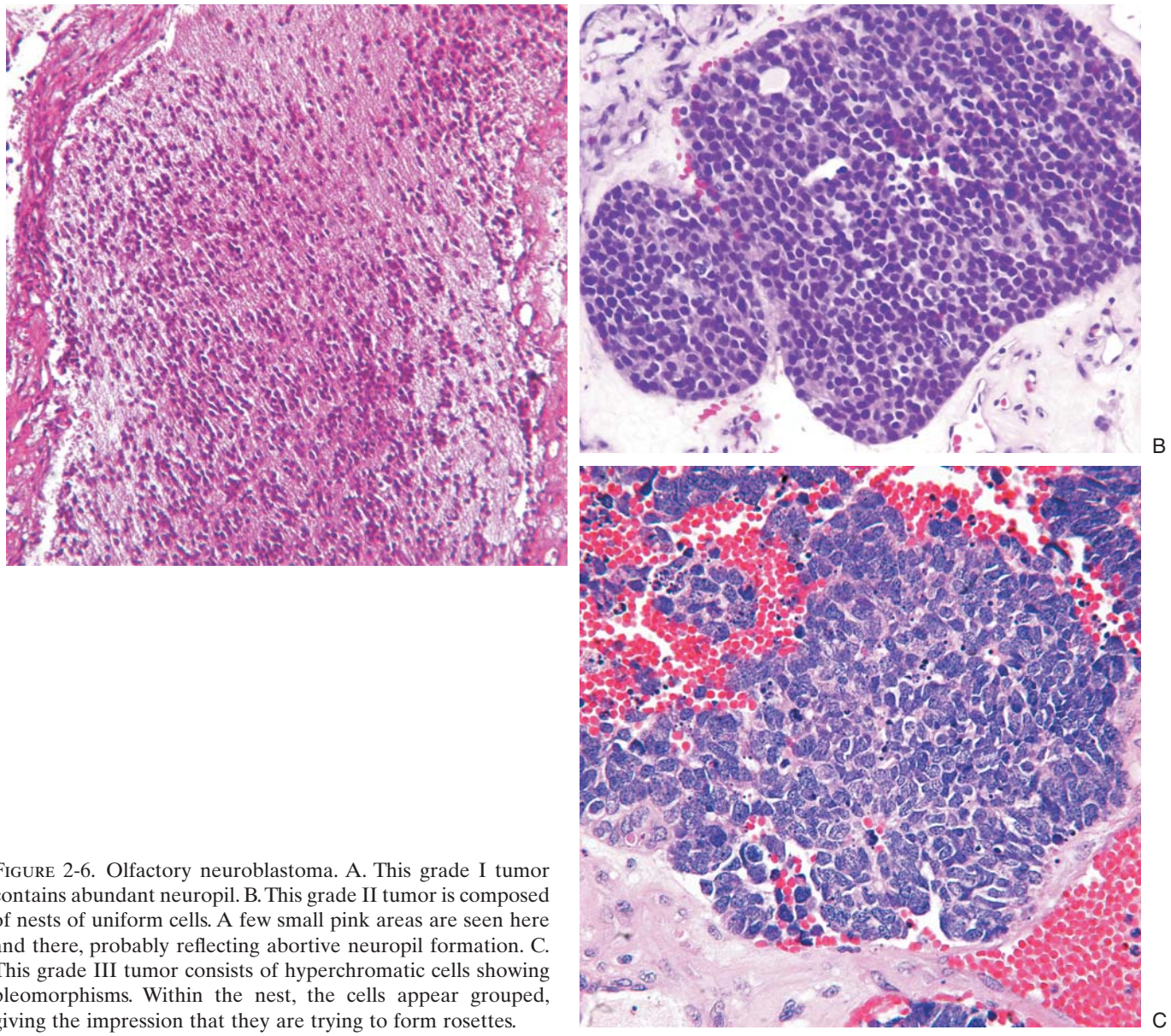


FIGURE 2-6. Olfactory neuroblastoma. A. This grade I tumor contains abundant neuropil. B. This grade II tumor is composed of nests of uniform cells. A few small pink areas are seen here and there, probably reflecting abortive neuropil formation. C. This grade III tumor consists of hyperchromatic cells showing pleomorphisms. Within the nest, the cells appear grouped, giving the impression that they are trying to form rosettes.

TABLE 2-3. Hyams grading system for olfactory neuroblastoma.

	Feature Grade			
	I	II	III	IV*
Lobular growth pattern	++	++	+/–	–
Pleomorphism of nuclei	–	–/+	+	++
Mitoses	–	–/+	+	++
Calcification	+/–	+/–	–	–
Necrosis/apoptosis	–	–	+/–	++
Neurofibrillary background	++	+	+/–	–
Rosettes (Homer-Wright or Flexner-Wintersteiner)	+ or ++	+/–	–/+	–

(*) Some grade IV olfactory neuroblastomas represent sinonasal undifferentiated carcinomas, from which they cannot always be distinguished with certainty.
–, absent; +, present
Source: Adapted from Mills SE et al. (2000) and Silverberg SG et al. (2006).

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3
Tumors of the Salivary Glands

Ossama Tawfik and Asraa Namiq

Introduction

Pathologists generally agree that histologic grading of some malignant salivary gland tumors is predictive of their clinical behavior (1,2). However, the data on the clinical utility of grading all salivary tumors are incomplete (Barnes et al., 2005). In addition, subjectivity of grading and interobserver variation appear to limit the impact of tumor grading.

Many malignant salivary gland tumors are considered either low- or high-grade malignancies, and are not graded (Silverberg et al., 2006). These 2 groups of tumors include the following microscopic forms of salivary carcinomas:

- **Low-grade malignant salivary gland tumors**. This group includes polymorphous low-grade adenocarcinoma (Figure 3-1), basal cell adenocarcinoma (Figure 3-2), acinic cell carcinoma (Figure 3-3), clear cell adenocarcinoma, epithelial-myoepithelial carcinoma, and cystadenocarcinoma.
- **High-grade malignant salivary gland tumors.** This group comprises relatively less common tumors, such as salivary duct carcinoma, squamous cell carcinoma, adenosquamous carcinoma, oncocytic carcinoma, sebaceous carcinoma, and undifferentiated large cell or small cell carcinomas.

The remaining malignant tumors, such as mucoepidermoid carcinoma, adenocarcinoma not otherwise specified (NOS), adenoid cystic carcinoma, and malignant mixed tumors, are graded according to generally accepted criteria.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland tumor (3,4). The primary sites include the parotid gland (50%) and minor salivary glands of the palate (20%), and less commonly the buccal mucosa, lips, retromolar region, and tongue. In a significant number of patients with this type, there is a history of radiation to the head and neck area.

While pathologists generally agree that MEC grading is an important prognostic factor, there is a lack of consensus regarding the histopathologic criteria that are most useful. Grading is dependent on many factors, either alone or in combination, including:

- Proportion of cystic spaces filled with mucus, as compared to solid areas of tumor. Low-grade tumors are typically cystic and contain mucus in the dilated lumina.
- Relative proportion of cell types. MEC are composed of 4 cell types: intermediate squamous cells, clear cells, keratinizing squamous cells, and mucus-secreting goblet cells, and their proportion varies among tumors.
- Degree of invasiveness. Low-grade tumors are characterized by a circumscribed growth, whereas intermediate and high-grade ones are overtly invasive.
- Pattern of invasion, and the presence of vascular and perineural invasion.
- Mitotic rate, cellular atypia, and necrosis. These signs of malignancy are found in high-grade tumors.
- Tumor site. It has been shown that grading MEC of the submandibular gland does not correlate with the biologic behavior of the tumor, as compared to tumors from other sites.

According to the system proposed by Goode et al. (3) and endorsed in the monograph of the Armed Forces Institute of Pathology (Ellis and Auclair, 1996), MEC is best graded on a scale from 1 to 3 and classified as a low-grade, intermediate-grade, or high-grade tumor, as follows (Figure 3-4):

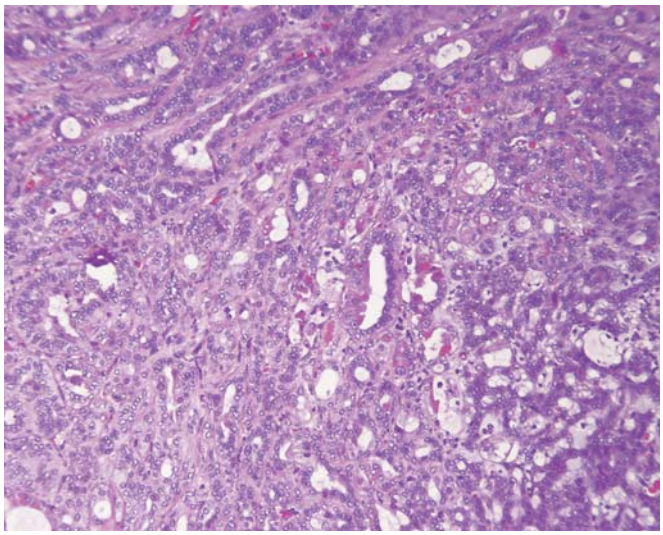

FIGURE 3-1. Polymorphous low-grade adenocarcinoma. This tumor is composed of tubular and trabecular components.

- **Low-grade mucoepidermoid carcinoma.** This tumor typically contains cystic spaces that are filled with mucin. Tumor nest are composed of intermediate squamous or clear cells, keratinizing squamous cells, and mucin-producing cells. The intermediate cells predominate, but the goblet cells are also prominent and often produce large amounts of mucin. The tumors are usually well circumscribed and lack invasiveness.

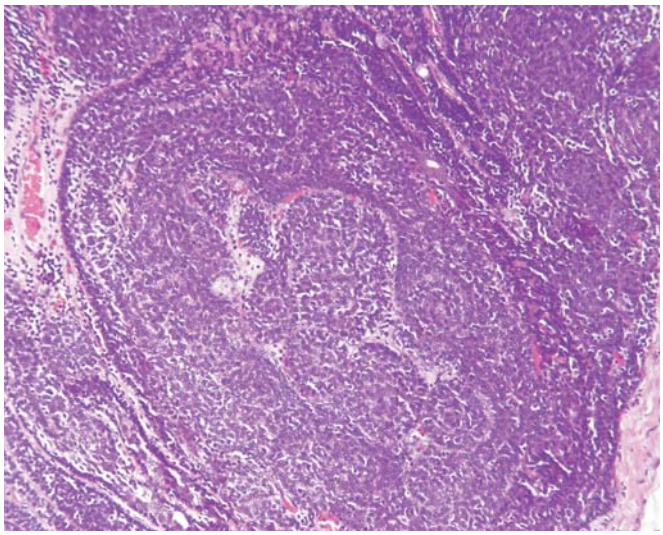

FIGURE 3-2. Basal cell adenocarcinoma. This tumor is composed of relatively uniform basaloid small blue cells, arranged into solid nests. At the periphery of the tumor nests, the cells appear palisaded.

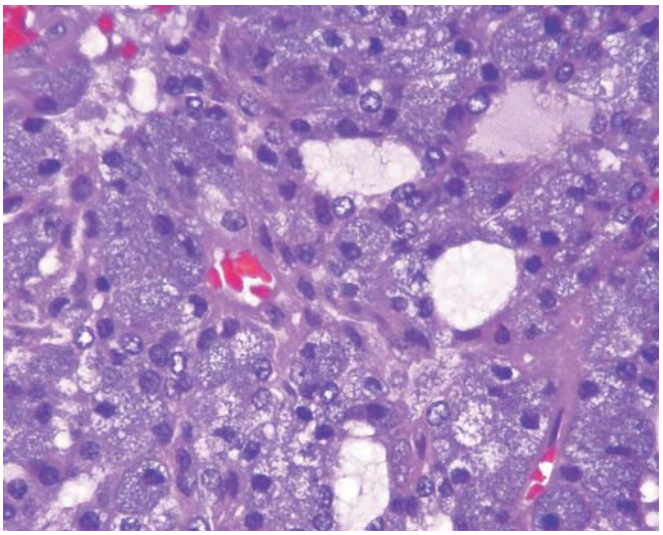

FIGURE 3-3. Acinic cell carcinoma. The solid sheets of cells in this tumor have a well-developed cytoplasm containing cytoplasmic granules.

- **Intermediate-grade mucoepidermoid carcinoma.** This tumor is predominantly solid, and cystic spaces do not account for more than 20% of the total mass. The tumor is composed predominantly of intermediate cells, but there are also keratinizing squamous cells, clear cells, and easily identifiable mucin-producing goblet cells. There is more pronounced nuclear anaplasia, and foci of necrosis may be found. These tumors are clearly invasive, and one may also find vascular or neural invasion.
- **High-grade mucoepidermoid carcinoma.** This tumor is almost entirely solid and does not contain cystic areas. It is mostly composed of intermediate squamous and clear cells, and may resemble nonkeratinizing squamous cell carcinoma. Scattered mucin-secreting cells may be seen, especial in slides stained with muci-

TABLE 3-1. Histological parameters for grading mucoepidermoid carcinoma and point values for each grade.

Microscopic parameters	Point Value
Intracystic component >20%	2
Neural invasion present	2
Necrosis present	3
Mitoses >4 per 10 high-power fields (hpf)	3
Anaplasia	4
Grade	**Total point Score**
Low grade	0–4
Intermediate grade	5–6
High grade	7 or more

Source: Modified from Ellis and Auclair, 1996.

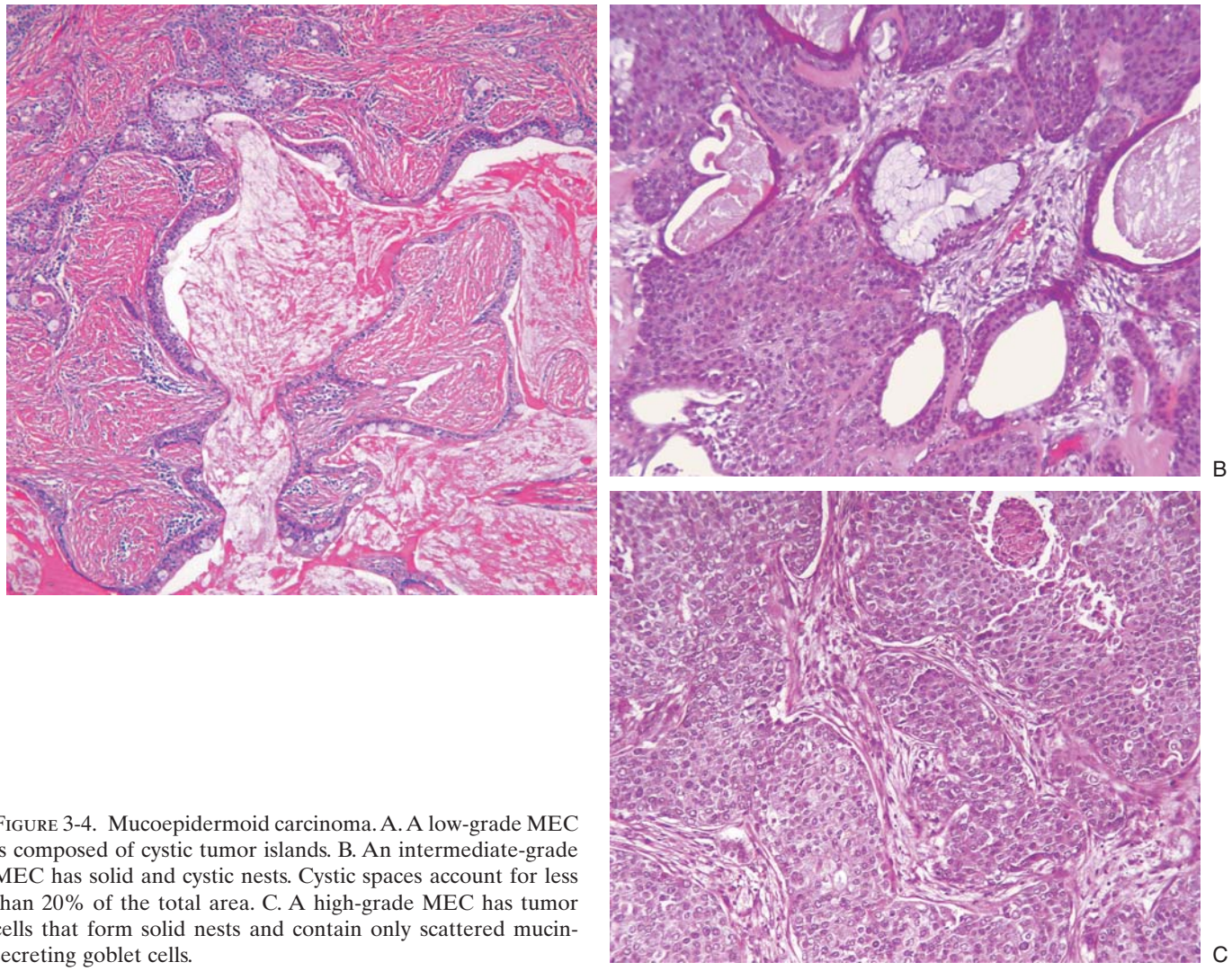

FIGURE 3-4. Mucoepidermoid carcinoma. A. A low-grade MEC is composed of cystic tumor islands. B. An intermediate-grade MEC has solid and cystic nests. Cystic spaces account for less than 20% of the total area. C. A high-grade MEC has tumor cells that form solid nests and contain only scattered mucin-secreting goblet cells.

carmine or p-aminosalicylic acid. Nuclei are vesicular and contain prominent nucleoli; anaplasia may be also seen. There is brisk mitotic activity (4 or more/10 hpf). While necrosis may be present, it is rarely extensive.

Comments

1. DNA analysis is somewhat helpful, especially for high-grade MEC, which is usually aneuploid.
2. Testing for proliferation markers may be of some added prognostic value, but it is not routinely recommended (5).
3. As pointed out by Rosai (2004), marked nuclear atypia, frequent mitoses, and extensive necrosis are not typical of mucoepidermoid carcinoma of any grade.

Adenocarcinoma, Not Otherwise Specified

This tumor type accounts for approximately 15% of all malignant salivary gland tumors. It is composed of tubular, ductular, or glandular structures that do not show any distinct resemblance to other salivary gland tumors (Figure 3-5). Hence, the diagnosis is usually reached by exclusion.

The grading is based on the degree of cytologic atypia, nuclear anaplasia, ductulo-glandular differentiation, the presence of mitoses and necrosis (Ellis and Auclair, 1996). Accordingly, adenocarcinomas NOS are graded as low-, intermediate-, and high-grade tumors (6). The essential features of this 3-tiered grading are summarized in Table 3-2.

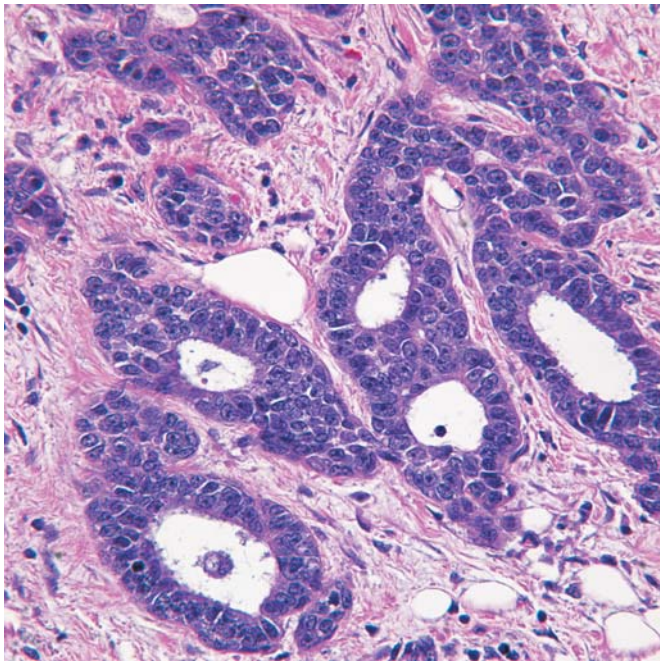

FIGURE 3-5. Adenocarcinoma, NOS. This moderately differentiated tumor shows tubule formation, but contains numerous solid nests and cords.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is the most common malignant tumor of minor salivary glands, but it also occurs in the major salivary glands (7,8). Despite a tendency to grow slowly, it is highly invasive and tends to spread along the nerves or metastasize to the lungs. Tumor location has an impact on the prognosis: those arising in minor salivary glands have a worse prognosis than those in major salivary glands.

Three main histologic patterns are recognized: cribriform, tubular, and solid (Figure 3-6). In tumors with a mixed growth pattern, a solid component with more than 30% of the tumor is indicative of a poor prognosis.

Adenoid cystic carcinoma can be graded as well differentiated, moderately differentiated, and poorly differenHtiated, as follows:

- **Well-differentiated adenoid cystic carcinoma.** Typically, this tumor has a tubular pattern and is composed of tubules or nests enclosed by hyaline material.
- **Moderately differentiated adenoid cystic carcinoma.** This tumor grows in a cribriform pattern and consists of nests and cords of tumor cells, with multiple cyst-like spaces resembling ductal lumina ("Swiss-cheese" pattern).
- **Poorly differentiated adenoid cystic carcinoma**. This tumor exhibits a solid pattern of growth and is composed of anaplastic tumor cells forming solid nests or sheets. Inside the solid nests, areas of comedo-like necrosis may be evident.

Malignant Mixed Tumor

Malignant mixed tumors most often develop due to the malignant transformation of a preexisting benign mixed tumor, but may also arise *de novo* as malignant biphasic tumors without a preexisting benign neoplasia (9,10). The rate of malignant transformation is approximately 8% (10).

- **Carcinoma ex pleomorphic adenoma**. This tumor typically contains a benign component that has all the features of a mixed salivary gland tumor. Tumors undergoing malignant transformation show more prominent mitotic activity, contain broad areas of hyalinization, and are usually larger than typical mixed tumors. The malignant component has the features of high-grade adenocarcinoma, but the mesenchymal-like component appears benign. Occasionally, the malignant component may have the microscopic

TABLE 3-2. Microscopic parameters for grading salivary gland adenocarcinoma, not otherwise specified.

Features	Low Grade	Intermediate Grade	High Grade
Nuclear morphology	Mostly uniform	Mild pleomorphism; nucleoli evident	Hyperchromatic; show pleomorphism
Mitoses	Rare	Easily found	Abundant
Necrosis	Absent	Occasional	Always present
Ductulo glandular-differentiation	Prominent	Present but solid nests abound	Few or no ducts; tumor composed of solid nests and cords

Source: Modified from Ellis and Auclair, 1996.

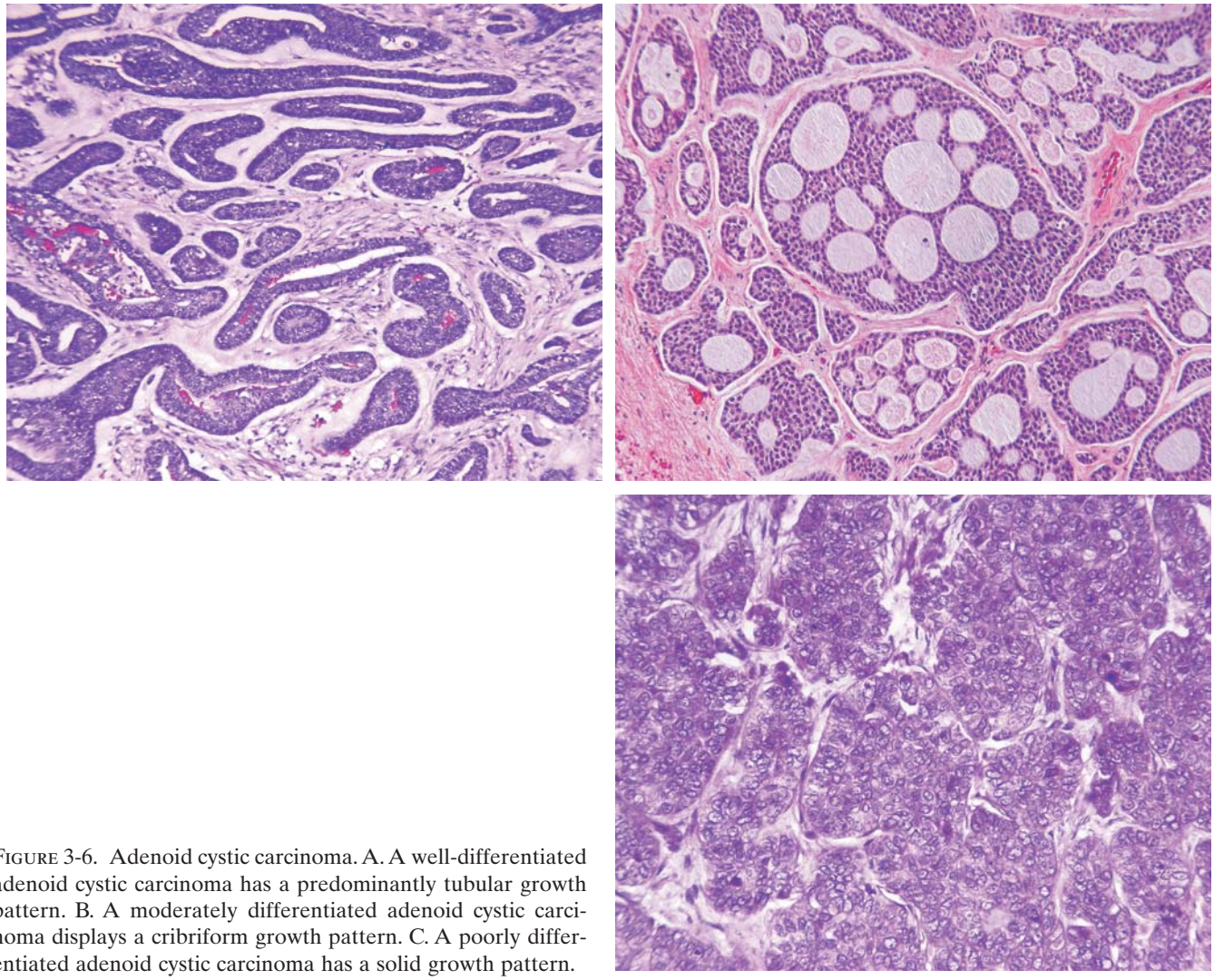

FIGURE 3-6. Adenoid cystic carcinoma. A. A well-differentiated adenoid cystic carcinoma has a predominantly tubular growth pattern. B. A moderately differentiated adenoid cystic carcinoma displays a cribriform growth pattern. C. A poorly differentiated adenoid cystic carcinoma has a solid growth pattern.

features of a low-grade carcinoma, such as polymorphous low-grade adenocarcinoma or basal cell adenocarcinoma, and such tumors have a better prognosis than the high-grade adenocarcinomas arising in mixed tumors. All carcinomas arising in preexisting benign tumors can be classified as localized or frankly invasive. Localized tumors have a better prognosis. Small areas of malignancy—those less than 8 mm in diameter—also have a better prognosis than larger lesions.

- **Primary malignant mixed tumor**. These tumors are also called carcinosarcomas, because both the epithelial and the mesenchymal-like components show microscopic signs of malignancy (11,12). The epithelial and mesenchymal components apparently stem from the same neoplastic clones (12). These tumors are highly aggressive and have a poor prognosis.

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4
Tumors of the Larynx and Hypopharynx

Nina Gale and Nina Zidar

Introduction

Most neoplastic lesions of the larynx and hypopharynx originate from the squamous epithelium. These tumors include benign lesions such as papillomas, as well as preinvasive intraepithelial neoplasms and invasive squamous cell carcinomas. This chapter reviews only the squamous intraepithelial lesions and invasive squamous cell carcinoma.

Squamous Intraepithelial Lesions

The different grades of epithelial lesions that appear during the process of laryngeal carcinogenesis are cumulatively called squamous intraepithelial lesions (SILs). Clinically, the lesions are described as chronic hyperplastic laryngitis, leukoplakia, or rarely, erythroplakia. The World Health Organization recently has adopted a system (Barnes et al., 2005) that incorporates the tenets of the European consensus system known as the Ljubljana classification (1,2).

According to the principles of the Ljubljana classification, SILs include the whole spectrum of microscopic changes, ranging from benign, reactive lesions (squamous cell hyperplasia and basal/parabasal cell hyperplasia), to potentially malignant lesions (atypical hyperplasia or risky epithelium) and carcinoma in situ (1,2).

- **Squamous cell hyperplasia.** This benign hyperplastic process shows thickening of the prickle cell layer. The basal and parabasal layers are unchanged (Figure 4-1).
- **Basal and parabasal cell hyperplasia.** In this lesion, there is an increased thickness of basal and parabasal cells in the lower half of the epithelium; the upper part contains regular prickle cells. Stratification is preserved. Augmented basal and parabasal cells show moderately enlarged nuclei, while rare regular mitoses may be seen in or near the basal layer (Figure 4-2).
- **Atypical hyperplasia or risky epithelium.** This potentially malignant lesion is characterized by the preserved stratification of squamous cells which, however, show mild to moderate cytological atypia. The cells also have an increased nuclear to cytoplasmic ratio. Altered epithelial cells are mainly perpendicularly oriented to the basement membrane and occupy the lower half or more of the entire epithelium. Mitoses are increased in number and are found in the lower two-thirds of the epithelium; they are rarely, if ever, abnormal. Dyskeratotic cells are frequently present. Two subtypes are recognized: basal and spinous cell type (Figure 4-3).
- **Carcinoma in situ.** This lesion characterized by a loss of the epithelial stratification, moderate to severe cytological atypia of epithelial cells, and increased number of mitotic figures within the whole epithelium, which are often abnormal. Two subtypes are basal and spinous cell type (Figure 4-4).

Comments

1. Despite a certain subjectivity in interpretation, traditional light microscopic examination remains the most reliable method for determining an accurate diagnosis of SILs.

2. The Ljubljana classification has been found to be precise for daily diagnostic work and provides data that have been shown to be closely correlated to the biological behavior of the lesions (1,2). The outcome of patients with SILs so graded justifies the proposal for separating the lesions into a benign group (squamous and basal/parabasal hyperplasia) and a potentially malignant group (atypical hyperplasia), showing malignant transformation in 0.9% and 11%, respectively (2).

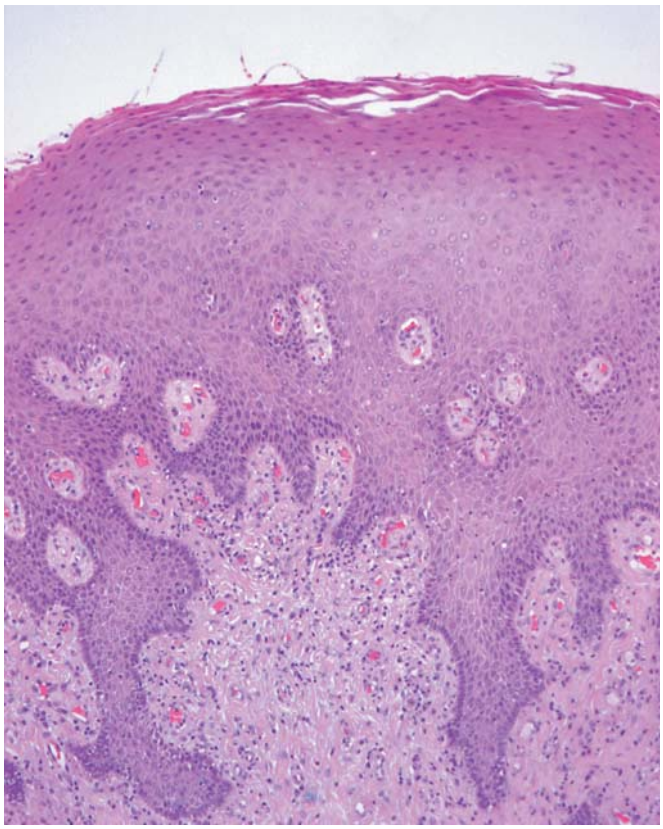


FIGURE 4-1. Squamous cell hyperplasia. The prickle cell layer is thickened, but the basal layer remains of normal thickness.

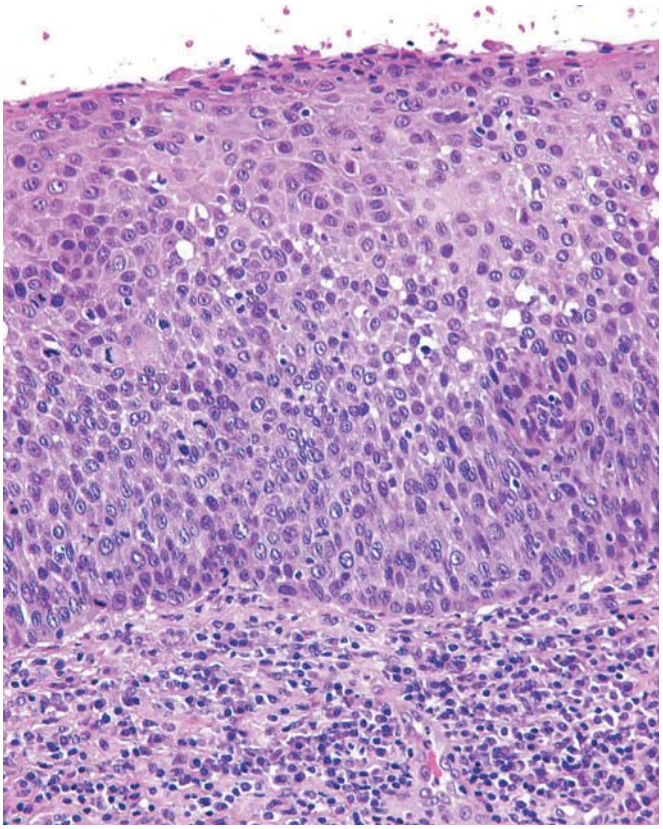


FIGURE 4-3. Atypical hyperplasia. The cells display mild to moderate atypia, but the stratification of cells is preserved. The cells also have an increased nuclear-cytoplasmic ratio.

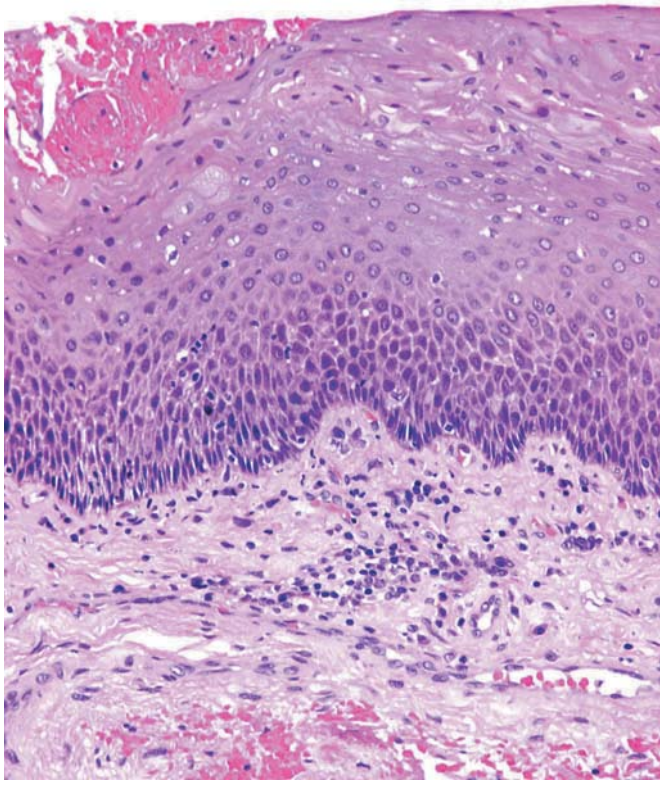


FIGURE 4-2. Basal and parabasal cell hyperplasia. The layers of basal and parabasal cells are thicker than normal, but the prickle cell layer shows no change.

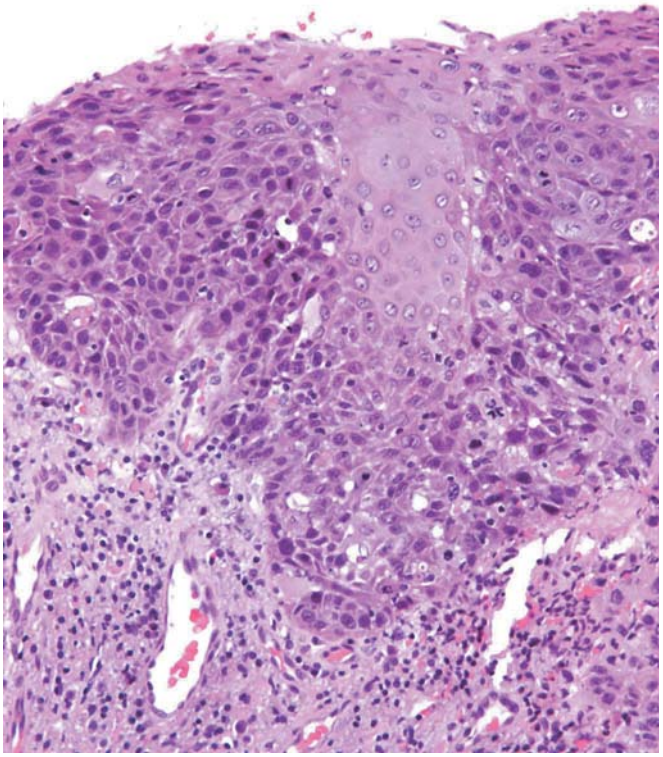
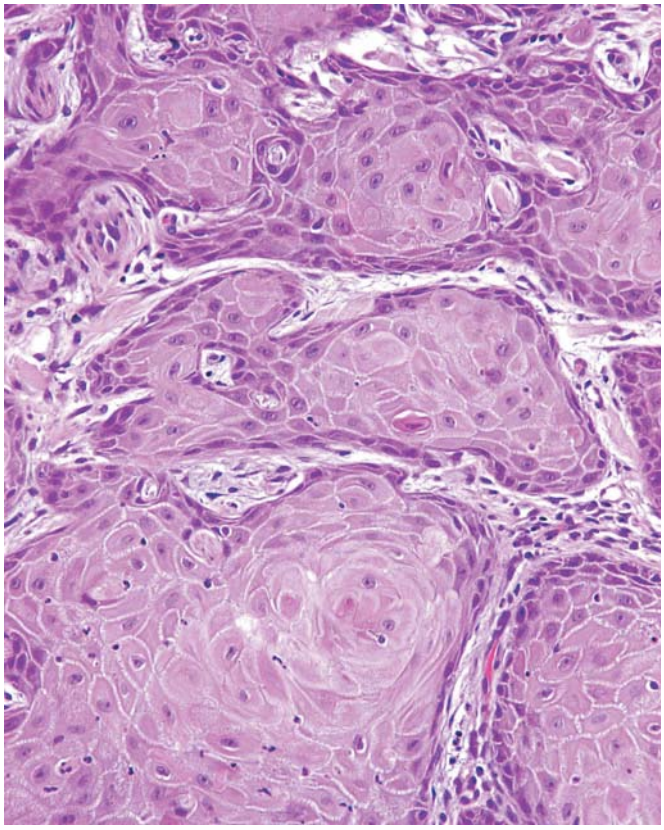


FIGURE 4-4. Squamous cell carcinoma in situ. The epithelium shows a loss of normal stratification, while the cells exhibit a moderate to severe atypia. Mitotic figures may be seen through the entire thickness of the epithelium.



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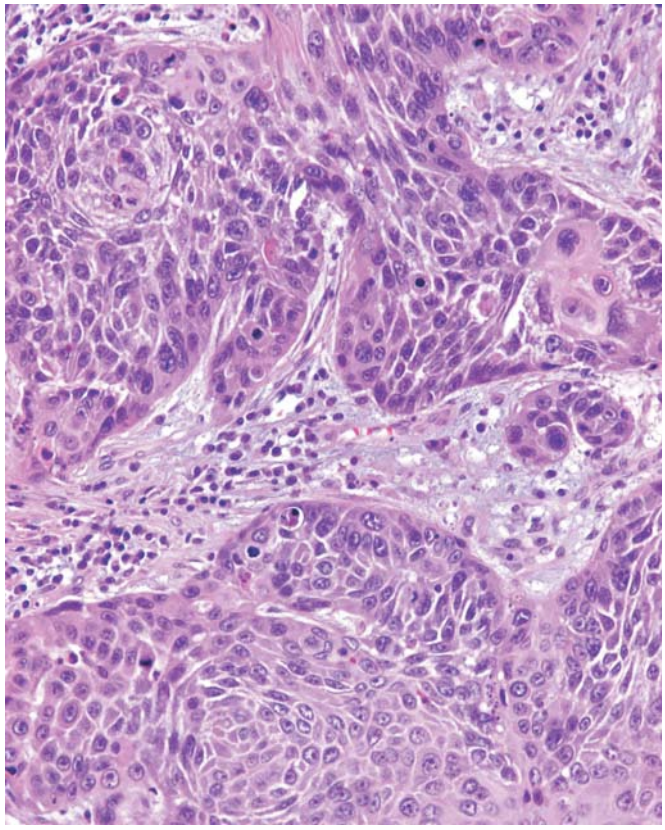

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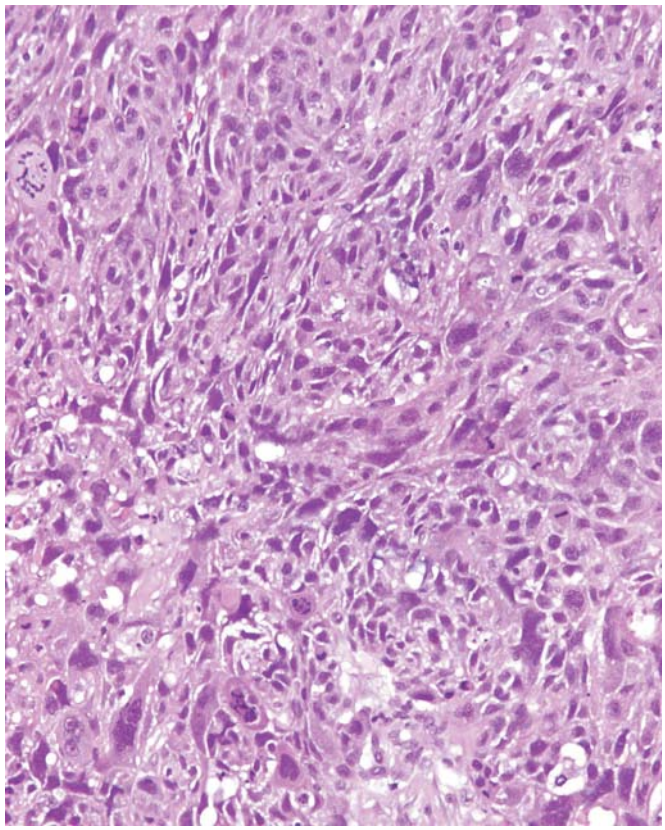

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FIGURE 4-5. Invasive squamous cell carcinoma. A. Well-differentiated squamous cell carcinoma of the larynx (grade 1). B. Moderately differentiated squamous cell carcinoma of the larynx (grade 2). C. Poorly differentiated squamous cell carcinoma of the larynx (grade 3).

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common malignant tumor of the larynx and hypopharynx, accounting for approximately 96% of all malignant tumors at this location. The majority are conventional type squamous cell carcinoma.

Squamous cell carcinoma of the larynx and hypopharynx are traditionally divided into well-differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated squamous cell carcinoma (grade 3), according to the degree of differentiation, cellular pleomorphism, and mitotic activity. Although keratinization is more likely to be present in well- or moderately differentiated squamous cell carcinoma, it should not be considered an important histological criterion in this grading (2).

- **Grade 1, well-differentiated squamous cell carcinoma.** This tumor closely resembles normal squamous epithelium and contains varying proportions of large, differentiated keratinocyte-like squamous cells, as well as small basal-type cells, which are usually located at the periphery of the tumor islands. Intercellular bridges are always present. Keratin pearls are found frequently; mitoses are scanty (Figure 4-5A).
- **Grade 2, moderately differentiated squamous cell carcinoma**. This tumor exhibits more nuclear pleomorphism and an increased number of mitoses, including abnormal mitoses; there is usually less keratinization (Figure 4-5B).
- **Grade 3, poorly differentiated squamous cell carcinoma.** Basal-type cells predominate in this tumor, with a high mitotic rate, including abnormal mitoses, barely discernible intercellular bridges, and minimal, if any, keratinization (Figure 4-5C).

Several variants of squamous cell carcinoma (SCC) also occur, including verrucous carcinoma, spindle cell carcinoma, basaloid SCC, papillary SCC, lymphoepithelial carcinoma, adenoid (acantholytic) SCC, and adenosquamous carcinoma. These tumors are similar to those in other head and neck areas (see Chapter 2). Their recognition is important, because most of them are true clinicopathologic entities, with a different prognostic implication: basaloid SCC, adenosquamous carcinoma, and lymphoepithelial carcinoma are more aggressive than conventional squamous cell carcinoma, while in contrast, verrucous SCC and arguably, papillary SCC have a better prognosis.

Comments

1. The majority of laryngeal squamous cell carcinomas are well to moderately differentiated, whereas the majority of hypopharyngeal squamous cell carcinoma are moderately to poorly differentiated.
2. Variations in differentiation are frequently observed within a single tumor, but grading must be based on the worst differentiated area.
3. The prognostic significance of traditional grading of squamous cell carcinoma is controversial. Some studies have suggested that the grade has a significant influence on prognosis (3,4), while others have not confirmed this observation (5).

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5
Tumors of the Lungs and Pleura

Saul Suster and Cesar Moran

Introduction

Carcinoma of the lung is a common malignant tumor. Histological typing of lung tumors has long been a source of controversy in pathology, in large part due to the marked heterogeneity that these tumors are capable of exhibiting (1-4). Although the bronchi and lungs may give rise to a wide variety of histopathologic types of malignant epithelial neoplasms, lung cancer grading is usually restricted to the 2 most common types of bronchogenic carcinoma included in the latest World Health Organization (WHO) classification: squamous cell carcinoma and adenocarcinoma. Neuroendocrine carcinoma of the lung constitutes a third major group of lung neoplasms for which grading is promising, as the histologic grading of these tumors appears to correlate with their clinical behavior and prognosis (5). The fourth major category of bronchogenic carcinoma in the WHO classification, large cell carcinoma, is not subject to grading, since it is by definition a high-grade neoplasm.

Other less common primary epithelial neoplasms of the bronchus, such as carcinomas of salivary gland-type, usually represent low-grade neoplasms that are rarely amenable to grading (6). Malignant mesotheliomas of the pleura that have an invariably poor prognosis are not commonly graded.

Squamous Cell Carcinoma

The grading system for squamous cell carcinoma of the bronchus is essentially the same as that for squamous cell cancer in other organs. The tumors are graded based upon the relative proportion of intercellular bridges and other features of keratinization, or the absence thereof. A variety of grading systems has been used in the past. The American Joint Commission on Cancer (Cancer Staging Manual, 2002) has proposed a 5-tiered system that includes: GX (grade cannot be assessed); G1 (well-differentiated); G2 (moderately differentiated); G3 (poorly differentiated); and G4 (undifferentiated). In clinical practice, however, most pathologists have traditionally employed a 3-tiered grading system that includes well, moderately, and poorly differentiated tumors.

- **Grade 1, well-differentiated squamous cell carcinoma.** This tumor is characterized by prominent keratinization throughout the lesion, as well as the presence of discernible intercellular bridges. Keratinization in well-differentiated squamous carcinoma usually adopts the form of squamous pearls—concentric laminated deposits of amorphous, eosinophilic, extracellular keratinous material (Figure 5-1A). These structures usually are located in the center of large tumor nests that show a "maturation" phenomenon, whereby the central portions of the nests or tumor islands show the most pronounced features of keratinization, while peripheral areas evince a decrease in tumor cell size, with the outermost layer composed of smaller cells with a more basaloid appearance. The cells within the tumor islands display a striking pavement-like architecture, and intercellular bridges resulting from the prominence of desmosomal cell junctions due to artefactual cell shrinkage can be readily observed at the light microscopic level (Figure 5-1B). The tumor cells generally have a polygonal shape, with well-defined cell membranes. Clearing of the cytoplasm due to accumulation of glycogen is a feature that is also observed in these tumors. Occasionally, focal accumulation of mucinous basophilic material that is stained positive with mucicarmine or periodic-acid Schiff' (PAS) can be seen in isolated tumor cells; however, this does not change the diagnosis to adenocarcinoma in a tumor otherwise showing features of well-differentiated squamous cell carcinoma.

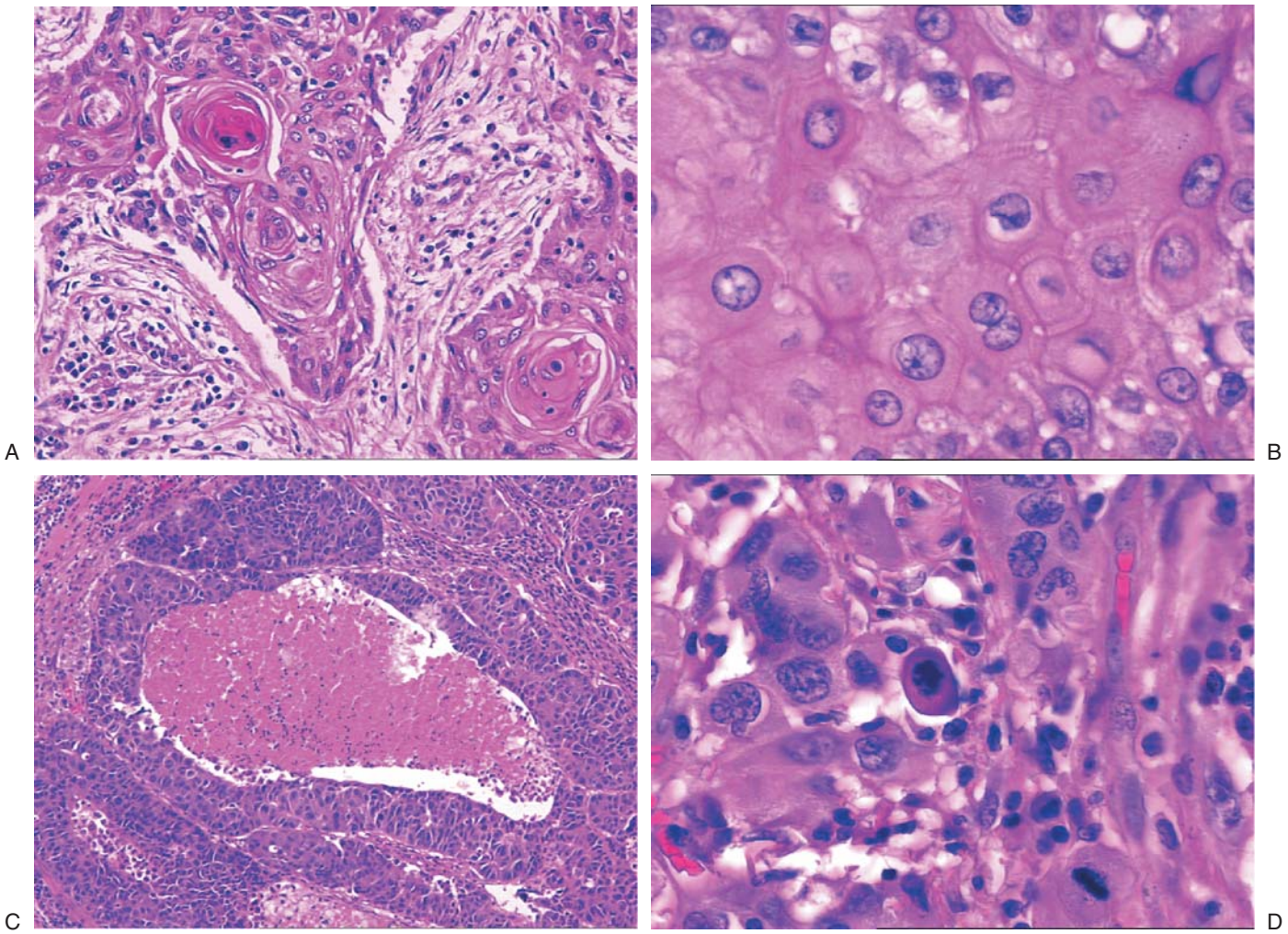

FIGURE 5-1. Squamous cell carcinoma of the lung. A. This well-differentiated tumor shows concentric laminated deposits of amorphous, keratinous material ("squamous pearls"). B. Higher magnification of a well-differentiated tumor reveals well-formed intercellular bridges. C. This moderately differentiated tumor shows central, comedo-like areas of necrosis and a decrease in the size of the surrounding tumor cells. D. A poorly differentiated carcinoma displays single cell keratinization (center), surrounded by poorly differentiated neoplastic cells.

- **Grade 2, moderately differentiated squamous cell carcinoma.** This tumor is characterized by a significantly decreased extent of squamous differentiation. Squamous pearls are few or absent, intercellular bridges are more difficult to find and seen only focally, and there is an increased number of smaller, basaloid cells in the tumor cell islands. Central comedo-like areas of necrosis are a common feature (Figure 5-1C). However, generally the pavement-like appearance of tumor cells with sharply defined cell borders is still preserved.
- **Grade 3, poorly differentiated squamous cell carcinoma.** This tumor shows marked loss of differentiation: intercellular bridges are rarely seen or not evident at all, and keratin pearls are absent. The tumor cells tend to grow in confluent sheets or form irregular islands, or infiltrate the tissue as single cells that have bizarre nuclear forms and show marked nuclear pleomorphism. Single cell keratinization is the most important feature for diagnosis; individually keratinized cells are usually round and have abundant, slightly refractile eosinophilic cytoplasm (Figure 5-1D). Their nuclei may be pyknotic or karyolitic, resembling apoptotic tumor cells. However, unlike apoptotic cells, they are surrounded by an ample rim of deeply eosinophilic cytoplasm. Often, small foci of tumor cells showing more advanced features of differentiation can be identified focally, including polygonal cells with a prominent pavement-like architecture, sharply delimited cell membranes, and small foci of keratinization.

Comments

1. The grading of squamous cell carcinoma is based on a tumor's predominant features. For this reason, grading is best reserved for complete resection specimens, since small biopsies may not be representative.

2. A few unusual histologic variants of squamous cell carcinoma of the lung have been described that may not be amenable to grading. These tumors are essentially regarded as high-grade (poorly differentiated) variants and include the following microscopic forms:

- Spindle cell ("sarcomatoid") squamous cell carcinoma
- Basaloid squamous cell carcinoma
- Small cell squamous cell carcinoma
- Lymphoepithelioma-like carcinoma

3. Immunohistochemical markers are of limited value for the diagnosis and grading of squamous cell carcinoma of the lung. Although in recent years a variety of immunohistochemical markers have been developed that have been associated with squamous differentiation (such as high-molecular weight cytokeratins, p63, and others), in our experience their patterns of expression have not been reliable enough to be useful for either separating squamous cell carcinoma from other types of epithelial lung cancers or for grading.

Adenocarcinoma of the Lung

The grading system for adenocarcinoma of the lung is primarily based on the ratio of glands to solid elements found within the tumor and the degree to which these glands resemble normal structures within the lungs (i.e., either alveolar spaces or bronchial glands).

- **Grade 1, well-differentiated adenocarcinoma.** This tumor has well-formed glandular or acinar structures that comprise more than 90% of its mass. Well-formed glands are lined by round or columnar cells with abundant cytoplasm and enlarged nuclei bearing a coarse chromatin pattern and visible nucleoli (Figure 5-2A). A distinctive variant is the bronchioloalveolar type, which is distinguished by a "lepidic" growth pattern, characterized by the growth of bland-appearing tumor cells along the alveolar walls (Figure 5-2B). The cells lining the alveolar spaces may be small and round to polygonal, with large "hobnail" hyperchromatic nuclei, or may be tall and columnar with abundant clear or lightly eosinophilic mucinous cytoplasm (Figure 5-2C). Two indispensable criteria must be met for a tumor to qualify as bronchioloalveolar: there should be no evidence of stromal invasion and desmoplasia, and the cell population should be relatively bland, with minimal nuclear pleomorphism, mitotic activity, or anaplasia.
- **Grade 2, moderately differentiated adenocarcinoma**. This tumor is characterized by a proliferation of glandular or acinar structures that comprise at least 50% of the total tumor volume, or which no longer closely resemble well-developed glands; the glands are poorly formed, with poorly developed or only abortive lumens, and are lined by cells showing solid areas with nuclear stratification (Figure 5-2D). Alternatively, the glands may show well-developed lumens but are lined by highly atypical cells with marked nuclear pleomorphism, frequent mitoses, and overt anaplasia.
- **Grade 3, poorly differentiated adenocarcinoma**. This tumor displays tumor cell proliferation containing fewer glandular or acinar structures (5% to 50% of the total tumor volume) and a predominance of solid areas containing frequent mucinous cells (5 or more mucin-positive cells in at least 2 high-power fields, or hpf). The few glands present usually are poorly formed and are lined by highly atypical cells with marked nuclear pleomorphism (Figure 5-2E).

Comments

1. Occasionally adenocarcinoma of the lung may also have a papillary growth pattern. A prominent papillary growth pattern is frequently observed in bronchioloalveolar cell carcinoma, in which the papillary structures are seen to invaginate and grow toward the lumen of the alveolar spaces. Under these circumstances, the cell population lining the papillae will be similar to that of the more conventional bronchioloalveolar cell carcinoma (i.e., cells devoid of significant cytologic atypia or anaplasia). A second, rarer type of tumor, papillary adenocarcinoma of the lung, is characterized by a predominant papillary growth pattern (7). Its papillary structures show complex branching and are lined by cells displaying marked nuclear pleomorphism, hyperchromasia, and high mitotic activity (Figure 5-2F). Such tumors behave in a much more aggressive fashion than bronchioloalveolar cell carcinoma and are more akin in their behavior to conventional adenocarcinoma of the lung.

2. A few other unusual variants of adenocarcinoma of the lung have been described, including the following microscopic forms:

- Signet-ring cell adenocarcinoma
- Mucinous ("colloid") adenocarcinoma

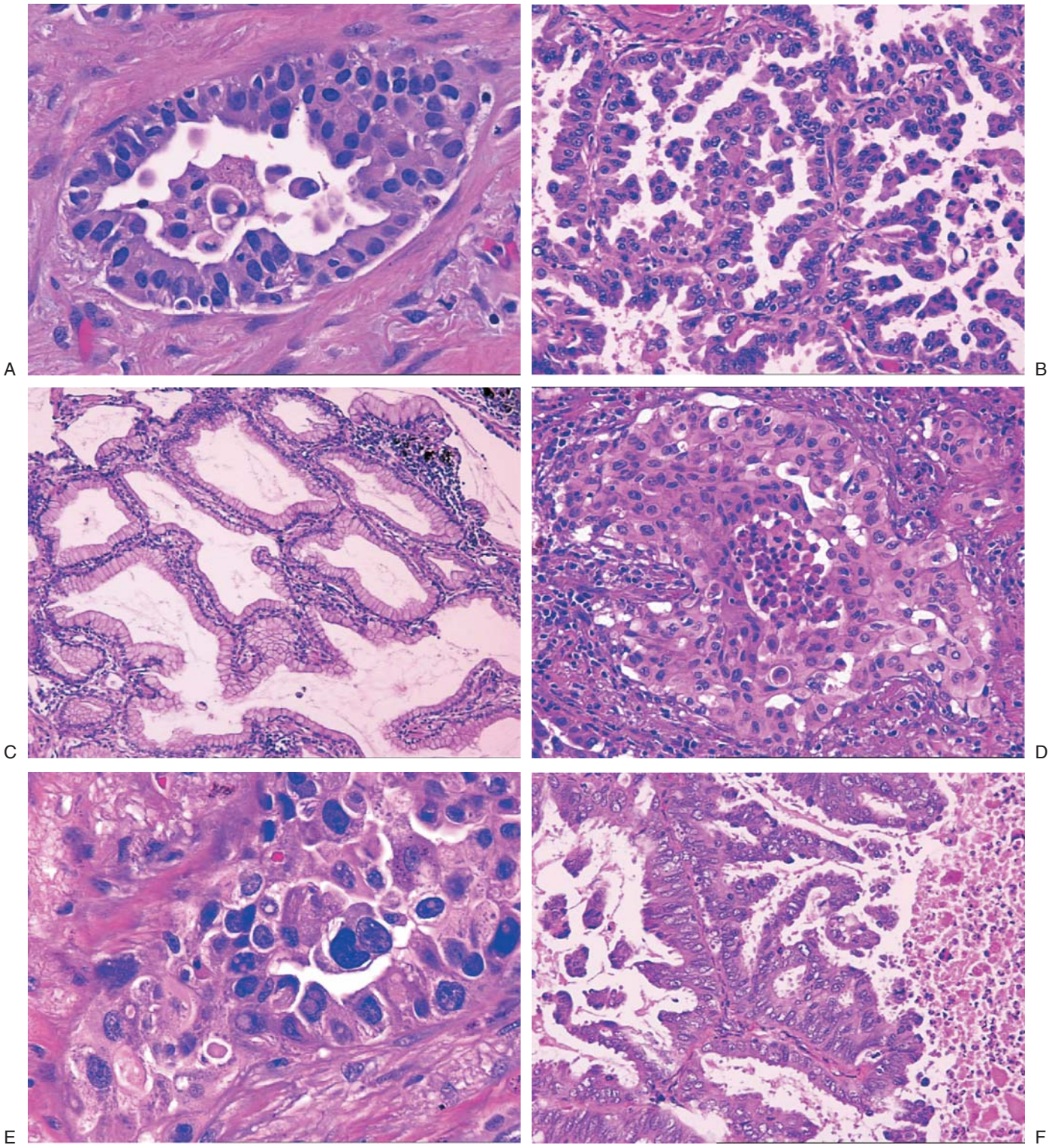

FIGURE 5-2. Adenocarcinoma of the lung and bronchioloalveolar carcinoma. A. This well-differentiated tumor consists of well-formed glands lined by a single layer of atypical columnar cells. B. The characteristic "lepidic" growth pattern of bronchioloalveolar cell carcinoma is evident, with a row of mildly atypical cells continuously lining the alveolar walls. C. Tall, columnar cells with abundant clear mucinous cytoplasm form this bronchioloalveolar cell carcinoma. D. This moderately differentiated adenocarcinoma is composed of ill-defined glands, with small, abortive lumina, lined by atypical cells. It also contains solid areas with nuclear stratification. E. A poorly differentiated adenocarcinoma exhibits ill-defined glands lined by highly atypical cells. F. Complex papillary structures are lined by markedly atypical cells in this papillary adenocarcinoma. Notice the foci of tumor necrosis in the lumen of the glandular structures.

- Adenocarcinoma with clear cell change
- Well-differentiated "fetal" adenocarcinoma ("monophasic pulmonary blastoma")

With the exception of the signet-ring cell carcinoma, the majority of these tumors correspond to low-grade, well-differentiated adenocarcinomas.

Neuroendocrine Carcinoma of the Lung

Neuroendocrine carcinoma (NEC) of the lungs occurs in several clinicopathologic forms, but their classification and grading have been the subject of much debate in recent years (5,8). This has been due mostly to the reluctance to abandon older terms such as "carcinoid tumor" and "atypical carcinoid" in favor of the more accurate designation of "neuroendocrine carcinoma" for this family of tumors. The new WHO classification recognizes the existence of a spectrum of lung lesions showing features of neuroendocrine differentiation ranging from very well-differentiated to very poorly differentiated. In deference to established custom, however, the terms carcinoid, atypical carcinoid, and small cell and large cell NEC have been retained in their proposed classification.

Another recent proposal has introduced a 4-tiered grading scheme for these tumors that employs terms similar to those adopted by the WHO schema, with the last category in their classification corresponding to "undifferentiated NEC." However, we believe the term "undifferentiated" as applied to these tumors should be abandoned because it is contradictory in this setting. The term undifferentiated, by definition, refers to a tumor displaying no features of differentiation; whereas the term neuroendocrine carcinoma by definition implies specific evidence of both epithelial and neuroendocrine differentiation. Poorly differentiated NEC would therefore be a more accurate and correct term. We also prefer a more simplified 3-tiered system that grades these tumors based on the degree of differentiation, and designates them as low-grade or well-differentiated NEC, intermediate grade or moderately differentiated NEC, and high-grade or poorly differentiated NEC, respectively.

- **Well-differentiated neuroendocrine carcinoma.** Essentially, this tumor corresponds to what has been previously termed "typical carcinoid." The defining criteria are twofold: architectural and cytologic. Architectural criteria include the presence of a well-developed neuroendocrine (or "organoid") pattern of growth in the majority (>80%) of the tumor, characterized by the arrangement of the tumor cells into well-defined nests, packets, cords, trabeculae, or ribbons, usually separated by fibrovascular septa (Figure 5-3A). Other growth patterns less frequently observed include the formation of epithelial rosettes, microacinar structures, or tumor cell islands with prominent peripheral palisading of the nuclei. The cytologic criteria include a fairly monotonous tumor cell population composed or relatively small cells with round to oval nuclei showing a characteristic, evenly dispersed chromatin pattern ("salt and pepper"), and surrounded by a rim of eosinophilic cytoplasm (Figure 5-3B). Nucleoli are generally absent or inconspicuous, and mitotic activity is minimal (>2 mitoses per 10 hpf).
- **Moderately differentiated neuroendocrine carcinoma.** This tumor is characterized by at least partial loss of the neuroendocrine growth pattern and more pronounced cytologic atypia with increased mitotic activity. Moderately differentiated NEC corresponds to the tumors previously designated "atypical carcinoid" in the literature. Cellular sheets and islands of relatively monotonous tumor cells that retain, at least focally, a recognizable "organoid" pattern of growth are typical of this tumor. Another distinctive feature is the presence of central, comedo-like areas of necrosis in many of the tumor cell islands (Figure 5-3C). Cytologically, this tumor has cells displaying enlarged nuclei, which can be round or oval, with an increase in chromatin pattern, occasional prominent nucleoli, and increased mitotic activity (2–10 mitoses per 10 hpf).
- **Poorly differentiated neuroendocrine carcinoma**. At present, 2 distinct variants are included in this category: small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC). The latter continues to be in dispute, and many authors contend that this tumor belongs in a different category, namely that of large cell/anaplastic carcinoma. It has not yet been determined whether the biologic behavior and response to chemotherapy is the same for the small cell and the large cell variants of NEC (7).

SCNEC is characterized by sheets of tumor cells with extensive tumor necrosis and without a readily identifiable neuroendocrine architectural growth pattern. The tumor cells are relatively small (compared to large cell or anaplastic carcinoma), and usually have a diameter that is roughly equivalent to that of 3 small lymphocytes. The cells display large nuclei with hardly any discernible cytoplasm. The nuclear chromatin is finely dispersed and often appears "smudged," with absent or small nucleoli as visualized in hematoxylin-eosin stained preparations on routine light microscopy (Figure 5-3D). Mitotic activity is usually high, with an average of 10 or more mitoses per 10 hpf.

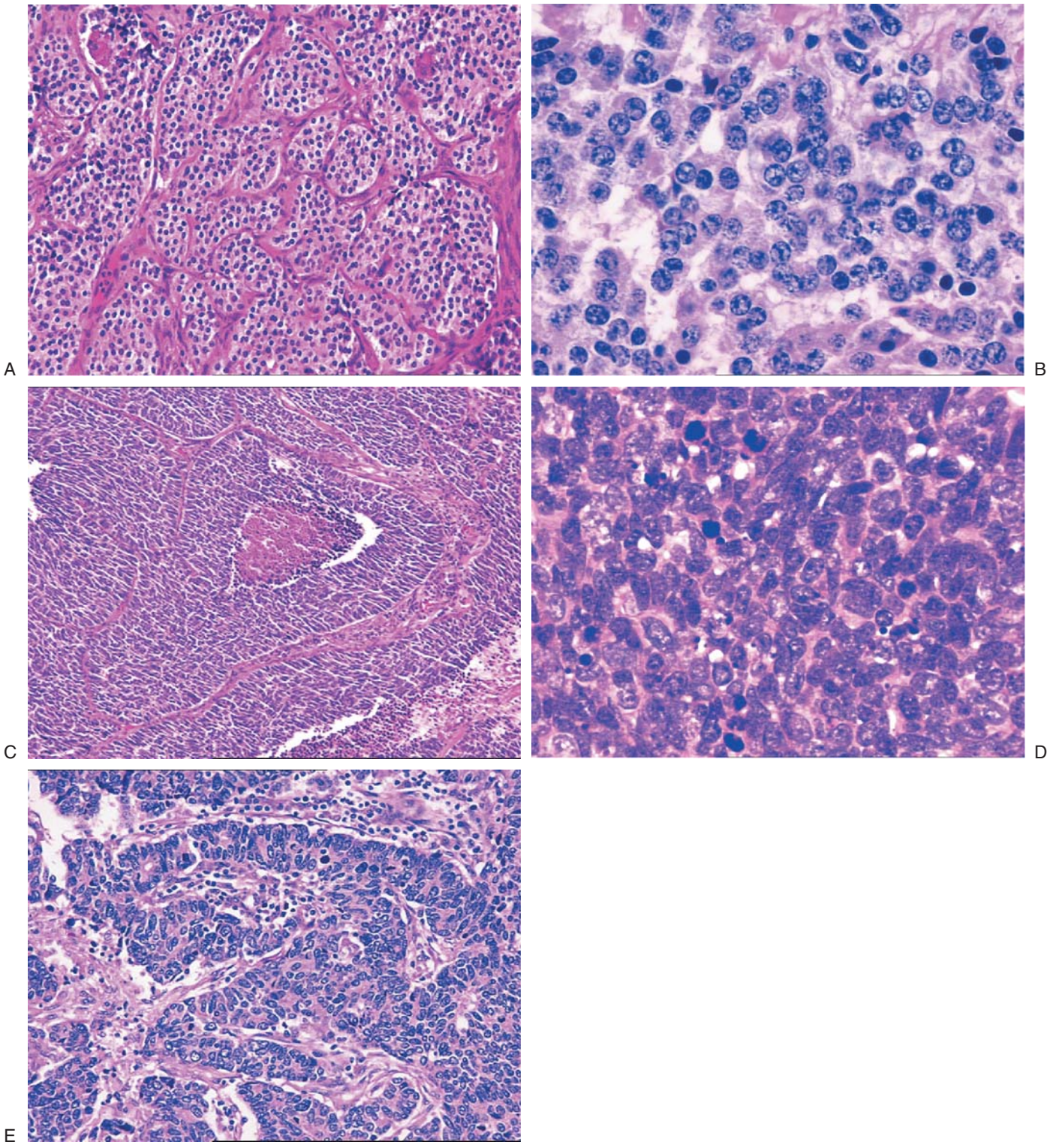

FIGURE 5-3. Neuroendocrine carcinoma. A. A well-differentiated neuroendocrine carcinoma ("carcinoid" tumor) is composed of a monotonous population of small, round tumor cells adopting a prominent "nesting" pattern separated by fibrovascular septa. B. A well-differentiated neuroendocrine carcinoma at a higher magnification. One can appreciate the monotonous population of tumor cells with "salt-and-pepper" nuclear chromatin pattern, the absence of prominent nucleoli and mitoses, and the indistinct rim of amphophilic to lightly acidophilic cytoplasm. C. Cells are arranged into large lobules with central, comedo-like areas of necrosis in this moderately differentiated neuroendocrine carcinoma of the lung ("atypical carcinoid"). D. A poorly differentiated neuroendocrine carcinoma of the lung, small cell type, has cells showing large, hyperchromatic nuclei with "smudged" chromatin. Mitoses are conspicuous. E. In a poorly differentiated neuroendocrine carcinoma of the lung, large cell type, the tumor cells are arranged into nests and cords. These cells are large and have abundant cytoplasm, adopting a vague "organoid" pattern. The tumor cells demonstrated positivity for chromogranin and synaptophysin by immunohistochemical staining.

LCNEC is currently defined as a lung tumor displaying a readily identifiable neuroendocrine architectural growth pattern (i.e., nest and cords of tumor cells, rosettes, trabeculae), but in which the tumor cells are much larger than those of SCNEC—at least double in size—with increased nuclear to cytoplasmic ratio, vesicular nuclei, and prominent nucleoli (Figure 5-3E). Mitoses are frequent, usually exceeding 10 per 10 hpf. Generally, tumor necrosis is prominent and may involve large zones. The diagnosis of LCNEC requires confirmation by immunohistochemistry (positivity for neuroendocrine markers such as chromogranin-A or synaptophysin), or demonstration of dense-core neurosecretory granules by electron microscopy.

Comments

1. A variable spectrum can sometimes be observed between well-differentiated NEC and moderately differentiated NEC, occasionally making exact distinction between them difficult. The most important criterion for separating them is mitotic activity.
2. Although it was initially thought that atypical carcinoid required more than 5 mitoses per 10 hpf, that threshold has been lowered recently, and tumors displaying 2 or more mitoses per 10 hpf are classified as moderately differentiated NEC.
3. Another important criterion is the presence of necrosis; even focal pinpoint areas of necrosis should raise the consideration of a moderately differentiated NEC when present in an otherwise well-differentiated tumor.
4. Cytologic atypia appears to be less reliable as a single criterion for separating these tumors. It is recommended that mitoses be counted in the areas of higher mitotic activity using a 40X objective with an eyepiece that has a field-of-view number of 20 (the area viewed in 1 hpf should equal 0.2 mm^2, or 2 mm^2 for 10 hpf).
5. Poorly differentiated neuroendocrine carcinomas may also show a variable admixture of small and large cell types within the same tumor. Such cases are designated as mixed small/large cell neuroendocrine carcinoma.
6. It must be noted that a subset of non-small cell carcinomas of the lung may display immunohistochemical or ultrastructural features of neuroendocrine differentiation, despite not showing a "neuroendocrine" architectural growth pattern. Neuroendocrine differentiation has been demonstrated by immunohistochemistry in up to 20% of squamous cell carcinomas, adenocarcinomas, and large cell carcinomas. These tumors have been collectively referred to as "non-small cell lung cancer with neuroendocrine differentiation." Their exact relationship to the group of LCNEC is still poorly defined and remains controversial.

Malignant Mesothelioma

Malignant mesothelioma is a neoplastic proliferation of mesothelial cells originating from the visceral and parietal pleura (9). Three basic types are described:

- Epithelioid mesothelioma
- Sarcomatoid ("spindle cell") mesothelioma
- Biphasic ("mixed epithelioid/sarcomatoid") mesothelioma

Less common variants include desmoplastic, deciduoid, lymphohistiocytic, clear cell, small cell, and poorly differentiated or anaplastic variants. These mesotheliomas must be distinguished from metastatic malignant tumors involving the pleura and the less common primary pleural tumors (10). Malignant mesothelioma may also resemble reactive mesothelial proliferative lesions (11).

Because of their uniformly dismal prognosis, malignant mesotheliomas are not commonly graded. The vast majority of malignant mesotheliomas (i.e., epithelioid malignant mesothelioma) actually display low-grade cytologic features and are characterized by a relatively bland-appearing, well-differentiated population of cells that closely resemble their benign counterpart (Figure 5-4A). The architectural growth pattern of these tumors—namely the formation of tubulopapillary structures—is also closely reminiscent of benign reactive mesothelium. The cells in sarcomatoid mesothelioma, on the other hand, no longer resemble normal mesothelium and instead may mimic a spindle cell sarcoma, due to their elongated shape and atypia. The latter could be conceptually regarded as a poorly differentiated or cytologically high-grade variant of malignant mesothelioma. The differences in behavior and prognosis for these tumors, however, are minimal, and their uniformly dismal outcome make distinction of little clinical significance. In rare instances, epithelioid malignant mesothelioma may grow as solid sheets composed of highly atypical and even anaplastic tumor cells with increased nuclear to cytoplasmic ratios, marked nuclear pleomorphism, and frequent mitotic figures; such tumors de facto represent a cytologically high-grade, poorly differentiated variant of epithelioid malignant mesothelioma (Figure 5-4B).

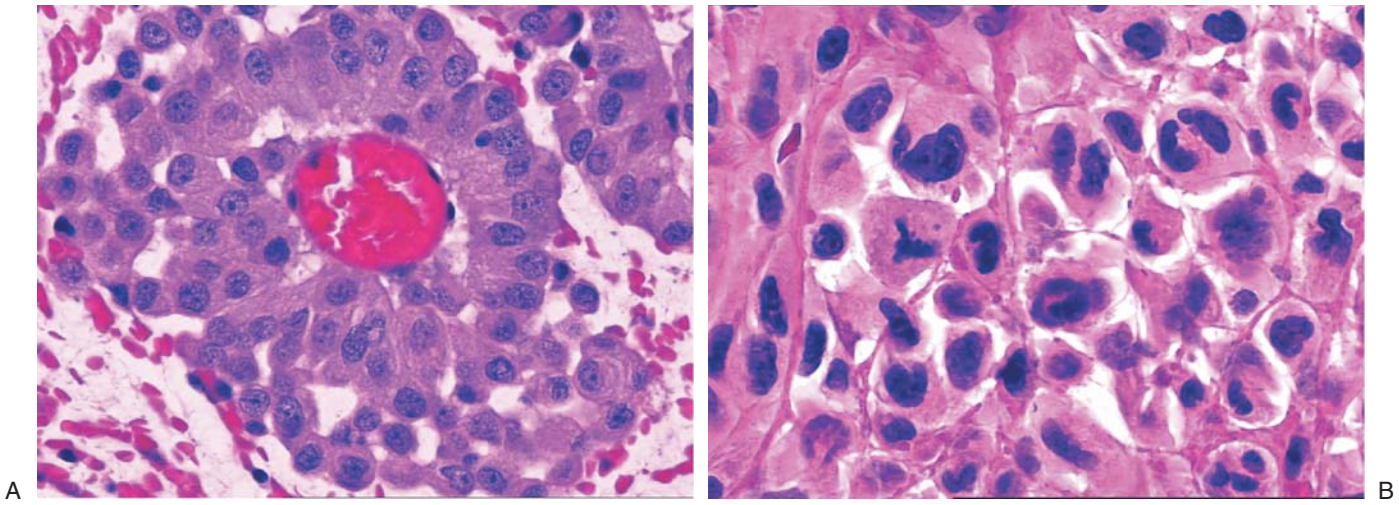

FIGURE 5-4. Malignant mesothelioma. A. This epithelioid mesothelioma is composed of large, round to polygonal tumor cells with abundant cytoplasm and minimal nuclear atypia. B. The tumor cells have high-grade nuclei showing marked nuclear pleomorphism, hyperchromatism, and abnormal mitoses.

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6
Tumors of the Thymus

Saul Suster and Cesar Moran

Introduction

Primary thymic epithelial neoplasms represent the most common type of tumors of the anterior mediastinum. These tumors have been a source of major controversy over the years, due to the difficulty of their histopathologic typing and their often unpredictable biologic behavior. Unlike malignant epithelial neoplasms arising in other organs, for many years it was thought that these tumors were unsuitable for histologic grading. In fact, the latest World Health Organization schema for the classification of thymic epithelial neoplasms does not even mention grading for these tumors.

More recent observations, however, have demonstrated that thymic epithelial neoplasms form part of a continuous spectrum of lesions that on one end may closely resemble their parent organ, and at the other extreme be very poorly differentiated (1). Based on these observations, recently a novel conceptual approach was introduced for the classification of thymic epithelial neoplasms, one that is based on the histologic degree of differentiation of the lesions (2). The histologic grading of these tumors is based on the premise that these lesions can range from well-differentiated to moderately or poorly differentiated neoplasms. This is supported by the observation of tumor progression in thymoma, whereby recurrences show transformation from a low-grade histologic type to that of a higher grade (3). The degree of differentiation in any tumor will depend on the presence or absence of the organotypical features of differentiation of the thymus, and on the degree of cytological atypia displayed by the tumor cells (Table 6-1).

Tumors displaying most or all of the organotypical features of thymic differentiation and an absence of cytological atypia are categorized as low-grade or well-differentiated thymic epithelial neoplasms (also designated, by convention, thymoma); tumors retaining only some of the organotypical features of the thymus but displaying mild to moderate cytologic atypia correspond to moderately differentiated thymic epithelial neoplasms (atypical thymoma); and those showing total loss of the organotypical features of the thymus and displaying overt cytologic evidence of malignancy correspond to high-grade or poorly differentiated thymic epithelial neoplasms (also designated, by convention, thymic carcinoma) (2,4). The grading is based on a combination of architectural and cytological parameters as observed on routine microscopy on hematoxylin-eosin—stained slides, and does not require the use of special stains or other ancillary techniques.

Well-Differentiated Thymic Epithelial Neoplasms (Thymoma)

The diagnosis of well-differentiated thymoma is based on the identification of the organotypical features of differentiation of the thymus as well as the absence of significant cytological atypia in the tumor cells. These organotypical features can vary depending on whether the tumor cells are attempting to recapitulate the normal, mature thymus of infants and adolescents, or whether they resemble the normal involuted thymus of the adult (see Table 6-1). In general, better differentiated tumors are characterized by a thick capsule, fibrous bands with prominent lobulation, and an overwhelming population of immature T-lymphocytes admixed with the neoplastic epithelial cells, thus closely resembling the thymic cortex in children and adolescents. Dilated perivascular spaces and so-called areas of "medullary" differentiation are other frequent features observed in these lesions. The neoplastic epithelial cells are characterized by large vesicular nuclei with prominent eosinophilic nucleoli, and are surrounded by an indistinct rim of abundant lightly eosinophilic or amphophilic cytoplasm (Figure 6-1). Mitoses are not a feature of the neoplastic cells, although in some cases they may be relatively frequent in the surrounding immature T-lymphocytic population. Well-

Table 6-1. Organotypical features of differentiation of the normal mature thymus of childhood and the normal involuted thymus of the adult.

Normal mature thymus of childhood or adolescence
Thick capsule with internal lobulation separated by fibrous septae
Dual (epithelial/lymphoid) cell population with variable numbers of immature T-lymphocytes
Dilated perivascular spaces
Areas of "medullary" differentiation
Absence of cytological features of malignancy
Normal involuted thymus of the adult
Thick capsule with internal lobulation
Spindle cell population devoid of cytologic atypia
Scant immature T-lymphocytes
Rosette-like epithelial structures
Cysts and glandular structures

Source: Adapted from Suster and Moran, 2003.

differentiated thymomas that resemble the normal involuted thymus of the adult are composed predominantly of a monotonous population of oval to spindle cells admixed with variable numbers of T-lymphocytes. The neoplastic spindle cells are characterized by bland-appearing oval nuclei, with dispersed chromatin and inconspicuous nucleoli surrounded by a scant rim of lightly eosinophilic cytoplasm (Figure 6-2). The cells are devoid of nuclear pleomorphism or mitotic activity.

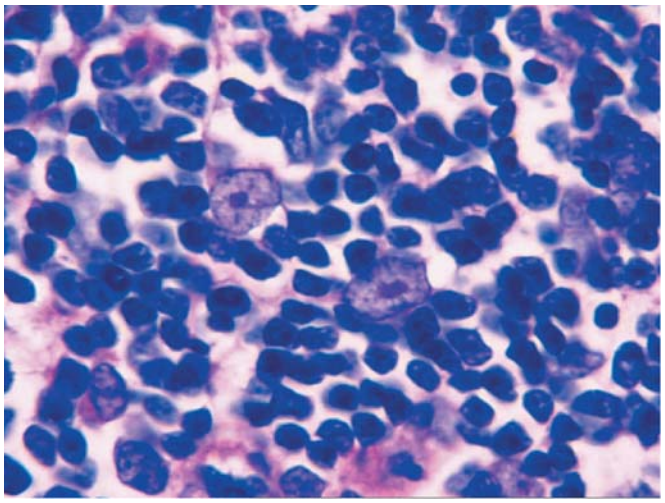

Figure 6-1. Well-differentiated thymoma. This lymphocyte-predominant type contains 2 neoplastic epithelial cells (center) surrounded by lymphocytes. The epithelial cells feature large, vesicular nuclei with prominent eosinophilic nucleoli enclosed by an indistinct rim of amphophilic cytoplasm.

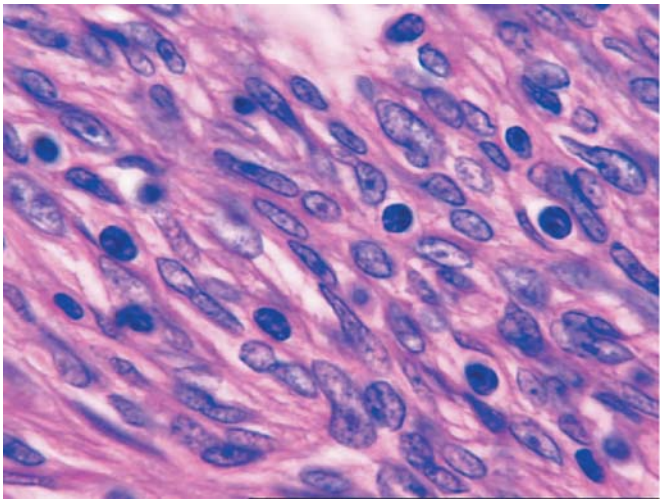

Figure 6-2. Well-differentiated thymoma of the spindle cell type. This tumor is composed of cells with oval to spindle nuclei. The nuclei have dispersed chromatin, and absent or inconspicuous nucleoli. There is no mitotic activity.

Moderately Differentiated Thymic Epithelial Neoplasm (Atypical Thymoma)

This tumor is characterized by partial loss of the organotypical features of differentiation of the normal thymus, with a mild to moderate increase in cytologic atypia of the neoplastic epithelial cells. Atypical thymoma may be composed of round/polygonal or oval/spindle cells, but the majority of these tumors are composed of large, round to polygonal epithelial cells admixed with scattered T-lymphocytes. Architecturally, the tumors may show some of the organotypical features commonly found in thymoma, such as a thick capsule, lobulation, and perivascular spaces (Figure 6-3). The tumor cells, however, are much larger than those in conventional thymomas, and are characteristically surrounded by abundant eosinophilic cytoplasm showing well-defined cell borders. The nuclei are also larger than in thymomas and display an increase in chromatin deposition, often with prominent eosinophilic nucleoli (Figure 6-4). Occasional mitotic figures can be observed in the epithelial cells; mitoses may be typical, or more rarely atypical, but usually are not numerous (usually <2 per 10 high-power fields). A distinctive feature of these tumors is the presence of well-defined cell membranes in the epithelial tumor cells, which contrasts with the indistinct cytoplasmic cell borders seen in thymoma. The polygonal shape of the cells and the sharply outlined, thick cell membranes often impart an epidermoid appearance to these tumors. In fact, microscopic foci displaying abrupt squamous differentiation are a frequent finding in these lesions. Perivascular spaces are often numerous marked by a tendency to display prominent peripheral

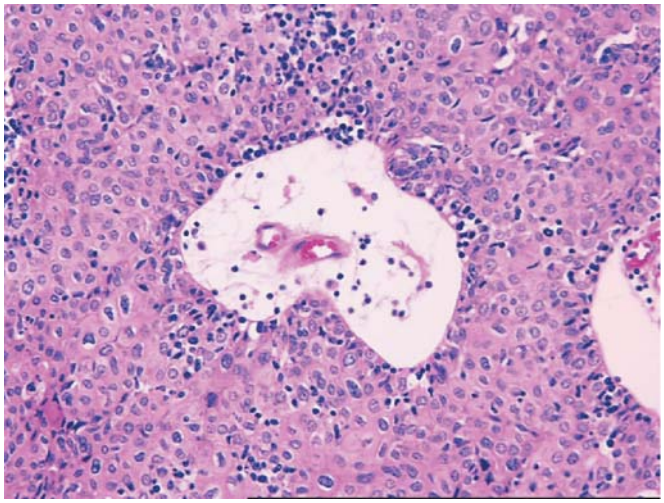

FIGURE 6-3. Moderately differentiated thymic epithelial neoplasm (atypical thymoma). Tumor cells form solid sheets around the dilated, thin-walled blood vessels. Epithelial cells predominate, but there are also scattered lymphocytes.

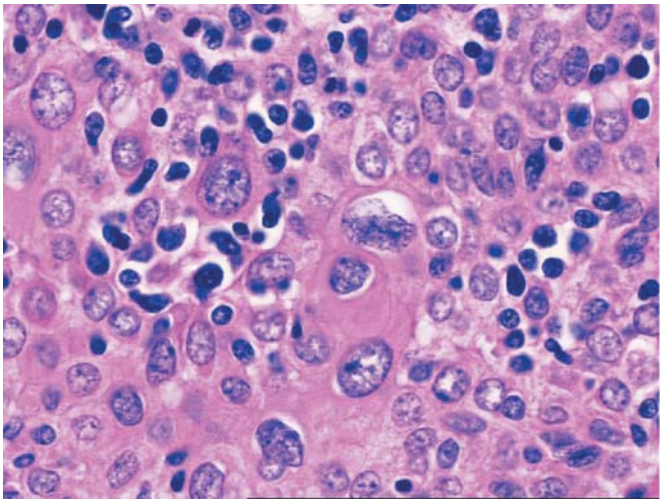

FIGURE 6-4. Moderately differentiated thymic epithelial neoplasm (atypical thymoma). Higher magnification of the tumor reveals large round to polygonal cells marked by sharply defined cell membranes and enlarged, hyperchromatic nuclei, with occasional prominent eosinophilic nucleoli.

palisading of tumor cells around the lumen of the vessels. Atypical thymomas composed of oval or spindle cells are also characterized by an increase in their nuclear size, with a heavy chromatin pattern, frequent eosinophilic nucleoli, and occasional mitotic figures.

Poorly Differentiated Thymic Epithelial Neoplasm (Thymic Carcinoma)

This tumors is defined as having lost the characteristic organotypical features of the thymus and by displaying overt cytologic evidence of malignancy. Thymic carcinoma can display a wide variety of microscopic appearances and may closely resemble carcinomas of other organs (5). As such, essentially this represents a diagnosis of exclusion, requiring strict clinical and radiographic demonstration of the absence of a primary tumor elsewhere. A large number of histologic varieties of thymic carcinoma have been described. In the study by Suster and Rosai (4), the tumors could be divided based on their morphologic features into those of low-grade and high-grade histology. It remains debatable whether some tumors in the low-grade category should be reclassified as moderately differentiated thymic epithelial neoplasms (atypical thymoma), a category that was not yet acknowledged at the time of publication of that study (4). The following are the categories of thymic carcinoma that have been described:

- **Squamous cell carcinoma** (well-differentiated and poorly differentiated, lymphoepithelioma-like carcinoma.)
- **Mucoepidermoid carcinoma** (Figure 6-5). (well, moderately, or poorly differentiated carcinoma).
- Clear cell carcinoma (Figure 6-6)
- Basaloid carcinoma (Figure 6-7)
- Adenosquamous carcinoma
- Small cell neuroendocrine carcinoma
- Sarcomatoid carcinoma
- Anaplastic carcinoma

The cytologic and architectural features of these tumors are essentially similar to those of their counter-

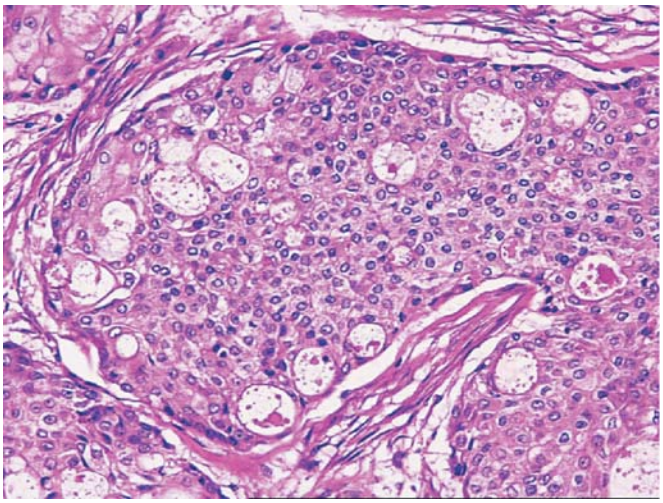

FIGURE 6-5. Poorly differentiated thymic epithelial neoplasm. This tumor has the features of a mucoepidermoid carcinoma. It is composed of islands of polygonal, epidermoid tumor cells containing cystic luminal spaces filled with mucin. There is no resemblance to the normal thymus.

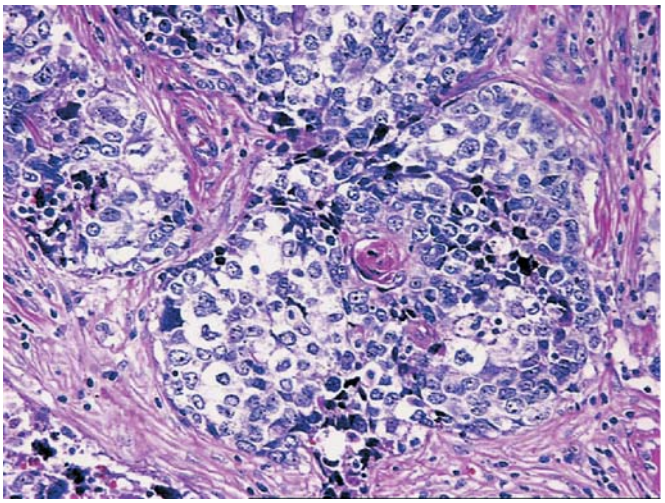

FIGURE 6-6. Clear cell carcinoma of the thymus. The tumor has clear cells, but also shows keratinization. The tumor does not display any of the organotypical features of differentiation of the normal thymus.

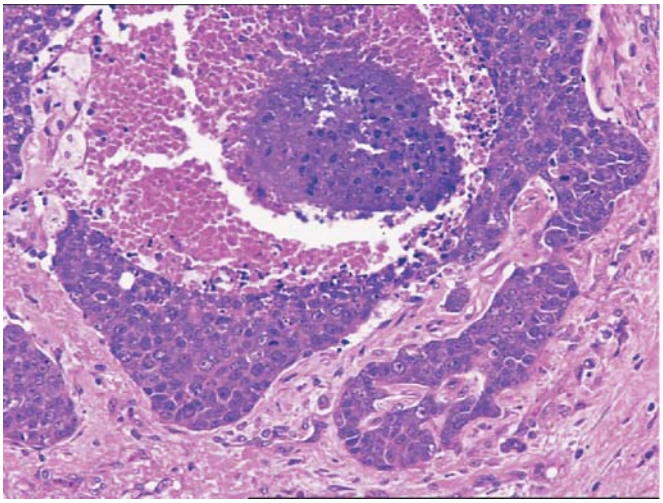

FIGURE 6-7. Basaloid carcinoma. This tumor displays hyperchromatic cells arranged into cohesive nests. There are also foci of necrosis.

parts in other organs (5). In general, thymic carcinoma is characterized by marked cytologic atypia, increased mitotic activity, and frequent areas of necrosis and vascular invasion.

Comments

1. There has been great controversy in the literature regarding the best approach to the classification of thymic epithelial neoplasms, which in recent years has centered on the issue of whether morphology alone is sufficient to predict the clinical behavior of these tumors. The consensus of opinion seems to be that morphology alone, particularly for the better differentiated (low-grade) variants of thymic epithelial neoplasms, is an unreliable predictor of clinical behavior, and that staging (i.e., the status of capsular integrity) is the most important parameter for the prediction of biologic behavior in these tumors.

2. The identification of moderately differentiated tumors (atypical thymoma) may be of significance, given their higher incidence of capsular invasion, the tendency for earlier recurrence, and the potential for transformation into a higher grade malignancy (1,4).

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7
Tumors of the Digestive System

Grace Guzman and Gregorio Chejfec

Introduction

The tumors of the tubular part of the digestive system, the liver, and the pancreas account for a significant portion of the day-to-day surgical pathology material in most diagnostic pathology laboratories. While many of these gastrointestinal tumors are microscopically identical to the homonymous tumors in other parts of the body, some are unique to the digestive system. This chapter reviews the grading of the most important neoplasms and related preneoplastic conditions of the digestive system.

Squamous Cell Carcinoma of the Esophagus

Two tumors, squamous cell carcinoma and adenocarcinoma, account for most of the malignant neoplasms of the esophagus. Other neoplasms are less common. All tumors, however, should be processed according to the recommendations formulated for optimal surgical pathology practice (1).

Squamous cell carcinomas of the esophagus, like other squamous cancers elsewhere, may be categorized by various grades based upon the relative proportions of keratinization, intercellular bridges, and primitive basal cells. A 3-grade system is generally accepted, in which the tumors are classified as well-differentiated or grade 1, moderately differentiated or grade 2, and poorly differentiated or grade 3.

- **Grade 1, well-differentiated squamous cell carcinoma.** Well-differentiated squamous cell carcinoma is composed of cells that closely resemble those in the normal squamous epithelium. Neoplastic cells in the center of tumor nests appear more mature and have more abundant eosinophilic cytoplasm in comparison to cells in the periphery. The cell-to-cell attachments (intercellular bridges) are well-defined. Keratin pearls (extracellular keratin arranged in whorls) are frequent. There is a paucity of compact basaloid cells.
- **Grade 2, moderately differentiated squamous cell carcinoma.** A moderately differentiated tumor has irregular nests and a higher proportion of primitive basal cells than that in well-differentiated tumors. The tumor cells, still recognizable as squamous, have less cytoplasm and form less keratin than those in well-differentiated tumors. Intercellular bridges are retained.
- **Grade 3, poorly differentiated squamous cell carcinoma.** Solid sheets lacking central keratin pearl formation characterize this tumor. The cells also form invasive tongues, columns, and strands extending into the underlying stroma. The tumor cells vary in size from small to large, and some have large, bizarre, polymorphic nuclei. The degrees of differentiation may vary considerably from area to area within a single tumor (Figure 7-1).

The key facts about these tumors are summarized in Table 7-1.

Comments

1. Moderately differentiated carcinomas account for almost 70% of all esophageal squamous carcinomas.
2. Various tumor grades may be seen in a single tumor, especially in grade 2 and 3 tumors.
3. The least differentiated component is the most important determinant of the prognosis for each tumors.

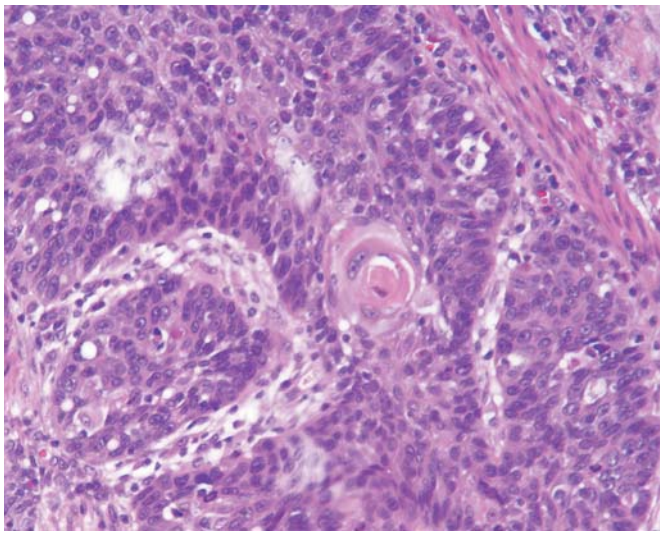

FIGURE 7-1. Squamous cell carcinoma of the esophagus. Poorly differentiated squamous cells show signs of focal keratinization.

Esophageal Adenocarcinoma and Its Precursors

Most adenocarcinomas of the esophagus develop from the intestinal epithelium forming the foci of metaplasia in Barrett esophagus. The sequence of events leading to the progression from normal intestinal epithelium to mild and severe dysplasia and intraepithelial carcinoma can be recognized in biopsy material. As summarized by Iacobuzio-Donahue and Montgomery (2005), the diagnosis is made by analyzing the following 4 aspects of these lesions: surface maturation, architecture, cytologic features, and inflammation and erosion of the epithelium (Figure 7-2).

- **Surface maturation.** In nondysplastic lesions, the basal glands of Barrett esophagus have larger nuclei than that in the surface epithelium. The nuclei on the surface tend to appear elongated and slim, and are located in the basal portion of the cytoplasm positioned perpendicularly to the basement membrane.
- **Architecture.** The nondysplastic lesions contain well-developed stroma surrounding the glands, which are of uniform shape and regularly distributed. Architectural abnormalities include crowding, back-to-back arrangement, cribriform glands, cystic dilatation, and necrotic debris.
- **Cytologic features.** Minor nuclear changes, such as nuclear enlargement and atypia, are part of intestinal metaplasia and are to be expected in the basal glands of Barrett esophagus. Significant dysplasia is characterized by an obvious enlargement of the nuclei, which become hyperchromatic, lose their polarity, and are arranged at random.
- **Inflammation and erosion.** Barrett esophagus is prone to inflammation that is often associated with surface erosions. Inflammation and regeneration of the epithelium may mask the neoplastic changes, but also may cause architectural distortion and nuclear changes that should not be confused with neoplastic atypia.

According to a consensus of gastrointestinal pathologists (see Iacobuzio-Donahue and Montgomery, 2005), esophageal biopsies containing the typical features of Barrett esophagus should be reported under 4 headings, as follows:

- **Barrett esophagus, negative for dysplasia.** In this lesion, there is appropriate surface maturation, and the glands are of uniform shape and enclosed in well-developed stroma. The nuclei have smooth contours and are polarized and located in the basal part of the well-developed cytoplasm. Nucleoli are not prominent. The cells contain and/or secrete mucin, albeit some mucin loss may be evident focally. Inflammation could induce reactive changes.
- **Barrett esophagus, indefinite for dysplasia.** The epithelium of this lesion shows good surface maturation, and there are only minor architectural abnormalities, such as the focal crowding of glands. The nuclei of basal glands show some hyperchromasia and slight irregularity of contour. Loss of nuclear polarity is not evident. Mitoses may be increased in the basal glands.
- **Barrett esophagus, low-grade dysplasia.** The surface epithelium of this lesion resembles the basal glands and shows only slight maturation. The glands are crowded, but still separated by connective tissue

TABLE 7-1. Microscopic grading of esophageal squamous cell carcinoma.

	Degree of differentiation		
Features	Well differentiated	Moderately differentiated	Poorly differentiated
Resemblance to normal epithelium	High resemblance	Still recognizable as squamous	Hardly recognizable as squamous
Keratin pearl formation	Frequent	Rare to none	None
Predominant cell population	Mature squamous	More basaloid, some squamous	Undifferentiated
Intercellular bridges	Distinct	Focally retained	Rare or none

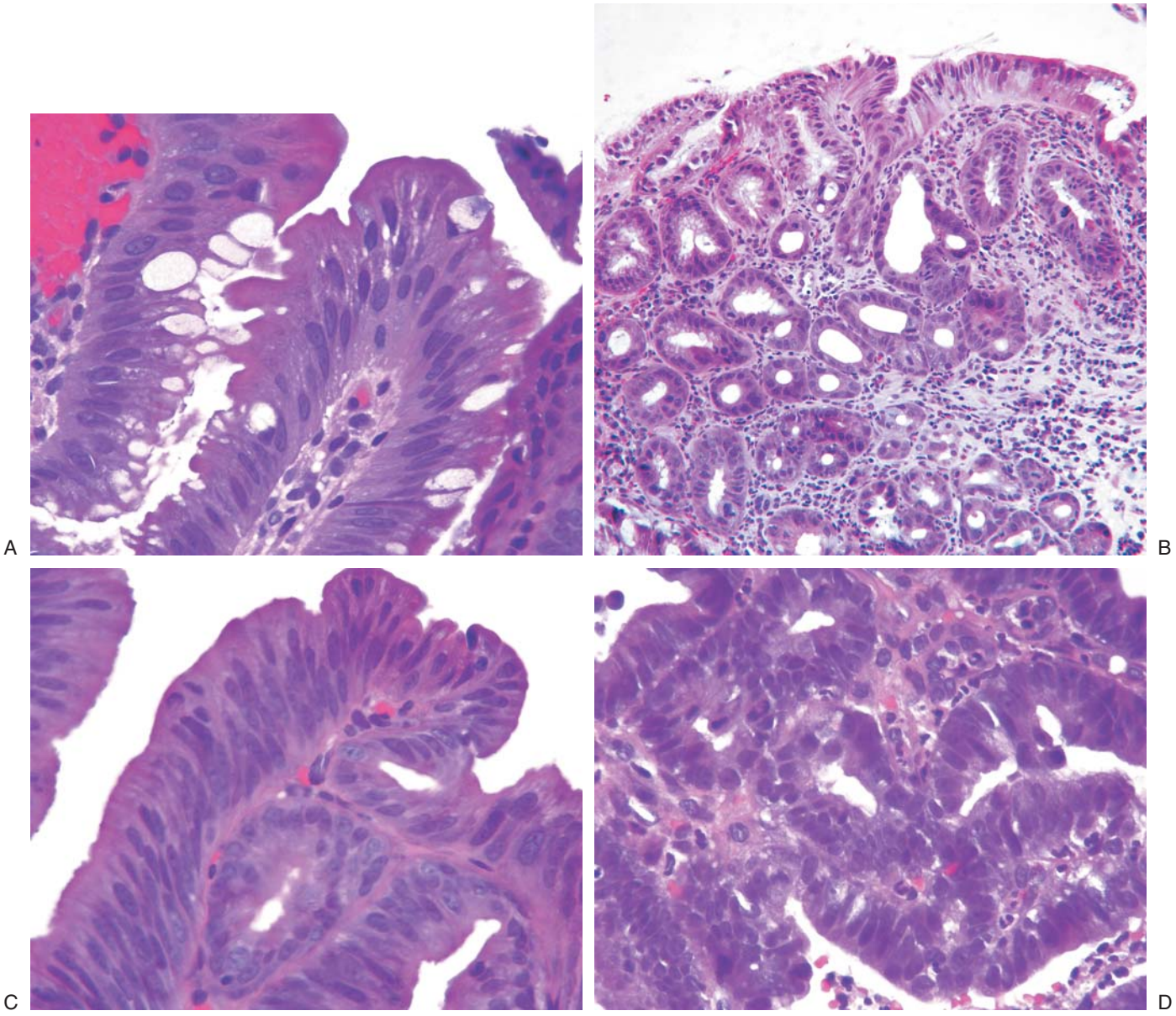

FIGURE 7-2. Barrett esophagus, with and without dysplasia. A. Barrett esophagus, indefinite for dysplasia. The surface epithelium reveals mild stratification of the nuclei and a depletion of mucus. There is no evidence of nuclear atypia. B. Barrett esophagus, low-grade dysplasia. At low magnification, it is possible to appreciate the complex branching pattern of the glands that appear crowded and irregular. However, the surface epithelium still shows regular stratification of the nuclei, which do not appear hyperchromatic and do not show severe atypia. C. Barrett esophagus, low-grade dysplasia. At higher magnification, the surface epithelium is lined by cells that have stratified nuclei with only mild atypia and hyperchromasia. D. Barrett esophagus, high-grade dysplasia. There is marked architectural disarray, and the glands are arranged back to back. The surface epithelium shows loss of nuclear polarity and hyperchromasia of vesicular and irregularly shaped nuclei.

stroma. The nuclei show hyperchromasia with chromatin clumping. The nuclei are still elongated, and even though they may have slightly irregular contours, they are still polarized. Nuclear stratification resembling the changes in tubular adenomas of the colon may extend all the way to the surface of the lesions. Nucleoli may be seen, but are not prominent.

- **Barrett esophagus, high-grade dysplasia.** Loss of surface maturation is the most important feature of this lesion. The glands appear crowded in the surface and basal parts of the epithelium, and the stroma is barely evident. The nuclei are often markedly enlarged and hyperchromatic. The chromatin is often clumped, and the nucleoli may be prominent. Nuclei have irregular

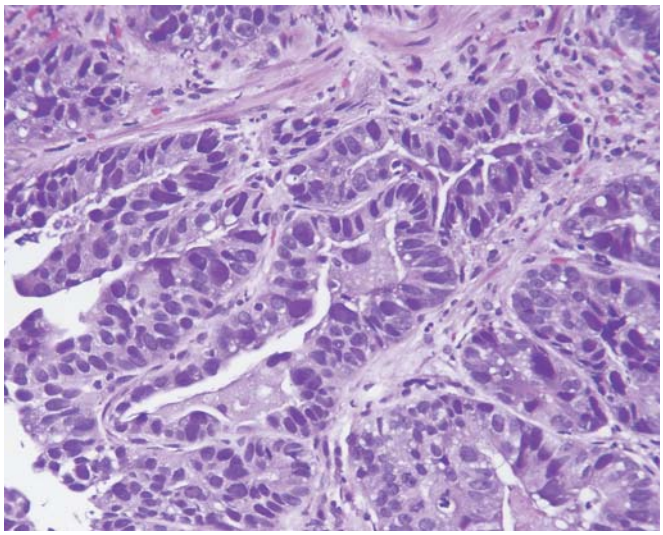

FIGURE 7-3. Adenocarcinoma of the esophagus. Atypical hyperchromatic cells form gland-like structures embedded in the connective tissue stroma.

contours, and there is obvious loss of nuclear polarity, which characteristically extends all the way to the surface of the lesions. Mitoses are prominent and may be seen in any part of the lesion. Typically, there is no or only minimal inflammation.

For intramucosal adenocarcinoma, the transition from dysplasia to carcinoma is gradual and is marked by subtle microscopic changes. Accordingly, Barrett esophagus with high-grade dysplasia may be difficult to separate from intramucosal carcinoma. These changes include extensive back-to-back growth of glands with a complete loss of intervening stroma, a syncytial growth pattern, and the separation of single cells lying freely in the stroma. Desmoplastic reaction is seen only after the intramucosal carcinoma invades the submucosa (Iacobuzio-Donahue and Montgomery, 2005).

Invasive esophageal adenocarcinomas are best graded using the guidelines of the American Joint Committee on Cancer (AJCC). According to this system, the tumors are graded by the proportion of fully formed glands seen in microscopic slides and classified as well-differentiated, moderately differentiated, and poorly differentiated (Figure 7-3). The key facts about these tumors are summarized in Table 7-2.

- **Well-differentiated carcinoma.** This tumor contains glands with open lumina in more than 95% of the total mass. The glands maybe regularly shaped, cystic, or tubular. The tumor cells are cuboidal or columnar. The nuclei are vesicular, with a coarse chromatin pattern and variable amount of eosinophilic or clear cytoplasm.
- **Moderately differentiated carcinoma.** This tumor forms glands in 50% to 95% of its mass. The tumor cells in nonglandular areas maybe arranged in irregular clusters or solid nests. The glandular regions show cribriform formation and extensive nuclear stratification.
- **Poorly differentiated carcinoma.** This tumor forms glands in 5% to 50% of its mass. Most of the cells are arranged into solid nests and invasive cords and sheets. Single cells invading the adjacent tissue also are found. The glands, if present, range from poorly formed to infiltrating the normal tissue and evoking an extensive desmoplastic fibrosis. The cells show considerable pleomorphisms and may assume signet ring-like features.

Comments

1. Various grades may be observed within a single tumor. If there is variation of histologic grade in the same tumor, the highest grade is designated to the tumor.
2. The majority of the tumors are moderately differentiated.
3. In early esophageal carcinoma, the histopathologic type (adenocarcinoma vs. squamous cell carcinoma) is an important independent prognostic factor.
4. Patients with early squamous cell carcinoma have a higher recurrence rate and are more often found to have a second primary tumor (2).
5. The depth of invasion in the esophageal wall and regional lymph node involvement were independent prognostic factors in the prognosis of patients with adenocarcinoma arising in Barrett esophagus (3,4).
6. The gross appearance and histologic differentiation were not found to impact prognosis.

TABLE 7-2. Features of adenocarcinoma of the esophagus.

Degree of differentiation	Extent of glandular	Appearance of glandular areas	Nonglandular differentiation areas
Well-differentiated	95	Cystic Tubular	Minimal to none
Moderately differentiated	50–95	Irregular glands	Solid or cribriform
Poorly differentiated	5–50	Narrow or cords Signet-ring cell	Solid sheets Desmoplasia

Gastric Adenocarcinoma

Adenocarcinoma is the most common malignant tumor of the stomach (Lewin and Appelman, 1996). Several systems have been proposed for classifying and grading these tumors. These classifications are known eponymously as the Ming (5), Lauren (6), and Goseki (7) classifications.

The Ming classification of gastric carcinomas is based on the pattern of tumor growth and infiltration (5). This 2-tiered classification divides gastric tumors into those that show an expansile pattern of growth, and those with an infiltrative growth pattern. The expansile growth pattern comprises about three-quarters of gastric carcinomas. These are well-differentiated intestinal-type adenocarcinomas with good prognosis. They are characterized by well-formed tubular glands with a clear-cut demarcation of infiltration between the tumor and the surrounding uninvolved stroma. On the other hand, the infiltrative type of carcinoma is more aggressive, characterized by tumor cells growing individually or in small clusters.

The Lauren classification divides tumors into 3 groups: tumors of intestinal type, tumors of diffuse type, and tumors of mixed type (Figure 7-4). Diffuse-type tumors are associated with a significantly worse prognosis than are intestinal-type tumors. The prognostic value of the Lauren classification is independent of the tumor stage.

The Goseki classification is 4-tiered and based on combining 2 of the morphological characteristics of gastric cancer, the degree of differentiation of the glandular tubules, and the amount of mucus in the cytoplasm (7). The groupings are as follows:

- **Group I.** This tumor shows good tubular differentiation. Tumor cells contain sparse mucus in the cytoplasm, or no mucus at all.
- **Group II.** This tumor shows good tubular differentiation. The mucus in the tumor cell cytoplasm is abundant.
- **Group III.** This tumor shows poor tubular differentiation. The cells do not contain mucus in their cytoplasm.
- **Group IV.** This tumor shows poor tubular differentiation. The cells contain abundant mucus in their cytoplasm.

Recent studies have found that the Goseki grading identifies subgroups of patients with a poorer prognosis than is predicted by TNM (tumor, nodes, metastasis) staging alone (8).

Irrespective of the classification system used, gastric adenocarcinoma can be further classified using a 3-tiered system that distinguishes the degree of resemblance to gastric or metaplastic intestinal glands. Tumors are graded as well-differentiated, moderately differentiated, or poorly differentiated (9).

- **Grade 1, well-differentiated adenocarcinoma.** This tumor has well-formed glands or papillae lined by mature cells of absorptive or goblet cell origin.
- **Grade 2, moderately differentiated adenocarcinoma.** This tumor features irregularly branching glands or complex or incomplete papillae.
- **Grade 3, poorly differentiated adenocarcinoma.** This tumor is characterized by poorly formed glands or infiltrating single cells.

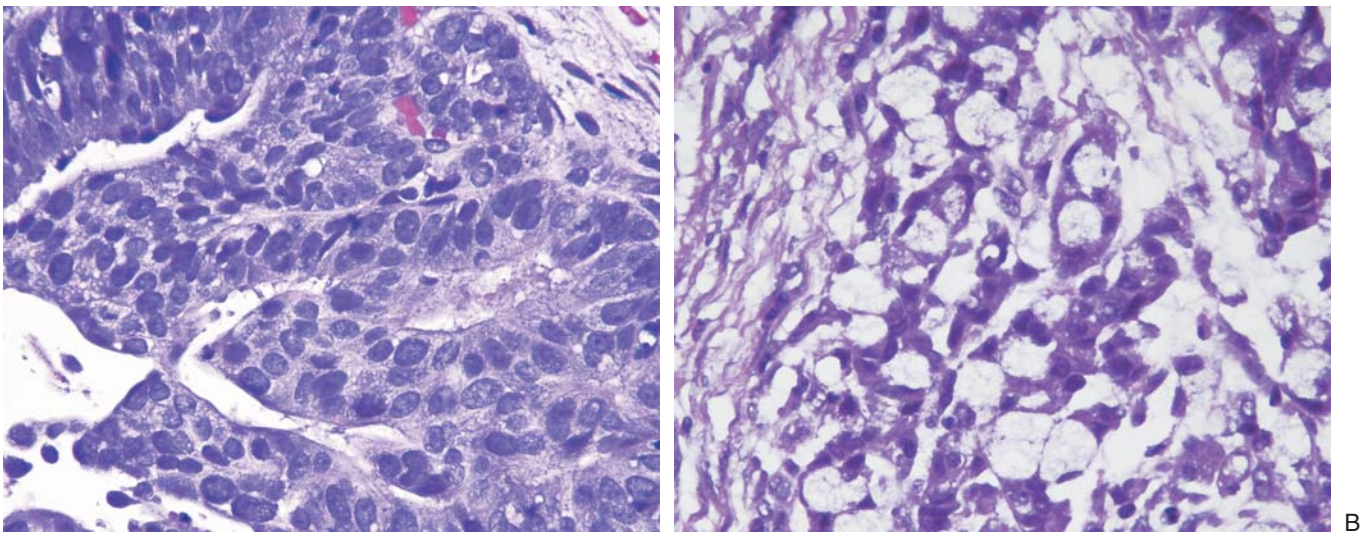

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FIGURE 7-4. Adenocarcinoma of the stomach. A. An intestinal-type tumor forms gland-like structures and resembles colonic carcinoma. B. Diffuse-type carcinoma is composed of signet ring cells growing without a distinct pattern.

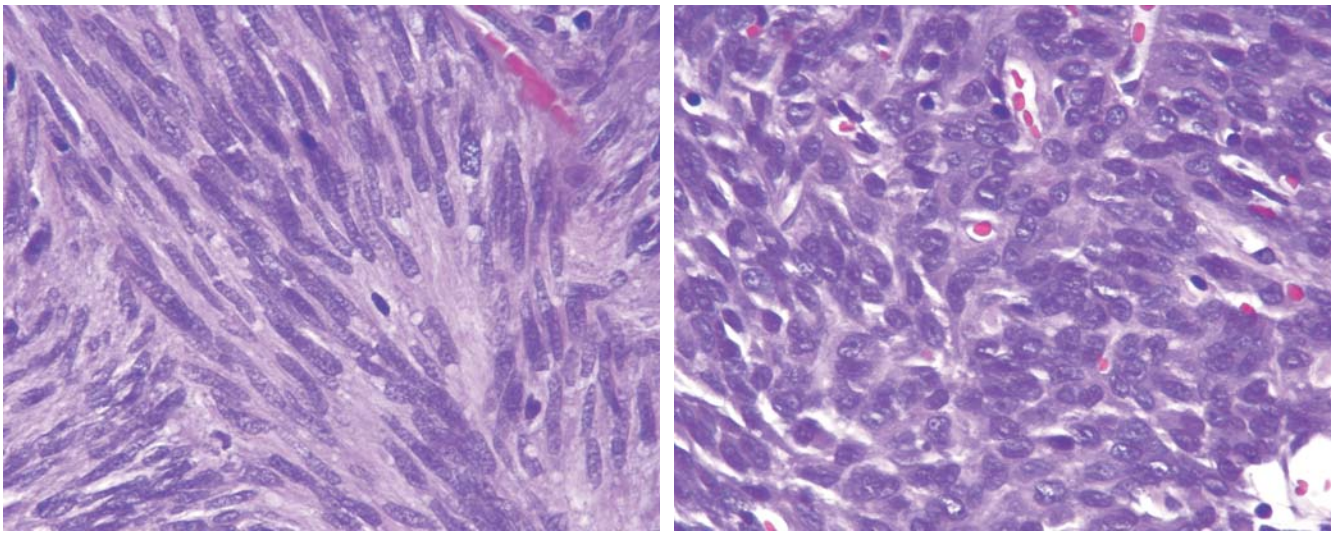

FIGURE 7-5. Gastrointestinal stromal tumor. A. A tumor composed of cells with abundant eosinophilic cytoplasm. B. A tumor composed of crowded cells that have less abundant cytoplasm.

Comments

1. Undifferentiated carcinomas do not display any differentiating features and may resemble other tumors such as lymphoma, poorly differentiated squamous carcinoma, or sarcomas. Immunohistochemical positivity for cytokeratins may be necessary to identify the epithelial nature of these tumors (10).
2. The Lauren classification provides prognostic indicators that are independent of the tumor grade and other data gathered about gastric adenocarcinoma.

Gastrointestinal Stromal Tumors

Mesenchymal tumors of the stomach are divided into 2 major groups. The first comprises the tumors that originate and/or are composed of cells that are ubiquitous, such as fibroblasts, fat cells, or endothelial cells. Tumors of this group, such as lipomas, schwannomas, and others, as well as their malignant counterparts do not differ from homonymous tumors in other parts of the body. The second group includes gastrointestinal stromal tumors (GIST), a type of neoplasia that predominantly occurs in the gastrointestinal tract and the abdominal cavity.

Gastrointestinal stromal tumors (GIST) are tumors of unknown histogenesis, which remain controversial. The tumors are composed of spindle-shaped cells that may have a well-developed or rather scant cytoplasm (Figure 7-5). Some have an epithelioid appearance, whereas others appear anaplastic. A definitive diagnosis usually requires immunohistochemical data and/or molecular biology facts. Most notably, these spindle cell tumors react with the antibodies to CD-117 and express mutations of c-KIT, encoding the receptor for a stem cell factor, or platelet-derived growth factor receptor α (PDGFRA), a receptor for the platelet-derived growth factor (11,12).

GISTs may be clinically benign or malignant. The guidelines for their grading, formulated by the panel of experts convened by the National Institutes of Health (NIH), are presented in Table 7-3.

TABLE 7-3. The NIH guidelines for the assessment of the risk for metastasis and adverse outcome of GIST.

Size	Mitoses/50 hpf*	Risk for metastasis
Small tumors (<2 cm)	Absent	Very low risk
2–5 cm	<5	Low risk
<5 cm	6–10	Intermediate risk
5–10 cm	<5	
Large tumors >5 cm	>50	High risk
10 cm	Any mitotic rate	
Any size	>10	

Abbreviations
hpf—high-power field

Source: Modified from Fletcher et al., 2002.

Colorectal Adenocarcinoma

Colorectal carcinoma is the most common malignant tumor of the digestive tract and the third leading cause of cancer-related deaths in the United States. At the time of diagnosis, approximately one-half of colorectal carcinoma patients already have metastases. Most tumors are classified as adenocarcinomas (13).

The grading of colonic adenocarcinoma is based on the proportion of tumor composed of well-defined glands relative to that of displaying solid sheets of tumor cells, poorly formed glands, or infiltrating individual tumor

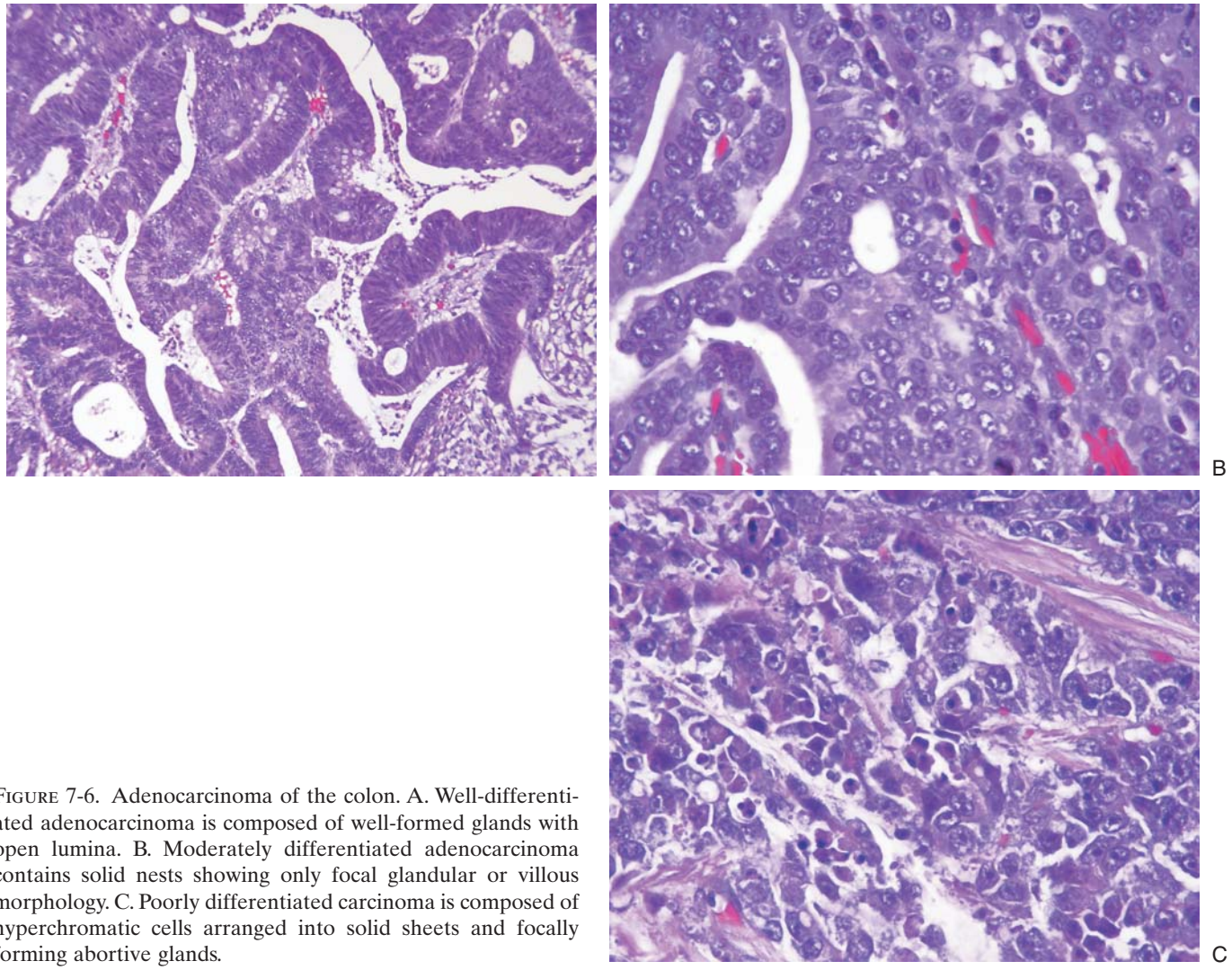

FIGURE 7-6. Adenocarcinoma of the colon. A. Well-differentiated adenocarcinoma is composed of well-formed glands with open lumina. B. Moderately differentiated adenocarcinoma contains solid nests showing only focal glandular or villous morphology. C. Poorly differentiated carcinoma is composed of hyperchromatic cells arranged into solid sheets and focally forming abortive glands.

cells (Figure 7-6). The grading of colorectal carcinoma pertains only to adenocarcinoma of the usual type. Signet-ring cell carcinoma and small cell carcinoma are always classified as poorly differentiated. Some authors consider mucinous adenocarcinoma (where mucin is equal or greater than 50% of the total surface area in the slides) as poorly differentiated.

The grading system as presented in the World Health Organization monograph (Hamilton and Aaltonen, 2000) on colonic adenocarcinoma is summarized in Table 7-4.

TABLE 7-4. Grading of colonic adenocarcinoma.

Grade	Differentiation	AJCC	% Glands descriptive grade
1	Well differentiated	Low grade	95
2	Moderately differentiated	Low grade	50–95
3	Poorly differentiated	High grade	>50
4	Undifferentiated	High grade	>5%

According to this system, colonic tumors can be assigned a grade on a scale from 1 to 4, as follows:

- **Grade 1, well-differentiated adenocarcinoma.** This tumor is composed of well-formed glands which comprise greater than 75% of the tumor mass. The tumor cells do not show a high-grade nuclear morphology. AJCC recommends that such tumors be designated as low grade.
- **Grade 2, moderately differentiated adenocarcinoma.** In this tumor, glands account for 50% to 75% of the mass. AJCC recommends designating these tumors as low grade.
- **Grade 3, poorly differentiated adenocarcinoma.** Well-formed glands comprise less than 50% of the tumor mass. The AJCC recommends designating grade 3 tumors as high grade.
- **Grade 4, undifferentiated carcinomas.** This is a distinct tumor subtype that has less than 5% glands, or shows almost no glandular differentiation. Signet ring carcinomas belong to this category. The AJCC recommends designating grade 4 tumors as high grade.

Using this classification, most colonic adenocarcinomas are designated as moderately differentiated, which account for 70% of all colonic tumors. Those classified as well-differentiated or poorly differentiated adenocarcinomas account for the remaining 30%.

Comments

1. Epidermal growth factor receptor (EGFR) is expressed in up to 75% of colorectal cancer tumors (14). In the near future, identification of EGFR should be common practice in the pathology work-up of colorectal carcinomas.
2. The term adenocarcinoma is used only for neoplastic lesions that invade through the muscularis mucosae and should not be applied to intramucosal lesions seen in adenomatous polyps (Odze et al., 2004). "Severe dysplasia" is the preferred term for the lesions that were previous called intraepithelial adenocarcinoma or carcinoma in situ.
3. Dysplasia is a precursor of adenocarcinomas that develop in ulcerative colitis and Crohn disease. Dysplastic changes may be reliably identified with the microscopic examination of colorectal biopsies (15), which are periodically performed on these patients. The biopsy findings in patients with chronic inflammatory bowel disease are reported as follows:
   - **Negative for dysplasia.** Special attention should be paid to the surface epithelium, which in these cases shows normal maturation. One should ignore the regeneration-related changes in the basal parts of the crypts, which may resemble adenomatous epithelium.
   - **Indefinite for dysplasia.** This category is reserved for instances when reactive changes cannot be differentiated from neoplastic changes with certainty. In such cases, the nuclei of regenerating cells appear slightly hyperchromatic and may acquire enlarged nucleoli. Yet they remain elongated, and there is surface maturation, which may not always be evident in a small biopsy.
   - **Positive for dysplasia, low grade.** This diagnosis is made in biopsies that show minimal distortion of the normal architecture of the colonic mucosa, which may even appear normal. The cell nuclei appear hypochromatic, overlapping each other, and pseudostratified, thus resembling those in tubular adenomas. The surface epithelium is usually flattened or protruding, with a reduced number of goblet cells. Generally, mitoses are easily found and are not limited to the basal part of the crypts.
   - **Positive for dysplasia, high grade.** This lesion is characterized by a loss of normal mucosal architecture and more pronounced nuclear changes than that seen in low-grade dysplasia. The normal mucosa is replaced by irregular glands in a back-to-back or cribriform arrangement. The nuclei vary in size and shape, appear irregularly hyperchromatic, and show a loss of polarity. Mitoses are more numerous than that in mild dysplasia, and they may be atypical. These changes extend all the way to the surface of the epithelium.

It is worth noting that invasive adenocarcinomas may develop in the course of chronic inflammatory bowel disease, showing either low-grade or high-grade dysplasia, but more often occurring in the context of high-grade dysplasia.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is not a common tumor in the United States, but worldwide it has a high prevalence, especially in parts of Africa and Asia. All cirrhotic patients of any etiology are at risk for the development of HCC, making it the fifth most common malignancy worldwide (Hamilton and Aaltonen, 2000).

HCC is most often of the classical type, in which the cells retain some resemblance to normal liver cells. Several other microscopic subtypes have been recognized, including the following:

- Clear cell
- Small cell
- Spindle cell
- Sclerosing
- Fibrolamellar
- Mixed hepatocellular-cholangiocellular carcinoma

The classical type of HCC may be classified as well-differentiated, moderately differentiated, or poorly differentiated (Figure 7-7).

- **Well-differentiated hepatocellular carcinoma.** This tumor measures less than 2 cm. There is minimal cytologic atypia and an increased nuclear-cytoplasmic ratio. The pattern is usually trabecular or pseudoglandular.
- **Moderately differentiated hepatocellular carcinoma.** This is the most common grade of HCC, usually seen in lesions greater than 3 cm. Pseudoglandular and trabecular patterns characterize this tumor. The nuclei are vesicular, hyperchromatic, and contain well-defined nucleoli.
- **Poorly differentiated hepatocellular carcinoma.** This form of HCC is composed of pleomorphic and even giant cells, usually arranged in solid nests. In poorly differentiated tumors, the blood vessels may be slit-like and the sinusoidal pattern is lost.

Comment

1. Most HCC develop in the background of cirrhosis. Invasive carcinoma is often associated and most likely preceded by premalignant changes that are poorly

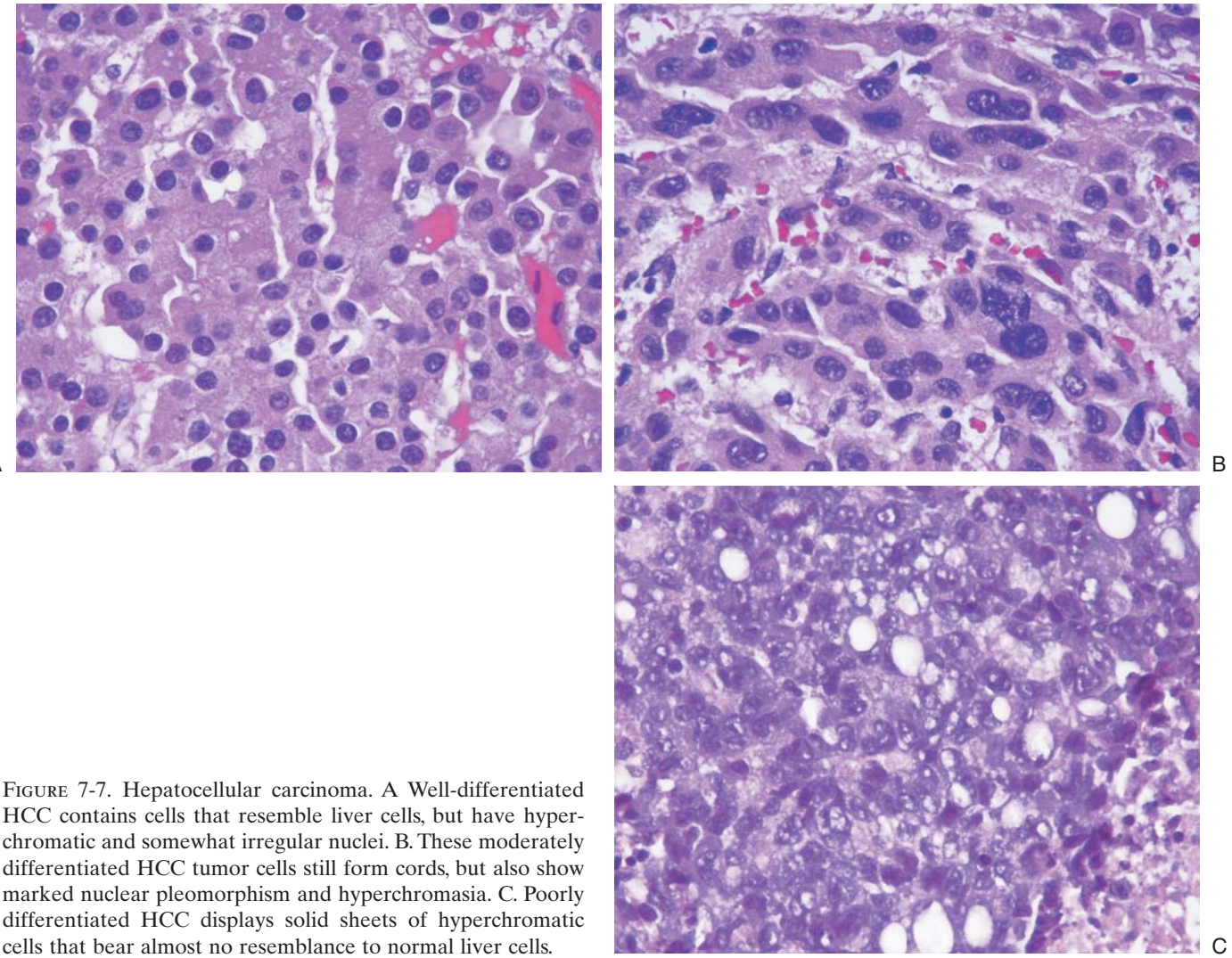

Figure 7-7. Hepatocellular carcinoma. A Well-differentiated HCC contains cells that resemble liver cells, but have hyperchromatic and somewhat irregular nuclei. B. These moderately differentiated HCC tumor cells still form cords, but also show marked nuclear pleomorphism and hyperchromasia. C. Poorly differentiated HCC displays solid sheets of hyperchromatic cells that bear almost no resemblance to normal liver cells.

defined and controversial. These lesions known under a variety of names, such as atypical adenomatous hyperplasia, small cell dysplasia, and large cell dysplasia, need to be distinguished from invasive HCC.

2. For many years, histological criteria have been the basis for diagnosis in HCC, but recently criteria which rely on imaging techniques have been devised, especially when associated with an elevation of serum alpha-fetoprotein (AFP) in excess of 400 ng/ml. (16)

Intrahepatic Cholangiocarcinoma

Cholangiocarcinoma is a relatively rare tumor in the United States, but it occurs more often in parts of Asia. This tumor may be graded as well-, moderately, or poorly differentiated, depending on the ability of the tumor to form glands and the degree of cytological and architectural abnormalities (Figure 7-8).

- **Well-differentiated cholangiocarcinoma.** Cuboidal cells form uniform glands and papillary structures in this tumor. The cells may contain mucus, or may be oncocytic or undergo squamous differentiation. The stroma is moderately well-developed, but some tumors may be highly desmoplastic.
- **Moderately differentiated cholangiocarcinoma.** This tumor is composed of cells showing more pleomorphisms. The cells form irregular glands, cribriform ductlike structures, cords, and solid nests. Desmoplastic stroma may be abundant.
- **Poorly differentiated cholangiocarcinoma.** This tumor has pleomorphic, hyperchromatic cells arranged into solid sheets, strands, and nests, and only focally forming cribriform glands. Some tumors are sarcomatoid, with spindle-shaped cells that almost imperceptibly intermingle with stromal cells. Desmoplastic reaction may sometimes completely overshadow the tumor cells, making them hard to find.

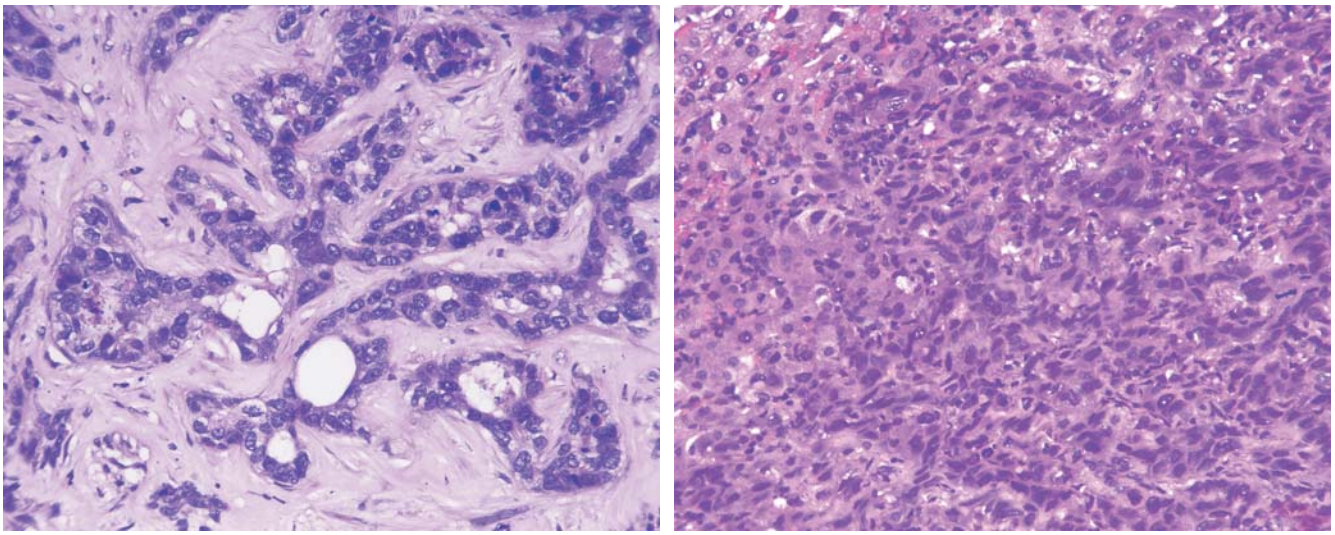

FIGURE 7-8. Cholangiocellular carcinoma. A. Well-differentiated carcinoma is composed of cuboidal cells forming irregular glands. B. Poorly differentiated carcinoma contains hyperchromatic cells arranged into solid sheets and cords.

Adenocarcinoma of the Biliary System and Gallbladder

Adenocarcinoma of the gallbladder may be graded as well-, moderately, and poorly differentiated tumors. This tumor is graded like the intrahepatic cholangiocarcinoma.

Adenocarcinoma of the Pancreas

Adenocarcinoma is the most common malignant tumor of the pancreas, and most of them arise from the ducts. Other tumors are less common, including mixed ductal-endocrine carcinoma, mucinous noncystic carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, intraductal papillary-mucinous carcinoma, invasive papillary-mucinous carcinoma, and acinar cell carcinoma.

The current grading scheme for pancreatic ductal adenocarcinoma (Klöppel's grading scheme, also endorsed by WHO) entails evaluation of gland-tubule formation, mucin production, mitotic count, and nuclear atypia (17). According to the refined WHO criteria (Hamilton and Aaltonen, 2000), the histopathological grade of pancreatic ductal carcinoma is an important independent prognostic factor, but the reproducibility of the grading depends on the expertise of the observer. Criteria that relate to cellular and structural differentiation seem to be more predictive than those related to proliferation (Table 7-5).

The histologic grading of pancreatic ductal adenocarcinoma recommended by AJCC uses a grading system from 1 to 4, as follows:

- **Grade 1, well-differentiated adenocarcinoma.** More than 95% of the tumor cells are arranged into ducts or glands.
- **Grade 2, moderately differentiated adenocarcinoma.** Between 50% and 95% of the tumor cells are arranged into ducts or glands. Ducts and glands are more numerous than solid cords and nests.
- **Grade 3, poorly differentiated adenocarcinoma.** Between 5% and 50% of the tumor cells are arranged into ducts or glands. Solid nests and cords are more numerous than the well-formed ducts and glands.
- **Grade 4, undifferentiated adenocarcinoma.** Fewer than 5% of all tumor cells are arranged into ducts or glands. The tumor consists predominantly of solid sheets of cells.

TABLE 7-5. Grading of pancreatic adenocarcinoma according to the scheme proposed by Klöppel and adopted by WHO.

Tumor grade	Differentiation	Mucin production	Mitoses	Nuclear pleomorphism
1.	Well-differentiated	Abundant	<5/10 hpf	Mild
2.	Moderately differentiated	Irregular	6-10/10 hpf	Moderate
3.	Poorly differentiated	Scant	>10 hpf	Marked

Abbreviation:
Hpf—high-power field
Source: Hamilton and Aaltonen, 2000.

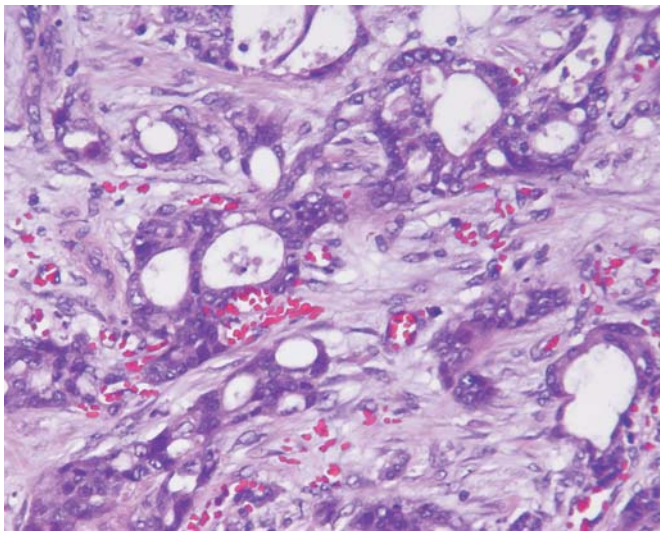

FIGURE 7-9. Adenocarcinoma of the pancreas. This grade 2 tumor is composed of low cuboidal cells forming inter-anastomosing glands that focally fuse into solid cords.

Most ductal carcinomas of the pancreas are well- to moderately differentiated (Figure 7-9). The interobserver variation in using these grading systems is considerable, limiting their usefulness. A new 3-tiered grading scheme, based on a simplified Gleason system for grading prostatic carcinomas, was proposed recently by Adsay et al. (18), but its reproducibility and advantages remain to be independently confirmed.

Comments

1. In most instances, invasive carcinoma of the pancreas is preceded by an intraductal carcinoma in situ, which is called pancreatic intraepithelial neoplasia (19).
2. Intraductal papillary-mucinous neoplasm (IPMN), a lesion that in approximately 30% of the cases is associated with invasive pancreatic adenocarcinoma, should be reported as:
   - IPMN-adenoma (low grade)
   - IPMN with moderate dysplasia
   - IPMN with severe dysplasia/carcinoma in situ
3. The participants of an international consensus study (20) have recommended that the IPMN be classified according to the type of epithelium found in the lesions, as listed in Table 7-6.

TABLE 7-6. Classification of pancreatic intraductal papillary-mucinous neoplasms.

Type of epithelium	Description	Degree of atypia
Gastric	Gastric foveolar-like epithelium	Low grade
Intestinal	Colonic villous adenoma-like	Moderate or high grade
Pancreatobiliary	Complex branching papillae with amphophilic, hyperchromatic cells	High grade
Oncocytic	Complex papillae with oncocytic cells with eosinophilic cytoplasm, round nuclei with nucleoli	High grade

Source: Furukawa et al., 2005.

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8
Tumors of the Endocrine System

Ivan Damjanov

Introduction

The grading of endocrine gland tumors has been difficult, inconsistent, and unrewarding. While the reasons for these problems vary from organ to organ, and from one tumor type to another, in general grading has been hampered by the following issues:

- In many endocrine organs, the transition of hyperplasia to benign neoplasia and then to malignancy includes a spectrum of morphologic changes that are not always easily defined.
- The proposed grading systems are often complex and include a number of variants that are not acceptable to all pathologists. The lack of consensus among pathologists has been one of the main hindrances to grading endocrine tumors.
- The correlation between the microscopic grading and the prognosis of tumors is often poor, and therefore with a few notable exceptions, clinicians do not find the pathologic grading of endocrine tumors to be as useful as that for tumors of other organs systems.

Pituitary Tumors

Most pituitary tumors are classified as adenomas, which are further subtyped as hormonally active or inactive. Hormonally active adenomas are classified on the basis of laboratory and immunohistochemical data as prolactinomas, growth hormone–secreting adenomas, corticotrophic adenomas, gonadotrophic adenomas, thyrotrophic adenomas, and plurihormonal mixed tumors.

Small tumors measuring less than 10 mm in diameter are called microadenomas; those that exceed 10 mm in diameter are macroadenomas. Some macroadenomas have an aggressive growth and tend to recur after surgical resection. Pituitary carcinomas with extracranial metastases are extremely rare (1).

Microscopic grading of pituitary tumors is of no clinical value, because it is not possible to predict which tumors will be aggressive and recur after surgical resection and which will be cured by the initial surgery.

Comments

1. The aggressiveness of pituitary adenomas cannot be predicted from their histologic appearance. Thus,one can disregard the following microscopic findings:
   - Areas of necrosis
   - Bizarre enlarged nuclei
   - Ring or giant nuclei
   - Prominent nucleoli
   - Mitotic figures
2. Prognostic indicators have been reviewed recently by Suhardja et al. (2). The use of modern techniques, such as DNA flow cytometry, has been found to be of no clinical predictive value in assessing the invasiveness or persistence/recurrence pituitary tumors (3).

Thyroid Tumors

Thyroid tumors are classified as benign or malignant. Thyroid adenomas outnumber carcinomas, which account for less than 1% of all thyroid neoplasms.

Thyroid carcinomas are a heterogeneous group of tumors that occur in many histologic forms. Papillary carcinoma accounts for approximately 80% of all such carcinomas, and along with follicular carcinoma, medullary carcinoma, and undifferentiated (anaplastic) carcinoma form the majority of all thyroid tumors seen in general surgical pathology practice. The grading of thyroid tumors is of relative limited clinical significance.

Comments

1. Papillary carcinoma of the thyroid may be graded microscopically (4,5). However, this grading system has not been widely used, and recent reviews of the prognostic factors indicate that the size of the tumor and TNM (tumor-nodes-metastasis) staging are still the best predictors of tumor recurrence or resistance to therapy (6–9).

2. Although follicular carcinoma cannot be graded adequately, the insular component, poorly differentiated carcinoma, the trabecular component, the serum thyroglobulin level before surgery, the patient's age at the time of presentation, the solid component, and vascular invasion have adverse prognostic implications (10,11). The search for insular components seems to be warranted, since this pattern of growth has proven to be an independent risk factor. Hürthle cell pattern also has an adverse prognosis (11).

3. Medullary carcinoma cannot be reliably graded. Nevertheless, it has been observed that certain microscopic findings correlate well with the aggressiveness of these tumors (12). These findings include:
   - High mitotic activity
   - Foci of necrosis
   - Small cell type
   - Squamous differentiation

   The prognosis is adversely affected by the finding of intravascular invasion, perineural invasion, extrathyroidal extension, and lymph node metastases (13). The use of molecular biology and other probes has not contributed significantly to predicting the outcome of treatment (13,14).

4. Undifferentiated carcinoma has an overall poor prognosis. Advanced age of the patient, the presence of necrosis (either focal or extensive), and mitotic count of more than 3 per 10 high-power fields (hpf) are associated with the worst outcome (15).

Parathyroid Tumors

Most parathyroid tumors are benign; parathyroid carcinomas are rare and may occur in both the usual location and ectopically (16,17). Microscopic grading of parathyroid tumors is not warranted, but the pathologist may be asked to contribute to a clinicopathologic effort to distinguishing parathyroid adenoma from parathyroid carcinoma.

Comments

1. Parathyroid adenomas often contain cells with enlarged hyperchromatic nuclei, but these nuclear changes are not a sign of malignancy (18).
2. The clinical and pathologic features favoring the diagnosis of parathyroid carcinoma are:
   - Large size of the tumor
   - Adhesion of a hard tumor to adjacent structures
   - Extremely high serum levels of calcium and parathyroid hormone
   - Persistence of hyperparathyroidism after surgery
   - Microscopic invasion of the capsule and adjacent tissues
   - Vascular invasion
   - Fibrous bands subdividing the tumor into segments
   - Spindle shaped nuclei of tumor cells
   - Mitotic activity
   - High labeling indices with MIB-1 antibodies
3. Many parathyroid tumors thought to be malignant do not recur, and better criteria to distinguish aggressive from nonaggressive parathyroid tumors need to be developed (19).

Adrenal Cortical Tumors

Adrenal cortical tumors can be benign or malignant, hormonally active or inactive (20). Most adrenocortical tumors are benign, and so are classified as adenomas. Adrenocortical carcinomas are rare, with an incidence in the population of 0.5 to 2.0 cases per million.

The malignancy of adrenal cortical carcinomas is not routinely graded. However, microscopic analysis is useful for distinguishing a malignant tumor from a benign adenoma.

Comments

1. The distinction of adrenocortical adenomas from carcinomas is not always simple. The tumor size is important: those weighing more than 50 g and measuring 5 cm or more at the greatest diameter are most likely malignant, whereas those that weigh less and are smaller are usually benign.

2. Several microscopic systems have been proposed to make the distinction more precise. Lau and Weiss (19) recently reviewed 4 of the most widely used systems. Here we present only the system developed by Weiss, because it is the simplest and the easiest to use.

3. The Weiss system for diagnosing adrenal cortical carcinoma and separating it from adrenal cortical adenoma requires finding at least 3 criteria from the following list:
   - High nuclear grade
   - Mitotic rate exceeding 5 mitoses per 50 hpf
   - Atypical mitoses
   - Cells with clear cytoplasm accounting for more than 25% of all cells

- Diffuse growth pattern in more than 30% of the tumor
- Necrosis
- Invasion into the veins
- Invasion into the sinusoids
- Invasion into the capsule

The nuclei are graded according to the system developed by Fuhrman for renal carcinoma, and "high nuclear grade" corresponds to Fuhrman grades 3 and 4. Aubert et al. (20) applied this system to their own material and found a correlation with clinical outcome in 98% of the cases. The same authors reported that immunohistochemical staining with MIB-1 also may help in predicting the malignancy of adrenocortical tumors.

Adrenal Medullary Tumors

Adrenal medullary tumors comprise 2 groups: peripheral neuroblastic tumors (pNT), including neuroblastoma, ganglioneuroblastoma, and ganglioneuroma, and pheochromocytomas, i.e., tumors composed of chromaffin cells that resemble adult medullary adrenal cells. Grading is an important part of the pathologic work-up of peripheral neuroblastic tumors. Pheochromocytomas are not graded microscopically, but microscopic study of these tumors may help in distinguishing the benign from the malignant.

Peripheral Neuroblastic Tumors

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma are tumors derived from immature sympathetic neuroblasts (21,22). Neuroblastomas most often occur in the adrenals of infants and children, and less commonly in the extra-adrenal locations of the abdomen and thoracic cavity. Ganglioneuroblastomas and ganglioneuromas also can occur in the adrenals, but more often are found in extra-adrenal sites.

For practical purposes, these tumors are grouped under the heading of peripheral neuroblastic tumors and stratified according to the criteria of the International Neuroblastoma Pathology Classification (INPC). The INPC is based on the system developed by Shimada et al. (23) in 1984 and revised subsequently to incorporate molecular/genetic indicators (24–27).

On the basis of clinical, pathologic, and genetic/molecular findings, pNT are classified as tumors with favorable indicators or unfavorable indicators (Table 8-1). By combining these 5 indicators, these patients can be subdivided into 3 groups: low risk, intermediate risk, and high risk (23–25).

The microscopic grading system is based on analysis of the differentiation of tumor cells into Schwann cell-rich stroma and by estimating the proliferative capacity of tumor cells by calculating the mitosis-karyorrhexis index (MKI).

Table 8-1. Classification of peripheral neuroblastic tumors according to the prognostic parameters.

Parameter	Favorable	Unfavorable
Age at diagnosis	Less than 1 year	1 year or more
Clinical stage	Stage 1 or 2 or 4S	Stage 3 or 4
Histopathology	Favorable	Unfavorable
MYCN oncogene	Nonamplified	Amplified
DNA ploidy	Hyperdiploid	Diploid
Urinary catecholamines	Elevated	Low

Source: Modified from Wenig et al. (1997) and Shimada et al (21).

The first step in the classification includes gross examination of tumors for the presence of nodules and a microscopic examination to determine the extent of schwannian differentiation. According to the degree of schwannian differentiation, pNT can be subdivided into 2 major groups (Figure 8-1): tumors that contain less than 50% of schwannian stroma (called "schwannian stroma-poor," or "stroma poor"), corresponding to neuroblastomas, and those with more than 50% of schwannian stroma ("schwannian stroma-rich or dominant," or "stroma rich"), ganglioneuromas, and ganglioneuroblastomas.

Stroma-Rich Peripheral Neuroblastic Tumors

The second step for evaluating schwannian stroma-poor pNT (neuroblastomas) is to analyze them microscopically and classify them into 3 groups undifferentiated, poorly differentiated, and differentiating neuroblastoma (Figure 8-2).

- **Neuroblastoma, undifferentiated**. This tumor is composed of undifferentiated cells whose neuroblastic nature can be definitely proven only by additional immunohistochemical or ultrastructural studies. These neuroblasts have small to medium-size nuclei surrounded with scant cytoplasm that has indistinct borders. The nuclei contain finely granular or stippled ("salt and pepper") chromatin and occasional nucleoli. There is no discernible neuropil between the cells. Foci of necrosis, exudates of fibrin, or collagenous stroma may be seen but should not be mistaken for schwannian differentiation.
- **Neuroblastoma, poorly differentiated**. This tumor contains undifferentiated neuroblasts but also has streaks of neuropil corresponding to focal schwannian differentiation. Up to 5% of all tumor cells differentiate into ganglion cells. These ganglion cells must be distinguished from neuroblasts that have pleomorphic and anaplastic or bizarre nuclei and multiple nucleoli. The extent of neuropil formation varies from tumor to

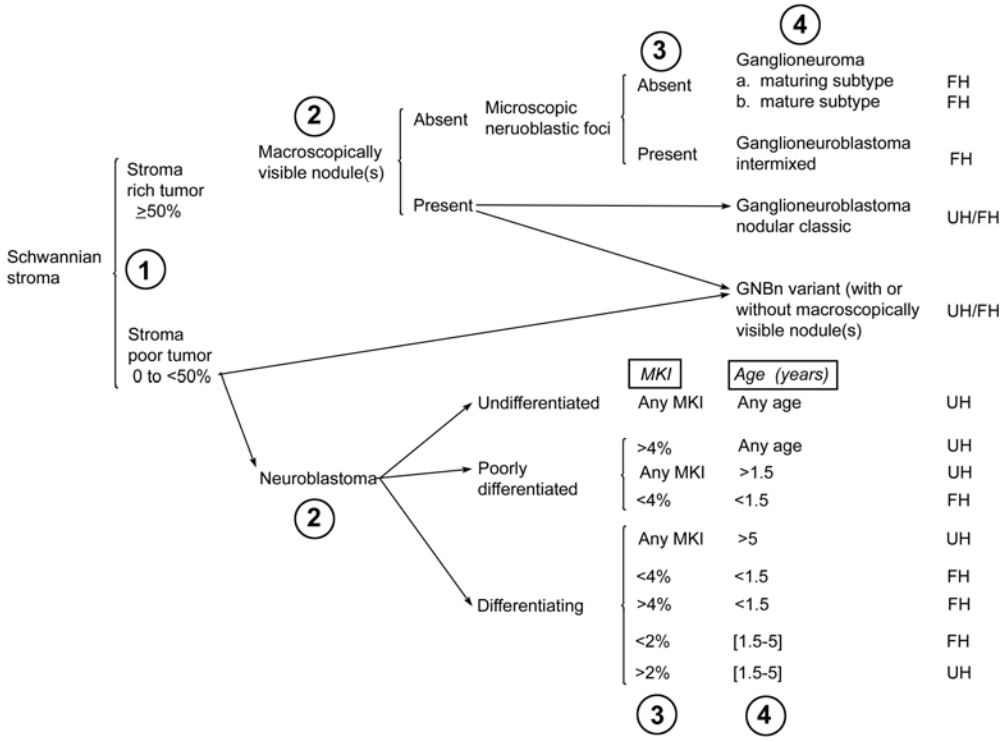


FIGURE 8-1. International Neuroblastoma Pathology Classification. The circled numbers correspond to the recommended steps described in the text, and are based on diagrams in the papers of Shimada et al. (21–23), and Peuchmaur et al. (24).

tumor, as well as from one section of the same tumor to another.

- **Neuroblastoma, differentiating**. This tumor is composed of neuroblastic cells that show focal neuronal differentiation. Differentiating neuroblasts and ganglion cells account for 5% or more of all tumor cells. Differentiating neuroblasts show synchronous enlargement of nuclei and cytoplasm. The vesicular nucleus of these cells is located excentrically in a well-developed cytoplasm, which appears eosinophilic or amphophilic and has clear-cut cell borders. Mature ganglion cells may be observed as well.

The extent of schwannian stroma formation varies, but by definition stroma comprises less than 50% of the entire tumor. The amount of schwannian neuropil is not critical for distinguishing poorly differentiated from differentiating neuroblastoma. It is usually most prominent at the periphery of tumor nests, but does not lead to the formation of nodules or a distinct separation of the undifferentiated from the differentiated part of the tumor. The continuity between the stroma-poor and stroma-enriched parts of differentiating neuroblastoma is an important feature of these tumors, allowing them to be distinguished from ganglioneuroblastoma nodular type.

The third step in evaluating schwannian stroma-poor pNT includes counting of mitoses and karyorrhectic nuclei (MKI). Mitotic figures are recognized by their rod-shaped condensation of chromatin, spiked projections of chromatin, and a lack of nuclear membrane. Karyorrhexis leads to condensation of the chromatin and fragmentation of nuclear material, accompanied by eosinophilic condensation of the cytoplasm. It is necessary to count 5000 cells and then express the MKI as low (2% [<100/5000]), intermediate (2–4% [100–200/5000]), or high (>4% [>200/5000]).

The fourth step involves inclusion of clinical data, primarily the age of the patient. Using the guidelines outlined in Figure 8-1, the histologic findings are then classified as favorable histology (FH) or unfavorable histology (UH).

Stroma-Rich Tumors

The second step for tumors that contain more than 50% of schwannian stroma, or "stroma-rich tumors," involves evaluation for nodularity. Nodules may be visible on gross examination or only microscopically.

The third step for evaluating tumors that show no nodularity includes a microscopic examination to determine whether the tumor contains neuroblastic cells. If no neuroblastic foci are found, the tumor is classified as ganglioneuroma, maturing subtype; if microscopic neuroblastic cells are present, it is classified as ganglioneuroblastoma, intermixed. Both of these tumors

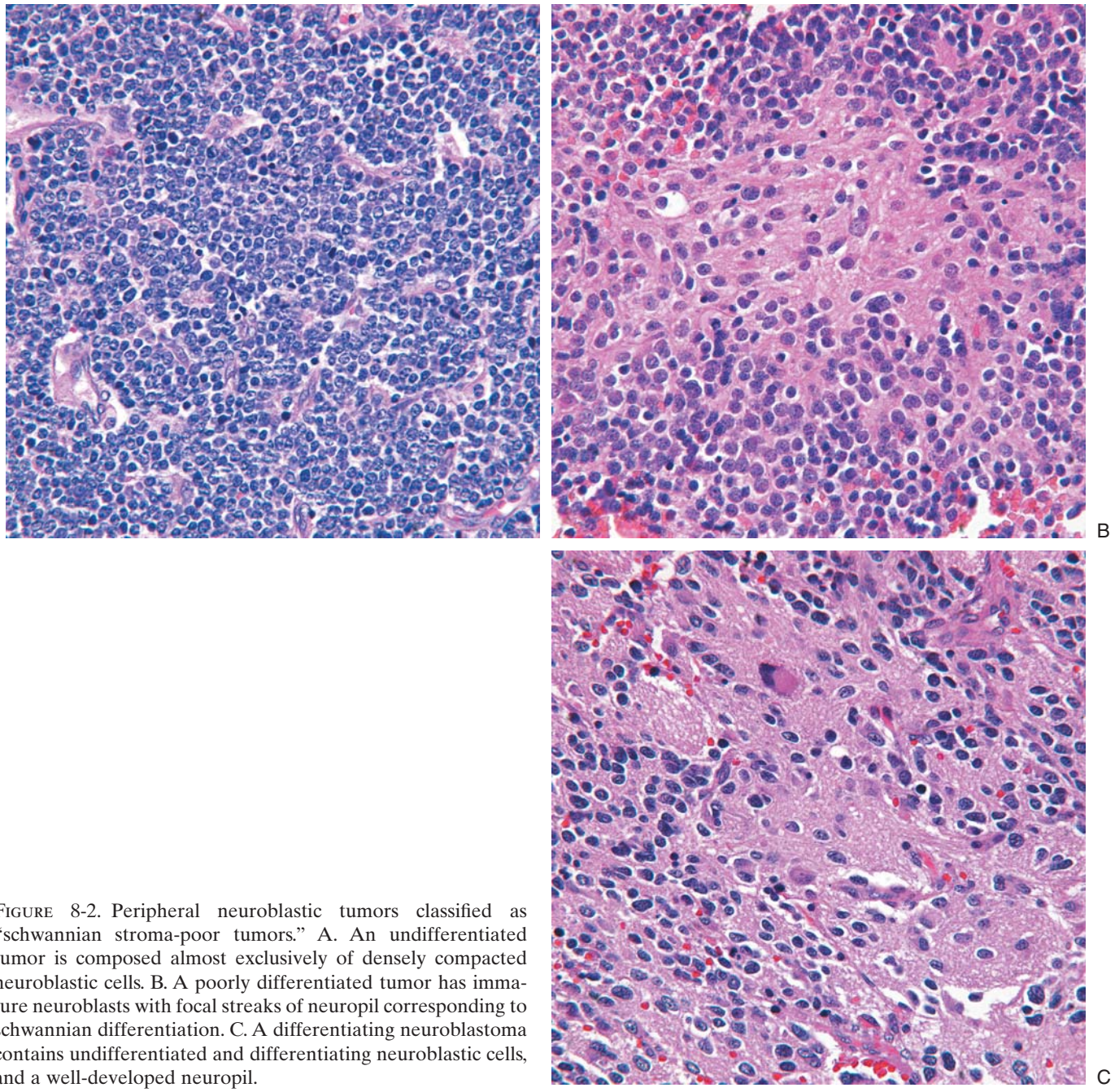
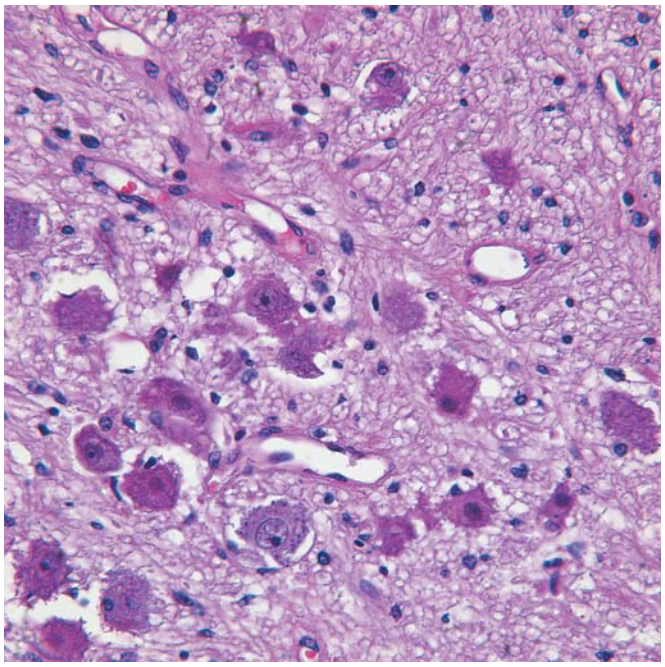


FIGURE 8-2. Peripheral neuroblastic tumors classified as "schwannian stroma-poor tumors." A. An undifferentiated tumor is composed almost exclusively of densely compacted neuroblastic cells. B. A poorly differentiated tumor has immature neuroblasts with focal streaks of neuropil corresponding to schwannian differentiation. C. A differentiating neuroblastoma contains undifferentiated and differentiating neuroblastic cells, and a well-developed neuropil.

have favorable histology. If macroscopically visible nodules are present, the tumor may be classified as ganglioneuroblastoma nodular, classic, or variant (GNBn). Some of the ganglioneuroblastoma variants have no macroscopically visible nodules, but are associated with metastases that show neuroblastomatous features.

The principal features of the stroma-rich tumor are illustrated in Figure 8-3 and briefly summarized as follows:

- **Ganglioneuroma.** This tumor is composed predominantly of ganglioneuromatous stroma. If it is composed of mature Schwann cells and ganglion cells, it is subclassified as ganglioneuroma, mature subtype. If it also contains foci of differentiating neuroblasts, it is subclassified as ganglioneuroma, maturing subtype. Maturing neuroblastomatous cells are intermixed with schwannian cells and do not form distinct nests, as in the intermixed form of ganglioneuroblastoma.
- **Ganglioneuroblastoma, intermixed**. Ganglioneuromatous tissue forms more than 50% of the tumor mass. However, this tumor also contains residual microscopic neuroblastic foci, and it must be differentiated from ganglioneuroblastoma, nodular subtype, a tumor that



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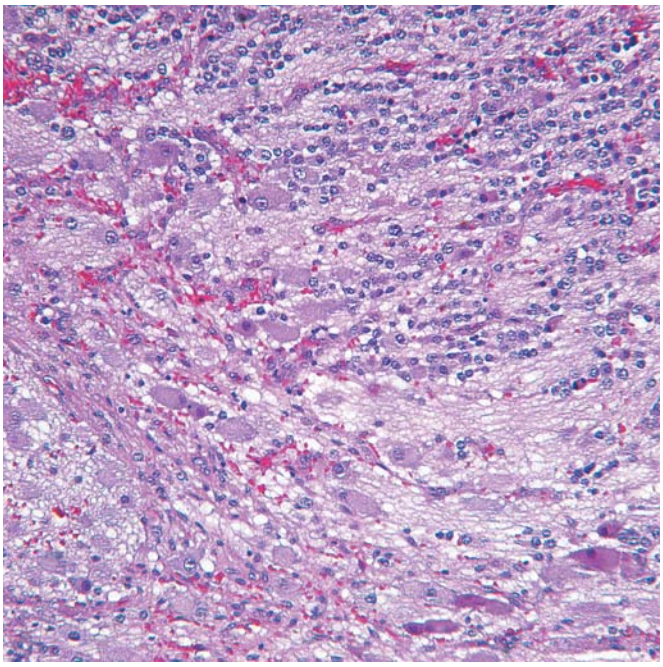

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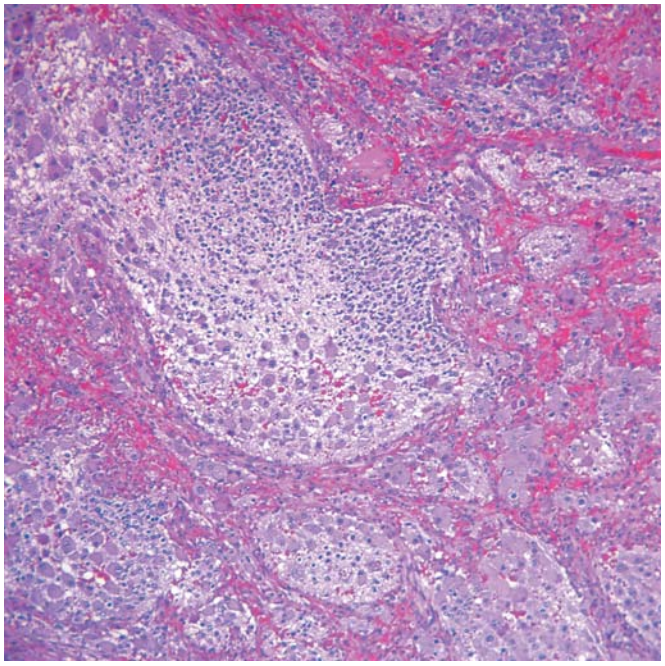

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FIGURE 8-3. Peripheral neuroblastic tumors classified as "schwannian stroma-rich tumors." A. A ganglioneuroma, mature, reveals ganglion cells and schwannian cells. B. A ganglioneuroma, maturing subtype, consists of maturing neuroblasts and ganglion cells in a schwannian stroma. C. Ganglioneuroblastoma, intermixed, is composed predominantly of ganglioneuromatous tissue, which forms more than 50% of the entire tumor. However, it also contains residual microscopic neuroblastic foci, seen as small blue cells.

contains a hemorrhagic nodule or nodules composed of highly aggressive tumor cells.

- **Ganglioneuroblastoma, nodular.** Typically, this tumor may present a single hemorrhagic nodule, or several hemorrhagic nodules surrounded by grayish white tissue. Microscopically, it has a characteristic composite nature, containing both stroma-rich and stroma-poor nodules. Thus, some nodules are composed of undifferentiated neuroblastic cells, whereas others have the features of ganglioneuroblastoma intermixed, and ganglioneuroma.
- **Ganglioneuroblastoma variant**. This tumor can be nodular on gross examination or show no nodularity (26). Those that are not nodular may have metastases. Some tumors in this category have more and some have less than 50% of schwannian stroma, and the nodules can be classified as favorable or unfavorable. The favorable nodules include poorly differentiating or differentiating, and low or intermediate MKI tumors in children under age 1.5 years. The unfavorable nodules in children under age 1.5 years are composed of undifferentiated cells and have a high MKI. In the age group

Table 8-2. Classification of pancreatic islet cell tumors.

Tumor type	Size (cm)	Mitoses (per 10 hpf)	Proliferation index (% cells reactive with Ki-67 or MIB-1)	Hormonal activity
Adenoma	<2	<2	<2	Yes
Tumor of uncertain malignant potential	>2	0–3	1–5	Yes
Low-grade endocrine carcinoma	>3	1–10	1–10	Yes
High-grade endocrine carcinoma	>10	>10	>10	No or weak

Source: Modified from Solcia et al. (1997).

from 1.5 to 5 years, the nodules are composed of undifferentiated or poorly differentiated tumors, with an intermediate or high MKI. In children over age 5 years, all tumors of this type are considered to have unfavorable histology.

Comments

1. The grading and prognostic stratification of peripheral neuroblastic tumors are constantly upgraded with data obtained by studies based on the application of cytogenetics, immunohistochemistry, and molecular biology (26,27). Ultimately, this will lead to new revisions of the INPC criteria.

2. Pheochromocytomas are not routinely graded. Most pheochromocytomas are benign, but approximately 10% are malignant (22). Microscopic data are used for predicting the malignancy of these tumors, although this might be extremely difficult (28). Findings favoring a diagnosis of malignancy include:

- Invasive growth such as capsular invasion, vascular invasion, or invasion of the periadrenal fat tissue
- Architectural features that include "large nests" exceeding 3 to 4 times the size of normal paraganglia, diffuse growth of tumor cells, increased cellularity with nuclear monotony, and central confluent necrosis
- Cellular and nuclear features such as spindle-shaped or small cells, cellular and nuclear pleomorphism, nuclear hyperchromasia, and macronucleoli
- Mitoses, with increased activity (>3 per 10 hpf) and atypical mitoses

Thompson has proposed a scoring system for predicting the malignancy of pheochromocytoma (29).

Islet Cell Tumors of the Pancreas

Tumors of the islets of Langerhans can be classified as hormonally active and hormonally inactive, and benign or malignant (30,31). Microscopic grading is not routinely practiced.

Comment

1. On the basis of microscopic findings, it is not easy to predict which islet cell tumor will be clinically benign and which will have more aggressive growth and metastasize. The only exception is the small cell carcinomas that resemble small cell ("oat-cell") carcinomas of the lungs, which are highly malignant and are readily identifiable microscopically.

2. The criteria for classifying islet of Langerhans cell tumors include:

- Macroscopic data, such as the size of the tumor and the presence of metastases
- Microscopic findings
- Immunohistochemical data
- Mitotic activity and immunohistochemical staining of nuclei with antibodies to proliferation markers (Ki-67 or MIB-1)
- Hormonal activity of tumors and hormonal syndromes

3. Overall, small and functionally active tumors and those that have few mitoses and show low proliferative activity tend to be benign, whereas the opposite is true for large tumors and those that have already metastasized. Thus, most insulin-secreting tumors are small and benign, but even in this group some are malignant (32). Keeping in mind that precision is not possible at present, it is advisable to apply a multimodal analysis to every islet cell tumor and try to classify it into 1 of the 4 possible categories: adenoma, tumor of uncertain malignant potential, low-grade endocrine carcinoma, and high-grade endocrine (small cell) carcinoma (Table 8-2).

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9
Tumors of the Kidney and the Male Urogenital System

Ivan Damjanov and Gregor Mikuz

Urogenital tumors are among the most common human tumors. Malignant tumors predominate, and the most important malignant neoplasms in this group are renal cell carcinoma, urothelial carcinoma of the urinary bladder, testicular carcinoma, and prostatic carcinoma. Testicular cancer is not generally assigned a microscopic grade, but the other 3 tumors are routinely graded according to well-established principles (Mostofi et al., 1998; Amin et al., 2004; Eble et al., 2004; Foster and Ross, 2004).

Renal Cell Carcinoma

Renal cell carcinoma can be graded according to several systems that use 2, 3, or 4 grades of malignancy. Although there is no consensus on the merits and reproducibility of the various systems, the grading system proposed by Fuhrman et al. (1) and the World Health Organization system developed by Mostofi and Davis are the most popular. The 4-tiered nuclear grading system originally proposed by Fuhrman et al. (1) has been the most widely used and will be presented here.

In the Fuhrman grading system, the tissue is examined at low magnification and the most anaplastic ("worst") area is identified for grading. The grading takes into account the size and shape of nuclei, the chromatin pattern, and the presence of nucleoli, as follows:

- **Grade 1.** The tumor cells have uniform, round, small nuclei (<10 µm) comparable to the nuclei of lymphocytes. The chromatin is condensed, and the nucleoli are not visible (Figure 9-1).
- **Grade 2.** The cells have somewhat larger, round vesicular nuclei (15 µm), with finely dispersed chromatin. The nucleoli are not present or are not clearly visible at low magnification (Figure 9-2).
- **Grade 3.** These cells have still larger nuclei (>20 µm), which are round or oval and contain finely dispersed chromatin. The nucleoli are easily seen at low magnification (Figure 9-3).
- **Grade 4.** The cells display irregularly shaped, hyperchromatic large nuclei (>20 µm) that vary in size and shape. The chromatin is irregularly distributed, and the nucleoli are large ("macronucleoli") (Figure 9-4).

The details of this grading system are summarized in Table 9-1.

Comments

1. The Fuhrman grade has been shown to be an independent prognostic factor for the classical renal cell carcinomas (3).
2. Most renal cell carcinomas (>80%) are classified as grade 2 or 3; grade 1 and 4 tumors are uncommon, accounting for only 5% to 10% of all cases (2).
3. Significant interobserver variability is a considerable drawback and has prompted attempts to consolidate the 4-grade system into a more reproducible 3- or 2-tiered system.
4. There is considerable controversy about the use of the Fuhrman system for grading papillary renal cell carcinomas. In daily practice, it is best to divide these tumors into 2 groups according to the 2-tiered system proposed by Delahunt and Eble (4), and then grade them according to Fuhrman.
5. The nuclei of chromophobe carcinomas are almost always grade 2; grade 3 and 4 nuclei are extremely rare (Murphy et al., 2004).

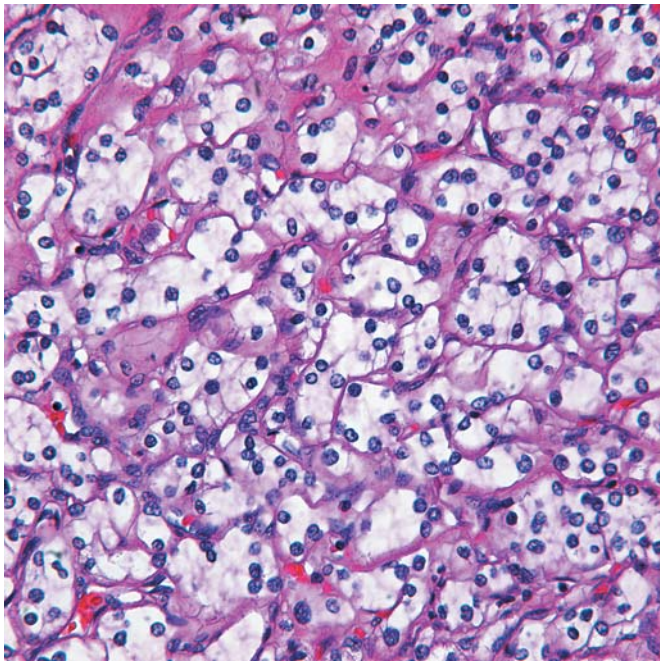


FIGURE 9-1. Renal cell carcinoma. This Fuhrman grade 1 tumor has small condensed nuclei.

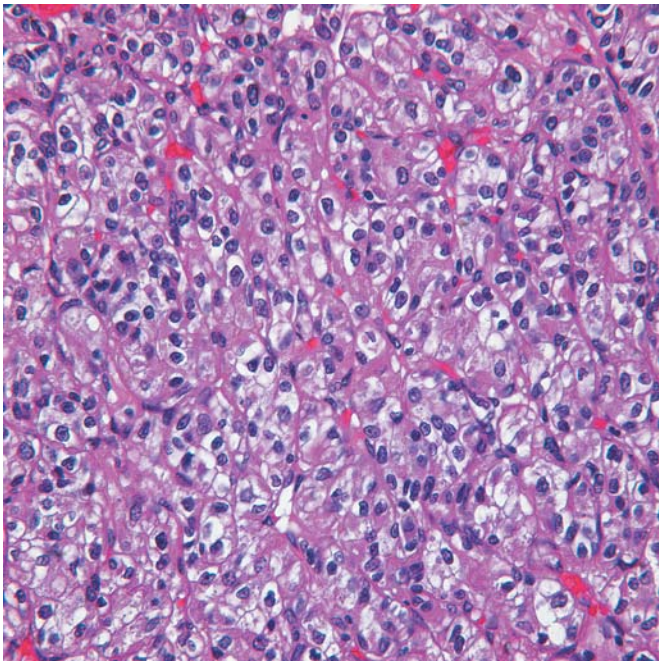


FIGURE 9-2. Renal cell carcinoma. This Fuhrman grade 2 tumor shows small vesicular nuclei, which contain no obvious nucleoli.

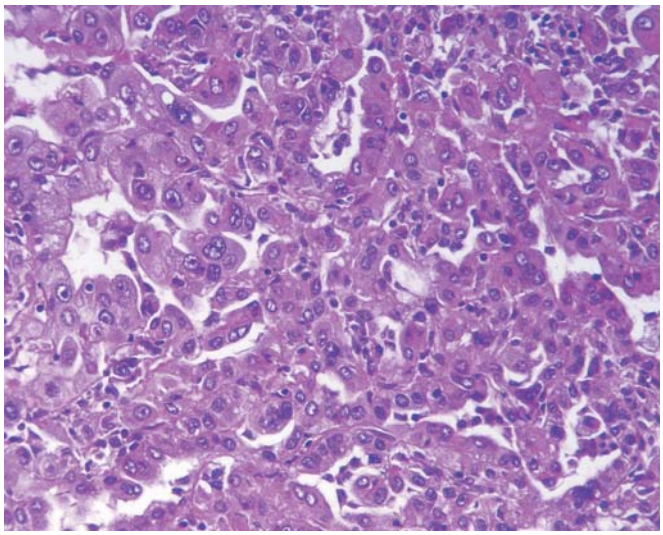


FIGURE 9-3. Renal cell carcinoma. This Fuhrman grade 3 tumor has enlarged vesicular nuclei, which contain obvious nucleoli.

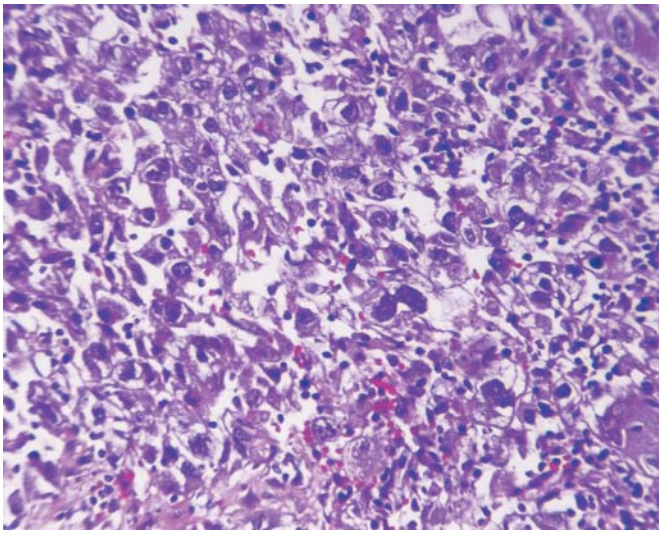


FIGURE 9-4. Renal cell carcinoma. Fuhrman grade 4 tumor nuclei show pleomorphism and appear hyperchromatic.

TABLE 9-1. Fuhrman grading of renal cell carcinoma.

Grade	Nuclear size	Nuclear shape	Chromatin pattern	Nucleoli
1	<10 μm	Round, uniform	Condensed	Not evident
2	15 μm	Round, uniform	Finely granular, dispersed	Rudimentary, not seen at low magnification*
3	20 μm	Round or oval, slightly variable	Coarsely granular	Clearly visible at low magnification*
4	>20 μm	Pleomorphic, multilobated	Hyperchromatic and clumped	Large ("macronucleoli")

*We prefer to use the 20x objective rather than the 10x objective recommended in the above listed reference, because it is much easier to distinguish nucleoli from coarse condensations of chromatin in grade 2 tumors.
Source: Modified from Murphy et al., 2004.

Carcinoma of the Prostate

Carcinoma of the prostate is the most common malignant tumor in men. It is mainly a disease of older men, and most cases have been relatively resistant to treatment. Core needle biopsy is essential for the diagnosis of prostatic carcinoma and is performed often (5). Grading of prostate carcinoma has major clinical implications for planning treatment and formulating a prognosis (6–9). The most widely used and the best clinically tested system is the one developed by Gleason (Figure 9-5) (6). The system is simple and reasonably reproducible. Although there is considerable interobserver variability, especially in the small needle biopsy specimens, the grades assigned to tumors with this approach correlate well with the clinical course and the final outcome of the malignant disease. The Gleason grading system is based on morphologic identification of distinct tumor growth patterns, which are graded on a scale from 1 to 5 (6–9). The specimen is examined to determine the predominant pattern, which is designated as the primary grade. The next most common pattern is then identified and designated as the secondary grade. These 2 are added together for the final Gleason score. Depending on the Gleason score, the tumors are stratified as follows:

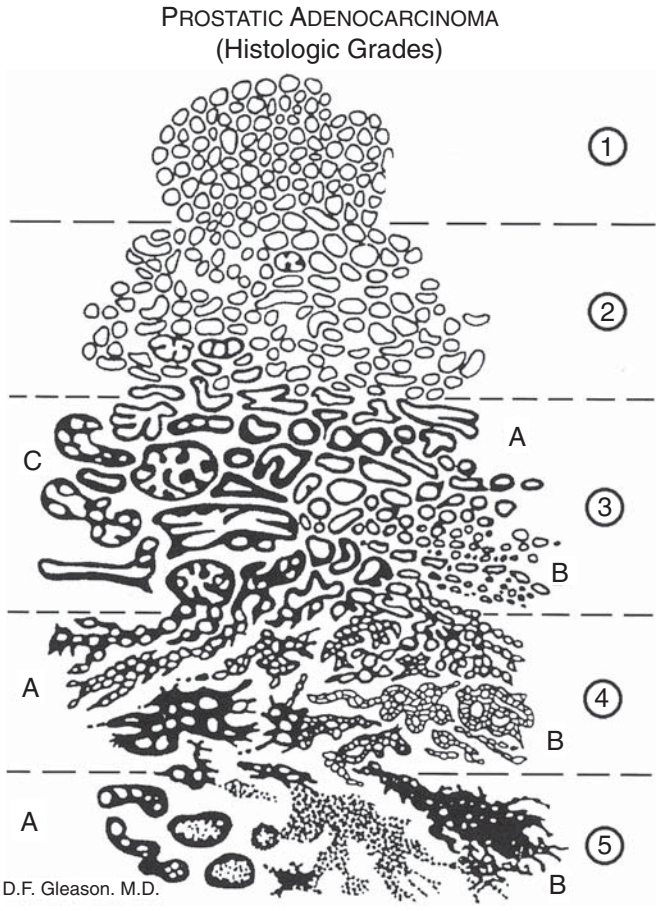


FIGURE 9-5. Gleason grading system. The original schematic drawing by Gleason illustrating the 5 patterns.

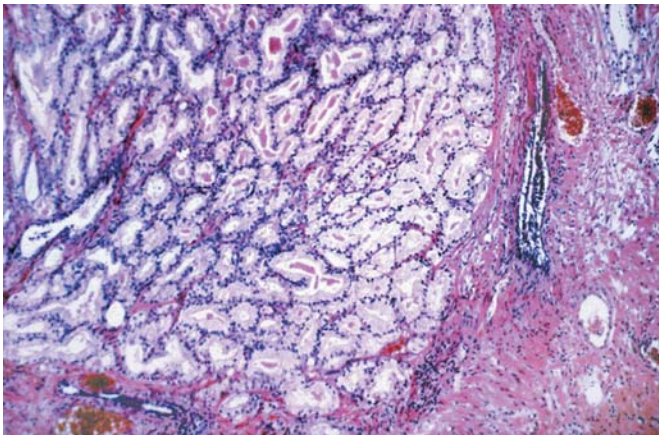


FIGURE 9-6. Gleason pattern 1. Uniform round glands are closely packed into nodules that have well-defined margins and pushing borders. The tumor stroma interface is smooth. The glands are medium-size and uniform. A distinct stroma is recognizable in between the glands. This pattern is very rare and could not be diagnosed in needle biopsies. It is the typical incidental carcinoma of the transitional zone, usually seen in transurethral resection specimens.

- Gleason score 2–4, well-differentiated
- Gleason score 5–7, moderately differentiated
- Gleason score 8–10, poorly differentiated

The grading of prostatic tumors is based on the assessment of histologic architectural features of neoplastic tissue at low- or medium-power magnification (4x or 10x objective lens). The neoplastic acini should be compared with adjacent normal acini, which typically have smooth and rounded or elongated contours.

- **Gleason pattern 1.** These tumors have simple round glands typically showing uniformity in size, shape, and spacing. Glands are closely packed into nodules that have smooth, well-defined, pushing margins (Figure 9-6). The nuclei and nucleoli are slightly enlarged, which is important for distinguishing this type of cancer from atypical adenomatous hyperplasia. Intraluminal crystalloids are found in more than 50% of cases. Gleason pattern 1 cannot be diagnosed reliably in small biopsies, and today it is rarely diagnosed.
- **Gleason pattern 2.** These tumors are composed of simple rounded glands similar to those in Gleason pattern 1; however, the glands show more variation in size and shape and are less evenly spaced (Figure 9-7). The separation is less than 1 glandular diameter. In contrast to Gleason pattern 1 tumors, the neoplastic nodules do not have round contours, but appear incompletely circumscribed, consistent with the invasiveness of this neoplasm.

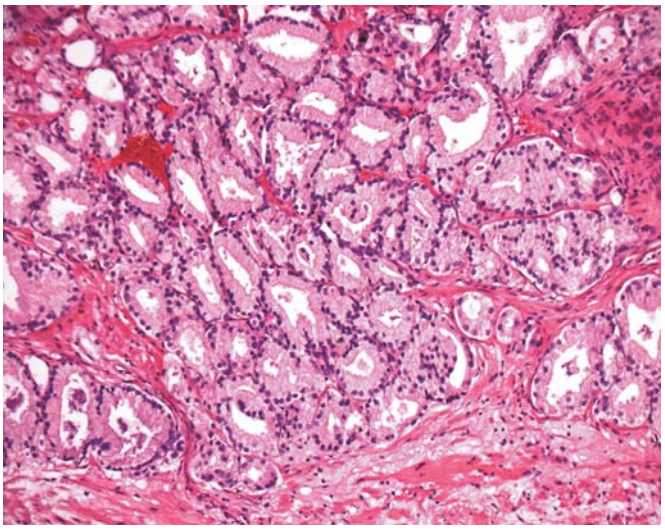


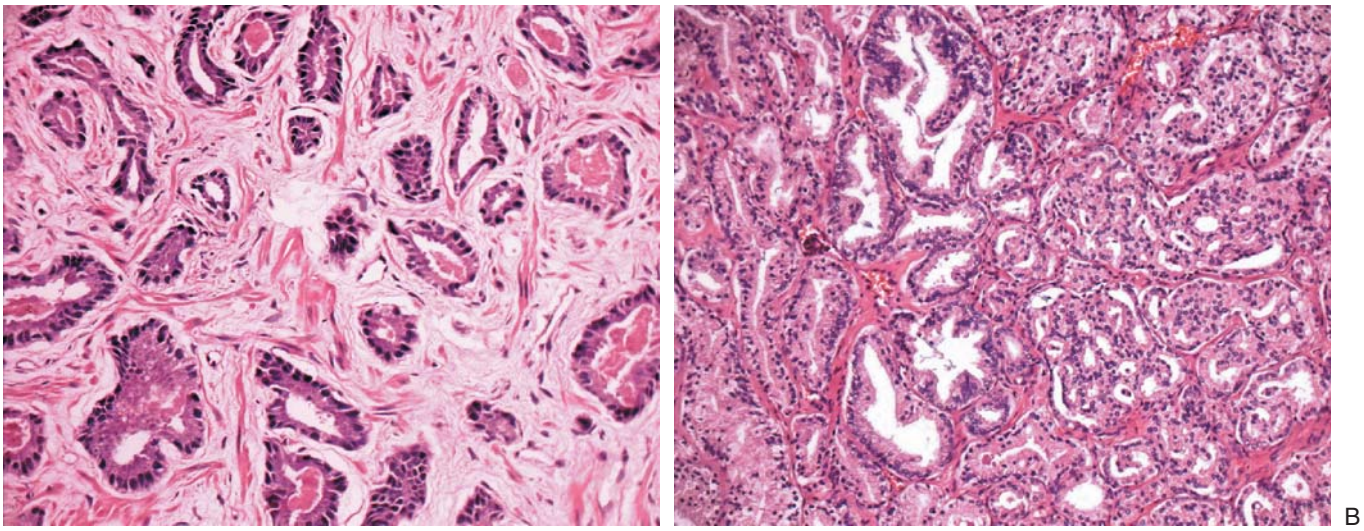
FIGURE 9-7. Gleason pattern 2. Rounded glands show more variation in size and shape and are less evenly spaced than those in Gleason pattern 1 tumors. In addition, the neoplastic nodules do not have round contours, but appear incompletely circumscribed. The stroma is more abundant. This pattern is also rarely seen in biopsy.

- **Gleason pattern 3.** The glands of these tumors show prominent variation in their size, shape, and spacing (Figure 9-8). Nevertheless, the glands are discrete and do not show fusion, as seen in Gleason grade 4. Neoplastic glands are arranged haphazardly and often are separated by prominent strands of fibrous stroma. This is the most common microscopic pattern of prostatic carcinoma.

  Pattern 3 can be divided into 3 subgroups, 3A, 3B, and 3C, although in routine there is no need to specify which of these 3 patterns predominates (7). Pattern 3A is characterized by infiltrating, medium-size glands of irregular shape and spacing, which extend irregularly into the stroma. Pattern 3B has the same growth pattern, but the glands are generally smaller. Pattern 3C is recognized by the presence of expanded cylinders or ducts and cribriform or papillary growth of the tumor cells.

  Several uncommon growth patterns are also included under this rubric: the pseudohyperplastic pattern, the glomeruloid pattern (in most instances, although some are pattern 4), foamy gland carcinoma, and tumors forming collagenous micronodules (7).
- **Gleason pattern 4.** These tumors are infiltrating carcinomas composed of irregularly shaped and often fused glands, and anastomosing cords and nests (Figure 9-9). The glands can be very small and closely packed, without any separation. Although the nuclei of tumor cells may be deceptively bland, the individual tumor cells or cords of tumor cells invade into the stroma. Most importantly, in contrast to pattern 3, the tumors have ragged infiltrative edges.

  Two subgroups are recognized, 4A and 4B; the latter designation is reserved for tumors that have clear cytoplasm and are called hypernephroid, because they resemble renal cell carcinoma. Mucinous adenocarcinomas belong to this group, although some show moderate differentiation and are assigned under pattern 3. Nonmucinous signet-ring carcinomas containing cytoplasmic vacuoles may be pattern 4, but some are pattern 5.
- **Gleason pattern 5.** These tumors have solid sheets of anaplastic cells showing abortive formation of glands (Figure 9-10). Two subtypes are recognized, 5A and 5B. Pattern 5A is characterized by cribriform nests with



A B

FIGURE 9-8. Gleason pattern 3. A. The tumor is composed of glands of variable size, shape, and spacing. The acini are discrete and separated by prominent strands of fibrous stroma. The glands are usually irregular with sharp, angular contours. B. Here more closely packed glands are surrounded with scant stroma; obviously, the amount of stroma may be highly variable.

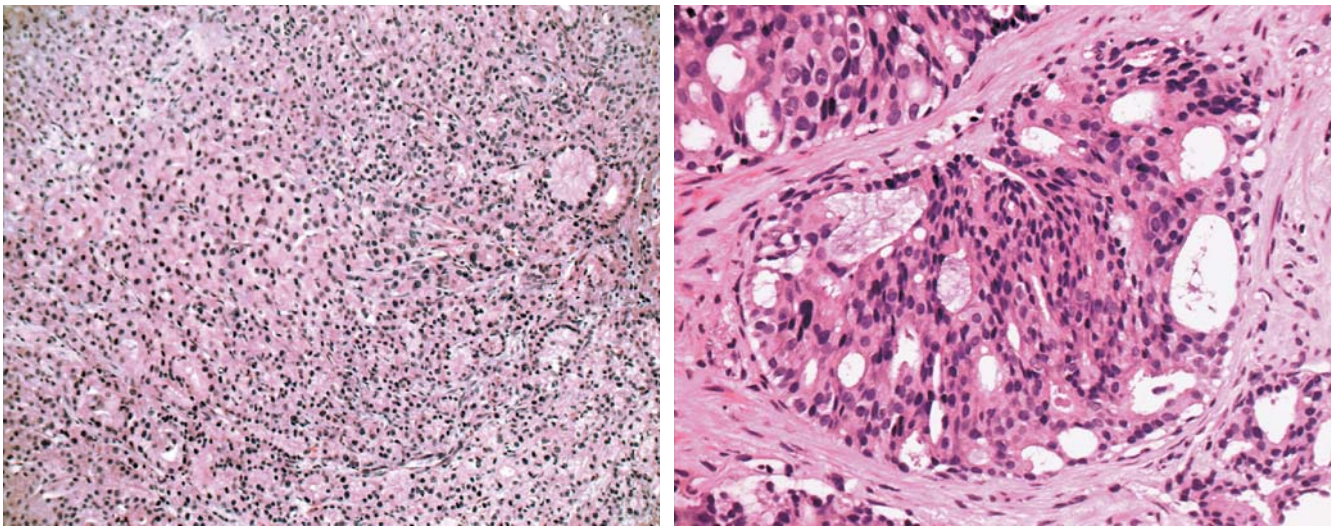


FIGURE 9-9. Gleason pattern 4. A. The tumor is composed of microglandular structures and prominently fused glands. This fusion of glands is the most important morphological feature of this pattern. B. Cribriform structures with fused glands are evident.

foci of comedo-like necrosis. These cribriform areas resemble Gleason pattern 3 glands, but in contrast to pattern 3 lesions, they contain foci of central necrosis similar to that in intraductal breast carcinoma. Pattern 5B features poorly differentiated tumor growth, and also includes variants such as signet-ring cell carcinoma and small cell undifferentiated carcinoma. Pleomorphic giant cell carcinoma belongs to this group as well.

Variant Forms of Prostatic Carcinoma

Besides the typical adenocarcinoma of the prostate, NOS (not otherwise specified) prostatic carcinoma may occur in several microscopic variant forms, as follows:

- **Ductal adenocarcinoma** (adenocarcinoma with endometrioid features). This tumor may have a papillary or cribriform growth pattern, or present as a polypoid or papillary mass protruding into the prostatic urethra. It is high grade.
- **Mucinous adenocarcinoma.** This is a high-grade tumor, but some are moderately differentiated. These tumors may respond to endocrine and radiation therapy. They are usually pattern 4, but some are pattern 3.
- **Signet-ring cell carcinoma.** This is a high-grade tumor.
- **Adenocarcinoma with vacuolated cytoplasm** (foamy gland carcinoma). This is a high-grade tumor.
- **Neuroendocrine carcinoma.** The grade of neuroendocrine tumors varies. Some resemble carcinoids and

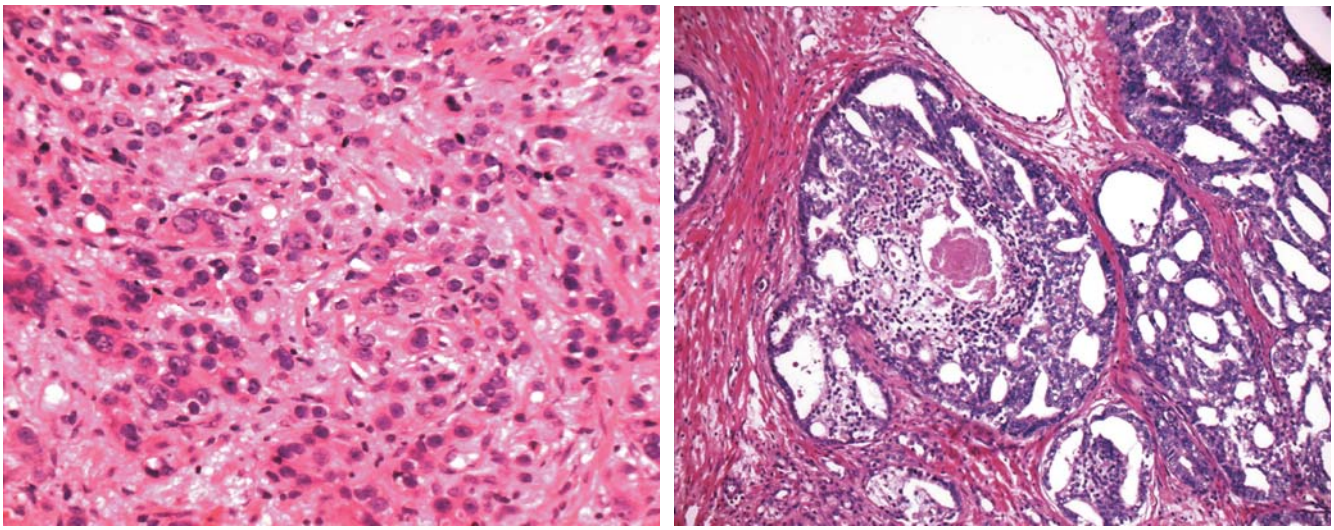


FIGURE 9-10. Gleason pattern 5. A. Solid nests of closely packed cells form no obvious glandular structures. Some cells are vacuolated. B. Comedo-like necrosis within some of the cribriform structure is visible. The image shows a combination of cribriform structures without and with necrosis, which corresponds to Gleason score 9 (4 + 5).

behave like low-grade malignant neoplasms, while others resemble oat-cell carcinoma of the lung and have a poor prognosis.
- **Sarcomatoid carcinoma (carcinosarcoma).** This is a high-grade tumor with a poor prognosis.
- **Pleomorphic giant cell carcinoma.** This is a high-grade tumor.
- **Basal cell/adenoid cystic carcinoma**. This is a rare low-grade tumor.

Comments

1. More than 2 patterns are found in over 40% of prostatectomy specimens, but only 2 grades—the predominant and the next most common—are listed. While the listing of the third grade is being considered, in most institutions it is not included in the final report.

2. The most predominant grade is listed as the first grade, even though it might not be the highest grade. For example, if there are 2 grades, grade 3 and grade 4, and grade 3 predominates, the results should be expressed as 7 (3 + 4). If grade 4 predominates, the score is 7 (4 + 3).

3. If the entire tumor shows the same growth pattern in all sections, the assigned grade is a duplicate (e.g., 8 [4 + 4]). Usually, pattern 3 is found in the pure form, and thus the most common Gleason score is 6 (3 + 3) (7).

4. If 2 or more tumors differing in grade are found in the same prostatectomy specimens, the scores for each of them should be reported.

5. At the latest international consensus conferences, it has been recommended that no Gleason pattern designation should be given to several microscopic variants of prostatic carcinoma, including the following tumors: small cell carcinoma, mucinous signet-ring cell carcinoma, sarcomatoid carcinoma, lymphoepithelioma, basal cell/adenoid cystic carcinoma, urothelial carcinoma, and squamous cell carcinoma (8).

Carcinoma of the Urinary Bladder

Like the renal pelvis, ureters, and parts of the urethra, the urinary bladder is lined with transitional epithelium. It is no wonder, then, that most tumors in these sites are epithelial and composed of transitional epithelium, which is also known as urothelium. Urothelial tumors are similar, irrespective of their site of origin. Most originate in the urinary bladder, and malignant tumors predominate.

Several systems for grading urothelial tumors have been proposed, but none of them has been universally accepted. The international classification and grading system proposed by the experts of the World Health Organization and the International Society of Urological Pathology (WHO/ISUP) is described here, since it seems to offer some advantages to clinicians and can be easily compared with others grading schemes (Table 9-2).

Table 9-2. Comparison of systems for the classification and grading of papillary urothelial neoplasms.

WHO, 1973	AFIP, 1994	WHO, 1999	WHO/ISUP, 1998
Papilloma	Papilloma	Papilloma LMP	Papilloma PUNLMP
Grade 1	Low grade	Grade 1	
Grade 2		Grade 2	PC-low grade
Grade 3	High grade	Grade 3	PC-high grade

Abbreviations:
PUNLMP—Papillary urothelial neoplasm of low malignant potential
LMP—Low malignant potential tumor
PC—Papillary carcinoma
Source: Based on Weidner et al (2003), and Murphy et al (2004).

Urothelial carcinomas are classified as invasive or noninvasive. The latter group comprises 2 categories: flat lesion and papillary lesions (10–12). Neoplastic lesions must first be distinguished from non-neoplastic lesions such as hyperplasia, which may be flat and of papillary or reactive atypia.

Flat neoplastic lesions are classified as low-grade intraepithelial neoplasia (dysplasia), or as high-grade intraepithelial neoplasia (carcinoma in situ). If hyperplasia cannot be confidently differentiated from dysplasia, the lesion is assigned to the category of atypia, of unknown significance.

Papillary neoplasms are classified as benign (exophytic papilloma and inverted papilloma) or malignant. Malignant tumors may be noninvasive or invasive. Noninvasive malignant tumors are classified as papillary tumors of low malignant potential, as papillary carcinoma, low grade, or as papillary carcinoma, high grade. If the papillary tumor shows invasiveness at the base, it is then classified as invasive carcinoma.

The reactive (non-neoplastic) and the neoplastic lesions of the urinary bladder mentioned above have the following morphologic features:

- **Hyperplasia.** In this benign lesion, the epithelium is thickened but still composed of normal urothelial cells showing no signs of nuclear atypia.
- **Reactive atypia.** This benign lesion typically results from chronic irritation with stones, medical instrumentation, or acute and chronic inflammation, which is evident in the microscopic slides. The urothelial cells have uniformly enlarged vesicular nuclei and prominent nucleoli. There is no nuclear atypia, hyperchromasia, nor any significant variation in the size and shape of the nuclei.
- **Atypia, of unknown significance.** This lesion resembles those with reactive atypia, but also shows some irregularities in the distribution of chromatin, nuclear

hyperchromasia and pleomorphism, and enlarged nucleoli. The nuclear changes are still mild but are out of proportion with the chronic inflammation in the underlying stroma.

- **Dysplasia, low-grade intraurothelial neoplasia.** In this preneoplastic lesion, the epithelium is disorganized and the generally enlarged nuclei show considerable variation in size and shape. The nuclei are hyperchromatic and often have enlarged nucleoli.
- **Carcinoma in situ, high-grade intraurothelial neoplasia.** The epithelium shows unequivocal signs of neoplastic transformation, and these changes include both nuclear and architectural irregularities. The nuclei vary in size and shape, but are often enlarged and of irregular shape and hyperchromatic. Such nuclei can be seen in all layers of the neoplastic epithelium. Mitotic figures are common and are evident in all layers of the epithelium. The surface umbrella layers may be preserved, or partially lost. The epithelium may be thickened and involved diffusely with the atypical neoplastic cells, or it might contain only scattered highly atypical cells and otherwise show only signs of dysplasia. The discohesive growth pattern of carcinoma in situ associated with shedding of tumor cells may result in the so-called "clinging urothelial carcinoma in situ," composed of only a few layers of neoplastic cells. Although the thickness of the epithelium of carcinoma in situ and the extent of atypia may vary, all carcinomas in situ are considered high-grade lesions.
- **Urothelial papilloma.** This is a rare benign exophytic lesion, usually found in young persons. It is composed of normal urothelial cells lining delicate papillae. The same epithelium may form inverted papillomas. Some papillomas have both inverted and exophytic features.
- **Papillary urothelial neoplasm of low malignant potential (PUNLMP).** In contrast to papillomas, this lesion is composed of cells that have uniformly enlarged nuclei. The number of cell layers covering the central fibrovascular core is increased, accounting for the obvious thickening of the epithelium (Figure 9-11), yet there is no nuclear or architectural atypia. Although enlarged, the nuclei show no variation in the size and shape; they are not hyperchromatic, and mitoses are not evident. The polarization and layering of nuclei resemble that of normal urothelium.
- **Papillary urothelial carcinoma, low grade.** This papillary tumor is characterized by a thickening of the epithelium lining the broader fibrovascular cores. The epithelium contains relatively uniform cohesive cells, which mostly show proper layering (Figure 9-12). Focally, there is nuclear crowding and loss of nuclear polarity. Unquestionable signs of cytologic atypia, evident even at low magnification, include enlargement of nuclei and a variation in their size and shape. Nucleoli are inconspicuous, but may be found. Mitoses are rare, usually in the basal layer, but may be found in other layers as well. For the assessment of the architectural features, one should evaluate only the properly oriented papillae, because the tangentially cut basal parts of the papillae may show much more architectural distortion. These tumors may invade the lamina propria and may occasionally (<5%) progress to a higher grade carcinoma.
- **Papillary urothelial carcinoma, high grade.** This tumor shows pronounced architectural and cytologic atypia, which are visible even at low magnification. The normal layering has been lost, and the disorganized tumor cells are arranged without obvious pattern, or appear crowded without any regularity (Figure 9-13). The nuclei are hyperchromatic and show marked clumping of the chromatin. There is prominent variation in the size and shape of the nuclei. Normal and abnormal mitoses may be present in all layers. In one-third of the cases, these tumors are either associated with invasive urothelial carcinoma or ultimately progress to invasive carcinoma.

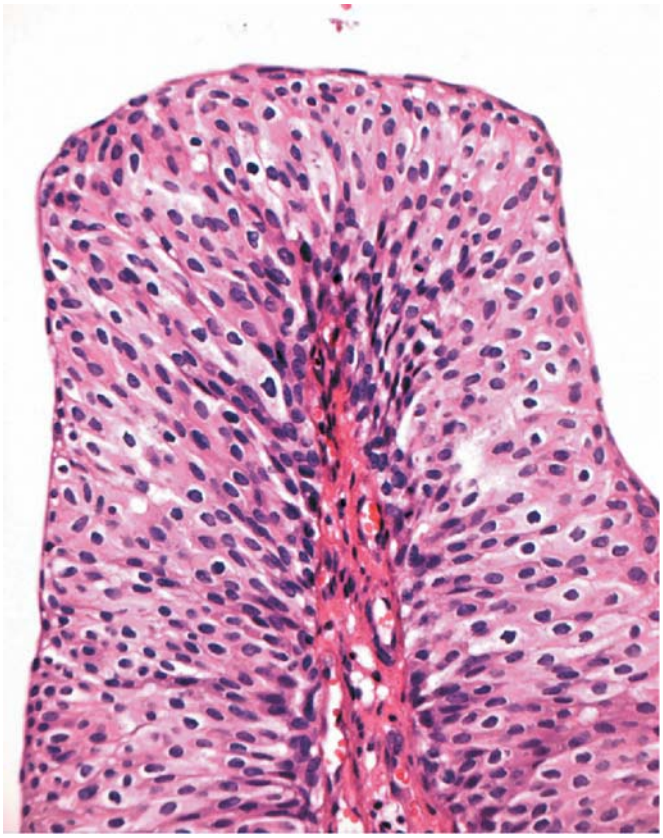


FIGURE 9-11. Papillary urothelial neoplasm of low malignant potential (PUNLMP). The papilla is lined by cells that have uniformly enlarged nuclei without atypia. The epithelium is thickened, but the cells still display proper layering and show no architectural atypia. The umbrella cells are well preserved.

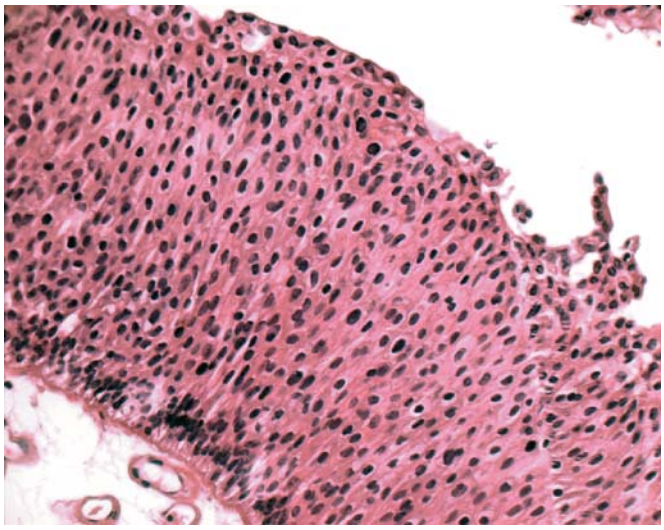


FIGURE 9-12. Papillary urothelial carcinoma, low grade. The papilla is lined by thickened epithelium with relatively uniform cohesive cells, and which mostly show proper layering. There is focal nuclear crowding and loss of nuclear polarity. The tumor cell nuclei are slightly enlarged and show mild variation in size and shape. The nucleoli are inconspicuous, and no mitoses are seen.

- **Invasive urothelial carcinoma.** In most instances, this tumor evolves from either flat or papillary noninvasive tumors. This is a high-grade lesion, and there is no benefit from further grading (Figure 9-14).

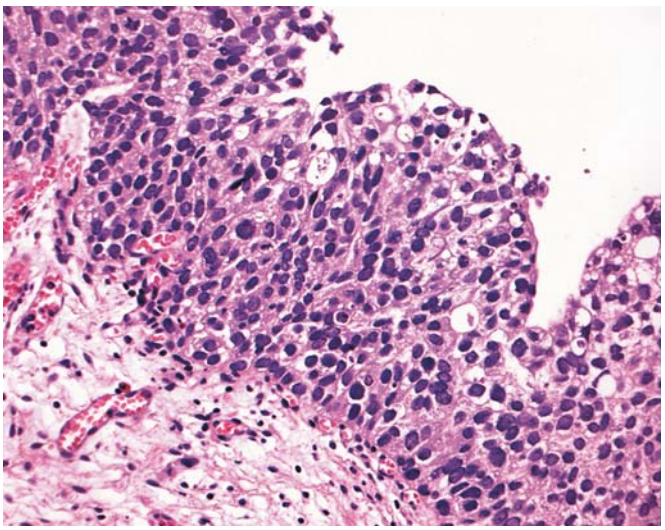


FIGURE 9-13. Papillary urothelial carcinoma, high grade. The tumor shows pronounced architectural and cytologic atypia. The normal layering of cells is lost. The polarity of the cells is only focally preserved. The nuclei are pleomorphic, hyperchromatic, and display prominent clumping of the chromatin. Nucleoli are evident.

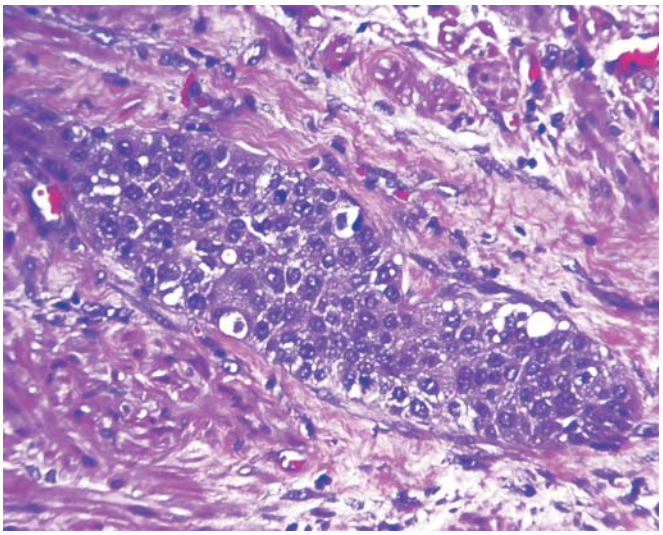


FIGURE 9-14. Invasive urothelial carcinoma. The tumor nest invading the muscle layer comprises cells that have retained few, if any, features of the normal urothelium.

Comments

1. If a papillary tumor shows more than 1 growth pattern, the tumor should be given the highest grade that was recognized on microscopic examination. However, small areas of high-grade neoplasia in an otherwise low-grade tumor can be ignored.

2. In papillary urothelial carcinoma, high grade, one may comment on the extent of nuclear atypia, but the clinical significance of these nuclear changes remains uncertain.

3. The invasion of tumor cells between the smooth muscle cell bundles of submucosa should not be confused with the invasion of the muscularis propria. The staging of urothelial carcinomas, which depends on proper determination of the depth of invasion, is still the best prognostic determinant of the outcome of malignant bladder disease.

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10
Tumors of the Female Genital Organs

Fang Fan and Ivan Damjanov

Introduction

Tumors of the female genital organs are often biopsied or surgically resected, and thus form a significant part of surgical pathology material in most institutions. Invasive tumors and premalignant or borderline lesions are routinely graded, and in many instances the grade assigned by the pathologist is an important determinant of the treatment for these conditions.

The parts of the female genital organs that are covered with squamous epithelium, namely the vulva, vagina, and the cervix uteri, give rise to squamous cell carcinoma. Squamous cell carcinoma and its precursors of the female genital organs are graded like the homonymous lesions in other anatomic sites. The mucosa of the endocervix, endometrium, fallopian tubes, and the surface epithelium of the ovary give rise to adenocarcinomas. These tumors are graded more or less the same way as adenocarcinomas in other anatomic locations, while those ovarian tumors that are unique to that organ are graded according to generally accepted schemes.

Vulvar Squamous Intraepithelial Neoplasia

Squamous cell carcinoma of the vulva is preceded by intraepithelial changes that can be recognized microscopically as vulvar squamous intraepithelial neoplasia (VIN) (1). VIN may be related to infection with human papilloma virus (HPV), but it can occur without HPV infection and in rare instances even in the background of lichen sclerosus with squamous hyperplasia.

Vulvar squamous intraepithelial neoplasia is graded on a scale from 1 to 3, as mild, moderate, or severe (Figure 10-1):

- **VIN 1, mild squamous dysplasia.** The epithelium is slightly thickened and has a disorganized basal layer showing mild nuclear atypia. Prominent koilocytosis is evident in the superficial layers. The surface may be covered with a hyperkeratotic layer and an underlying layer of granular cells, resembling those in the skin.
- **VIN 2, moderate squamous dysplasia.** The epithelium shows disorganized layering, nuclear enlargement and irregularity, and mitotic activity in the lower two-thirds of the squamous epithelium. Squamous maturation with proper layering is retained toward the surface.
- **VIN 3, severe squamous dysplasia/carcinoma in situ.** In this condition, the epithelium is thickened, but its thickness varies from case to case, and even within the same patient site to site. The entire thickness of the epithelium has been replaced by small atypical hyperchromatic basaloid cells that show no signs of maturation. A thin layer of parakeratosis or abortive layering may be seen on the surface. In some cases of VIN 3, there is prominent surface hyperkeratosis and the entire lesion has a verrucous appearance (warty type VIN 3). Occasionally, VIN has the features of well-differentiated squamous cell carcinoma in situ of the skin (simplex type VIN 3).

Invasive Squamous Cell Carcinoma of the Vulva

Invasive squamous cell carcinoma of the vulva is graded according to the same principles as that for squamous carcinoma of other anatomic locations:

- **Grade 1, well-differentiated squamous cell carcinoma.** The tumor cells resemble normal squamous epithelium, with frequent formation of concentrically laminated keratin pearls. The cells are polygonal and have well-developed eosinophilic cytoplasm. The intercellular bridges are clearly seen at high magnification.

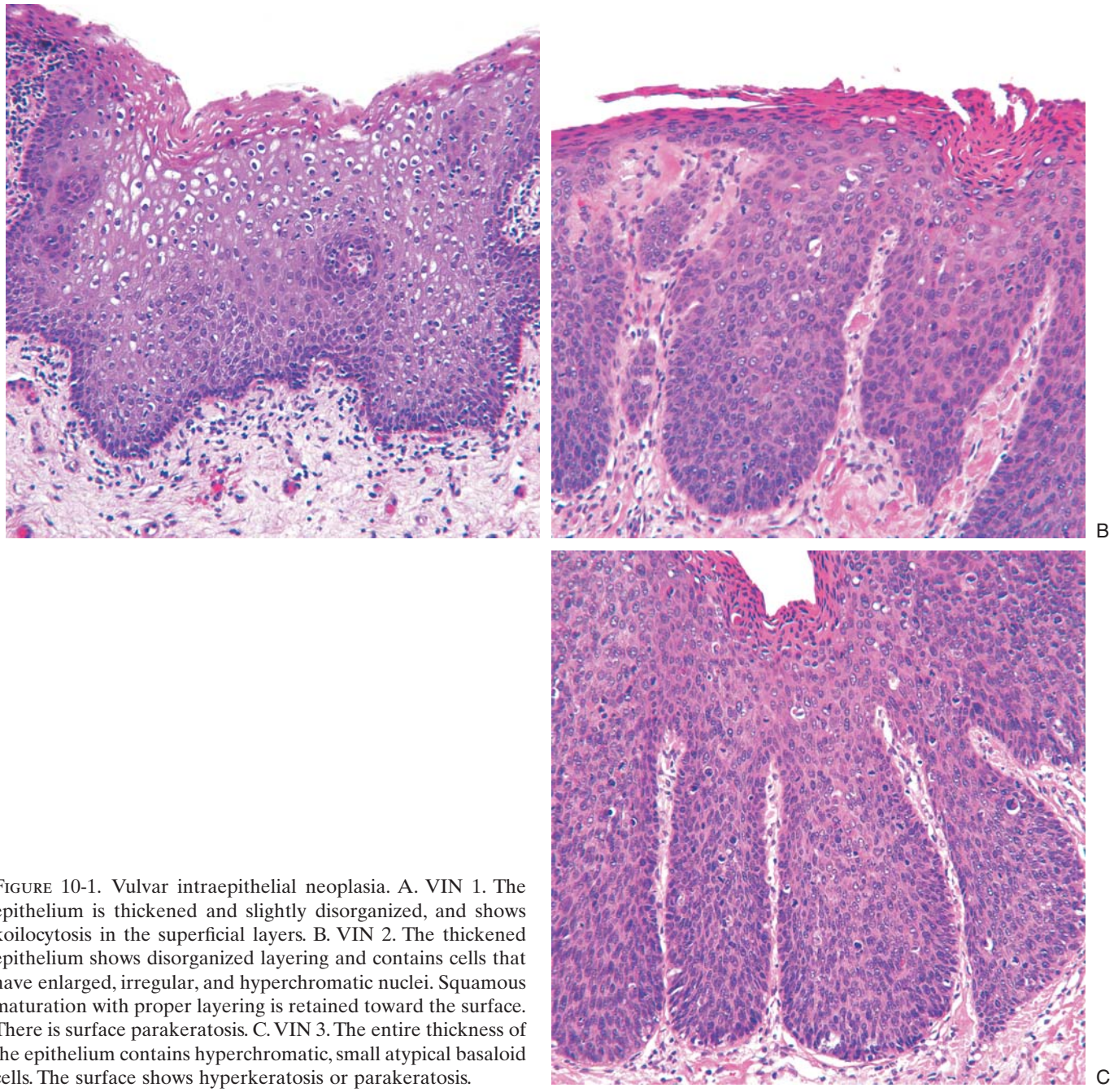


FIGURE 10-1. Vulvar intraepithelial neoplasia. A. VIN 1. The epithelium is thickened and slightly disorganized, and shows koilocytosis in the superficial layers. B. VIN 2. The thickened epithelium shows disorganized layering and contains cells that have enlarged, irregular, and hyperchromatic nuclei. Squamous maturation with proper layering is retained toward the surface. There is surface parakeratosis. C. VIN 3. The entire thickness of the epithelium contains hyperchromatic, small atypical basaloid cells. The surface shows hyperkeratosis or parakeratosis.

Nuclei show mild atypia with inconspicuous nucleoli, and there are occasional mitoses.

- **Grade 2, moderately differentiated squamous cell carcinoma.** The tumor cells have variable amounts of cytoplasm and pleomorphic nuclei. Squamous differentiation of the cells is still recognizable by occasional keratin pearl formation and individual cell keratinization. Mitoses are easily identified.
- **Grade 3, poorly differentiated squamous cell carcinoma.** Tumor cells have a high nucleocytoplasmic ratio and show nuclear hyperchromasia and pleomorphism. Individual cell keratinization may be observed, but no keratin pearls are found. In some tumors, the nests are composed of small basaloid cells that show almost no signs of squamous differentiation. Mitoses are prominent and often atypical.

Invasive squamous cell carcinoma also may be classified as keratinizing and nonkeratinizing. The keratinizing squamous cell carcinoma is usually well-differentiated, whereas the nonkeratinizing squamous cell carcinoma is moderately to poorly differentiated. Several additional

microscopic subtypes are recognized, and these rare forms include the following:

- **Basaloid squamous cell carcinoma.** This tumor is composed of sheets of small, ovoid cells resembling those in VIN 3. It tends to occur in younger women infected with HPV.
- **Sarcomatoid squamous cell carcinoma.** This is a poorly differentiated carcinoma, and immunohistochemistry may be needed to distinguish it from sarcoma.
- **Verrucous squamous cell carcinoma.** This rare well-differentiated squamous cell carcinoma forms papillary fronds and resembles condyloma acuminatum. It is related to HPV infection, and typically it evokes an inflammatory reaction in the underlying stroma. It occurs in younger women.
- **Warty squamous cell carcinoma.** This is a rare exophytic tumor, composed of papillae covered with a thick layer of parakeratosis and keratosis. It contains koilocytes, and typically is associated with HPV infection.
- **Keratoacanthoma-like squamous cell carcinoma.** This low-grade tumor grows fast but does not invade or metastasize. Typically, it occurs on the hair-covered part of the vulva and is identical to keratoacanthoma-like squamous cell carcinomas on other parts of the skin.

Comments

1. Most vulvar and vaginal squamous cell carcinomas are moderately differentiated. Well-differentiated and poorly differentiated squamous cell carcinomas occur less frequently.

2. The tumor grade is directly related to the risk for lymph node metastasis and the overall prognosis (2).

3. Grading and staging are important prognostic predictors for vulvar squamous cell carcinomas. Additional immunohistochemical studies do not seem to contribute significantly to the data obtained by thorough clinicopathologic work-up (2,3).

Tumors of the Vagina

Tumors of the vagina are less common than those of the vulva or the cervix. Most of these tumors originate from the squamous epithelium. Glandular and mesenchymal tumors are rare.

Squamous cell neoplasms of the vagina, which account for over 95% of all vaginal cancers, occur in invasive and pre-invasive form. Pre-invasive neoplasms are identical to intraepithelial squamous cell lesions of the vulva and cervix. These lesions are called vaginal intraepithelial neoplasia (VAIN), and are graded on a scale from 1 to 3, as mild, moderate, or severe, respectively. Invasive tumors present as keratinizing or nonkeratinizing squamous cell carcinomas are identical to those in the vulva or the cervix.

Cervical Intraepithelial Neoplasia

Essentially, all squamous cell carcinomas of the ectocervix are preceded by cervical intraepithelial neoplasia (CIN), and in most instances are related to infection with human papilloma viruses (4,5). CIN can be diagnosed reliably by exfoliative cytology and in histologic sections of the cervical lesions.

CIN is graded on a scale from 1 to 3, designated as mild, moderate, or severe squamous dysplasia, respectively. The rubric CIN 3 includes not only severe dysplasia but also carcinoma in situ of the cervix; these 2 lesions cannot be separated objectively.

Intraepithelial lesions also may be graded in a binary system as low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL). A comparison of the 3-tiered and the 2-tiered grading systems, the Bethesda cytologic system, and the HPV risk group is presented in Table 10-1.

Although there is still some interobserver variation (6), the 3-tiered system of grading is currently the most

Table 10-1. Grading and classification of intraepithelial lesions of the cervix.

Descriptive terminology	Three-tiered grading system	Two-tiered grading system	Bethesda system (cytology)	HPV-risk category
Mild squamous dysplasia	CIN 1	Low-grade CIN	LSIL	Low to high
Moderate squamous dysplasia	CIN 2	High-grade CIN	HSIL	High
Severe squamous dysplasia	CIN 3	High-grade CIN	HSIL	High

Abbreviations:
CIN—cervical intraepithelial neoplasia
LSIL—Low-grade squamous intraepithelial lesion
HSIL—high-grade squamous intraepithelial lesion
Source: Modified from Dallenbach-Hellweg et al., 2006.

widely used (Figure 10-2). It includes the following categories:

- **CIN 1, mild squamous dysplasia.** This lesion results from HPV infection, causing disorderly proliferation of cells in the lower third of the epithelium. These layers are widened and lack normal polarization, but are still distinct from the 2 surface layers, which show layering and signs of squamous maturation. The cells have enlarged hyperchromatic nuclei. In the lower layers, nuclear enlargement results in a high nucleocytoplasmic ratio. In the upper layers, nuclear enlargement results in the formation of koilocytes, which have an optically clear cytoplasm and contain enlarged hyperchromatic nuclei of irregular contours ("raisinoid nuclei"). These nuclei are excentrically located and appear to be in contact with the cell membrane on 1 side. Mitoses may be observed, but they are confined to the basal layer and do not show morphologic atypia.
- **CIN 2, moderate squamous dysplasia.** This lesion shows marked cellular atypia and a loss of cellular polarity throughout the lower two-thirds of the epithelium, while the upper third shows good layering of cells and surface squamous maturation. Nuclear enlargement, atypia, and hyperchromasia are prominent, but mitoses are limited to the lower two-thirds of the epithelium. Abnormal mitotic figures may be present.
- **CIN 3, severe squamous dysplasia/carcinoma in situ.** The epithelium displays no signs of layering or maturation. From bottom to top, it is composed of atypical cells that have a high nucleocytoplasmic ratio. These basaloid cells (called thus because they resemble normal basal cells) have spindle-shaped or irregularly shaped enlarged hyperchromatic nuclei, arranged disorderly and without polarization. Mitotic figures are numerous and are found at random, at all levels. The surface may show focal parakeratosis or hyperkeratosis. Abnormal mitoses are common.

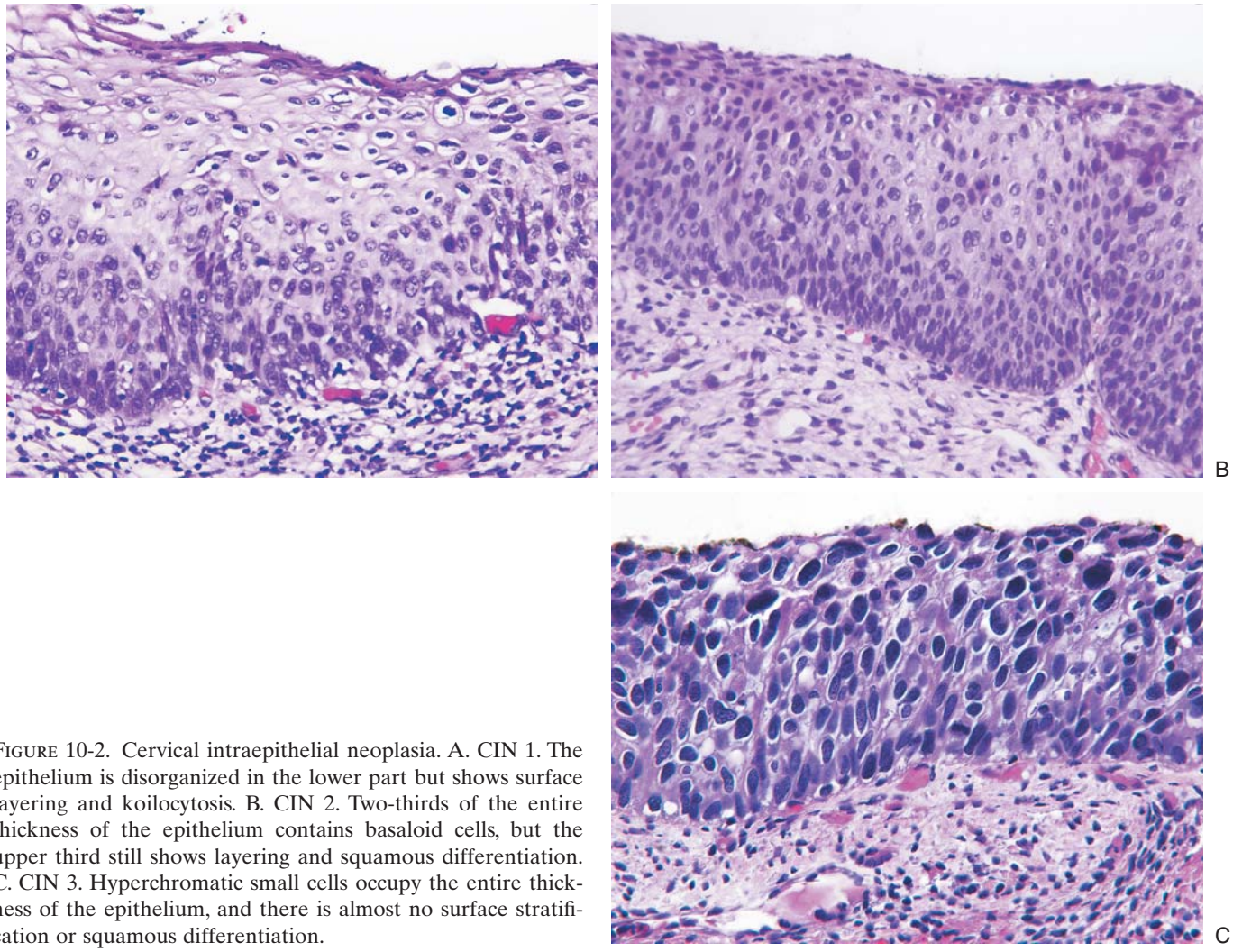


FIGURE 10-2. Cervical intraepithelial neoplasia. A. CIN 1. The epithelium is disorganized in the lower part but shows surface layering and koilocytosis. B. CIN 2. Two-thirds of the entire thickness of the epithelium contains basaloid cells, but the upper third still shows layering and squamous differentiation. C. CIN 3. Hyperchromatic small cells occupy the entire thickness of the epithelium, and there is almost no surface stratification or squamous differentiation.

Comments

1. CIN can involve foci of intraglandular squamous metaplasia in the endocervix. These changes must be distinguished from metaplasia and should not be mistaken for invasive carcinoma.

2. CIN 3 may be associated with micro-invasive or overtly invasive squamous cell carcinomas. However, even with the modern technology available in the laboratory, it is difficult to predict which CIN will progress to invasive carcinoma (7). The transition of CIN into invasive squamous cell carcinoma should be suspected in all cases that show any of the following features:
   - Involvement of broad areas of the cervix
   - Multifocal and deep extension into the glands of the endocervix
   - Marked thickening of the dysplastic epithelium and exophytic papillary growth pattern
   - Foci of squamous differentiation scattered at random, and especially if found in the basal zones
   - Foci of surface necrosis of the dysplastic epithelium
   - Extensive chronic inflammation in the stroma underneath the dysplastic epithelium

3. Immunohistochemistry with antibody MIB-1 (Ki-67) shows high proliferative activity in all layers of CIN 3. This is in sharp contrast to the normal epithelium and low-grade dysplasia, in which MIB-1 reacts with nuclei of the basal and parabasal layer only (see Dallenbach-Hellweg et al., 2006).

Invasive Squamous Cell Carcinoma of the Cervix

Invasive squamous cell carcinoma is graded the same way as is squamous cell carcinoma in other anatomic sites:

- **Grade 1, well-differentiated squamous cell carcinoma.** This tumor is composed of cells that resemble normal squamous epithelium, with frequent formation of concentrically laminated keratin pearls and evident intercellular bridges. The cells have abundant eosinophilic cytoplasm, and their nuclei show mild atypia, with inconspicuous nucleoli and occasional mitosis.
- **Grade 2, moderately differentiated squamous cell carcinoma.** This tumor has cells with moderate amounts of cytoplasm and pleomorphic nuclei. Squamous differentiation of the tumor cells is still recognizable by occasional keratin pearl formation and individual cell keratinization. Mitoses are easily identified.
- **Grade 3, poorly differentiated squamous cell carcinoma.** The tumor cells have a high nucleocytoplasmic ratio, marked nuclear pleomorphism, and abundant mitosis, including some atypical forms. Individual keratinized cells may be observed, but no keratin pearl formation is identified. Rarely, spindle-shaped tumor cells predominate, resembling sarcoma.

Squamous cell carcinoma of the cervix is moderately differentiated in about two-thirds of all cases (Figure 10-3); the well-differentiated and poorly differentiated forms are less common. Several microscopic variants are recognized, as follows:

- **Nonkeratinizing squamous cell carcinoma.** This is the most common form of cervical cancer, accounting for 65% of all cases. Most of them show only abortive squamous differentiation and are classified as moderately differentiated squamous cell carcinoma.
- **Keratinizing squamous cell carcinoma.** This tumor shows signs of squamous differentiation (intercellular bridges, keratohyalin granules, and dyskeratosis) and forms keratin pearls. They are usually well- or moderately differentiated squamous cell carcinoma.
- **Basaloid squamous cell carcinoma.** This high-grade, aggressive tumor is composed of small hyperchromatic cells bearing some resemblance to the basaloid cells in CIN 3.
- **Papillary squamous cell carcinoma.** This tumor contains papillae lined by epithelium that resembles CIN 3, and also shows focal invasion of the stroma. It reveals focal areas of squamous differentiation and is usually classified as moderately differentiated.
- **Verrucous squamous cell carcinoma.** This tumor is well-differentiated and shows prominent surface keratinization.
- **Lymphoepithelioma-like squamous cell carcinoma.** These tumors resemble those of the nasopharynx and

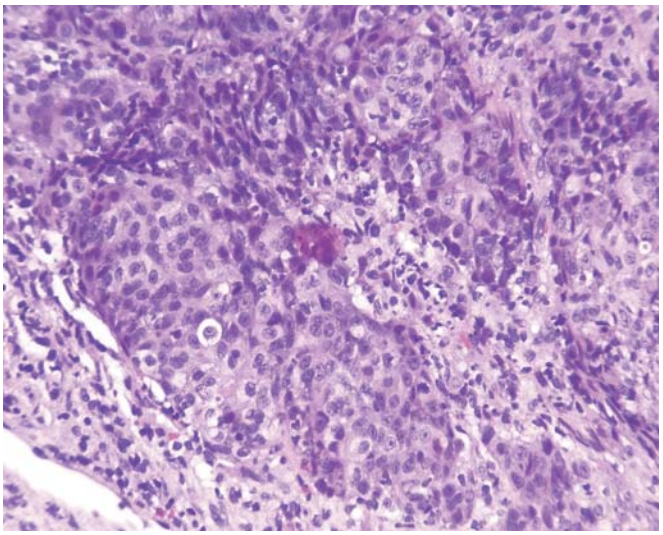


FIGURE 10-3. Invasive squamous cell carcinoma of the cervix. The tumor is composed of sheets of squamous cells that show minimal keratinization.

are composed of nests of poorly differentiated squamous cells intermixed with lymphocytes.

Adenocarcinoma of the Cervix

In most instances, invasive adenocarcinoma of the cervix is preceded by intraepithelial neoplasia (8). Invasive adenocarcinoma is graded as follows:

- **Grade 1, well-differentiated adenocarcinoma.** This neoplasm consists mainly of glands, with the solid components forming only 5% of the entire tumor.
- **Grade 2, moderately differentiated adenocarcinoma.** This tumor has glands, but solid areas comprise 5% to less than 50% of the mass.
- **Grade 3, poorly differentiated adenocarcinoma.** Poorly differentiated cells form solid masses that account for more than 50% of the entire tumor mass.

In addition to adenocarcinomas that cannot be further classified (adenocarcinoma, NOS, or not otherwise specified), several microscopic subtypes of endocervical carcinoma are recognized (9):

- **Mucinous adenocarcinoma.** This tumor may occur in several grades, i.e., well-differentiated, moderately differentiated, or poorly differentiated. Several variants are recognized, including minimal deviation adenocarcinoma, as well as endocervical, intestinal, villoglandular, and signet ring variants of endocervical adenocarcinoma.
- **Endometrioid adenocarcinoma.** This tumor is usually well to moderately differentiated and resembles endometrioid carcinomas of the uterus.
- **Clear cell adenocarcinoma.** This high-grade tumor consists of clear or hobnail-like cells arranged into solid areas and tubular glands or lining papillae. It resembles clear cell carcinomas of the ovary.
- **Serous adenocarcinoma.** This high-grade tumor resembles serous adenocarcinoma of the ovary.
- **Mesonephric adenocarcinoma.** This tumor develops from mesonephric remnants in the lateral and posterior wall of the cervix. It forms several glandular patterns, and hyaline material may be found in the lumen. It may be well-, moderately, or poorly differentiated.
- **Adenosquamous carcinoma.** This is an aggressive tumor and tends to metastasize more often than common adenocarcinomas or squamous cell carcinomas.
- **Adenoid cystic carcinoma.** This rare tumor is a low-grade neoplasm and may be found incidentally in cervices biopsied or removed for some other conditions.

Comments

1. Adenocarcinoma (NOS), mucinous, and endometrioid carcinomas account for the vast majority of all endocervical cancers. The prognosis is mostly stage dependent, and the grading is of limited prognostic significance.
2. Early adenocarcinoma showing subtle invasiveness may be difficult to identify in biopsy material.
3. Invasive adenocarcinoma of the endocervix may resemble adenocarcinomas of the endometrium, and from which it may be impossible to distinguish in some cases. Similarly, if a serous or clear cell carcinoma is identified in the cervix, it is important to first exclude a metastasis from an ovarian tumor, before a diagnosis of a primary cervical tumor is made.

Adenocarcinoma of the Endometrium

Endometrial adenocarcinoma is the most common malignant tumor of the uterus. These tumors can be subdivided into 2 major groups:

- **Type I.** This group comprises estrogen-related endometrioid carcinomas, which account for the majority (80%) of endometrial carcinomas.
- **Type II.** Tumors of this group are not pathogenetically related to estrogen, and occur more often in postmenopausal women. These tumors often resemble ovarian carcinomas and include several microscopic forms.

Type I, Estrogen-Related ("Endometrioid") Adenocarcinoma

This tumor develops in women in age 40 to 65 years, usually in the context of endometrial hyperplasia. The most recent revisions of the grading and staging systems devised by the International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization recommend that the endometrial adenocarcinomas be graded using both architectural and nuclear features.

Nuclear grading of endometrioid endometrial adenocarcinoma according to FIGO takes into account the size and the shape of nuclei. Three nuclear grades are recognized:

- **Grade 1.** Tumors of this group have mildly enlarged, oval, or round uniform nuclei with evenly dispersed chromatin and inconspicuous or very small nucleoli. Nuclei are in a single row or slightly stratified. Mitoses are rare.

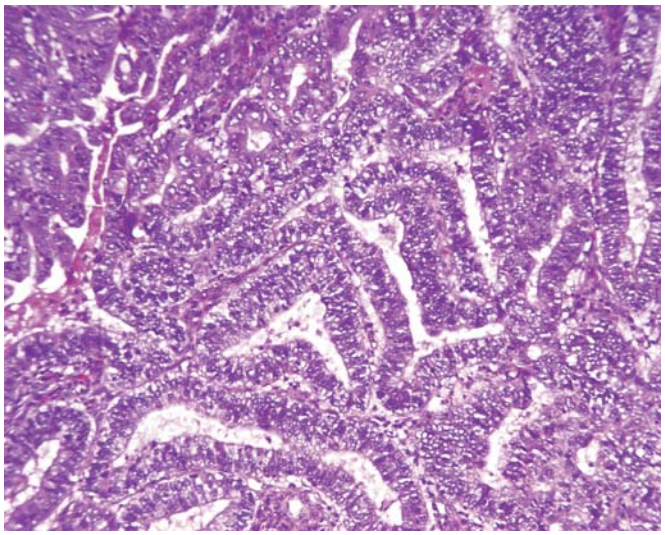
- **Grade 2.** The tumor cells have moderately enlarged nuclei, which vary in size and shape. The nucleoli are small but evident. There is variable mitotic activity.
- **Grade 3.** The tumor cells have markedly enlarged and pleomorphic nuclei that contain irregularly coarse chromatin and prominent nucleoli. Mitoses are frequent and may occur in atypical forms.

FIGO's architectural grading of endometrial adenocarcinoma takes into account the proportion of glandular and solid areas (Figure 10-4). The tumors are graded as well-differentiated (50%), moderately differentiated (35%), and poorly differentiated (15%), as follows:

- **Grade 1, well-differentiated adenocarcinoma.** This tumor is composed almost entirely of well-formed glands; solid areas account for less than 5% of the total mass. It may contain foci of squamous epithelium or show morular growth, but these should not be counted as solid areas.
- **Grade 2, moderately differentiated adenocarcinoma.** This tumor has well-formed glands as well, but also contains 6% to 50% solid areas. As in grade 1 tumors, squamous and morular areas should not be taken into account when calculating the extent of the solid areas.
- **Grade 3, poorly differentiated adenocarcinoma.** The solid parts predominate in this tumor, forming more than 50% of the mass.

Several variants of endometrioid adenocarcinoma are recognized, (10–12) which can also be graded according to FIGO. These variants include the following:

- Variant with squamous differentiation
- Villoglandular variant
- Secretory variant
- Ciliated cell variant



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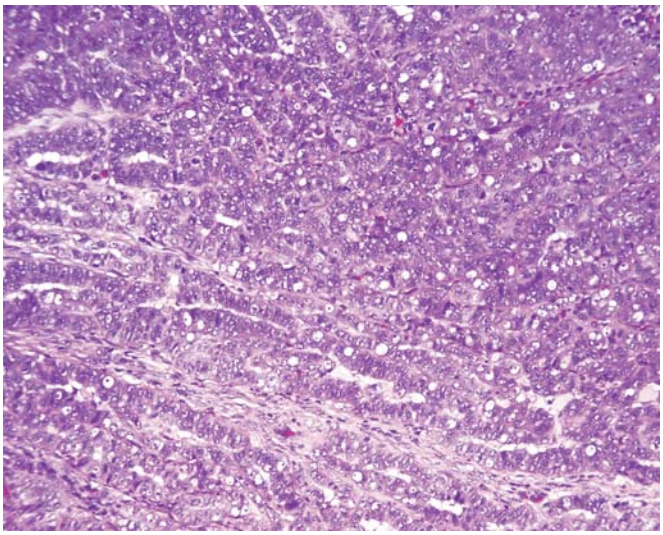

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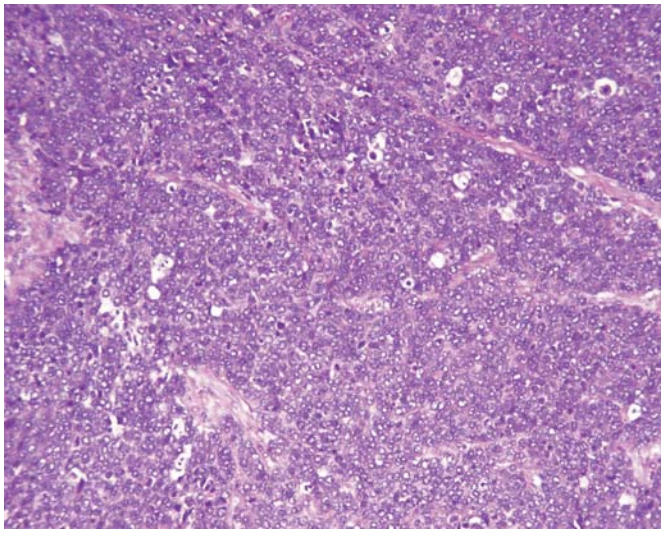

C

FIGURE 10-4. Endometrioid adenocarcinoma. A. Grade 1, well-differentiated adenocarcinoma, shows cells forming glands. B. Grade 2, moderately differentiated adenocarcinoma, consists of solid and glandular areas. C. Grade 3, poorly differentiated adenocarcinoma, contains mostly solid sheets of cells.

Type II, Non-Estrogen-Related Adenocarcinoma

These tumors are less common than endometrioid adenocarcinomas, and usually develop in older women and in the background of endometrial atrophy. This group includes the following tumor types:

- **Mucinous adenocarcinoma.** This tumor is usually low grade.
- **Serous adenocarcinoma.** This tumor is high grade.
- **Clear cell adenocarcinoma.** This tumor is high grade.
- **Squamous cell carcinoma.** The grade of this tumor varies.
- **Transitional cell carcinoma.** This tumor is usually grades 2 and 3.
- **Small cell carcinoma.** This high-grade tumor resembles oat cell carcinoma of the lung.
- **Undifferentiated carcinoma.** This tumor is high grade.

Comments

1. The nuclear and the architectural grades of endometrioid adenocarcinoma usually correspond to each other. In the presence of marked nuclear atypia and of bizarre nuclei, one should raise the architectural FIGO grade of grade 1 tumors to 2, and of grade 2 tumors to 3.

2. Adenocarcinoma with squamous differentiation is graded according to the nuclear grade of the glandular component.

3. In serous adenocarcinoma, clear cell adenocarcinoma, and squamous cell carcinoma, the nuclear grade takes precedence over the architectural grade.

4. Mixed adenocarcinoma is a term used for tumors that contain both type I endometrioid and type II non-estrogen-related adenocarcinoma. The minor component must exceed 10% of the total tumor mass. Tumors containing more than 25% of type II tumors have a poor prognosis.

Smooth Muscle Cell Tumors

Smooth muscle cell tumors may be divided into 3 groups: benign (leiomyoma), malignant (leiomyosarcoma), and tumors of unknown malignant potential (STUMP) (13,14).

Leiomyoma is the most common benign uterine tumor. It is composed of smooth muscle cells and fibroblasts (Figure 10-5). Microscopically, the tumors are composed of fascicles of uniform spindle cells with elongated, blunt-ended nuclei, fine chromatin, small nucleoli, and eosinophilic abundant cytoplasm. Mitoses are infrequent (usually less than 5 per 10 high-power fields [hpf]). Hemorrhage, edema, myxoid degeneration, and hyaline fibrosis are common.

Several forms of leiomyoma are recognized. The most important that could be mistaken for leiomyosarcoma are:

- **Cellular leiomyoma.** This variant is characterized by prominent cellularity when compared to the surrounding myometrium. However, there is no coagulative tumor necrosis, and no nuclear atypia or mitotic activity, which allow these tumors to be distinguished from leiomyosarcoma.
- **Mitotically active leiomyoma.** This variant has all the cellular and architectural features of typical leiomyomas, but shows an increased mitotic activity (>5 per 10 hpf) . This diagnosis should be limited to tumors that display no significant marked nuclear atypia, and contain no atypical mitosis, and no coagulative necrosis.

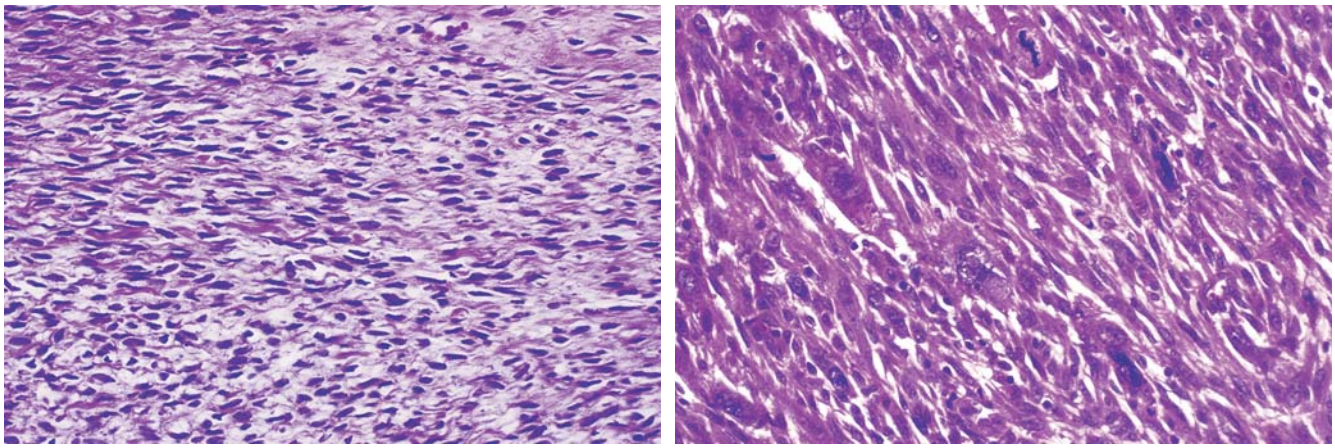

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FIGURE 10-5. Smooth muscle cell tumors of the uterus. A. Leiomyoma is composed of uniform smooth muscle cells and fibroblasts. B. Leiomyosarcoma is composed of hyperchromatic cells showing nuclear pleomorphism. Mitotic figures are numerous.

- **Atypical leiomyoma.** This tumor, also known as symplastic, pleomorphic, or bizarre leiomyoma, shows marked nuclear atypia and intranuclear inclusions of cytoplasm. However, these nuclear changes are not associated with other features of malignancy of smooth muscle cell tumors. Thus, they show low mitotic activity (<10 mitoses per 10 hpf) and contain no areas of coagulative tumor cell necrosis.
- **Smooth muscle tumor of uncertain malignant potential (STUMP).** This term is used for tumors that cannot be histologically diagnosed with certainty as benign or malignant. In general, STUMPs differ from leiomyomas and have some but not all features of leiomyosarcomas. The uterine smooth muscle cell tumors are diagnosed as STUMPs when the tumors have the following features:
  1. Coagulative necrosis is present, but there is no increased mitotic activity and the nuclear atypia is not diffuse.
  2. Increased mitotic activity (up to 15 mitoses per 10 hpf) is combined with focal atypia, but there is no diffuse atypia or any evidence of necrosis.
  3. There is diffuse atypia, but there is no increased mitotic activity or any evidence of coagulative necrosis.
- **Leiomyosarcoma.** While this is a rare tumor, it represents the most common uterine sarcoma. Microscopically, it is hypercellular and composed of atypical spindle cells with hyperchromatic nuclei. The diagnosis is based on finding coagulative necrosis, increased mitotic activity, or cellular atypia, in any of the following combinations:
  1. Coagulative necrosis, more than 10 mitoses per 10 hpf, with or without cellular atypia.
  2. Coagulative necrosis, 10 or fewer than 10 mitoses per hpf, with moderate to severe cellular atypia.
  3. No evidence of necrosis, but more than 10 mitoses per 10 hpf, and diffuse moderate to severe cellular atypia.

Adenocarcinoma of the Fallopian Tube

Adenocarcinoma of the fallopian tube is rare. Morphologically, it has the same features as endometrial or ovarian carcinomas and is graded according to the same principles (15).

Ovarian Adenocarcinoma

Ovarian epithelial tumors account for two-thirds of all ovarian neoplasms and the vast majority of malignant ovarian tumors (16,17). Depending on the type of epithelial differentiation, they are classified as serous, mucinous, endometrioid, clear cell, and transitional or squamous epithelial-like. Clinicopathologically, these tumors are classified as benign, malignant, or borderline malignant.

Malignant epithelial tumors of the ovary generally are classified as adenocarcinoma and are graded according to the FIGO classification of endometrial adenocarcinomas. Thus, adenocarcinomas of the ovary are given both a nuclear and an architectural grade on a scale from 1 to 3.

The nuclear grade according to FIGO is assigned as follows:

- **Grade 1.** Tumors of this group have mildly enlarged, uniform nuclei with evenly dispersed chromatin and inconspicuous or very small nucleoli. The nuclei are in a single row or slightly stratified, and mitoses are rare.
- **Grade 2.** These tumor cells have moderately enlarged nuclei, which vary in size and shape. The nucleoli are small but evident. There is variable mitotic activity.
- **Grade 3.** These tumor cells show markedly enlarged and pleomorphic nuclei that contain irregularly coarse chromatin and prominent nucleoli. Mitoses are frequent, with atypical forms.

The FIGO architectural grade is assigned as follows:

- **Grade 1, well-differentiated adenocarcinoma.** These tumors are composed predominantly of glands, with solid areas forming less than 5% of the total tumor mass.
- **Grade 2, moderately differentiated adenocarcinoma.** These tumors are composed of glands, but contain prominent solid areas occupying 6% to 50% of the total tumor mass.
- **Grade 3, poorly differentiated adenocarcinoma.** In these tumors, the solid areas predominate, comprising more than 50% of the tumor mass.

Comment

1. The prognosis of ovarian adenocarcinomas is predominantly stage dependent, and grading is of limited prognostic value.

Germ Cell Tumors

Ovarian germ cell tumors are classified as benign or malignant. Teratoma, the most common benign germ cell tumor, accounts for more than 90% of the tumors in this group. Secondary malignancy can occur in teratomas that have been allowed to stay in the body until the woman reaches an older age. Such malignant tumors are rare and are classified as squamous cell carcinoma, adenocarcinoma, neuroectodermal tumors, or sarcomas. Primary malignant germ cell tumors are also uncommon and include dysgerminoma, embryonal carcinoma, yolk sac tumor, and choriocarcinoma. Except for dysgerminoma, all other primary germ cell tumors are high-grade malignancies and are not graded.

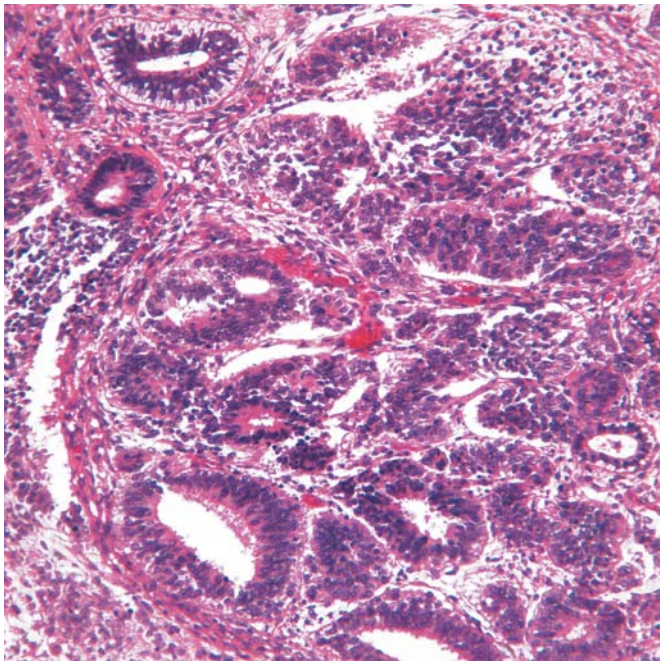

FIGURE 10-6. Immature teratoma of the ovary, grade 3. The tumor contains numerous neural tubes and rosettes.

Immature teratoma is the only germ cell tumor that is worth grading. Like the classical teratomas, these tumors contain various mature somatic tissues but also have immature tissues, most notably in the form of neuroectodermal tubes and rosettes (Figure 10-6)(18). Immature teratomas are graded on a scale from 1 to 3, as follows:

- **Grade 1.** This tumor contains only rare foci of immature neuroepithelial tissue, occupying less than 1 low-power field (lpf) in any slide.
- **Grade 2.** This tumor has more immature neuroepithelial tissues, which occupy more than 1, but less than 4, lpf.
- **Grade 3.** This tumor contains abundant neuroepithelial elements, occupying more than 4 lpf in any slide.

Comments

1. Immature ovarian teratomas may form peritoneal implants. These implants are composed of neuroepithelial tissue and should also be graded microscopically.
2. For proper grading, multiple sections of the primary tumor and the implants must be submitted.

Sex Cord Stromal Tumors

Sex cord stromal tumors account for less than 10% of all ovarian tumors. While they are mostly benign, some may be malignant. This group of tumors includes adult and juvenile granulosa cell tumors, Sertoli-Leydig cell tumors, fibromas, thecomas, and sclerosing stromal tumors of the ovary. These tumors are usually not graded, except for Sertoli-Leydig cell tumors.

All adult granulosa cell tumors are potentially malignant, and certain microscopic subtypes portend a more aggressive tumor growth. For example, adult granulosa cell tumors that are classified as diffuse (sarcomatoid) have a more aggressive behavior than microfollicular, macrofollicular, insular, or trabecular granulosa cell tumors. If removed in stage I, juvenile granulosa cell tumors have an excellent prognosis, but larger and more advanced tumors may progress and have a less favorable outcome. Microscopic grading has no clinical utility in either adult or juvenile granulose cell tumors, but it does in larger tumors.

Ovarian thecomas and fibromas are generally benign tumors. Fibrosarcoma, the malignant equivalent of fibroma, has all the features of malignancy and can be readily distinguished from benign stromal tumors.

Sertoli-Leydig Cell Tumor

Sertoli-Leydig cell tumors account for less than 1% of all ovarian tumors. This tumor occurs in several microscopic forms that predict their clinical behavior (Prat, 2004). The following are the variants and grades of Sertoli-Leydig cell tumors:

- **Well-differentiated.** This tumor consists of Sertoli cells arranged into tubules, surrounded by fibrous stroma and solid nests of Leydig cells.
- **Intermediate differentiation.** This tumor contains large nests of polygonal Leydig cells surrounded by immature Sertoli cells. These 2 components may be focally intermixed, and the Sertoli cells may even form abortive tubules.
- **Poorly differentiated (sarcomatoid variant).** This tumor is composed mainly of mitotically active, hyperchromatic, and anaplastic stromal cells and scattered foci of Leydig cells.
- **Retiform Sertoli-Leydig cell tumor.** This tumor resembles rete testis and is composed of inter-anastomosing clefts lined by cuboidal cells that often project into the lumen in form of papillae.
- **Sertoli-Leydig cell tumor with heterologous elements.** In about 20% of cases, Sertoli-Leydig cell tumors contain heterologous epithelial or stromal elements. Most Sertoli-Leydig cell tumors are benign. Poorly differentiated tumors, which account for 10% of all tumors in this group, are malignant. Adverse prognosis is also heralded by the presence of heterologous stromal elements (e.g., rhabdomyosarcoma-like cells) or carcinoid-like neuroendocrine nests.

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11
Tumors of the Breast

Fang Fan and Patricia A. Thomas

Introduction

Breast carcinoma is the most common malignant tumor in women in North America and Europe. Invasive mammary carcinoma, like the pre-invasive tumors that typically precede it, can be readily recognized and graded in surgically removed or biopsied tissue samples. The grading and staging of these tumors are of considerable clinical significance and are performed routinely.

Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) is a precursor of invasive carcinoma. Grading for DCIS is meaningful in predicting prognosis and guiding treatment. While there is no universally agreed-upon grading system for ductal carcinoma in situ, current practice is to grade it on the basis of nuclear characteristics in combination with necrosis, and not according to architectural features.

The current grading system published in the World Health Organization (WHO) monograph is a 3-tiered system (Tavassoli and Devilee, 2003). It incorporates the basic tenets of the Van Nuys grading scheme (1) and the approach outlined by Scott et al. (2), and is a refinement of the original classification published by Lagios et al. in 1989 (3). Like the classifications that preceded it, it is based on grading the tumor cell nuclei on a scale from 1 to 3, and by evaluating the intraluminal groups of tumor cells for the presence or absence of necrosis.

The nuclear grade is based on the size of the nuclei, the distribution of chromatin, and the presence or absence of nucleoli.

- **Grade 1.** The nuclei are small, round, and uniform. The nuclei of the tumor cells are of the same size as a red blood cell, or slightly larger. Their diameter does not exceed by more 1.5 times that of normal red blood cells. The nuclei contain uniformly dispersed chromatin, and the nucleoli are not apparent. Mitoses are rare.
- **Grade 2.** The tumor cell nuclei are enlarged and their diameter is equivalent to 1.5 to 2 times the size of red blood cells. The chromatin is coarse, but the nucleoli are infrequently seen. There are sparse mitoses.
- **Grade 3.** The tumor cell nuclei have a diameter greater than 2.5 that of red blood cells. The nuclei are vesicular, filled with irregularly clumped chromatin and of irregular contour. The nuclei contain 1 or more prominent nucleoli. There are frequent mitotic figures, but their presence is not required for grading.

Necrosis is either present or absent; if present, it typically involves the centrally located cells inside the ducts. Necrotic cells undergo karyorrhexis or pyknosis, and these signs of cell death are associated with a loss of nuclear details, clumping of chromatin, and fragmentation of nuclei. Necrosis must be distinguished from inspissated eosinophilic secretions, hemorrhage, foam cells, or debris without karyorrhexis of the tumor cells.

The final grade is assigned as follows:

- **Grade 1, low-grade DCIS.** The tumor cells have a nuclear grade of 1 or 2, and there is no necrosis (Figure 11-1).
- **Grade 2, intermediate-grade DCIS.** The tumor cells have nuclear grade of 1 or 2, but there is also necrosis (Figure 11-2).
- **Grade 3, high-grade DCIS.** The tumor cells have a nuclear grade of 3, with or without necrosis (Figure 11-3).

Ancillary methods may be used but are not essential for grading DCIS. They may be useful under certain circumstances to support the diagnosis and exclude other possibilities, as follows:

- Immunohistochemical stains for myoepithelial cells, including smooth muscle actin, calponin, and collagen

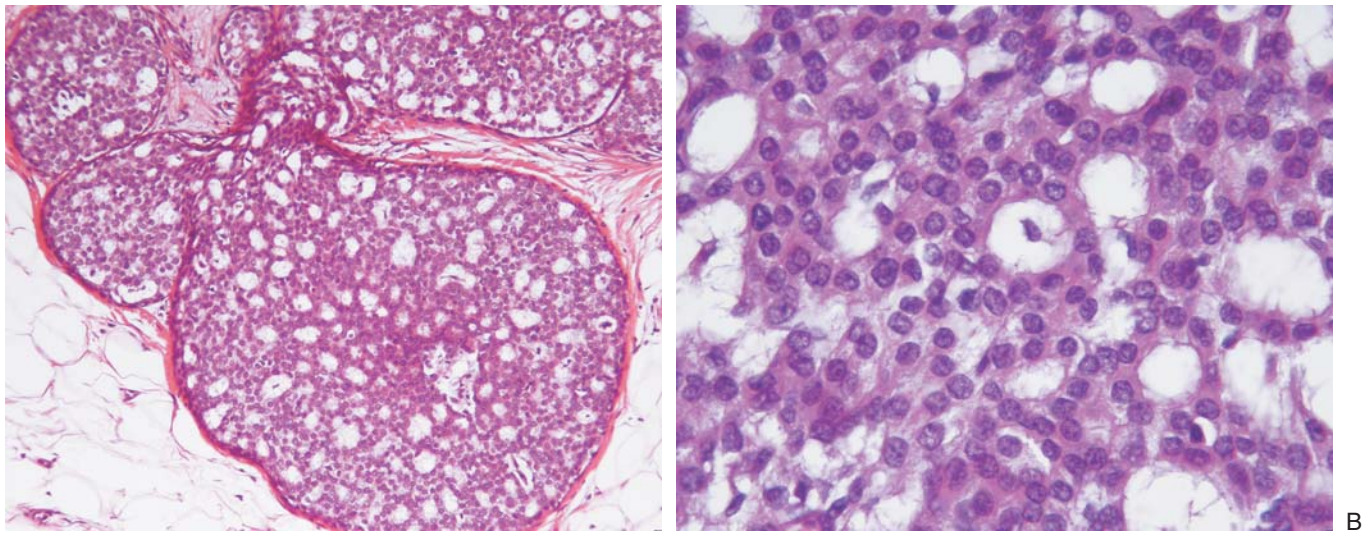

FIGURE 11-1. Low-grade DCIS, cribriform architecture. A. The ducts are distended by a monotonous population of cells with small, round to oval nuclei. No central necrosis is present. B. The cells have small nuclei (1–1.5 times that of red blood cells), dispersed chromatin, and indistinct nucleoli (nuclear grade 1).

IV, can be useful in cases where invasion is suspected (4).

- Immunohistochemical stains for E-cadherin and antibody 34βE12 to high molecular–weight keratin can help differentiate low-grade, solid type DCIS (E-cadherin positive, 34βE12 negative) from lobular neoplasia (E-cadherin negative, 34βE12 positive) (5).
- Immunohistochemical staining for estrogen receptor, progesterone receptor, and Her2/neu expression have prognostic, predictive, and therapeutic values.

Comments

1. The architecture pattern of ductal carcinoma in situ (comedo, cribriform, solid, papillary, and micropapillary) should be included in the pathology report, because certain architectural patterns carry independent prognostic significance (6, 7). DCIS with comedo necrosis is associated with a high risk of local recurrence and progression to invasive cancer. Micropapillary DCIS may be associated with more extensive disease in multiple quadrants.

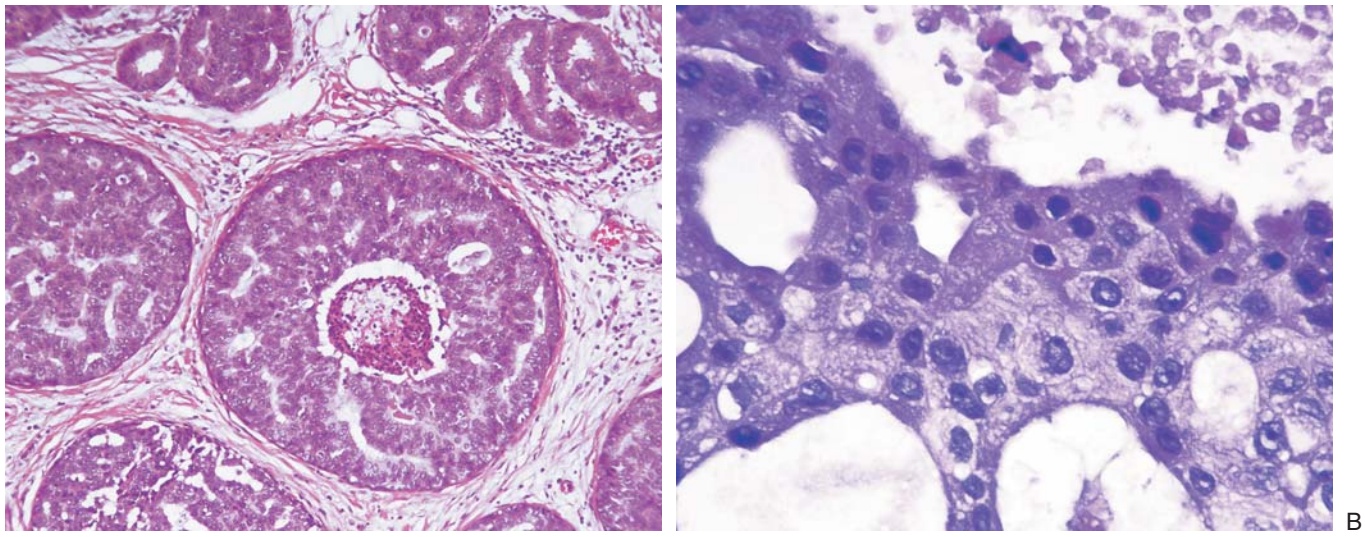

FIGURE 11-2. Intermediate-grade DCIS, cribriform architecture. A. The overall pattern is similar to low-grade lesions. There is a central area of necrosis. B. The nuclei are moderately enlarged (1.5–2 times that of red blood cells), with coarse chromatin and occasional prominent nucleoli (nuclear grade 2).

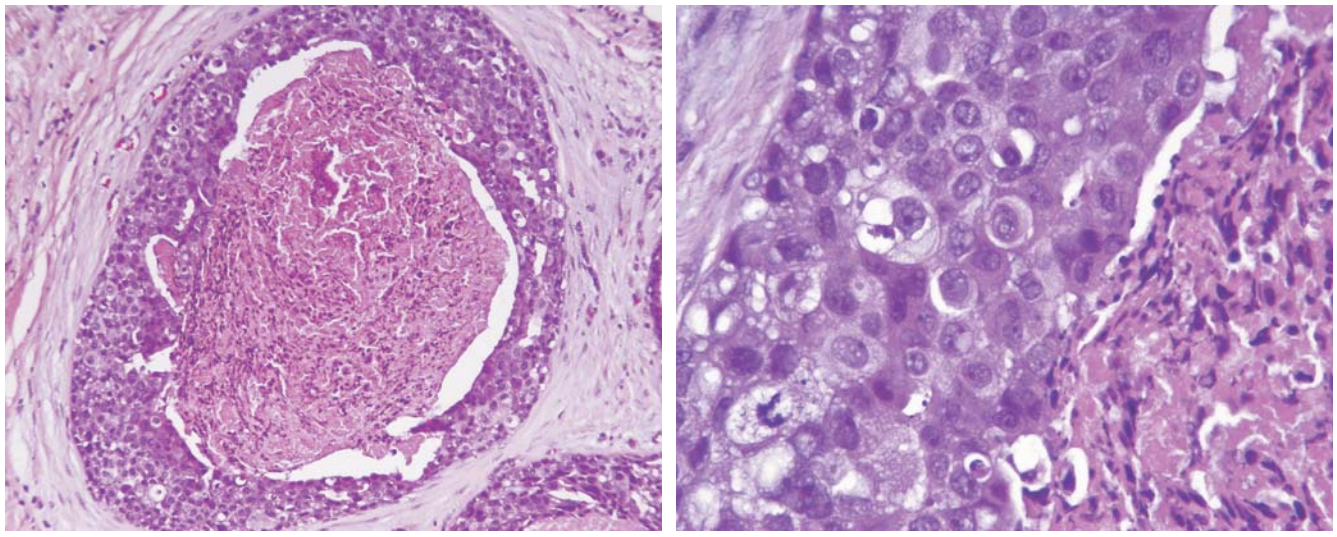

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FIGURE 11-3. High-grade DCIS, comedo type. A. Extensive central necrosis is surrounded by a rim of highly anaplastic tumor cells. B. The tumor cells have high-grade nuclei (greater than 2.5 times that of red blood cells in diameter) with marked pleomorphism, prominent nucleoli, and mitotic figures (nuclear grade 3).

2. The margin status and the extent (size) of disease are the other 2 important prognostic factors in the local control of DCIS, and should be documented in the pathology report (8).

3. There is no consensus on the approach to the grading of uncommon types of DCIS, such as apocrine, clear cell, spindle cell, signet ring, and neuroendocrine types.

4. The presence of microcalcifications must be documented and the microscopic findings correlated with mammographic films and/or specimen imaging.

Lobular Carcinoma In Situ

Tavassoli has proposed a 3-level scheme for stratifying lobular intraepithelial neoplasia (LIN 1, LIN 2, and LIN 3) (8). However, no grading system for lobular carcinoma in situ has been endorsed by the WHO expert panel on breast diseases.

Invasive Mammary Carcinoma

The relationship between breast cancer morphology or histology and survival was documented in 1920s and 1930s. Greenhough and his colleagues were the first to propose the idea of histologic grading in 1925. These investigators reviewed 73 cases of radical mastectomy specimens and assessed 8 morphological factors, including the degree of gland formation, the presence of secretory vacuoles, cell size, nuclear size, variation in the size of cells and nuclei, the degree of nuclear hyperchromatism, and the number of mitoses. Based on the overall evaluation of these 8 features, tumors were assigned a grade in a 3-tiered grading system. A clear association between tumor grade and 5-year "cure" was demonstrated. Current breast cancer grading studies stem from this work.

Patey and Scarff (9) followed Greenhough's method and developed their own grading systems, emphasizing the amount of tubule formation, variation in nuclear size, and hyperchromatism. They also found associations between grade and survival. However, the idea of breast grading did not gain much popularity among clinicians and pathologists at that time, in part due to the complexity and subjectivity of the grading system, and to the limitation of treatment options corresponding to different grades of the tumor.

In 1950, Bloom (ironically, a radiotherapist) reviewed the literature on breast cancer grading and decided to follow the Patey and Scarff method. He divided tumors into low, moderate, or high-grade malignancy according to the following 3 factors: (1) the degree of tubule formation, (2) the regularity in the size, shape, and staining character of the nuclei, and (3) nuclei hyperchromasia and mitotic activity. He found a clear correlation between tumor grading and 5- and 10-year survival. Following this, in 1957, Bloom and Richardson (10) first proposed a numerical scoring system to facilitate the grading effort. Each of the above 3 features was examined and given a score of 1, 2, or 3, with a total possible score of 3 to 9 points. Then the final grade was assigned as grade I for a score of 3 to 5, II for a score of 6 to 7, and III for a score of 8 to 9. This method was later recommended as the preferred grading system for breast cancer by WHO experts in 1968.

In the meantime, Black and colleagues concluded that only nuclear morphology is the most significant prognostic factor. Their nuclear grade evaluation was based on the regularity of the nuclear outline, the delicacy of the chromatin, nucleoli, and the presence and number of mitotic figures. However, this 5-grade system was in reverse numerical order to common practice in that grades 0 and 1 represent the most poorly differentiated nuclei. In 1980, Fisher and colleagues modified Black's system, reducing it to a 3-grade system and reversing its numerical order to be consistent with other grading schemes. He then combined nuclear grade and tubule formation in evaluating the histologic grade of a tumor.

It was not until the early 1990s that Elston and Ellis (11) re-examined and modified the grading system by combining the Bloom and Richardson system with Black's approach. The most important modification was to delete the "nuclear hyperchromasia" in the Bloom and Richardson system and introduce an objective and numerical method to assess the mitotic count. They also clearly defined the criteria for the other 2 features examined (tubule formation and nuclear pleomorphism). This Elston and Ellis system, also referred to as the Nottingham modification of the Bloom-Richardson system, soon became popular and widely used. It has held up as a statistically significant prognostic factor. It is currently recommended by the World Health Organization for use in all cases of invasive breast cancers.

Elston and Ellis's modification of the Scarff-Bloom-Richardson method is the most widely used grading system of invasive breast carcinoma. Recently, it has been recommended by the panel of WHO experts and is outlined in the monograph edited by Tavassoli and Devilee (2003). It includes 3 components: evaluation of the extent of the formation of tubules and glands, an estimation of the degree of nuclear pleomorphism, and the counting of mitoses.

Tubule and gland formation are assessed and given 1 to 3 points, as follows:

- One point. Tubules or glands formed in >75% of the tumor.
- Two points. Tubules or glands formed in 10% to 75% of the tumor.
- Three points. Few, if any, tubules formed, accounting for <10% of the tumor.

Nuclear pleomorphism is assessed and given 1 to 3 points, as follows:

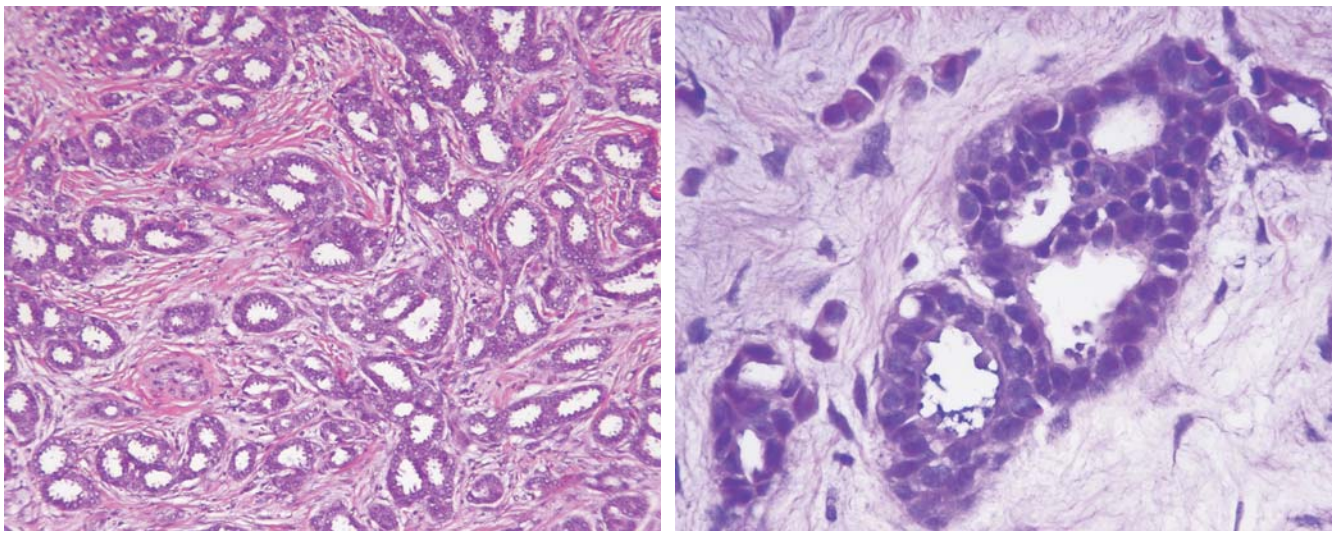
- One point. Tumor nuclei are small, regular, and uniform.
- Two points. Tumor nuclei are moderately increased in size and show variability.
- Three points. Tumor nuclei show marked variation.

Mitotic figures are counted, and the scores are converted into 1 to 3 points, as follows:

• Field diameter (mm)	0.44	0.59	0.63
• Field area (mm^2)	0.152	0.274	0.312
• One point. Mitotic count	0–5	0–9	0–11
• Two points. Mitotic count	6–10	10–19	12–22
• Three points. Mitotic count	>11	>20	>23

The final grade, combining values of the above 3 features, is calculated as follows:

- **Grade 1, well-differentiated carcinoma**. 3 to 5 points (Figure 11-4)



A B

FIGURE 11-4. Invasive well-differentiated ductal carcinoma. A. The majority of tumor is formed of well-recognized tubules/glands (tubule formation >75%, score 1). B. Tumor nuclei are small and uniform, with minimal pleomorphism (nuclear grade 1). Mitosis is rare (score 1). The final histological grade is 3 out of a total score of 9, indicating a grade 1 (well-differentiated) breast carcinoma.

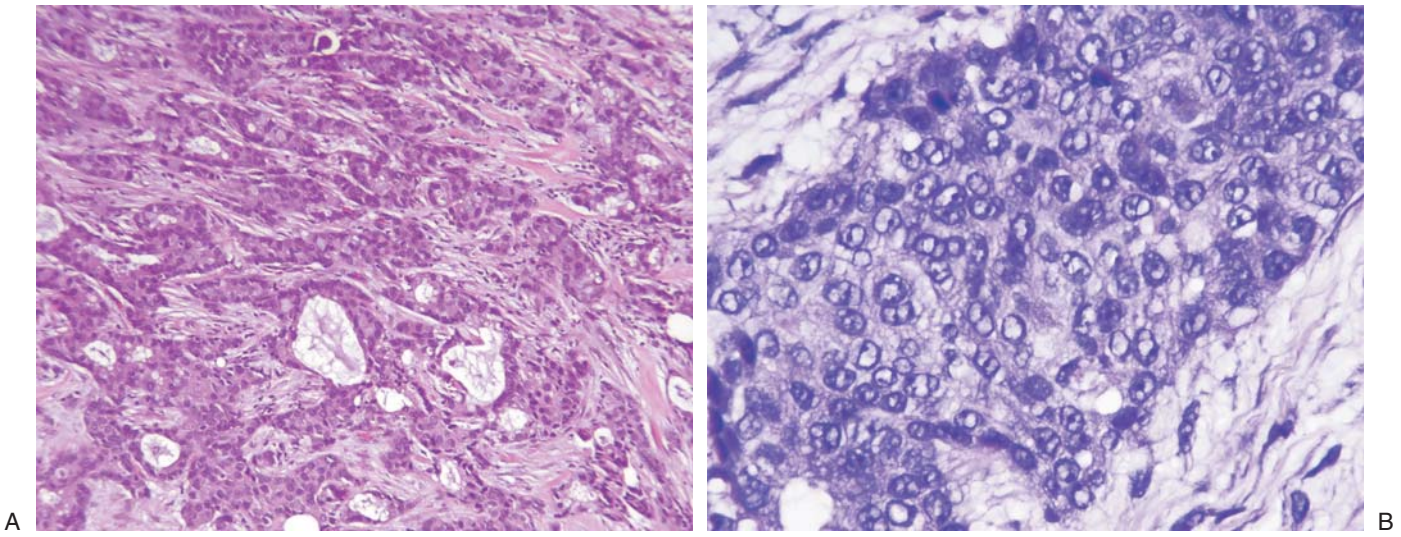


FIGURE 11-5. Invasive moderately differentiated ductal carcinoma. A. Tumor cells grow in solid cords and nests, with occasional recognizable tubules/glands (tubule formation <10%, score 3). B. Tumor nuclei are moderately increased in size, with mild pleomorphism (nuclear grade 2). Rare mitoses are seen (2/10 hpf, 0.59 field diameter, score 1). The final histological grade is 6 out of a total of 9, indicating a grade 2 (moderately differentiated) breast carcinoma.

- **Grade 2, moderately differentiated carcinoma.** 6 to 7 points (Figure 11-5)
- **Grade 3, poorly differentiated carcinoma**. 8 to 9 points (Figure 11-6)

Ancillary methods are not essential for grading, but they may be used for special purposes, as follows:

- Immunohistochemical stains for epithelial and myoepithelial markers can be helpful in cases when invasion is questionable.
- Immunohistochemical stains for E-cadherin can be useful in differentiating invasive ductal carcinoma (E-cadherin positive) from invasive lobular carcinoma (E-cadherin negative).
- Immunohistochemical staining for estrogen receptor, progesterone receptor, and Her2/neu expression have prognostic and therapeutic values and should be performed in all invasive carcinoma cases.
- Ki-67 has been suggested as an objective substitute for mitotic counts in the grading system (12–14).

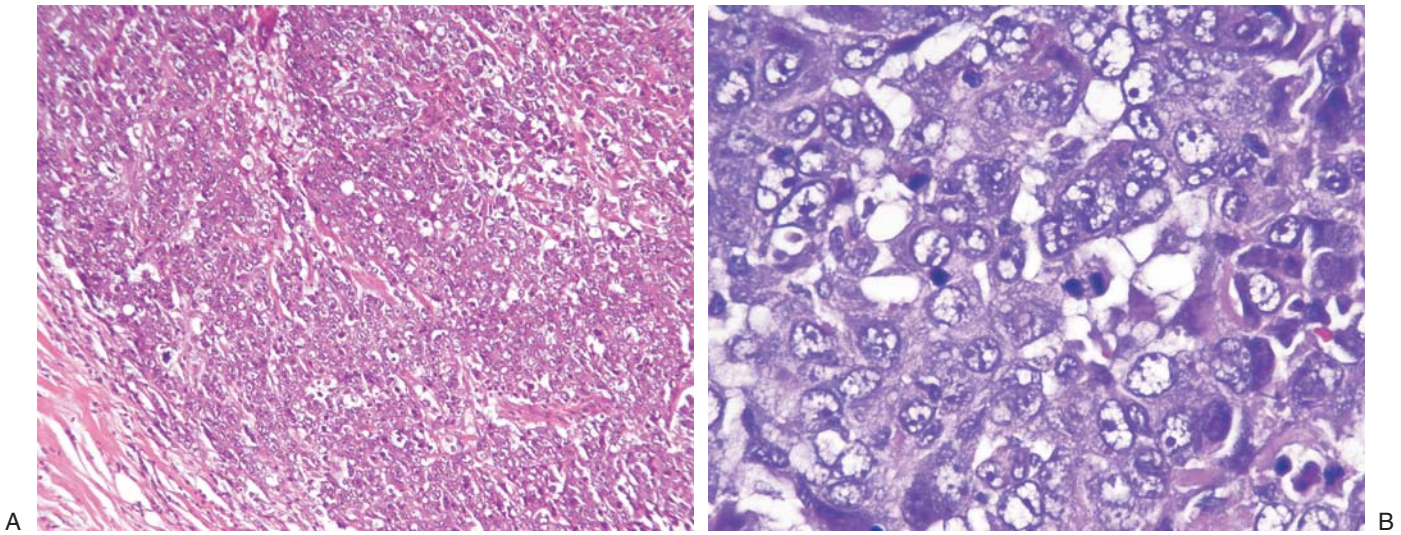


FIGURE 11-6. Invasive poorly differentiated ductal carcinoma. A. There is no evidence of glandular formation (tubule formation <10%, score 3). B. Tumor cells are large with marked pleomorphism (nuclear grade 3). Numerous mitoses are seen, with some atypical forms (more than 20 per 10 hpf, 0.59 field diameter, score 3). The final histological grade is 9 out of a total of 9, indicating a grade 3 (poorly differentiated) breast carcinoma.

- Measurement of the degree of genomic instability in breast carcinomas may improve grading at the genetic level (15).

Comments

1. Nuclear grade is an independent prognostic marker in addition to the histologic grade, and should be mentioned separately in the pathology report.
2. All invasive carcinomas, including invasive ductal carcinoma, invasive lobular carcinoma, and special types (medullary carcinoma, tubular carcinoma, mucinous carcinoma, and the like) are graded using this system.
3. Tumor size and margin should be documented in the pathology report.

Phyllodes Tumors

Phyllodes tumors are biphasic tumors characterized by leaf-like structures lined by a double-layered epithelial component, surrounded by overgrowing hypercellular stroma. Depending on the cellularity and atypia of the stromal component, they may have features of benign tumors and resemble fibroadenomas, or be malignant and share features with breast sarcoma.

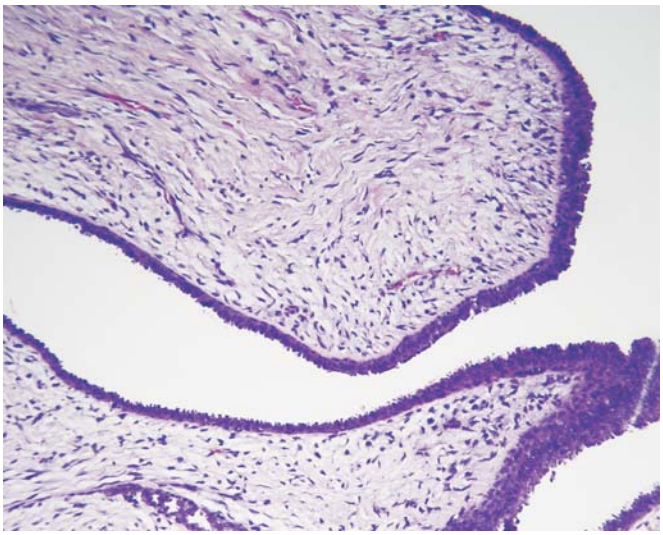
The grading of phyllodes tumors is described in detail in the WHO monograph (Tavassoli and Devilee, 2003). On the basis of stromal cellularity, cellular pleomorphism, mitotic activity, the appearance of margins, and stromal distribution, phyllodes tumors are divided into 3 groups and labeled either benign, borderline, or malignant.

- **Benign phyllodes tumor.** This tumor shows modest stromal cellularity, mild cellular pleomorphism, and no or only a few mitoses, and has well-circumscribed pushing margins. The stromal distribution is uniform (Figure 11-7A).
- **Borderline phyllodes tumor.** This tumor displays modest stromal cellularity, moderate cellular pleomorphism, and moderate mitotic activity (< 10/10 hpf), and has partially infiltrative margins. There is stromal overgrowth, but it is typically uneven.
- **Malignant phyllodes tumor.** This tumor has marked stromal cellularity and cellular pleomorphism, along with numerous mitoses (>10/10 hpf) and widely invasive margins. Invariably, it shows clear stromal overgrowth (Figure 11-7B).

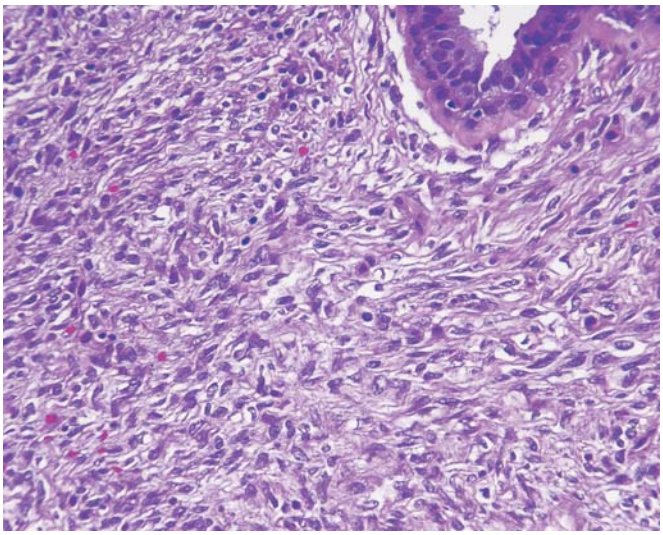
Ancillary methods are not required for grading, but an immunohistochemical stain for indicators of proliferative activity, especially MIB-1 (Ki-67), may be a valuable prognostic factor in malignant phyllodes tumor (16).

Comments

1. The term "cystosarcoma phyllodes" is inappropriate and should be abandoned, because most of these tumors follow a benign course, and thus the term "sarcoma" is misleading.
2. A sampling of 1 block for every 1 cm of maximal tumor dimension is necessary for an accurate grading of phyllodes tumors, due to the presence of structural variability.
3. The tumors should be graded according to the areas of highest cellularity and atypia.



A



B

FIGURE 11-7. Phyllodes tumor. A. Benign phyllodes tumor. There is a leaf-like structure lined by benign epithelium, with underlying cellular stroma. The stroma is composed of uniform spindle cells, with only rare mitoses. B. Malignant phyllodes tumor. The stroma is frankly sarcomatous and contains numerous mitotic figures.

4. Stromal overgrowth is defined as the absence of epithelial elements in at least 1 low-power field (lpf) (40×) (17).

5. It has been suggested that the mitotic count be related to the field diameter instead of high-power fields (hpf), because the size of the high-power fields varies among microscopes (18).

6. In malignant phyllodes tumors, the epithelial component may only be identified after examining multiple sections, due to overgrowth of the sarcomatous component.

7. The sarcomatous component in malignant phyllodes tumor is usually fibrosarcoma. However, heterologous differentiation including liposarcoma, osteosarcoma, chondrosarcoma, or rhabdomyosarcoma may occur, and such changes should be documented in the diagnostic report.

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12
Tumors of the Lymphoid and Hematopoietic Systems

Lawrence M. Weiss and Karen L. Chang

Introduction

The grading of tumors plays a less significant role in the hematopoietic and lymphoid systems than perhaps for any other organ system. While grading was once an integral part of the classification of non-Hodgkin lymphomas, it is now considered more relevant to give a precise classification to provide the information that the clinician requires for prognosis and treatment planning. Nonetheless, for certain neoplasms grading plays an accepted and sometimes important role. In the future, ancillary methods such as immunohistochemistry, flow cytometry, and cytogenetics (already of great importance), as well as gene profiling, will likely play an even more critical role in determining prognosis and response to therapy in lymphoid and hematopoietic neoplasms.

Follicular Lymphoma

While for years the grading of follicular lymphoma has been accepted as having clinical relevance (1–3), the optimal method of grading and the specific clinical implications have yet to be determined. The recent World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues has proposed specific guidelines that, while not validated, provides a standardized methodology that should prove to be reproducible.

According to the WHO classification, follicular lymphoma is graded by counting the number of centroblasts in 10 neoplastic follicles, expressed per 40× high-power microscopic field (hpf), based on hpf of 0.159 mm (2). Centroblasts (also called large noncleaved cells) are large lymphoid cells characterized by round to oval and occasionally indented nuclei, a vesicular chromatin pattern, 1 to 3 nucleoli usually situated at or near the nuclear membrane, and a narrow rim of cytoplasm. Centroblasts must be distinguished from large centrocytes (large cleaved cells), which also have large nuclei but show a more angulated and elongated nucleus and a more condensed chromatin pattern, with inconspicuous nucleoli; they are also distinct from follicular dendritic cells, which often are multinucleate and possess a finer chromatin pattern, have nucleoli that tend to be more centrally placed, and show a finer nuclear membrane.

On the basis of the recommended WHO criteria, follicular lymphomas (Figures 12-1 to 12-4) are graded as follows:

- **Grade 1.** These tumors have 0–5 centroblasts/hpf.
- **Grade 2.** These tumors have 6–15 centroblasts/hpf.
- **Grade 3.** These tumors have >15 centroblasts/hpf. Centrocytes still present, and solid sheets of centroblasts are observed.

The 0.159 mm^2 field is derived from a microscope with a 40× objective and an 18 mm field of view ocular. Appropriate adjustments must be made when using other magnification objectives or different size ocular fields. Each high-power field should be counted within a different follicle, without selecting the follicles. If discrete areas of grade 3 follicular lymphoma are present in a case that is otherwise of lower grade, a second grade is given, with the approximate amount of each grade reported as a percentage.

Diffuse variants of follicular lymphoma are graded 1 and 2, based on the criteria given above. There is no grade 3 diffuse variant of follicular lymphoma, as this is regarded as diffuse large B-cell lymphoma.

Comments

1. Grades 1 and 2 follicular lymphoma are traditionally regarded as indolent or low-grade follicular lymphoma; grade 3 follicular lymphoma has been shown to behave in a more aggressive fashion and is usually regarded as intermediate grade.

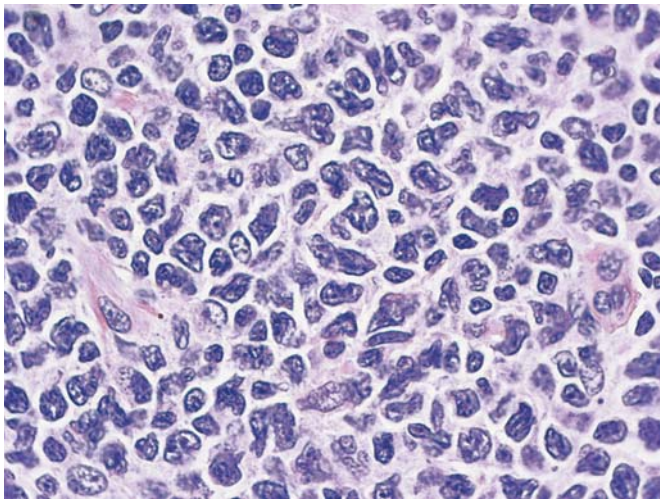

FIGURE 12-1. Follicular lymphoma, grade 1. This case is composed almost entirely of small cleaved cells, with only rare centroblasts.

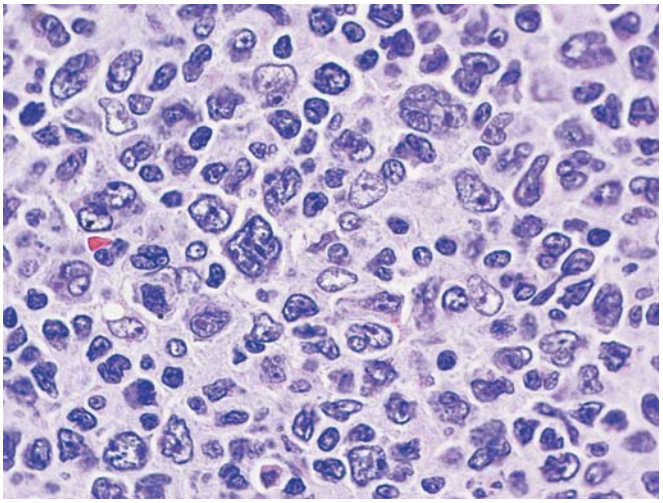

FIGURE 12-3. Follicular lymphoma, grade 3a. There are large numbers of centroblasts, but small cleaved cells are still present.

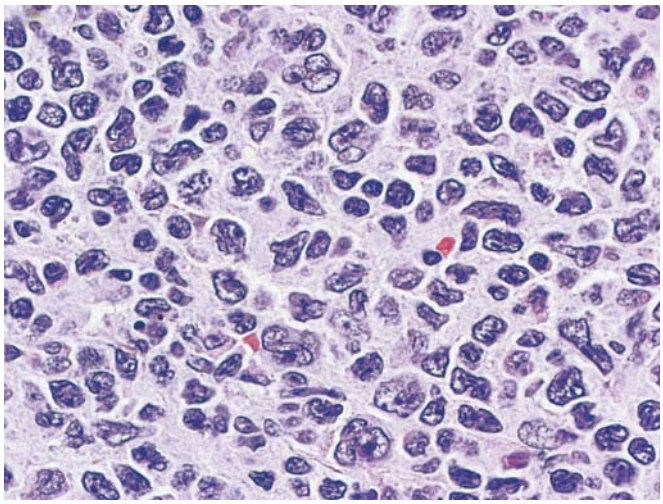

FIGURE 12-2. Follicular lymphoma, grade 2. Scattered centroblasts are seen. Note the increase in number from Figure 1.

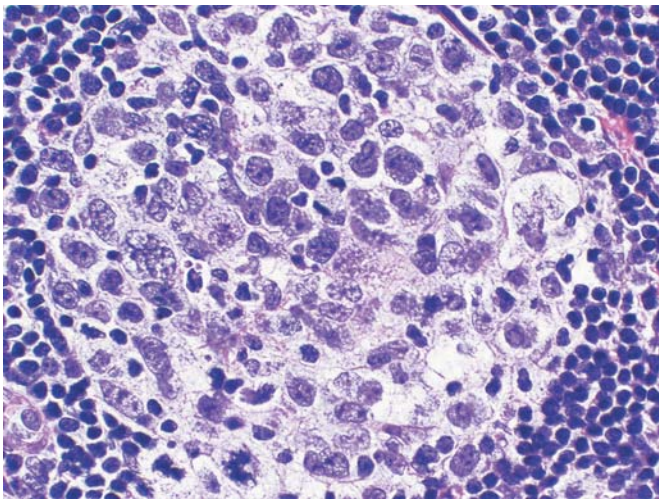

FIGURE 12-4. Follicular lymphoma, grade 3b. This neoplastic follicle contains almost a pure population of centroblasts.

2. The cytologic subtypes of grade 3 follicular lymphoma have not been shown to predict survival; however, the presence of a significant diffuse component has predicted for survival (4).

3. The presence of diffuse areas may have an adverse impact on survival, particularly in grade 3 neoplasms.

Mantle Cell Lymphoma

While there is no formal grading system, cases of mantle cell lymphoma can be divided into classic and blastic (blastoid) types. The classic type has a median survival period of 4 to 5 years, with the majority being not curable. In most studies, blastic mantle cell lymphoma has a poor prognosis, with a median survival period usually of less than 2 years.

Classical mantle cell lymphoma is composed of a relatively monotonous population of small to medium-size lymphoid cells, in either a diffuse, vaguely nodular, or mantle zone distribution. The lymphoid cells have irregular nuclear outlines, a relatively mature lymphoid chromatin pattern with inapparent or inconspicuous nucleoli, and an inapparent rim of cytoplasm. The mitotic rate averages about 20 per 10 hpf. Rare variants may show features mimicking the cells of chronic lymphocytic leukemia/small lymphocytic lymphoma, or that of a marginal zone B-cell lymphoma.

There are 2 main types of blastic mantle cell lymphoma. In the more common type, sometimes termed

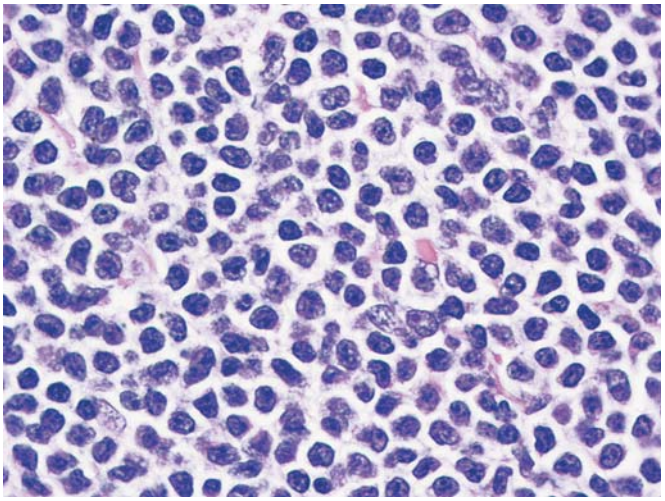

FIGURE 12-5. Mantle cell lymphoma, typical case. This case shows a homogeneous population of small lymphoid cells with somewhat irregular nuclear outlines.

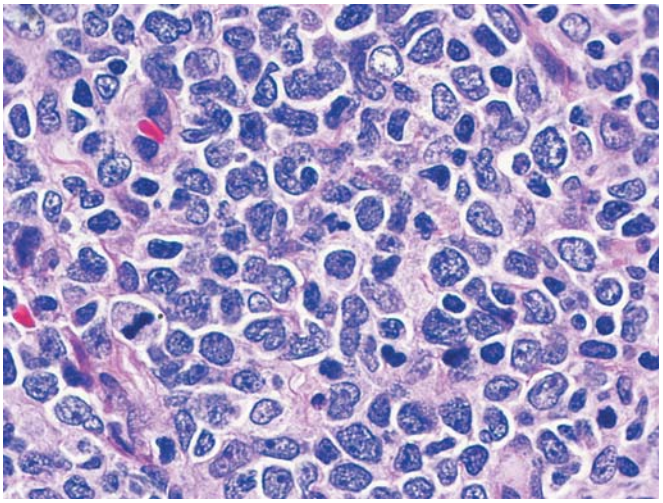

FIGURE 12-7. Mantle cell lymphoma, pleomorphic/large cell blastic variant. Although the cells are large, note the relatively fine chromatin pattern. This case expressed nuclear cyclin D1.

classic or lymphoblastoid, the cells have a close morphologic resemblance to the cells of precursor lymphoblastic leukemia/lymphoma, with a fine chromatin pattern, inapparent or inconspicuous nucleoli, and an inapparent rim of cytoplasm. The mitotic rate is greater than 30 per 10 hpf, and usually averages 50 per 10 hpf. In the second type, also known as pleomorphic or large cell, the cells are more heterogeneous, resembling those found in typical cases of mantle cell lymphoma to larger cells with larger cleaved to oval nuclei, clearly discernible nucleoli, and a rim of pale cytoplasm. Other cases feature the presence of large blast-like cells and may be virtually indistinguishable from diffuse large B-cell lymphoma. The grading of mantle cell lymphoma (Figures 12-5 to 12-7) is as follows:

- Mantle cell lymphoma, typical
- Mantle cell lymphoma, blastic
  Classic/lymphoblastoid
  Pleomorphic/large cell

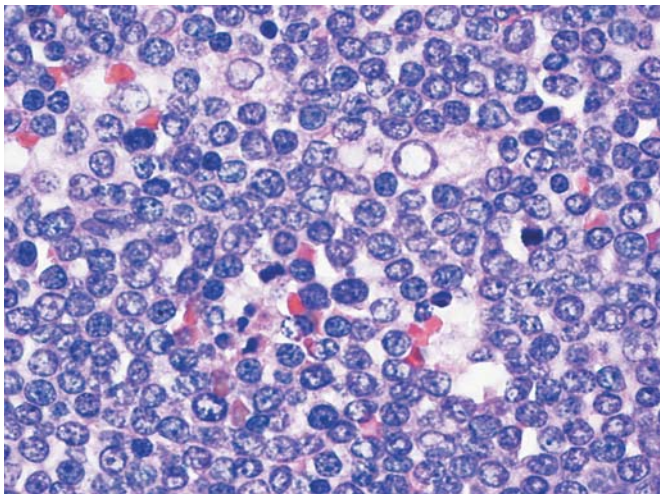

FIGURE 12-6. Mantle cell lymphoma, classic blastic/lymphoblastoid variant. There is a fine chromatin pattern, closely resembling a lymphoblastic neoplasm. This case expressed nuclear cyclin D1.

Comments

1. Cyclin D1 immunohistochemical staining, while not absolutely sensitive or specific, is useful in confirming a mantle cell lymphoma diagnosis. Demonstration of evidence of a t(11;14) by molecular studies may also be useful. Blastic variants of mantle cell lymphoma tend to have frequent bcl-1 rearrangements at the major translocation cluster region, tetraploid chromosome clones, and increased incidence of p53 mutations and overexpression (5,6). Gene array studies have shown that blastic cases have a lower expression of caspase 7, but an increased expression of TOP1 and CDK4 as compared to other cases of mantle cell lymphoma (7).

2. Gene expression microarray studies have provided a precise measurement of tumor cell proliferation, based on the expression of proliferation signature genes, identifying patient subsets that differed by more than 5 years in median survival (8).

3. When considering a diagnosis of blastic mantle cell lymphoma, it is important to rule out a lymphoblastic malignancy or a diffuse large B-cell lymphoma.

4. Approximately 10% to 15% of cases of mantle cell lymphoma will be of the blastic subtype.

Classical Hodgkin Lymphoma, Nodular Sclerosis Type

Hodgkin lymphoma is currently divided into nodular lymphocyte predominant and classical types. Classical Hodgkin lymphoma, which accounts for more than 95% of cases, is subdivided into nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted forms. With modern therapy, there are no significant differences in prognosis among the subtypes. The nodular sclerosis subtype represents approximately two-thirds of all cases of classical Hodgkin lymphoma, so there has been some interest in trying to establish a grading system that can distinguish prognostically significant subgroups within this large group of patients. The most successful system has been that proposed by the British National Lymphoma Investigation.

The British National Lymphoma Investigation grading of nodular sclerosis classical Hodgkin lymphoma (9,10) (Figures 12-8 and 12-9) can be summarized as follows:

- **Grade 1.** All cases not meeting the criteria for grade 2.
- **Grade 2.** These tumors show any of the following features:
  a. More than 25% of the cellular nodules display reticular or pleomorphic lymphocyte depletion
  b. More than 80% of the cellular nodules show the fibrohistiocytic variant of lymphocyte depletion
  c. More than 25% of the nodules contain numerous bizarre and highly anaplastic-appearing Hodgkin cells, without depletion of lymphocytes (sheets of cells filling a 40×hpf)

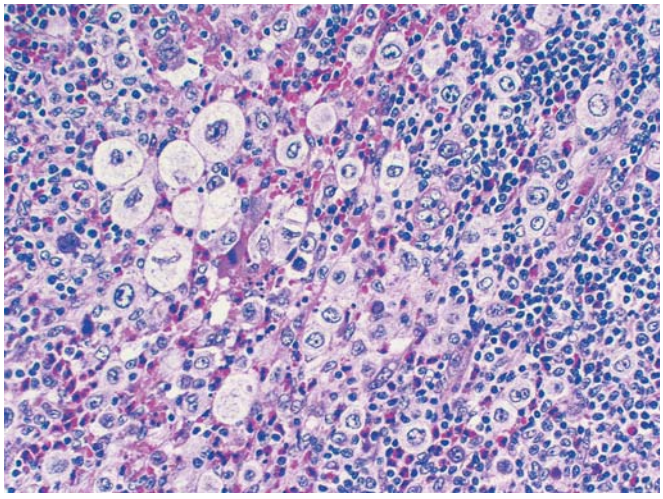

FIGURE 12-8. Nodular sclerosis classical Hodgkin lymphoma, grade 1. A typical case of nodular sclerosis is seen, with a large (but not unusually so) number of lacunar cells.

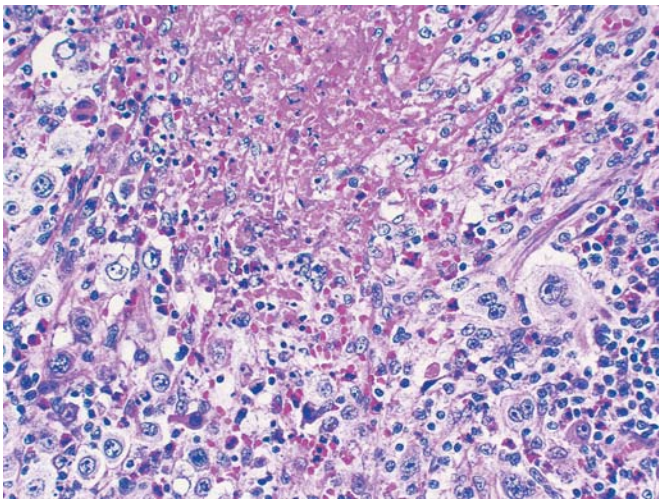

FIGURE 12-9. Nodular sclerosis classical Hodgkin lymphoma, grade 2. Sheets of lacunar cells are observed at the edge of an area of central necrosis. This case also met the criteria for the syncytial variant of nodular sclerosis.

Comments

1. Grade 2 nodular sclerosis is somewhat similar to what has been termed nodular sclerosis with lymphocyte depletion in some studies (11), and overlaps with the syncytial variant of nodular sclerosis in others (12).
2. This system is somewhat hard to learn, although some studies have shown good reproducibility.
3. Some studies have shown that the patients classified as grade 2 have a significantly worse prognosis than those classified as grade 1; however, other studies have not confirmed this finding. In general, large numbers of patients must be studied for an effect on prognosis to be demonstrated.
4. In general, this grading scheme has not been extensively used in daily practice, and WHO does not require its use for routine clinical purposes.

Mycosis Fungoides: Lymph Node Involvement

Mycosis fungoides is a distinctive cutaneous T-cell lymphoma. Aside from the skin, the lymph nodes are the most common site of involvement. The clinical stage is the single most important prognostic factor, with stage II representing enlargement of lymph nodes but no involvement histologically, and stage III representing lymph node involvement documented by histology. Unfortunately, it is extremely difficult to establish a histologic diagnosis of mycosis fungoides involving lymph nodes, particularly when enlarged lymph nodes in these patients generally show extensive dermatopathic changes. Several investigators have established a histologic grading system

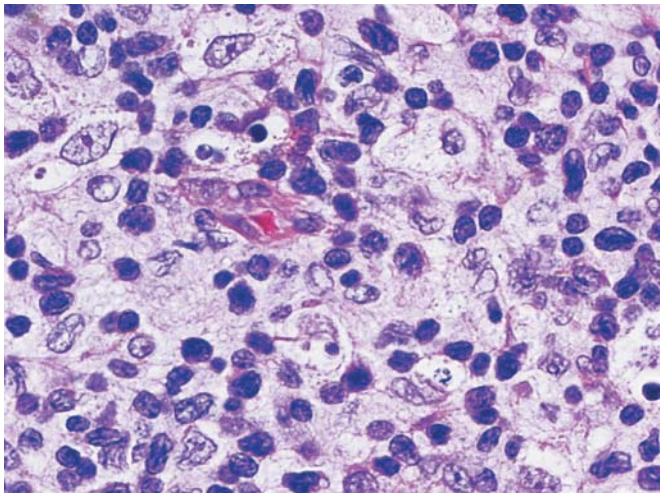

FIGURE 12-10. Lymph node involvement by mycosis fungoides, category I (LN-1). Only rare atypical small lymphoid cells are seen in this area that otherwise has the features of dermatopathic lymphadenitis.

for the assessment of lymph nodes in patients with mycosis fungoides, as a way of communicating a degree of certainty in the diagnosis. The grading system (13,14), in part illustrated in Figures 12-10 to 12-13, includes 3 categories of lesions as follows:

- **Category I.** The lymph nodes show no involvement by mycosis fungoides.
  LN-0—Reactive changes are present, but no atypical lymphocytes are evident.
  LN-1—Only a few atypical lymph nodes are noted in the paracortex (Figure 12-10).
  LN-2—Atypical lymphocytes occur both singly or in small clusters, generally of fewer than 3 to 6 cells in the paracortex (Figure 12-11).
- **Category II.** Lymph nodes show early involvement by mycosis fungoides.
  LN-3—Large clusters of atypical lymphocytes, generally in aggregates of 15 or more cells, are interspersed between and tend to separate the paracortical histiocytes, often accompanied by large immunoblastic cells.
- **Category III.** Lymph nodes show massive involvement by mycosis fungoides.
  LN-4—Partial or complete obliteration of the architecture by atypical lymphocytes is evident.

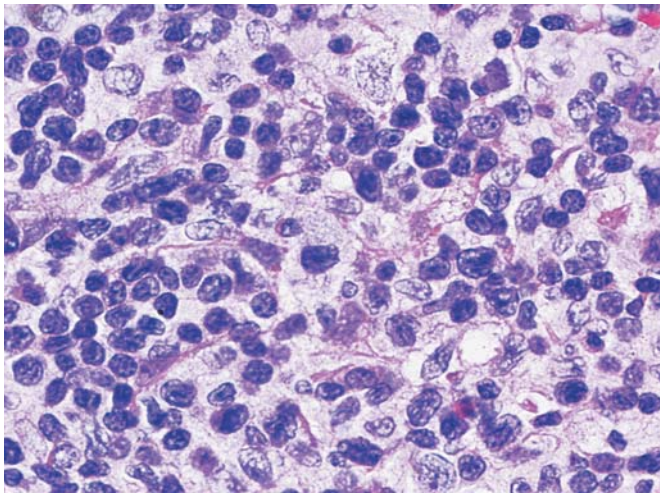

FIGURE 12-11. Lymph node involvement by mycosis fungoides, category I (LN-2). Although dermatopathic changes are present, small clusters of atypical small lymphoid cells are visible.

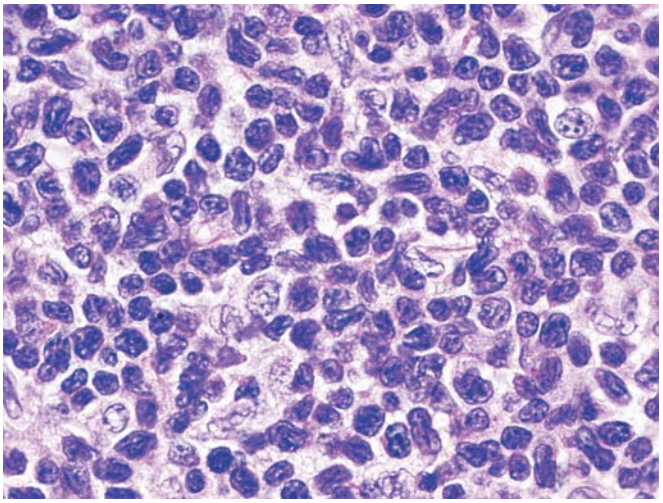

FIGURE 12-12. Lymph node involvement by mycosis fungoides, category II (LN-3). Numerous atypical small lymphoid cells are seen, along with occasional larger forms.

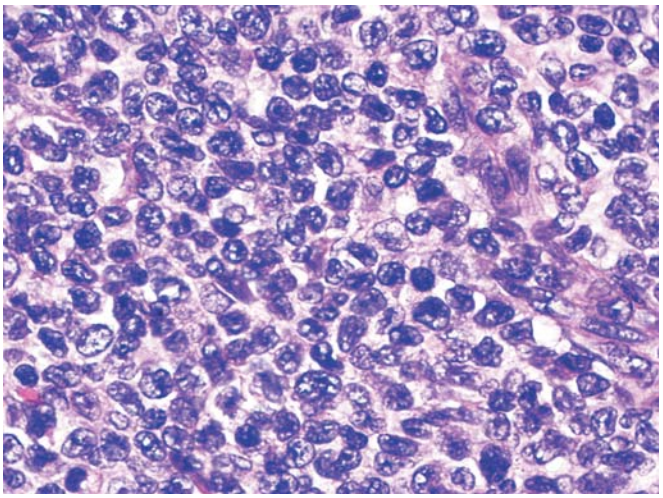

FIGURE 12-13. Lymph node involvement by mycosis fungoides, category III (LN-4). There is complete architectural obliteration by atypical lymphoid cells, including many with large cell features.

Comments

1. Immunohistochemical studies are of limited utility in establishing a diagnosis of lymph node involvement by mycosis fungoides. Most commonly, aberrant loss of CD7 antigen is seen, but this is not completely specific to mycosis fung-oides (15).
2. Clonal T-cell receptor gene rearrangements can be detected in a subset of cases of category I, usually those in LN-2, and in the large majority of cases of categories II and III (16). Some studies have suggested that the identification of clonal T-cell populations in category I lymph nodes may adversely impact prognosis, so this test is recommended in all category I lymph nodes; positive results may be used to upstage the patients.
3. Patients with mycosis fungoides as well as other skin diseases often show changes of extensive dermatopathic lymphadenopathy, due to disruption of the blood-skin barrier. This condition is marked by a proliferation of Langerhans cells and other dendritic cells, histiocytes, and lymphoid cells. The lymphoid cells may have irregular nuclear contours, mimicking the atypical cells seen in mycosis fungoides (17).

Myelodysplastic Syndromes

The myelodysplastic syndromes represent a group of clonal hematopoietic stem cell diseases characterized by abnormal and inefficient hematopoiesis in 1 or more of the major hematopoietic cell lineages. There may be an increase in the percentage of myeloblasts, but the presence of 20% or more indicates a diagnosis of acute leukemia rather than a myelodysplastic syndrome. The recent WHO classification recognizes 7 specific morphologic subtypes and acknowledges an additional category of myelodysplastic syndrome, unclassified. These subtypes can be stratified into 2 risk groups based on the duration of survival and incidence of evolution to acute leukemia. Thus, these risk groups represent a kind of grading system.

The groups of low-grade forms of myelodysplastic syndrome, illustrated in part in Figures 12-14 to 12-16, comprise the following:

- **Refractory anemia (RA).** This unilineage dysplasia affects only the erythroid lineage. Myeloblasts account for <1% in the blood and <5% in the bone marrow.
- **Refractory anemia with ringed sideroblasts (RARS).** This unilineage dysplasia also affects only the erythroid lineage. Myeloblasts are absent from the blood and account for <5% cells in the bone marrow. The bone marrow contains >15% ringed sideroblasts.
- **Myelodysplastic syndrome associated with isolated del(5q) chromosome abnormality (5q- syndrome).** This is a clonal proliferation characterized by an isolated del(5q) abnormality in which there are <5% myeloblasts in the blood and bone marrow.

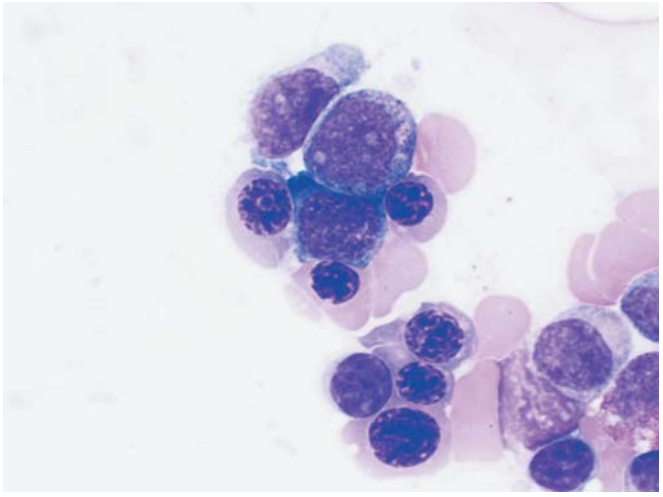

FIGURE 12-14. Refractory anemia. The erythroid series is hyperplastic. The nucleated erythroid precursors show minimal nuclear-to-cytoplasmic dyssynchrony. (The myeloid precursors and megakaryocytes appear normal.)

The high-grade forms of myelodysplastic syndrome, illustrated in part in Figs. 12-17 to 12-19, comprise the following:

- **Refractory cytopenia with multilineage dysplasia (RCMD).** Dysplasia is seen in >10% of the cells in 2 or more of the myeloid cell lineages, with <1%

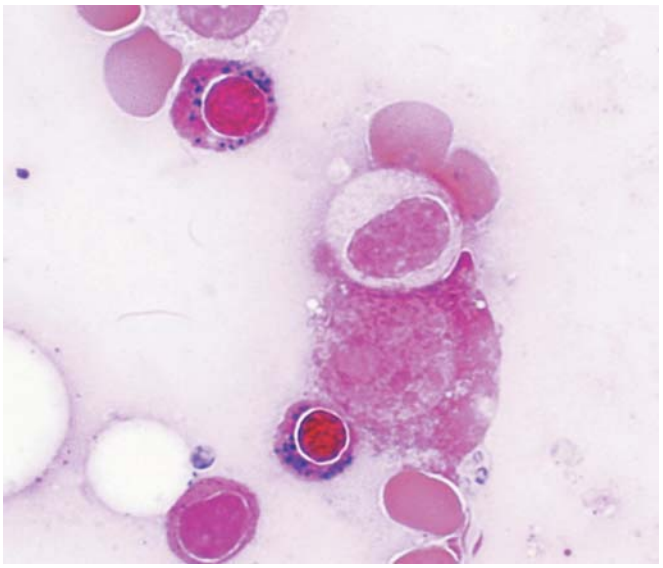

FIGURE 12-15. Refractory anemia with ringed sideroblasts. The morphologic features are similar to refractory anemia, except for the presence of abnormal iron incorporation affecting >15% of nucleated erythroid precursors. The iron granules are distributed concentrically around the erythroid nucleus.

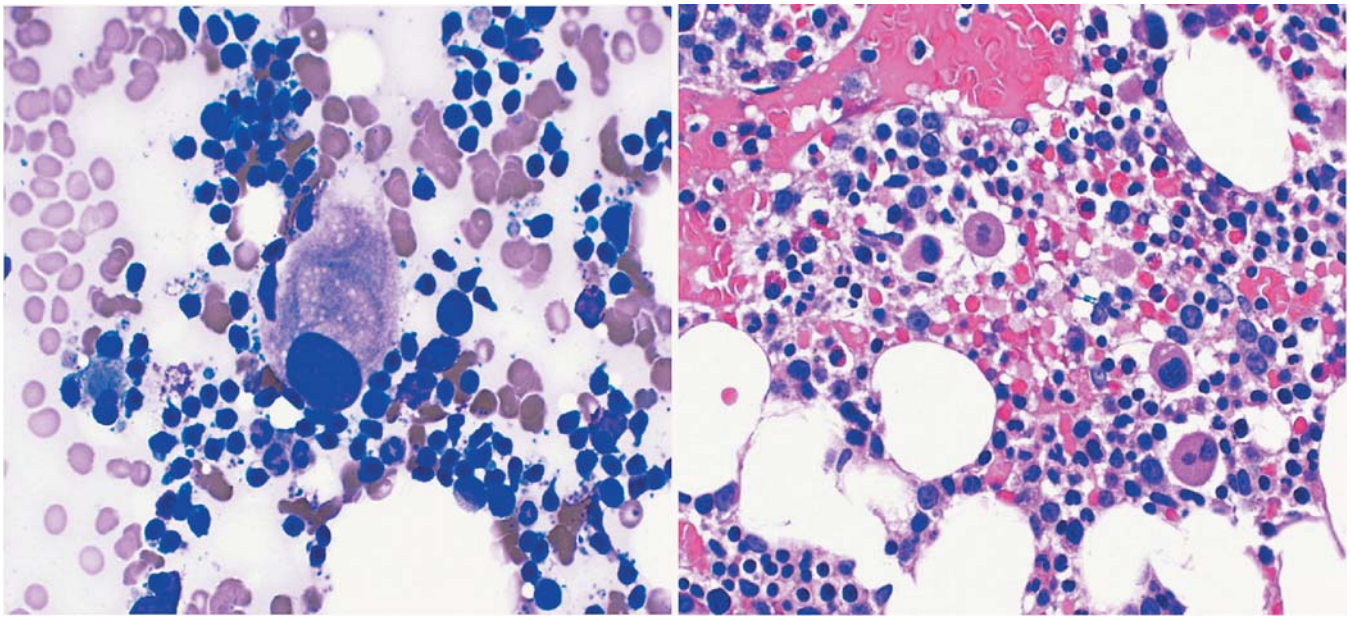

FIGURE 12-16. 5q- syndrome. The low-power impression of the aspirate smear includes numerous hypolobated megakaryocytes amidst a background of erythroid hyperplasia. Often the H&E sections are more helpful for viewing the megakaryocytes, which show abnormal lobulation and variation in size.

myeloblasts in the marrow, absent Auer rods, and <15% ringed sideroblasts.

- **Refractory anemia with multilineage dysplasia and ringed sideroblasts (RCMD-RS).** The bone marrow shows the same changes as seen in RCMD, but it also contains >15% ringed sideroblasts.
- **Refractory anemia with excess blasts-1 (RAEB-1).** This may present as unilineage or multilineage dysplasia, with <5% blasts in the blood, 5% to 10% blasts in the bone marrow, $<1 \times 10^9$/L monocytes, and absent Auer rods.
- **Refractory anemia with excess blasts-2 (RAEB-2).** It may present as unilineage or multilineage dysplasia with 5% to 19% blasts in the blood, 10% to 19% blasts in the bone marrow, and $<1 \times 109$/L monocytes.

Comments

1. Cytogenetics is an important prognostic indicator in myelodysplasia (18). This variable has been combined with the percentage of blasts and the presence of various cytopenias to derive a scoring system (19).

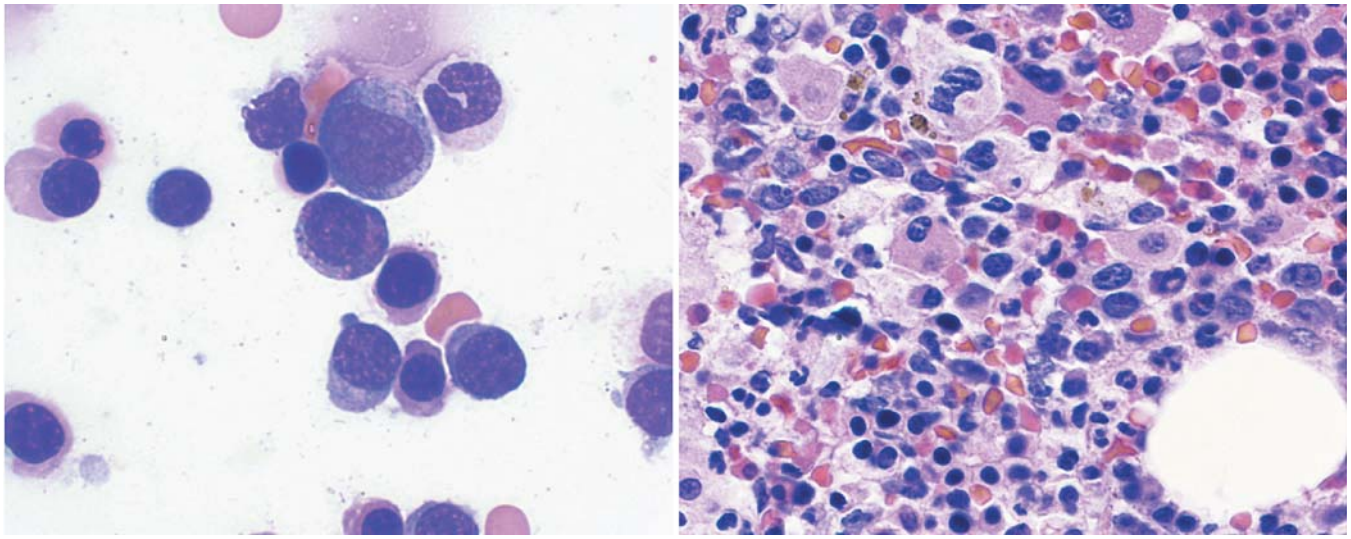

FIGURE 12-17. Refractory cytopenia with multilineage dysplasia. Most commonly the erythroid and myeloid series show marked dysplasia, but often all 3 cell lineages show dysplastic features. This patient had complex cytogenetic abnormalities.

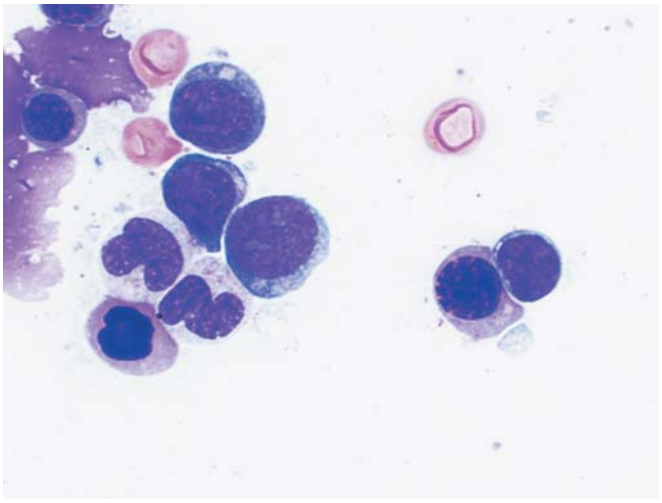

FIGURE 12-18. Refractory anemia with excess blasts-1. This case displays moderate dyserythropoiesis and dysgranulopoiesis. Cases of RAEB-1 are defined by 5% to 9% bone marrow blasts and <5% blasts in the blood.

Favorable-prognosis cytogenetics include -Y, del(5q), del(20q), and normal cytogenetics, poor-prognosis cytogenetics include complex (>3) or chromosome 7 abnormalities, while intermediate-prognosis cytogenetics include all other clonal abnormalities.

2. In addition to the hematologic findings and cytogenetics, age has been found to be a predictor of survival, with improved survival seen in patients of younger age.

3. The median survival is approximately 5 to 6 years in RA, RARS, and 5q- syndrome; 3 years in RCMD and RCMD-RS; 1.5 years for RAEB-1; and 1 year for RAEB-2.

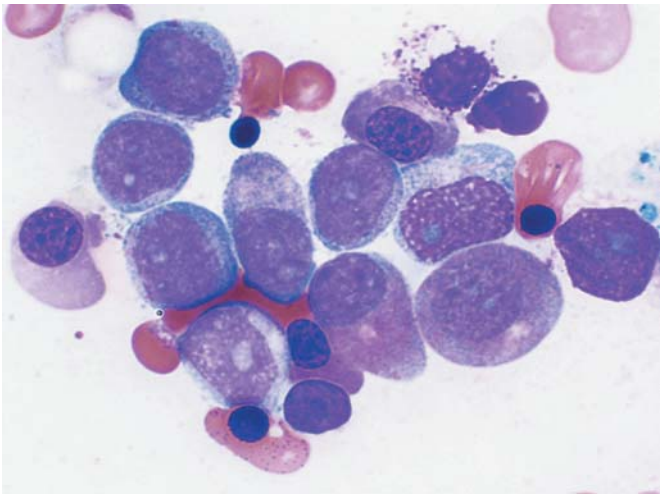

FIGURE 12-19. Refractory anemia with excess blasts-2. This case shows moderate nuclear-to-cytoplasmic dyssynchrony in the erythroid and myeloid series. Two blasts are present.

4. As the natural history is that of progression from a lower grade to a higher grade, as well as from myelodysplastic syndrome to acute leukemia, the disease process should be re-evaluated each time additional findings appear.

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13
Tumors of the Musculoskeletal System

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Introduction

Tumors of the soft tissues and bones form a heterogeneous group that includes common benign neoplasms as well as other less common, variably malignant neoplasms (sarcomas). Recent advances in molecular and cell biology have influenced considerably the present clinical approach to these tumors. As the classifications of these tumors, most notably that of soft tissue sarcomas, are constantly refined by the addition of new data, the grading of soft tissue and bone sarcomas remains a work in progress (1,2). Accordingly, only the most established grading systems used in daily surgical pathology practice are presented here.

Soft Tissue Sarcoma

For years, the grading of soft tissue sarcoma (STS) was controversial, mainly due to the uncertainty of how to uniformly apply the grading principles to the diverse variety of soft tissue neoplasms, and how to weigh the importance of factors such as differentiation level, mitotic rate, and tumor necrosis. The system introduced in 1984 by Costa et al. (3), later known as the National Cancer Institute (NCI) system, was widely used in the United States. The grading system proposed by the French Federation of Cancer Centers (Federation Nationale des Centres de Lutte Contre le Cancer, FNCLCC) (4,5) has gained considerable popularity in many countries of Europe, and according to some accounts is the most widely used system (6). It is also validated by the largest number of patients studied, and its reproducibility tested with a large number of participating pathologists (7).

The prognostic value of the NCI and FNCLCC systems were compared in a series of 410 adult patients with soft tissue sarcomas (8), with follow-up. The prognostic value of both systems was examined using univariate and multivariate (Cox's model) analyses, and special attention was devoted to tumors with discordant grades. In univariate analysis, both the NCI and FNCLCC systems were of prognostic value to predict metastasis development and tumor mortality. In multivariate analysis, high-grade tumors (irrespective of the system used), a size of 10 cm or greater, and deep locations were found to be independent prognostic factors for the advent of metastases. Tumor grade had a higher predictive value than size or depth, and higher prognostic weight was assigned to the FNCLCC grading system in Cox models. Grade discrepancies were observed in 34.6% of the cases. An increased number of grade 3 soft tissue sarcomas, a reduced number of grade 2 soft tissue sarcomas, and a better correlation with overall and metastasis-free survival within subpopulations with discordant grades were observed in favor of the FNCLCC system.

Many issues remain unresolved in both of these systems (2,9), and neither the FNCLCC nor the NCI system has been formally endorsed by either the World Health Organization (WHO) or the Association of Directors of Anatomic and Surgical Pathology (10). However, the French system, which is more precisely defined, appears to be the more reproducible system for practicing pathologists (2).

The French Federation of Cancer Centers (FNCLCC) grading system of soft tissue sarcomas of adults is based on the total score obtained from the summation of points for 3 factors: differentiation, mitotic rate, and tumor necrosis (Table 13-1).

Each soft tissue sarcoma type has been assigned 1 to 3 points for differentiation based on the histologic type and level of differentiation (the differentiation score, see Table 13-2). The mitotic count per 10 high-power fields (hpf) is used to assign an additional 1 to 3 points, and the extent of tumor necrosis (absent, less than half of tumor material, or more than half of tumor material) provides for the final 0 to 2 points. The sum of the all points determines the tumor grade: 2 or 3 points for low grade (grade

Table 13-1. Grading system* of the French Federation of Cancer Centers.

	Score
Tumor differentiation (according to Table 13-2)	1–3
Well-differentiated tumors	1
Defined histogenetic types	2
Poorly differentiated tumors and undefined histogenetic types	3
Mitotic count	
0–9/10 hpf	1
10–19/10 hpf	2
≥20/10 hpf	3
Tumor necrosis	
None	0
≤50%	1
>50%	2
Histologic grade	Sum of the preceding scores
I	2 or 3
II	4 or 5
III	6, 7, or 8

*This grading system formulates the overall grade based on the total points of scores from tumor differentiation, mitotic rate, and tumor necrosis.
Abbreviations:
hpf—high-power field
Source: Modified from Guillou et al., 1997.

I), 4 or 5 points for intermediate grade (grade II), and 6 or more points for high grade (grade III).

Examples of a low-grade and a high-grade myxofibrosarcoma are shown in Figure 13-1.

The Pediatric Oncology Group grading system for non-rhabdomyosarcomatous soft tissue sarcomas in children (12), addressing issues specific for childhood sarcomas, is presented in Table 13-3. It relies significantly on histologic type as the basis for grade, especially for low-grade (grade 1) and high-grade (grade 3) neoplasms. It also incorporates the extent of necrosis and mitotic counts as grading parameters in some (but not all) histologic types, as follows:

- **Grade 1 pediatric tumor.** This group is defined by certain histologic types alone, regardless of their cytologic features, the amount of necrosis, or mitotic activity.
- **Grade 2 pediatric tumor.** This groups comprises tumors that do not belong to group 1 or group 3 by virtue of histologic diagnosis or the fact that they have <5 mitoses/10 hpf, and or <15% geographic necrosis.
- **Grade 3 pediatric tumor.** This group contains certain tumors known to be clinically aggressive by virtue of histologic diagnosis and non-grade 1 tumors with >4 mitoses/10 hpf, or >15% necrosis.

This grading system may result in underestimating the potential of cellular myxoid liposarcoma, which is placed unconditionally in the low-grade group.

Comments

1. Although in principle grading could be applied to any sarcoma type, it has been specifically validated only for the more common tumors, especially spindle cell sarcomas. For malignant peripheral nerve sheath tumors, grading was not found to provide significant prognostic information in the most recent FNCLCC series (5). However, Wong et al. (13) reported that tumor size, grade, and histologic subtype were independent predictive factors for distant disease control in a series of 134 cases of MPNST.

There are no studies to address the grading of rare sarcomas, such as epithelioid sarcoma, clear cell sarcoma, and alveolar soft part sarcoma. However, assuming low mitotic rate and limited, if any, necrosis, these tumors

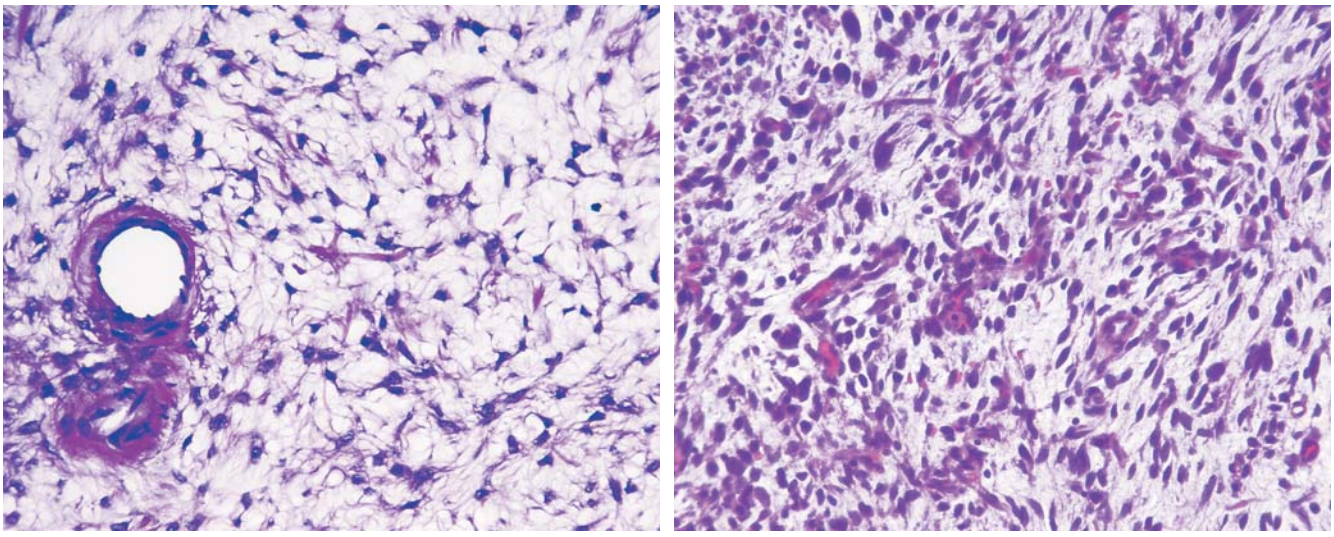
Table 13-2. Tumor differentiation score, according to the updated version of the French Federation of Cancer Centers grading system.

Differentiation score 1
Well-differentiated sarcoma (fibrosarcoma, liposarcoma, leiomyosarcoma, chondrosarcoma), well-differentiated MPNST*

Differentiation score 2
Conventional fibrosarcoma
Myxoid sarcomas (MFH, liposarcoma, chondrosarcoma)
Storiform-pleomorphic MFH
Conventional leiomyosarcoma
Well-differentiated malignant hemangiopericytoma
Conventional angiosarcoma
Conventional MPNST

Differentiation score 3
Poorly differentiated fibrosarcoma
Giant cell and inflammatory MFH
Round cell liposarcoma
Pleomorphic sarcomas (liposarcoma, leiomyosarcoma)
Rhabdomyosarcoma (except spindle cell in children)
Poorly differentiated and epithelioid angiosarcoma
Triton tumor, epithelioid MPNST
Extraskeletal mesenchymal chondrosarcoma
Extraskeletal osteosarcoma
Ewing family tumors
Synovial sarcoma
Clear cell sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Malignant rhabdoid tumor
Conventional malignant hemangiopericytoma
Poorly differentiated MPNST
Undifferentiated sarcoma
Dedifferentiated liposarcoma**

Abbreviations:
MPNST—malignant peripheral nerve sheath tumor
MFH—malignant fibrous histiocytoma
*See Comment (1)
**Low-grade dedifferentiation in liposarcomas may be seen in a minority of cases, but the survival rates do not significantly differ between high- and low-grade dedifferentiation (11).
Source: Modified from Guillou et al., 1997.



A B

FIGURE 13-1. Myxoid tumors A. Low-grade myxofibrosarcoma. B. High-grade myxofibrosarcoma.

would generally be assigned an intermediate grade, given their differentiation scores of 3.

2. Limited or inadequate sampling impairs the accuracy of grading and can make it impractical. Ideal sampling is generally considered to be 1 histologic section per each centimeter of greatest tumor diameter. Needle biopsies or other small biopsies can only give a minimum grade, due to the potentially nonrandom distribution of mitoses, necrosis, and overall differentiation. Because gross sampling of tumors is frequently biased against the inclusion of necrosis, the percentage of necrosis is often underestimated from histologic sections. Ideally the most accurate estimate on necrosis would be made based on gross observations, radiologic studies, or by randomized sampling.

3. The counting of mitoses has not been universally standardized, and there is considerable interobserver variability as to what constitutes a mitotic figure. Sometimes karyorrhectic debris and pyknotic or apoptotic nuclei may be counted. However, mitotic figures in nonneoplastic components should be excluded. The obtained counts may also depend on microscope field size; the number of counted fields should be adjusted, keeping in mind that the field size of 0.174 mm^2 was used to establish the grading system. The level of effort in screening the sections for the mitotically most active areas and section thickness may also influence the mitotic counts.

4. The definition of tumor necrosis can be problematic. In the FNCLCC grading system, necrosis related to ulceration, surgery, or hemorrhage has been excluded for consideration.

5. Grading is generally not applied in postchemotherapy or postradiation specimens, as the treatment tends to reduce mitotic counts, increase necrosis, and sometimes seemingly induce differentiation or cause selection for more differentiated components.

6. Different tumor types in the same histologic grade can markedly vary in their metastatic potential. This is perhaps most evident in the low-grade (grade 1) tumors. For example, well-differentiated lipoma-like liposarcoma

TABLE 13-3. The Pediatric Oncology Group grading system for nonrhabdomyosarcomatous soft tissue sarcomas of children.

Grade 1
Dermatofibrosarcoma protuberans
Infantile fibrosarcoma, well-differentiated (children not over age 4 years)
Infantile hemangiopericytoma, well-differentiated
Well-differentiated and myxoid liposarcoma
Well-differentiated MPNST
Extraskeletal myxoid chondrosarcoma
Angiomatoid (malignant) fibrous histiocytoma
Grade 2
Sarcomas not included in grades 1 and 3 with <15% of necrosis and no more than 5 mitoses/10 hpf
No marked atypia, no markedly high cellularity*
Includes noninfantile fibrosarcomas, poorly differentiated infantile fibrosarcomas, leiomyosarcomas, and MPNSTs fitting these criteria
Grade 3
Round cell and pleomorphic liposarcoma
Mesenchymal chondrosarcoma
Extraskeletal osteosarcoma
Malignant Triton tumor
Alveolar soft part sarcoma
Sarcomas not included in grade 1 with >15% of necrosis, or with >5 mitoses/10 hpf

*Marked atypia and cellularity may also result in assignment into grade 3.
Abbreviations:
MPNST—malignant peripheral nerve sheath tumor
MFH—malignant fibrous histiocytoma
hpf—high-power field
Source: Modified from Parham et al., 1995.

has no metastatic potential, whereas even the best-differentiated or least cellular variants of myxoid liposarcoma have significant metastatic potential.

7. Tumor stage is a description of the extent of the tumor, and it also incorporates grade as an element, as defined in the current TNM (tumor, nodes, and metastasis) and the American Joint Committee for Cancer Staging System for Soft Tissue Sarcomas; the 2 systems have merged. The other elements of stage are tumor size (whether over 5 cm or not), depth (whether superficial/suprafascial or deep/intrafascial), and localized or disseminated (presence or absence of lymph node and distant metastases).

8. Some histopathologic characteristics other than those used in grading may be prognostically important. The status of surgical margins is one of the strongest predictors of local recurrence in soft tissue tumors, and the presence of vascular invasion—whether intratumoral or extratumoral—has been shown as an adverse prognostic factor for some tumor types (14).

9. Numerous studies have suggested cell cycle parameters to have prognostic significance (15,16). Among these, proliferation index by Ki-67 analogs detecting cells that have entered the cell cycle and immunohistochemically determined p53 (over)expression are reported to have prognostic significance, but there is no data to support the systematic application of these results to the diagnosis and grading of sarcomas in general.

10. Gene expression cDNA arrays will likely provide additional parameters of assessing the biologic potential of soft tissue sarcomas, in addition to their contribution toward biologically more accurate tumor classification (17–19). Many of these parameters could be assessable by tissue immunohistochemistry in the future.

11. Gene expression studies, combined with mutation analyses, can also identify potential therapeutic targets in soft tissue sarcomas, such as pathologically activated receptor tyrosine kinases (19). Recently, tyrosine kinase inhibitor drugs, such as imatinib mesylate (Gleevec, Novartis Pharma) for KIT and PDGFRA have become available for the treatment of gastrointestinal stromal tumors. Similar treatments will probably become available for other soft tissue sarcomas in the future. The growing availability of new and often tumor-specific treatments emphasizes the importance of accurate classification and grading (19,20).

12. Separate from grading, a managerial classification has been introduced for soft tissue tumors (see Kempson et al., 2001). This divides different tumor types into clinically benign, intermediate, and sarcoma categories. Each category is subdivided based on expected frequencies of recurrence or metastasis and generally advisable treatment types.

13. Recently, nomograms that assess multiple clinical and histologic parameters including tumor size, site, depth, histologic type, grade (low vs. high), and patient age have been used to extrapolate prognosis (21,22).

Bone Tumors

Bone tumors are a heterogeneous group that includes neoplasms of bone-forming, cartilaginous, and other mesenchymal cells. There is no unified histologic grading system for bone sarcomas (23), but the overall emphasis is on a multidisciplinary approach that involves not only pathologists, but also radiologists, orthopedic surgeons, and molecular biologists (see Fletcher et al., 2002). There are also radiology-based grading systems that principally assess the tumor aggressiveness by cortical destruction and sclerotic versus permeative margins.

Perhaps the best grading system for bone sarcomas is the one used by the Mayo Clinic (24). This system has adapted the principles of Broders, who originally described grading for squamous cell carcinoma of the lip and subsequently applied it to fibrosarcoma. The elements of grading are as follows:

- Cellularity (the relative ratio of cells to extracellular matrix)
- Nuclear atypia (enlargement, hyperchromasia, and irregularity of nuclear contours)
- Mitotic count
- Presence and extent of tumor necrosis

Representative, well-processed, and sectioned material should be used for grading. Grading should be carefully preceded by histologic diagnosis, and assessment of whether the tumor is benign or malignant, based on synthesis of histologic, clinical, and radiologic information. Histologic grading can generally be applied to pretreatment material only. The grading applies to osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, chondrosarcoma, and hemangioendothelioma/angiosarcoma. According to the Mayo Clinic system, osteosarcoma, fibrosarcoma, and MFH are assigned grades of 1 to 4, and chondrosarcoma and angiosarcoma/hemangioendothelioma are assigned grades of 1 to 3.

For clinical purposes, bone tumors are best classified as low-grade and high-grade sarcomas, as follows:

- **Low-grade sarcoma.** This tumor is generally characterized by a low level of nuclear atypia, abundant extracellular matrix (e.g., collagen, osteoid, mineralized bone, and cartilagineous matrix), and low to moderate cellularity. Occasional mitoses are found.
- **High-grade sarcoma.** This tumor is cellular and produces variable amounts of abnormal, immature, and disorganized matrix. The neoplastic cell populations are often pleomorphic or anaplastic, and mitotic activity is often brisk. Necroses are prominent.

TABLE 13-4. Grading according to the AJCC classification of bone tumors.

Grade	Microscopic designation	Clinical designation
GX	Grade cannot be assessed	–
G1	Well-differentiated	Low-grade tumor
G2	Moderately differentiated	Low-grade tumor
G3	Poorly differentiated	High-grade tumor
G4	Undifferentiated*	High-grade tumor

*Ewing sarcoma is always assigned to the G4 group
Source: American Joint Committee on Cancer, 2003.

A microscopic grade is required for the evaluation and staging of bone sarcomas according to the American Joint Committee on Cancer (AJCC), which recognizes 5 categories as listed in Table 13-4. For the sake of expediency, the clinical designation should be included as well.

Some bone tumor types are assigned a grade by histologic type alone, either because there is limited variation within the tumor type, or because attempted grading has not yielded prognostically significant information (Table 13-5). In addition, some specific types of osteosarcoma and chondrosarcoma are by definition classified as low or high grade. Multiple myeloma and lymphomas of the bone are exempted from grading.

Osteosarcoma

On the basis of clinicopathologic data, osteosarcomas can be divided into 3 major groups, as follows:

- Conventional (central or medullary) osteosarcoma. These tumors occur in several histologic forms, including osteoblastic, chondroblastic, fibroblastic, telangiectatic, small cell, giant cell-rich, and epithelioid osteosarcoma.
- Intramedullary (central) well-differentiated osteosarcoma
- Surface (cortical and parosteal) osteosarcoma

The grade is largely determined by the subtype (Table 13-6). Most conventional central (medullary) osteosarcomas are high-grade lesions. Low-grade central osteosarcomas occur infrequently. The opposite is true, however, for cortical and parosteal lesions, among which low-grade variants such as parosteal osteosarcoma predominate. Periosteal osteosarcoma—a rare subtype that typically features chondroblastic differentiation, often with high-grade features—is exempted from grading; this tumor has a rather favorable prognosis.

The microscopic features of high-grade and low-grade osteosarcomas are illustrated in Figures 13-2 and 13-3, respectively.

TABLE 13-5. Primary bone tumors other than osteosarcoma and chondrosarcoma that are exempted from formal grading but are sometimes assigned a definitional grade.

Low grade by definition	High grade by definition	Exempted from grading
Adamantinoma	Ewing family of tumors	Myeloma
Chordoma*		Lymphoma

*Transformation into high-grade tumors can occur, and occasionally some tumors are high grade from inception.
Source: Adapted from AJCC, 2003 and Inwards and Unni, 1995.

TABLE 13-6. Grading principles for osteosarcoma.

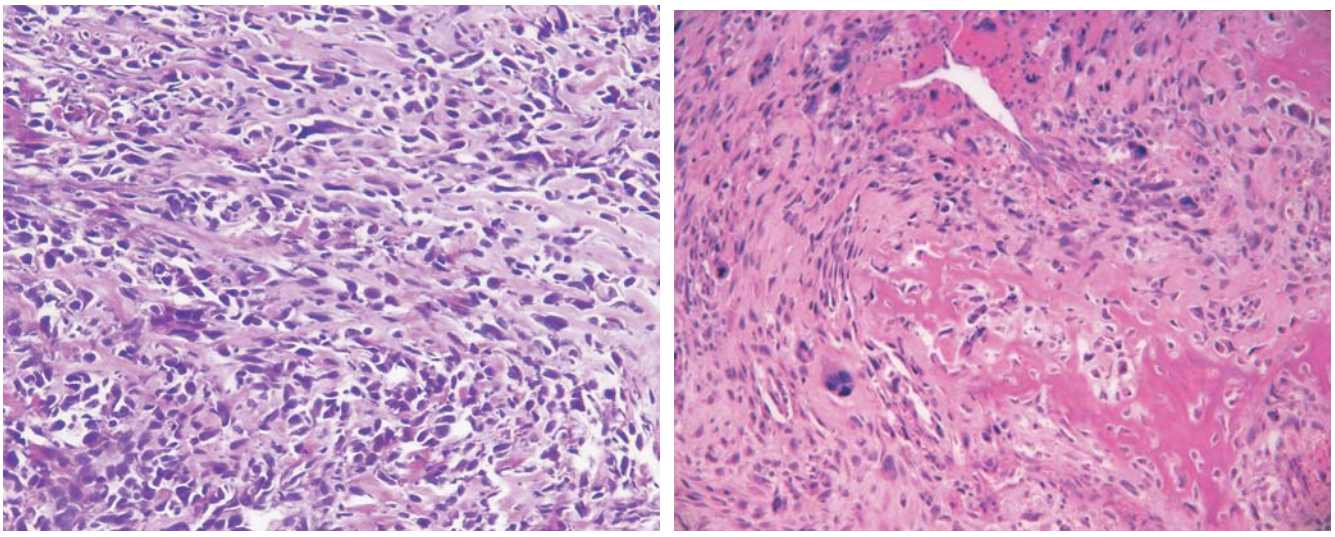
Low grade by definition*	High grade by definition*
Parosteal osteosarcoma**	Conventional medullary osteosarcoma
Low-grade central (medullary) osteosarcoma	High-grade surface osteosarcoma
	Telangiectatic osteosarcoma
	Small cell osteosarcoma

*Low-grade tumors are subjectively divided into grades 1 and 2, and high-grade tumors into grades 3 and 4, based on cellularity and atypia.
**High-grade dedifferentiation may occur.
Source: Adapted from Inwards and Unni, 1995.

Chondrosarcoma

Several systems for grading chondrosarcoma have been proposed, but none of them has been generally accepted (see Fletcher et al., 2002). Once the malignant nature of the cartilage forming neoplasm is established based on correlation between radiologic, clinical, and histopathologic evidence, grading should be performed based on cellularity, the cytologic features of the chondrocytes, and mitotic activity (24–27). Necrosis can be seen, particularly in high-grade neoplasms. Conventional chondrosarcoma is graded on a scale of 1 to 3; 60% are grade 1, 35% grade 2, and 5% grade 3. By definition, clear cell chondrosarcoma is low grade and mesenchymal chondrosarcoma is high grade.

- **Grade 1 chondrosarcoma.** This tumor features a well-developed chondroid matrix resulting in low cellularity, which is nevertheless higher than that of typical enchondromas (Figure 13-4A). The chondrocyte nuclei are small, round, and densely staining. Some nuclei may be slightly enlarged and contain nucleoli. Isolated areas with some pleomorphism are not indicative of a higher grade, as long as there is no increased cellularity and mitotic activity. The peripheral margins are irregular and infiltrative rather than round and well-circumscribed. All clear cell chondrosarcomas are considered to be low-grade tumors.
- **Grade 2 chondrosarcoma.** This tumor is moderately cellular (Figure 13-4B). The nuclei are twice the size of normal chrondrocytes, and there are occasional mitoses (less than 2 per 10 hpf). The nuclei have



A B

FIGURE 13-2. High-grade osteosarcoma. A. The tumor contains no extracellular matrix. B. The tumor contains a well-developed extracellular matrix, but the cells show prominent hyperchromasia and pleomorphism of their nuclei.

irregular contours and appear either hyperchromatic or vesicular, with clearly visible nucleoli. Binucleate cells are readily found. Cellularity is particularly prominent at the edges of the tumor lobules.

- **Grade 3 chondrosarcoma.** This tumor is hypercellular and shows mitotic activity in excess of 2 per 10 hpf (Figure 13-4C). High cellularity and pleomorphism may obscure the chondroid nature of some of these tumors. The nuclei are hyperchromatic, contain nucleoli, and show prominent pleomorphism. Bizarre multinucleated cells may be present. Mesenchymal chondrosarcoma and dedifferentiated chondrosarcoma are by definition considered to be high-grade tumors and are included in this group.

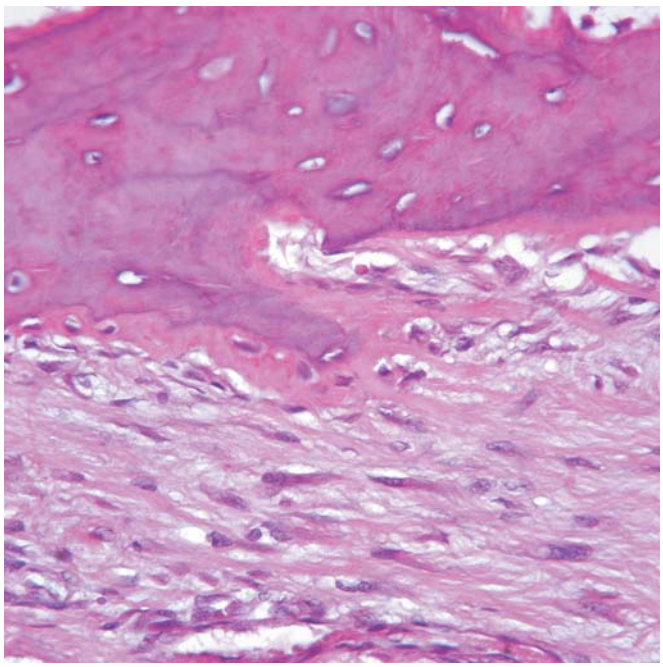


FIGURE 13-3. Low-grade parosteal osteosarcoma. The tumor cells are enclosed in a well-developed matrix.

Other spindle cell sarcomas, such as primary osseous fibrosarcoma, malignant fibrous histiocytoma, and leiomyosarcoma, may be graded in a manner similar to that already described for their soft tissue counterparts, although 3-tiered grading could be modified to a 4-tiered system. These tumors are rare, and the microscopic grade does not seem to reflect the clinical course of the disease and prognosis. Angiosarcoma, whose low-grade variants are often termed as hemangioendothelioma, has a spectrum from low to high grade. Grading is based on the degree of vasoformation and endothelial cell atypia, but necrosis and degree of mitotic activity are also factors.

Comments

1. The grading of chondrosarcoma correlates with the immunohistochemical staining for the proliferation marker MIB-1 (28).
2. Measurements of deviation from the normal chromosomal number and the so-called "DNA malignancy grade" are independent prognostic factors for the outcome of disease in patients with chondrosarcoma (29).
3. Microscopic study of tumors treated with neoadjuvant therapy is used to separate the responders showing more than 90% necrosis from non-responders (<90% necrosis). Genetic analysis of these tumors can also predict those that will respond to chemotherapy (30).

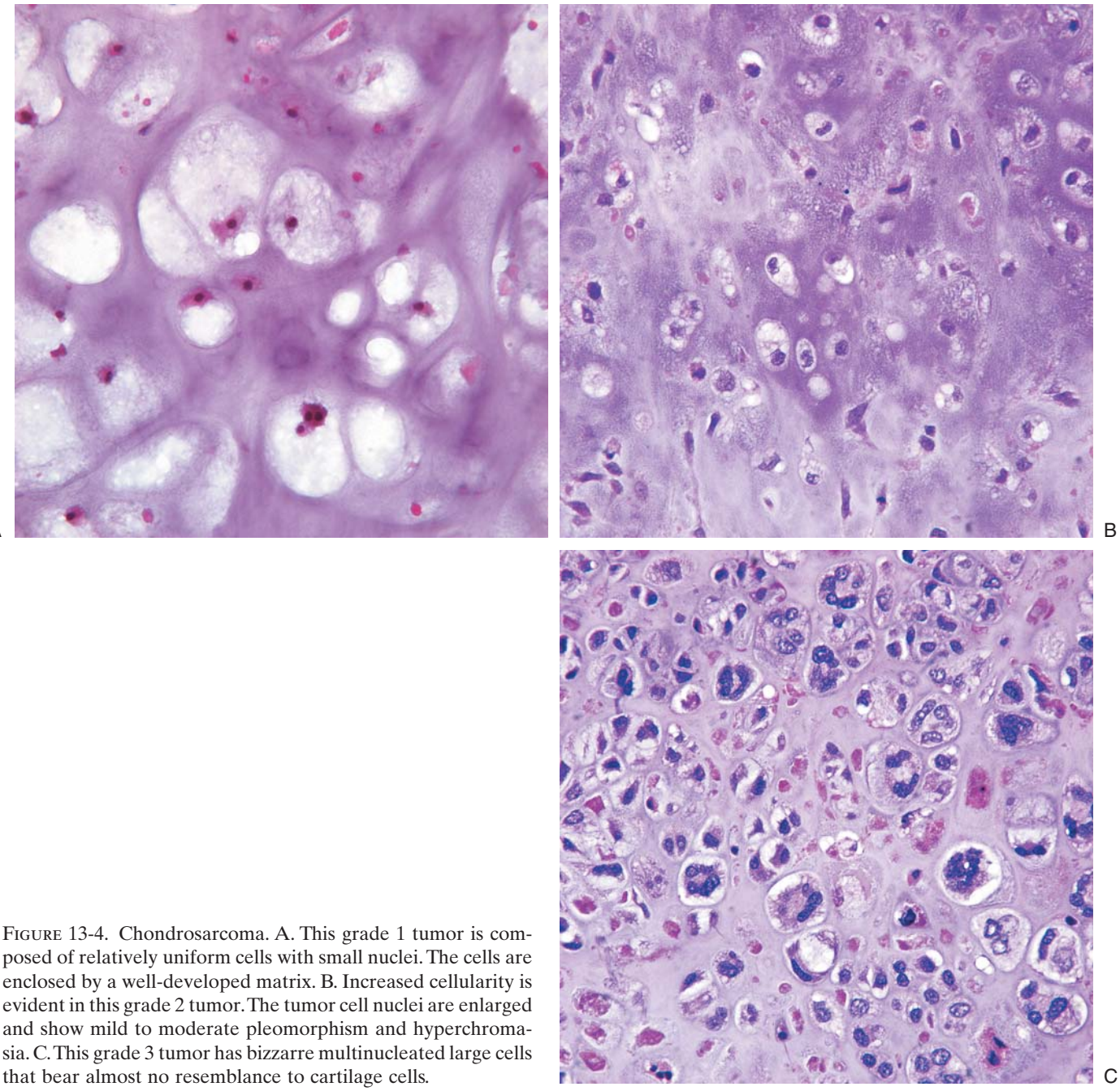


FIGURE 13-4. Chondrosarcoma. A. This grade 1 tumor is composed of relatively uniform cells with small nuclei. The cells are enclosed by a well-developed matrix. B. Increased cellularity is evident in this grade 2 tumor. The tumor cell nuclei are enlarged and show mild to moderate pleomorphism and hyperchromasia. C. This grade 3 tumor has bizzarre multinucleated large cells that bear almost no resemblance to cartilage cells.

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14
Tumors of the Skin

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Introduction

Although skin tumors are common, they are rarely graded. This chapter covers only the grading of basal cell carcinoma, squamous cell carcinoma, and some mesenchymal and pigmented lesions.

Basal Cell Carcinoma

Basal cell carcinoma, the most common cancer, results from a malignant transformation within the basal layer of the epidermis and/or the basal cells of the epithelium of the hair follicle (1,2). These tumors occur in several microscopic forms (Figure 14-1). Over a dozen histologic variants have been described, but they are usually detected within 1 of the 5 most common architectural patterns. The most important microscopic subtypes are as follows:

- Superficial basal cell carcinoma
- Nodular basal cell carcinoma
- Micronodular basal cell carcinoma
- Infiltrative basal cell carcinoma
- Morpheaform basal cell carcinoma

Nodular and superficial basal cell carcinomas are much less likely to recur following complete excision, in contrast to micronodular, infiltrative, and morpheaform basal cell carcinoma, which are more prone to recurrence. One or more patterns may be present within a single specimen.

Approximately 10% of all basal cell carcinomas are superficial basal cell. Classically, it demonstrates basophilic budding of tumor cell from the epidermis with extension into the papillary dermis. As with all basal cell carcinomas, its features may include peripheral nuclear palisading, fibromyxoid stroma, and stromal retraction. Histologic margins are often difficult to ascertain, as skip areas are common.

Nodular basal cell carcinoma is the most common architectural subtype of basal cell carcinoma. The tumor presents in the form of well-circumscribed, basophilic nodules that reside within the dermis and frequently demonstrate epidermal attachment. Multifocal lobules of varying size and shape exhibit peripheral palisading and central haphazard array of cells. The entire tumor demonstrates an expansile growth pattern. Cystic degeneration or central necrosis may be prominent.

Although similar to the nodular variant, micronodular basal cell carcinoma is composed of basal cell islands that are smaller and rounded. Peripheral palisading is less prominent, and the tumor frequently infiltrates throughout the dermis into the subcutis. Local recurrence is more likely, given its propensity for deep invasion.

The infiltrating type of basal cell carcinoma is composed of elongated strands of basophilic cells intercalate between collagen bundles within the dermis that lack extensive fibrosis. Jagged or spiking projections may protrude from infiltrating strands. A nodular component is commonly observed in the overlying dermis. This architectural subtype is present in approximately 5% of all basal cell carcinomas. Because of indistinct borders, adequate tumor margins may be difficult to achieve. Stromal retraction and peripheral palisading is frequently absent.

Morpheaform basal cell carcinoma is an aggressive histologic variant that accounts for approximately 5% to 10% of all basal cell carcinomas. It is composed of basophilic cells forming narrow strands and small tumor islands that are embedded within a sclerotic dermis. The tumor is poorly circumscribed, with frequent invasion of the deep dermis and subcutis. Keloidal collagen may be prominent. Because the tumor cells permeate the dermis in an infiltrative manner with extensive subclinical extension, margin evaluation may be challenging.

Comments

1. Basal cell carcinoma demonstrates various types of differentiation (sebaceous, apocrine, eccrine) and numerous cytologic features. For example, a basal cell carcinoma

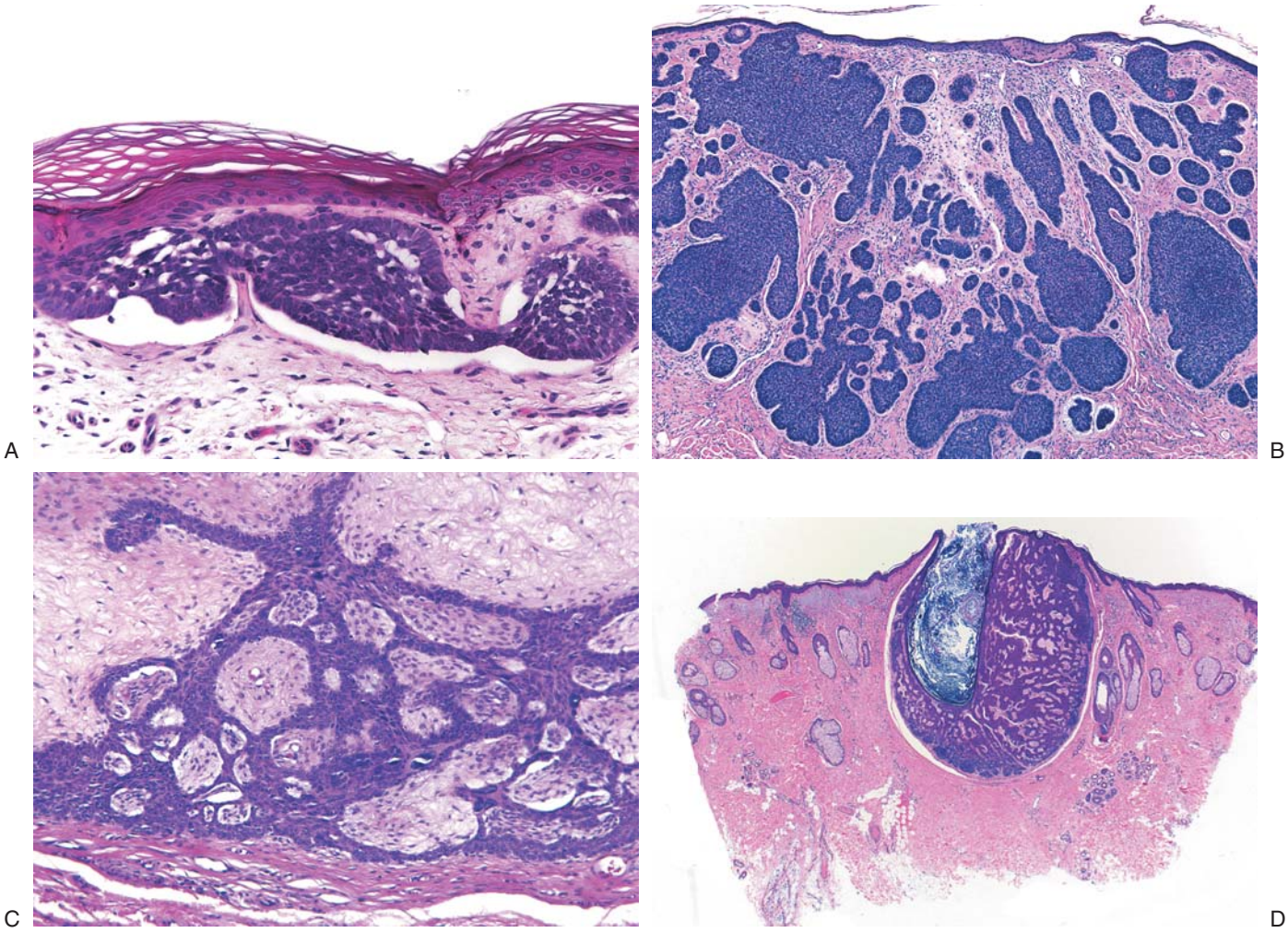

FIGURE 14-1. Basal cell carcinoma. A. Superficial basal cell carcinoma. Nests of basophilic cells in the upper dermis are seen in continuity with the overlying epidermis. B. Nodular basal cell carcinoma. The relatively circumscribed mass consists of basophilic cells arranged into lobules of variable size and shape. C. Fibroepithelioma of Pinkus. The tumor is composed of thin, anastomosing strands of basaloid cells associated with loose fibromyxoid stroma. D. Infundibulocystic basal cell carcinoma. This rare tumor has basaloid cells with squamous features. It consists of small aggregates and anastomosing cords of cells and a small keratin cyst. There is clefting at the epithelial interface.

may have adenoid features, pigmentation, granular cytoplasm, clear cell features, or prominent squamous differentiation. These subtypes are best described within the setting of the overall architectural pattern.

2. Histologic variants that bear mention include fibroepithelioma of Pinkus and infundibulocystic basal cell carcinoma. Fibroepithelioma of Pinkus is comprised of thin, anastomosing strands of basaloid tumor, associated with loose fibromyxoid stroma. Infundibulocystic basal cell carcinoma is a rare tumor of basaloid cells with squamous features. In this unique variant, small aggregates and anastomosing cords of cells are accompanied by small keratin cysts and stromal-stromal clefts.

3. Metastasizing basal cell carcinomas are rare. Microscopically, it is not possible to predict which tumors will have such an aggressive behavior (3).

Squamous Cell Carcinoma and Related Lesions

Cutaneous squamous cell carcinoma (SCC) results from malignant transformation of epidermal keratinocytes (1,4). These lesions can be classified as pre-invasive (intraepithelial) and invasive, with obvious metastatic potential. Several morphologic subtypes are recognized as distinct

clinicopathologic entities. Invasive tumors are most commonly classified based upon the degree of differentiation, rather than the degree of cytologic and architectural atypia. Perineural invasion, perivascular spread, and poor differentiation connote a poor prognosis.

Intraepithelial Squamous Cell Neoplasia

These lesions occur most often on the sun-exposed surface of the face, neck, and upper extremities, but may be found on other skin surfaces. The most important lesions in this group are actinic keratosis and squamous cell carcinoma in situ.

In actinic keratosis, the cellular atypia is confined to the lower layers of the epidermis (Figure 14-2). The nuclei of neoplastic cells exhibit crowding, pleomorphism, and loss of polarity. Epidermal thickness is variable, ranging from a thin epidermis (atrophic type) to a thick epidermis (hypertrophic type). Alternating areas of parakeratosis and orthokeratosis are frequently described in this tumor. The dermis shows solar elastosis and inflammatory infiltrates, but the extent of these changes varies from case to case.

Squamous cell carcinoma in situ (Bowen disease) is defined as full thickness epidermal atypia (Figure 14-3). The neoplastic keratinocytes display nuclear enlargement, hyperchromatism, and disorderly maturation. Mitotic figures, cellular crowding, and epidermal acanthosis may be identified. In a few cases, cells with a pale cytoplasm may be observed—the so-called pagetoid variant of Bowen disease. The granular layer is typically absent, and individual keratinocytes frequently undergo keratinization.

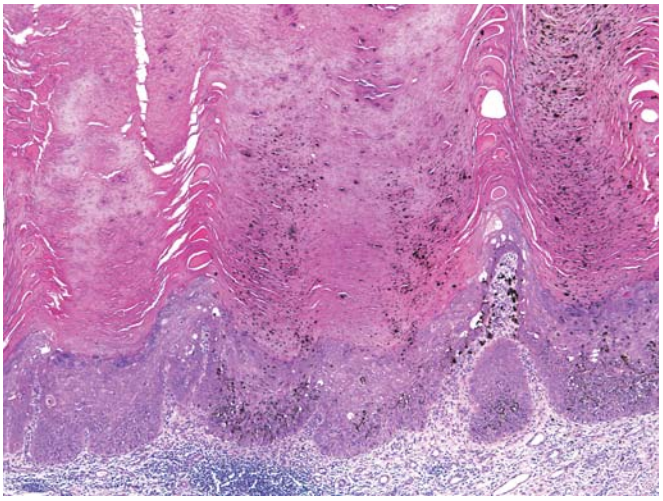

FIGURE 14-3. Squamous cell carcinoma in situ. A. The epidermis contains atypical hyperchromatic cells in all layers, except for the surface layer, which appears hyperkeratotic.

Invasive Squamous Cell Carcinoma

Invasive well-differentiated SCC is an easily recognizable neoplasm most often found on the sun-exposed surface of the face and hands. Its histological features are similar to those of normal epithelium, including abundant eosinophilic cytoplasm and keratinization (Figure 14-4). At higher magnification, it is possible to see intercellular bridges (desmosomes). Keratinization takes place within horn pearls, which are composed of concentric layers of keratin. In these particular neoplasms, the neoplastic cells are present within the dermis, and there is a potential for metastasis.

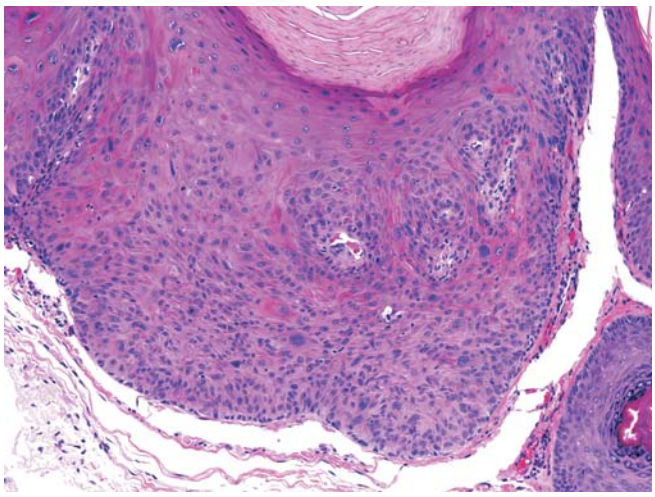

FIGURE 14-2. Actinic keratosis, hypertrophic type. A thickened epithelium is composed of atypical cells and covered with a thick layer of parakeratosis.

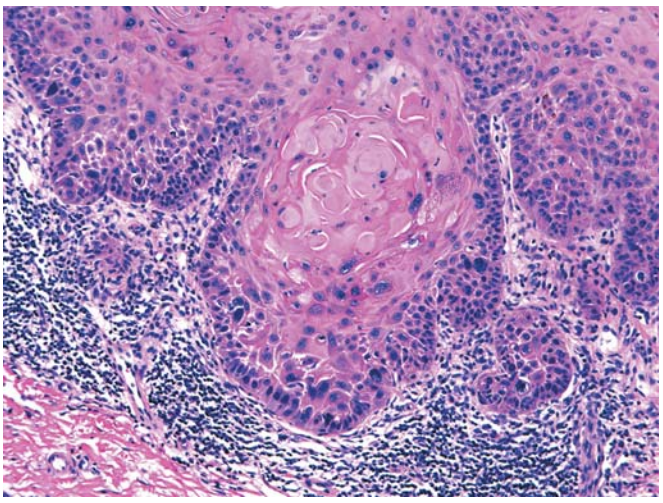

FIGURE 14-4. Squamous cell carcinoma. The hyperchromatic tumor cells show considerable pleomorphism and irregular keratinization, and focally invade into the superficial dermis.

Invasive moderately differentiated squamous cell carcinoma is characterized by increasing degrees of nuclear atypia of keratinocytes forming irregular lobules. Keratinization is much less prominent, and horn pearls may be incompletely formed. Intracellular bridges become less conspicuous, but are still focally retained.

Invasive poorly differentiated squamous cell carcinoma is formed of undifferentiated and often bizarre, pleomorphic cells comprising poorly circumscribed lobules or strands and islands invading the stroma. Individual tumor cells lying freely in the stroma are common. Intracellular bridges are difficult to discern, and tumor cells demonstrate individual keratinization. Atypical mitotic figures abound. In many cases, immunohistochemical stains may be needed to make the correct diagnosis.

Variants of Squamous Cell Carcinoma

Several morphologic variants of squamous cell carcinoma are recognized as distinct clinicopathologic entities (5). These tumors are not graded, but are by definition classified as low-grade or high-grade lesions. The most important variants are:

- **Spindle cell squamous cell carcinoma.** This rare form of anaplastic squamous cell carcinoma is composed of spindle-shaped cells that have scant cytoplasm and usually show nuclear pleomorphism. There are numerous mitoses and few signs of squamous differentiation. Immunohistochemistry with antibodies to keratins is essential for correct diagnosis and for distinguishing these tumors from atypical fibroxanthoma and spindle cell melanoma.
- **Adenoid (pseudoglandular) squamous cell carcinoma.** This tumor typically occurs on the skin of the head and neck of elderly men. The tumors show central gland-like structures resulting from acantholysis of dyskeratotic keratinocytes. These tumors are usually considered to be low-grade neoplasms, but larger lesions may metastasize.
- **Verrucous carcinoma.** This tumor presents as slow-growing, wart-like lesions on the plantar surface of the lower extremities and the crural and genital areas. Microscopically, there is papillomatosis, acanthosis, and hyperkeratosis, and minimal atypia. Mitoses are rare, and invasion occurs in the form of broad-based bulbous protrusions. This tumor grows slowly and may recur, but does not metastasize.
- **Keratoacanthoma.** This tumor, previously considered benign, is a low-grade malignancy and is best called "well-differentiated squamous cell carcinoma with features of so-called keratoacanthoma." It occurs on the sun-exposed surface of the skin and upper extremities, and presents as a rapidly enlarging nodule that may involute on its own (6). Microscopically, it has the shape of a crater that is filled with keratinized squames. The lateral sides of the crater contain well-differentiated squamous epithelium, composed of cells that have abundant eosinophilic cytoplasm and relatively small nuclei. Foci of invasion may be found, but the tumor does not metastasize.

Cutaneous Angiosarcoma

Angiosarcomas are malignant neoplasms with vascular differentiation and can be classified as low and high grade.

Low-Grade Angiosarcoma

Low-grade angiosarcoma of the skin includes the following types: epithelioid hemangioendothelioma, Dabska tumor, and retiform hemangioendothelioma (7–11).

Epithelioid hemangioendothelioma usually appears as a solitary, slightly painful tumor, which in some cases may ulcerate (7,8). It may occur at any age, but is rare during childhood. It affects both sexes in approximately equal proportion. Histologically, epithelioid hemangioendothelioma presents as a circumscribed dermal or subcutaneous nodule. The neoplasm is composed of cords, strands, and nests of plump, epithelioid cells embedded in a fibromyxoid or sclerotic stroma. Many of the neoplastic cells contain vacuoles in their cytoplasm as a sign of primitive vascular differentiation. Slight cellular pleomorphism and occasional mitotic figures may be observed. Rarely, large, distinct vascular channels are present, mainly in the central areas of the neoplasm. In many cases, epithelioid hemangioendothelioma is difficult to differentiate from metastatic adenocarcinoma, which contains mucin vacuoles within the neoplastic cells; a feature that helps to distinguish them is the presence of erythrocytes in the vacuoles of epithelioid hemangioendothelioma.

Endovascular papillary angioendothelioma, or Dabska tumor, clinically presents as enlarging cutaneous lesions that occur either as a diffuse swelling or intradermal tumors (9). Affected sites include the head, neck, and extremities. In most cases, the neoplasms are located in the skin and subcutaneous fat, and preferentially affect infants and young children; however, cases in adults have also been reported. Histopathologically, the neoplasm is composed of interconnecting vascular channels lined by atypical endothelial cells. The vascular spaces vary in size and shape, ranging from narrow channels to large vascular structures. The most characteristic histopathologic feature consists of papillary plugs of atypical endothelium, with a central sclerotic core of connective tissue, projecting into the lumina and producing a glomeruloid appearance. The endothelial cells are round to polyhedral, with an atypical, hyperchromatic, and eccentrically

placed nuclei located in the luminal border of the cell, producing a surface bulge, for which they are known as "hobnail" or "matchstick." The cytoplasm of some hobnail endothelial cells contains vacuoles as an expression of primitive lumen formation. Mitotic figures may be seen, but are uncommon.

Retiform hemangioendothelioma lesions are commonly found on the lower and upper limbs, although isolated lesions may present on the scalp, trunk, or penis. The majority of these cases occur in adults, but cases have also been reported in children (10,11). Clinically, lesions of retiform hemangioendothelioma present as slow-growing exophytic masses or plaque-like dermal and subcutaneous nodules, preferentially located on the extremities. They consist of elongated, arborizing blood vessels involving the dermis, arranged in an architectural pattern reminiscent of that of the normal rete testis. Monomorphic hobnail endothelial cells line the vessels composing the neoplasm. Cytologic atypia is minimal in the hobnail cells of retiform hemangioendothelioma, and few or no mitotic figures are seen. In some areas, the retiform pattern is obscured by the presence of a dense inflammatory infiltrate of mature lymphocytes. In addition, there are also more solid areas composed of epithelioid or spindle cells and some dilated vascular channels with intraluminal papillary projections similar to those seen in Dabska tumor. Dabska tumor and retiform hemangioendothelioma likely are closely related neoplasms. Examples have been described that combine features of these 2 hemangioendotheliomas in the same lesion, and the term "composite hemangioendothelioma" has recently been proposed to designate vascular neoplasms that show a combination of benign, low-grade malignant, and malignant components of hemangioendothelioma (12).

High-Grade Angiosarcoma

High-grade angiosarcoma of the skin includes the following types: cutaneous angiosarcoma of the face and scalp of elderly patients, cutaneous angiosarcoma associated with lymphedema, radiation-induced cutaneous angiosarcoma, and epithelioid angiosarcoma.

Angiosarcoma of the face and scalp affects predominantly elderly patients and is usually located on the scalp and upper forehead. Men are affected more frequently than women (13). Clinically, the lesions appear as ill-defined, bruise-like areas that simulate a hematoma. In some cases, it begins with facial edema, especially of the eyelids, with only minimal erythema. More advanced lesions present as indurate plaques with raised, nodular, and occasionally ulcerated components accompanied by smaller satellite lesions in the vicinity.

For angiosarcoma associated with chronic lymphedema, more than 90% occur following mastectomy for breast carcinoma (14), but it has also been described in areas of lymphedema secondary to other mechanisms. The arm—most often the upper inner aspect—is the most frequent site for early involvement. Less commonly, the tumor may appear more distally, on the elbow or the forearm. Clinically, these lesions appear as bruise-like areas or violaceous nodules superimposed on the brown, nonpitting edema of the affected limb (15). After the appearance of the lesions, there is a rapid increase in their number and size, and they may undergo ulceration. Advanced cases spread distally to the hands and proximally to the chest wall.

Postirradiation cutaneous angiosarcoma is a rare condition that has been described following the use of radiotherapy for the treatment of diverse conditions, both benign and malignant (16). The ensuing angiosarcoma usually manifests itself after a long interval, ranging from 4 to 40 years (mean 23.3 years) when radiation therapy was administered for benign conditions, and from 4 to 25 years (mean 12.3 years), for patients in whom radiation therapy was used for malignant tumors. Clinically, the lesions present as diffuse infiltrative plaques, papulonodules, or ulcers. They affect the area of irradiation or its immediate vicinity, and because most cases appear following radiation for breast and genitourinary malignant tumors, the chest wall and the lower abdominal wall are the most frequently involved sites.

Regardless of the clinical variant, angiosarcomas are histopathologically similar. Microscopically, these tumors can be classified as well-differentiated and poorly differentiated, as follows:

- **Well-differentiated angiosarcoma.** This tumor appears as irregular, dilated vascular channels lined by flattened endothelial cells with an innocuous appearance (Figure 14-5A). It can be confused with benign tumors, such as hemangioma or lymphangioma, or inflammatory lesions. However, careful observation of these lesions reveals the presence of irregular vascular channels dissecting through the dermis. These channels tend to communicate, forming an anastomosing network. Furthermore, some of the endothelial cells appear large, hyperchromatic, and pleomorphic, and may protrude into the vascular lumina in the form of short papillae.
- **Poorly differentiated angiosarcoma.** This tumor displays solid proliferation of polygonal or spindle-shaped pleomorphic endothelial cells, with prominent mitotic activity and poorly formed vascular spaces (Figure 14-5B). Sometimes it may be difficult to distinguish this tumor from carcinoma, melanoma, or a high-grade fibrosarcoma (15); the presence of cytoplasmic vacuoles within the neoplastic cells is valuable to help in diagnosis of these cases. Patchy lymphoid infiltrates are also a common finding. The number of erythrocytes present within the vascular spaces varies from a few to

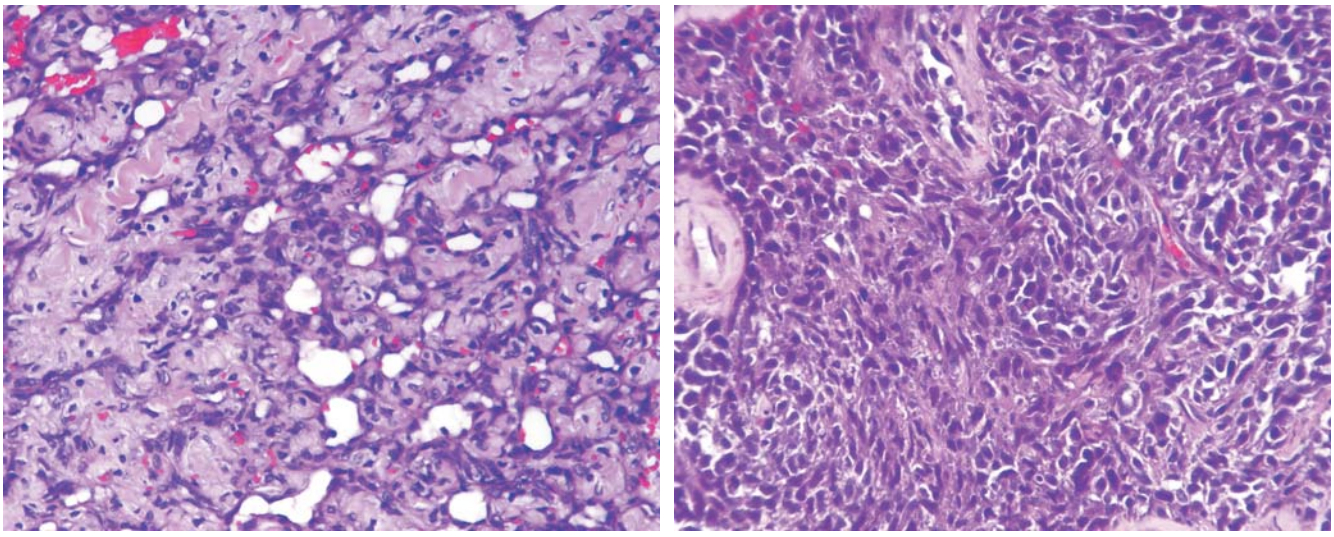

FIGURE 14-5. Angiosarcoma. A. Well-differentiated angiosarcoma is composed of inter-anastomosing vascular spaces lined by neoplastic endothelial cells. B. Poorly differentiated angiosarcoma is composed of spindle cells forming solid sheets and only a few vascular spaces.

none in the poorly differentiated areas. Preexisting adnexal, neural, and vascular structures of the dermis are frequently involved and destroyed by the tumor.

Uncommon cytologic variants of cutaneous angiosarcoma of the face and scalp include granular cell angiosarcoma (17,18) and angiosarcoma with foamy cells. In some angiosarcomas, numerous single necrotic neoplastic cells are scattered throughout the neoplastic aggregations of endothelial cells, giving the lesions a starry-sky appearance (19).

Dysplastic Nevus

The term dysplastic nevus is highly controversial (20–26). Many authors believe this type of nevus is just a variant of a common acquired nevi, while others consider this lesion to be a precursor to melanoma. Dysplastic nevi have certain clinical and histologic features in common with melanoma. Clinically, they vary in size, often measuring greater than 5 mm. They continue to arise through middle age, showing features of asymmetry, irregular borders, and variegated color pattern, and may be surrounded by erythema or an eczematous halo.

Microscopically, the dysplastic nevus is characterized by epidermal hyperplasia with elongation of the rete ridges, bridging of these structures, and stromal fibroplasias (Figure 14-2) (21,22). The melanocytic component is characterized by the presence of single melanocytes and nests at the dermal-epidermal junction (junctional nevus) or the dermal-epidermal junction and dermis (compound nevus). When the lesion is a compound nevus, the epidermal component extends beyond the dermal component—that is, the shoulder of the lesion.

The lesions are divided into 2 groups: those with mild atypia, and those with moderate to severe atypia. Although the designation of architectural disorder within nevi is fairly reproducible between pathologists, studies have documented discordance with the diagnosis of mild versus moderate cytologic atypia, and between moderate and severe atypia. Therefore, it is becoming a common practice to only use the terms mild or severe when describing cytologic atypia in these lesions.

- **Dysplastic nevus with mild atypia.** In cases where the degree of atypia is mild, both individual melanocytes and nests are seen in the lower parts of the epidermis; the nests tend to be fairly equidistant, and the epidermis shows regular hyperplasia (Figure 14-6). Individual melanocytes show a nucleus that is 1.5 to 2 times its normal size, with chromatin that is condensed with loss of all detail. The nucleolus is not visible. The cytoplasm is present as a small rim that is eccentrically located around the nucleus.
- **Dysplastic nevus with severe atypia.** In severe cases, there is some variation in the size and shape of the nests, and focal areas of confluence are seen. Occasional melanocytes present above the dermal-epidermal junction (Figure 14-7). Individual melanocytes contain a nucleus that is 2 times its normal size, with attenuated chromatin present as widely spaced aggregates in a pale background and condensation on the nuclear membrane. Often, there are multiple nucleoli that are large

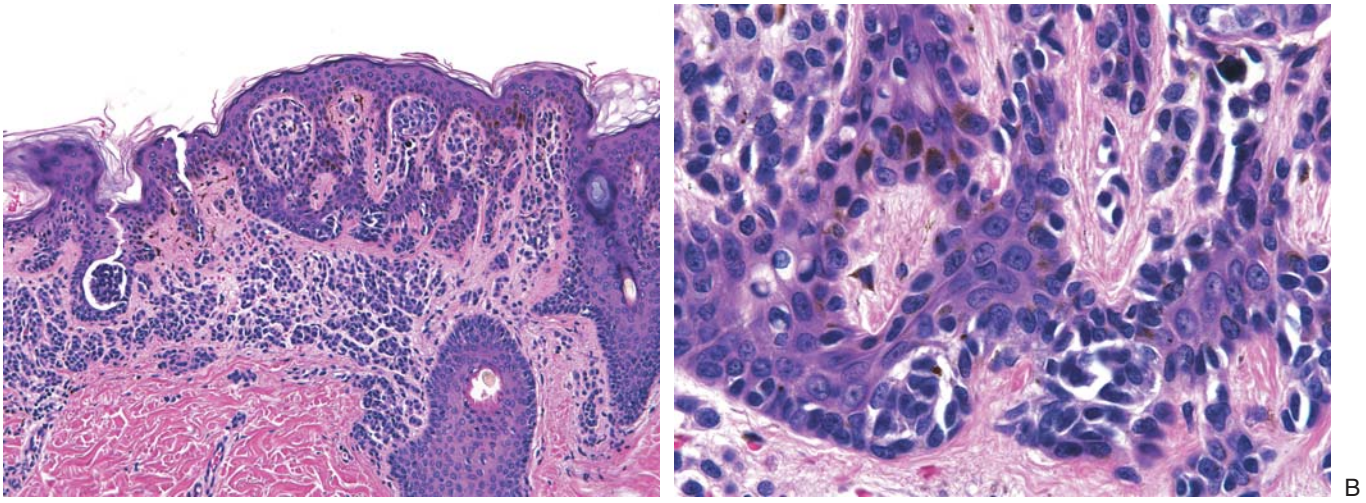

FIGURE 14-6. Dysplastic nevus with mild atypia. A. Both individual melanocytes and nests are seen in the lower parts of the epidermis. The nests tend to be fairly equidistant, and the epidermis shows regular hyperplasia. B. A higher power view of the atypical melanocytes.

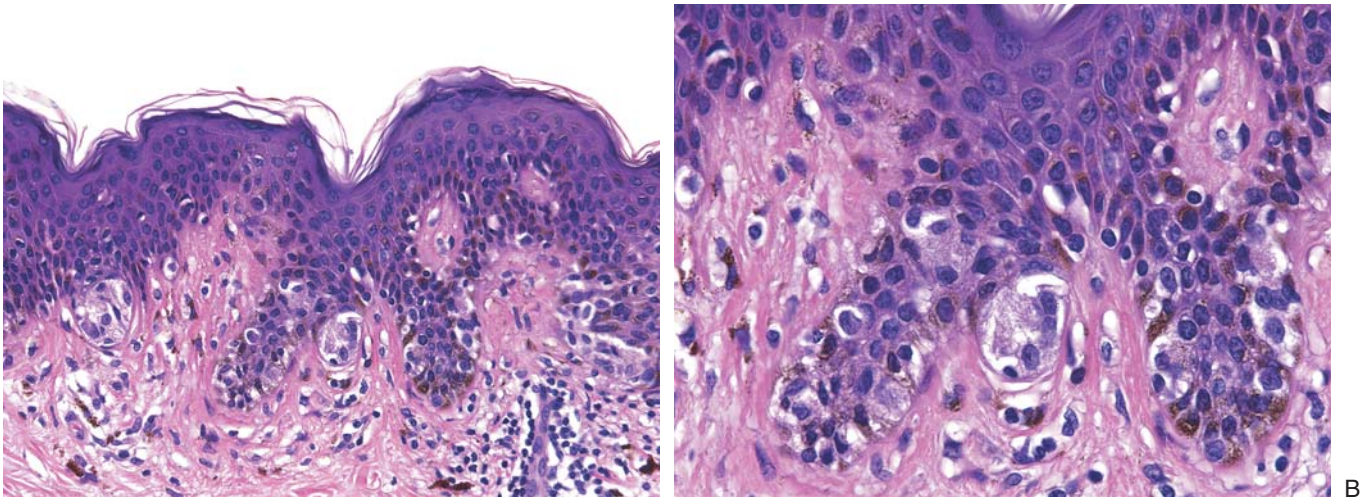

FIGURE 14-7. Dysplastic nevus with severe atypia. A. The nevus shows some variation in the size and shape of the nests. Foci of confluence are evident. B. Higher magnification illustrates the nuclei of atypical melanocytes that vary in size and shape. There are also scattered single melanocytes.

and pale. The cytoplasm is pale pink, is increased in volume, and is finely granular and eccentrically placed around the nucleus.

Comments

1. In 1992, the National Institutes of Health Consensus Development Conference on the Diagnosis and Treatment of Early Melanoma (20) standardized the criteria and nomenclature for dysplastic nevi, recommending a standardized reporting system that describes these lesions clinically as atypical moles and histologically as nevi with architectural disorder. If cytologic atypia is present, the severity should be stated.

2. The possibility that dysplastic nevi are precursor lesions to melanoma continues to be a source of debate. However, it is well established that these nevi are associated with an increased melanoma risk as part of the familial atypical mole and melanoma syndrome and the atypical mole syndrome. In addition, sporadic dysplastic nevi and numerous common, acquired nevi appear to be associated with patients who are at increased risk of melanoma.

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15
Tumors of the Central Nervous System

M. Joe Ma

Introduction

The first significant histologic classification of tumors of the central nervous system (CNS) was proposed by Bailey and Cushing in 1926. Thereafter, several major revisions were introduced, and numerous consensus conferences were held. The grading of CNS tumors is an integral part of these revisions and is routinely applied to primary intracranial and spinal tumors. Rare tumors will not be discussed in this concise chapter.

Astrocytoma

Diffusely infiltrating or fibrillary astrocytomas constitute the majority of those encountered in the human central nervous system. The most widely accepted grading system for this type is the World Health Organization (WHO) classification of tumors, last published in 2000 (Kleihues and Cavenee, 2000). It determines the grade, on a scale of I to IV, of a diffusely infiltrating astrocytoma according to several microscopic features: cellularity, nuclear atypia, mitotic activity, vascular proliferation, and tumor necrosis. However, grading based on these criteria has been reported to show poor interobserver agreement, especially in stereotactic biopsies (1). In 1988, Daumas-Duport and colleagues proposed a more reproducible grading system of adult diffusely infiltrating astrocytomas, (2) generally known as the St. Anne/Mayo grading system. Assigning equal importance to each of 4 specific pathologic features—nuclear atypia, mitosis, vascular proliferation, and necrosis—the St. Anne/Mayo grade of a diffusely infiltrating astrocytoma on a scale of 1 to 4 is determined by the number of feature(s) present plus 1. This system is similar, but not identical to, the WHO classification. For instance, finding 1 mitotic figure in an otherwise well-differentiated, diffusely infiltrating astrocytoma qualifies it as grade 3 in the St. Anne/Mayo system, but it may still be considered a WHO grade II lesion. On the other hand, a small biopsy showing predominantly necrosis rimmed by a few viable atypical astrocytes without mitosis is diagnosed as glioblastoma (grade IV) by the WHO criteria, but remains a St. Anne/Mayo grade 3 lesion. Since both systems are defined by positive features, grading fibrillary astrocytomas based on small biopsies is subject to errors of "undergrading."

The WHO classification of astrocytic tumors includes the following:

- **Grade I, fibrillary astrocytoma.** This tumor is exceedingly rare. It shows a mild increase of cellularity and minimal cytologic atypia without other pathologic features. This grade also includes variants of astrocytoma with specific pathology, radiology, and indolent clinical behavior, i.e., pilocytic astrocytoma and subependymal giant cell astrocytoma.
- **Grade II, well-differentiated or diffuse astrocytoma.** This tumor shows a mild to moderate increase of cellularity (Figure 15-1), mild to moderate degree of nuclear atypia (Figure 15-2), minimal mitotic activity, and no vascular proliferation or tumor necrosis.
- **Grade III, anaplastic or malignant astrocytoma.** This tumor has moderate to high cellularity (Figure 15-3), prominent nuclear atypia, and readily identified mitotic figures. When neither tumor necrosis nor vascular proliferation is recognized, the distinction between grade II and grade III astrocytoma may be subjective. The use of the MIB-1 labeling index to differentiate more aggressive astrocytomas from less aggressive ones has been suggested (3); however, topographic variation of staining limits its practical use, especially in small specimens.
- **Gemistocytic astrocytoma.** This tumor is usually graded as a WHO grade III lesion. It represents a form of diffusely infiltrative astrocytoma. Gemistocytic astrocytomas are composed of neoplastic astrocytes with

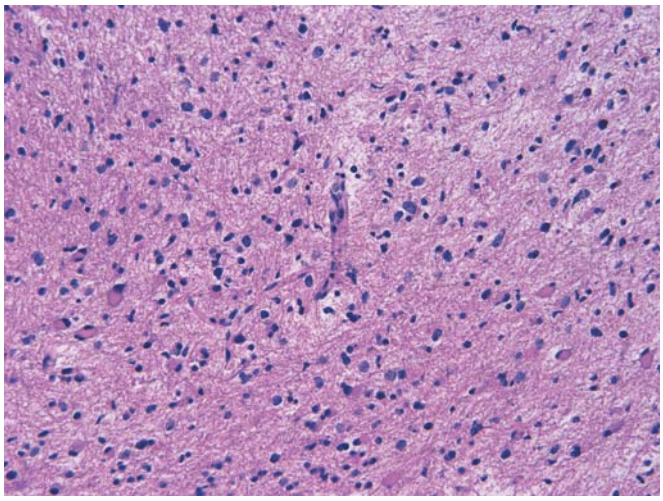

FIGURE 15-1. Astrocytoma. This WHO grade II diffusely infiltrating (fibrillary) astrocytoma shows mild hypercellularity.

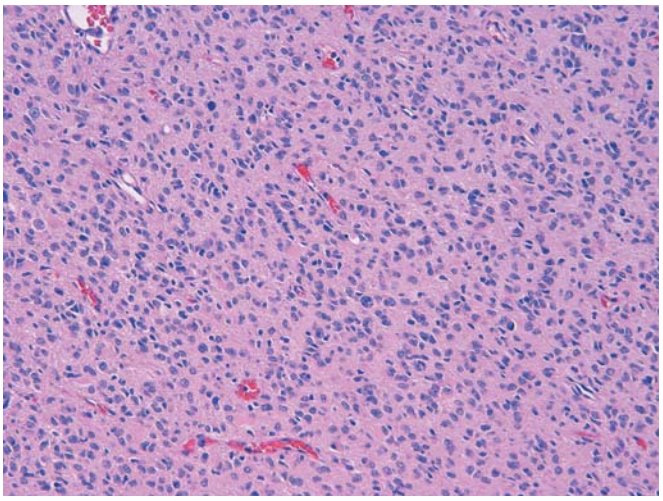

FIGURE 15-3. Anaplastic astrocytoma. Moderate hypercellularity and cytologic atypia are seen in this WHO grade III tumor.

eccentric nuclei, small nucleoli, plump, eosinophilic, glassy and fibrillary cytoplasm (Figure 15-4). There is usually perivascular inflammation. Mitotic figures are few and may be not evident at all.

- **Grade IV, astrocytoma (glioblastoma).** This group of tumors includes astrocytomas that show not only nuclear atypia but also exhibit either necrosis (pseudopalisaded or not) (Figure 15-5) or vascular proliferation (Figure 15-6), or both. As the old term glioblastoma multiforme implies, the architectural pattern and cytologic details of neoplastic cells are variable. Small cells, clear cells, giant cells with bizarre hyperchromatic nuclei, cells with eosinophilic granular cytoplasm, and spindled cells in fascicles can be seen in various combinations or, less often, in pure forms. Aberrant epithelial (squamous and/or glandular) differentiation is rarely seen in glioblastomas and should not to be mistaken as collision cancer (carcinoma metastatic to glioblastoma), although it does occur.
- **Gliosarcoma.** This WHO grade IV tumor contains a glioblastoma component and a malignant mesenchymal component derived from vessel walls or associated meninges (Figure 15-7).

Special Variants of Astrocytoma

In addition to the common variety astrocytomas, several other forms are recognized, including:

- **Pilocytic astrocytoma (PA).** The WHO grade I pilocytic astrocytoma is often cystic, with an enhanced

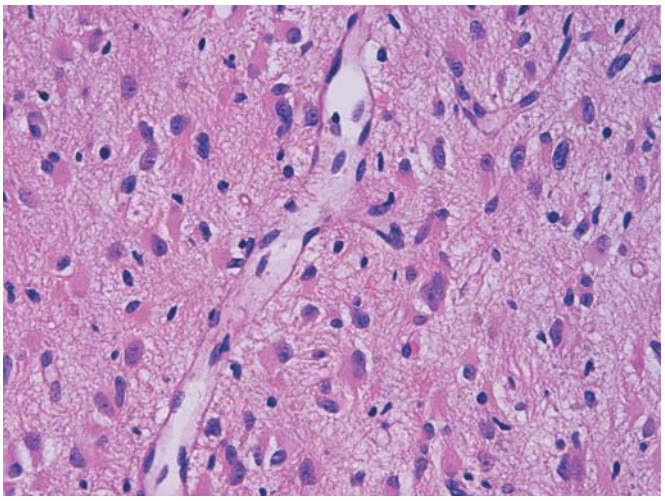

FIGURE 15-2. Astrocytoma. This WHO grade II tumor displays nuclear atypia, which is not accompanied by vascular proliferation or tumor necrosis.

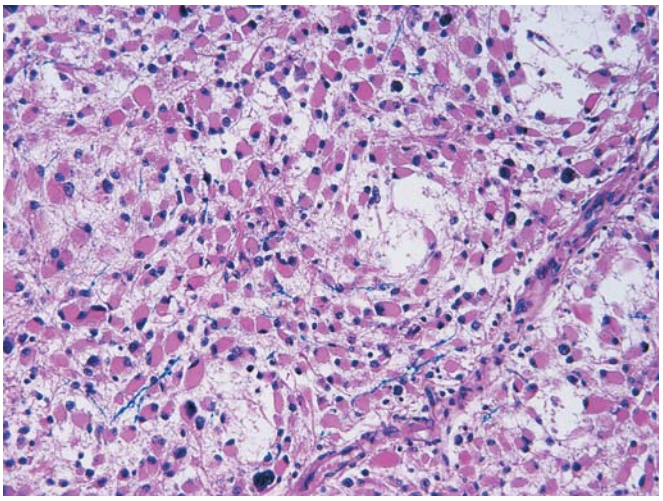

FIGURE 15-4. Gemistocytic astrocytoma. This WHO grade III tumor has moderate atypia (luxol fast blue/HE stain).

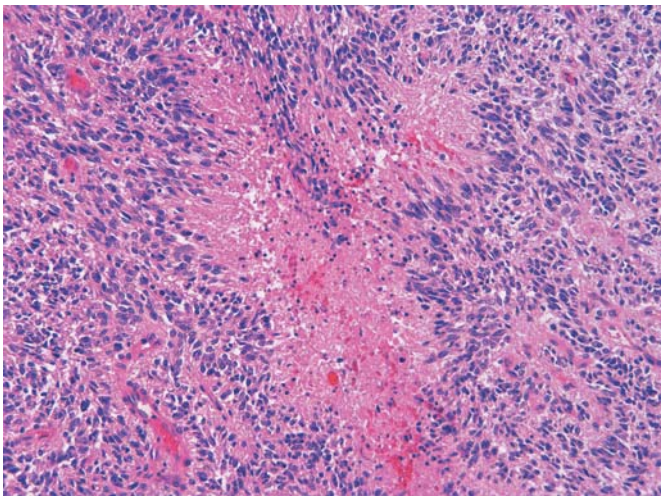

FIGURE 15-5. Glioblastoma multiforme. This WHO grade IV tumor shows pseudopalisaded necrosis.

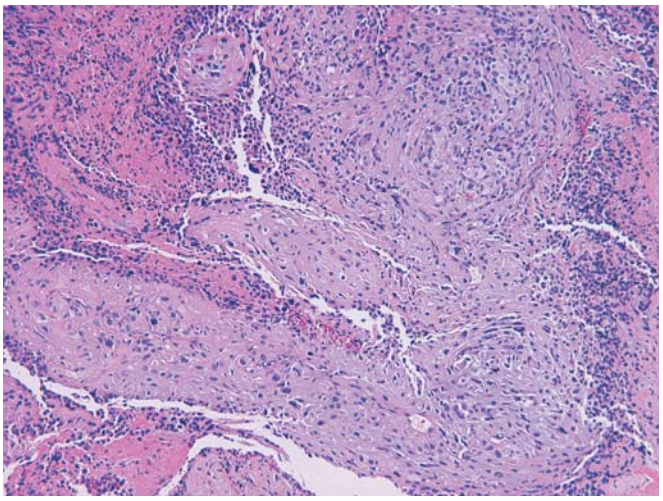

FIGURE 15-7. Gliosarcoma. This WHO grade IV tumor contains atypical mesenchymal cells, which are seen in the perivascular stroma.

mural nodule. It is usually well circumscribed but may show microscopic infiltration in the surrounding parenchyma. It often occurs in or near the midline of neuraxis (e.g., cerebellum, hypothalamus, optic nerve) in children and young adults, but cases have been observed in all age groups and at all anatomic locations. The microscopic appearance of PA varies tremendously. Classic features include a biphasic growth pattern—fibrillary compact areas containing piloid cells and fibrillary processes with or without Rosenthal fibers, alternating with loose microcystic areas containing protoplasmic astrocytes in loose mucin (Figure 15-8)—uniform cells, bland nuclei, eosinophilic granular bodies (Figure 15-9), bipolar slender fibrillary cytoplasmic processes, and calcospherites. Other characteristics include a mild degree of cellular pleomorphism, nuclear atypia, giant cells with floret-like nuclei, hyalinized blood vessels, perinuclear halos, leptomeningeal infiltration, central infarctive necrosis, vascular proliferation, and palisaded spongioblastoma-like growth pattern. By themselves, necrosis and vascular proliferation are of no prognostic significance. In general, mitotic figures are rare and the MIB-1 labeling index is low (<4%). Very rare cases of cerebellar PA with malignant features have been reported (WHO grade III, with hypercellularity, high mitotic activity, and pseudopalisaded tumor necrosis, in addition to vascular proliferation). Rarely, a PA may undergo malignant transformation after irradiation, with characteristics of WHO grade III to IV anaplastic astrocytoma or glioblastoma (4, 5).

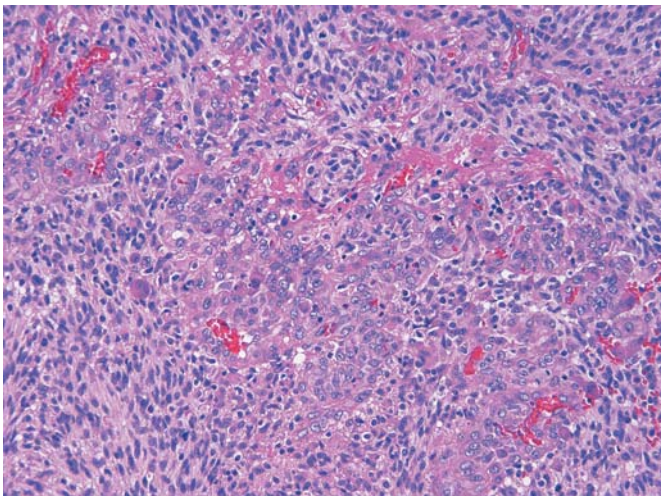

FIGURE 15-6. Glioblastoma multiforme. Characteristic vascular proliferation is evident in this WHO grade IV tumor.

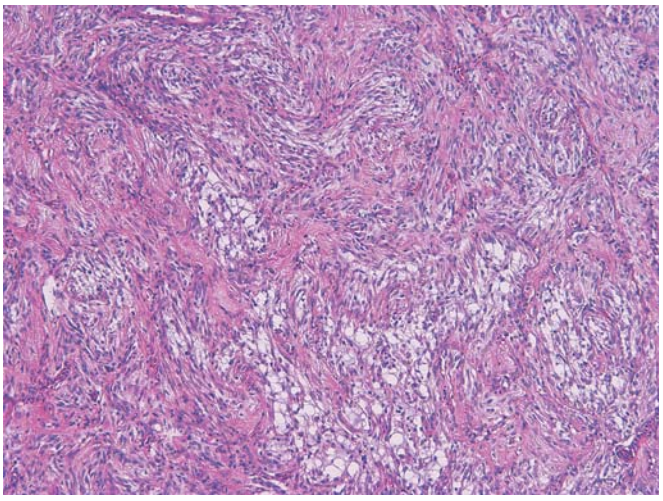

FIGURE 15-8. Pilocytic astrocytoma. This WHO grade I tumor is biphasic and shows a fibrillary and loose, microcystic growth pattern.

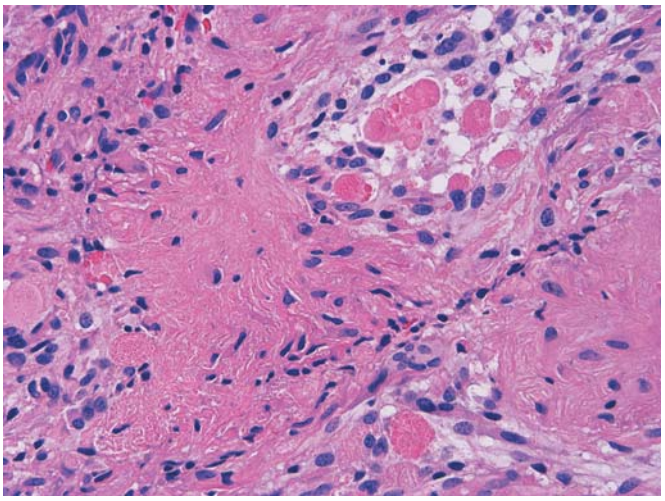

FIGURE 15-9. Pilocytic astrocytoma. Numerous eosinophilic granular bodies can be observed in this WHO grade I tumor.

- **Subependymal giant cell astrocytoma (SEGA).** This WHO grade I circumscribed ventricular wall tumor is found either incidentally or after presentation with obstructive hydrocephalus. The majority of patients with this tumor have tuberous sclerosis; 6% to 16% of patients with this disease develop SEGA. Classic features include a loose or packed collection of large polygonal or elongated cells, with plump or fibrillary eosinophilic cytoplasm in between hyalinized blood vessels (with or without perivascular pseudopalisading) and calcospherites. Some polygonal cells may contain large, round to oval and ganglionic (neuronal) nuclei with a single, central prominent nucleoli (Figure 15-10). Mild cellular pleomorphism, binucleation and occasional mitoses may be seen, but tumor necrosis and vascular proliferation are rare and do not portend malignancy.

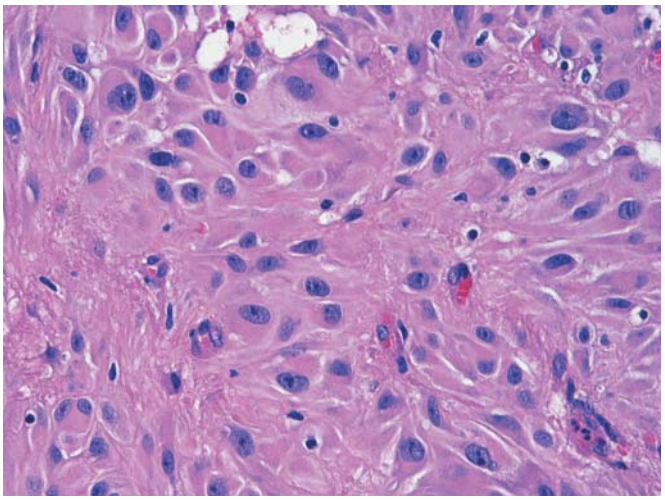

FIGURE 15-10. Subependymal giant cell astrocytoma. In this WHO grade I tumor, large neoplastic cells are seen, with round nuclei, central prominent nucleoli, plump eosinophilic cytoplasm, and occasional binucleation.

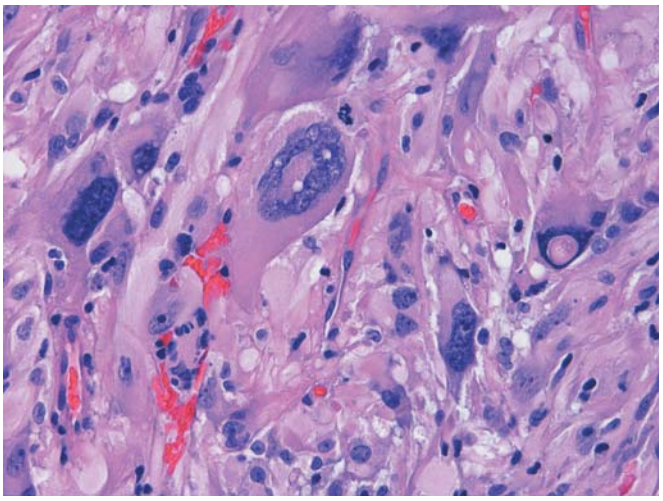

FIGURE 15-11. Pleomorphic xanthoastrocytoma. Large cells with bizarre hyperchromatic nuclei, intranuclear pseudoinclusions, and vacuolated cytoplasm form this WHO grade II tumor.

- **Pleomorphic xanthoastrocytoma (PXA).** This WHO grade II tumor usually presents as a circumscribed, often partially cystic, superficial tumor in children and young adults. Characteristic features include elongated astrocytes, scattered giant cells with large hyperchromatic nuclei, intranuclear pseudoinclusions, vacuolated (lipidized) cytoplasm (Figure 15-11), scattered eosinophilic granular bodies, perivascular inflammation, and pericellular deposition of reticulin fibers. Most cases are controlled or cured by complete surgical resection. A minority (15% to 20%) of PXA manifest tumor necrosis, vascular proliferation, and brisk mitotic activity (>5 per 10 hpf). These so-called PXA with anaplastic features may have a less favorable prognosis; however, they should not be confused with giant cell glioblastoma (6).
- **Desmoplastic cerebral astrocytoma of infancy (DCAI) and desmoplastic infantile ganglioglioma (DIGG).** These rare WHO grade I massive neoplasms of young children present as large, solid, and cystic cerebral tumors often associated with the dura and leptomeninges. Microscopically, desmoplastic hypocellular zones containing plump fibrillary astrocytes (Figure 15-12) transform to hypercellular zones of round or spindled cells with atypia and high nucleocytoplasmic ratios (Figure 15-13). In spite of the readily found mitotic figures and their alarming size, these neoplasms have a good prognosis following resection. The histopathology of both are similar, except for the presence of small or large cells with neuronal differentiation.
- **Rare variants of astrocytoma.** This group, not discussed here, includes several microscopic variants: protoplasmic astrocytoma, gliomatosis cerebri, chordoid glioma

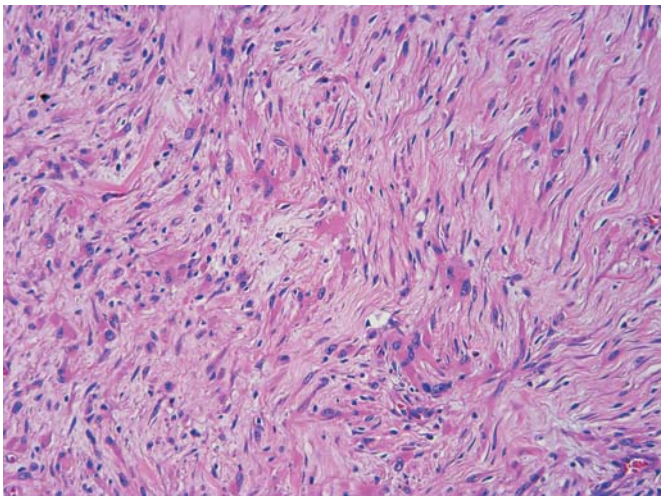

FIGURE 15-12. Desmoplastic infantile ganglioglioma. This WHO grade I tumor consists of neoplastic astrocytes that have a plump fibrillary cytoplasm and are embedded in sclerotic areas.

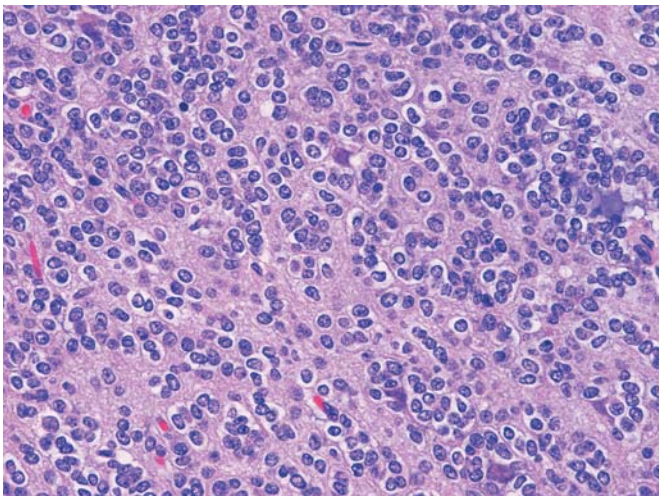

FIGURE 15-14. Oligodendroglioma. This WHO grade II tumor has uniform neoplastic cells with round nuclei and perinuclear halos.

of the third ventricle, granular cell astrocytoma, astroblastoma, pilomyxoid astrocytoma of the suprasellar region in young children and infants, gliofibroma, and sarcoglioma. For grading of these tumors, see specialized neuropathology textbooks and original articles.

Oligodendroglioma

The WHO classification of tumors recognizes 2 grades of oligodendroglioma: well-differentiated (WHO grade II) and anaplastic (malignant) (WHO grade III). It should be noted that clinical response of many oligodendrogliomas to certain chemotherapeutic agents—such as a PCV regimen (procarbazine, lomustine or CCNU, vincristine) and temozolomide—has been associated with loss of chromosome 1p and/or 19q (7).

- **WHO grade II, well-differentiated oligodendroglioma.** The classic features of well-differentiated oligodendroglioma include superficial parenchymal (cortical) involvement, uniform cells with round nuclei and perinuclear halos (Figure 15-14), scant cytoplasm without processes, or globular eccentric eosinophilic cytoplasm with fibrillary processes (mini- or microgemistocytes) (Figure 15-15), a delicate capillary network, associated calcospherites, mucinous microcysts, and occasional hypercellular nodules. Mitotic activity (mitotic count and MIB-1 labeling index) is quite variable.

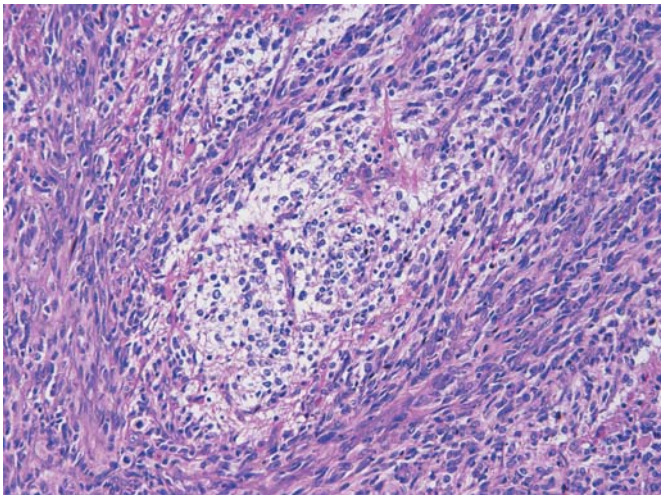

FIGURE 15-13. Desmoplastic infantile ganglioglioma. This WHO grade I tumor contains variably hypercellular areas composed of small, oval, or elongated cells with scant cytoplasm.

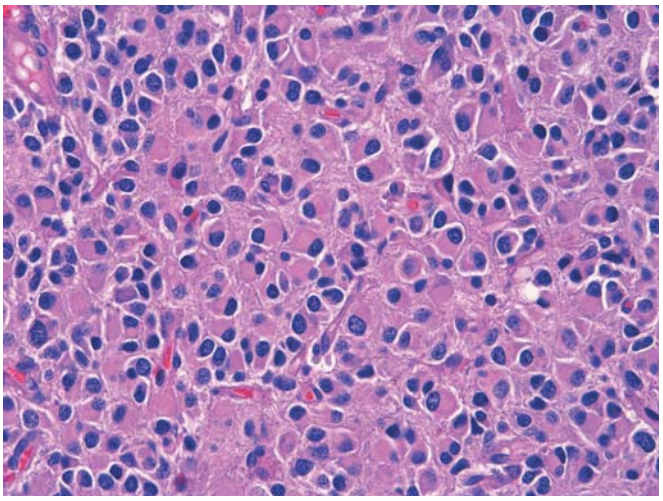

FIGURE 15-15. Oligodendroglioma. This WHO grade II tumor contains mini- or microgemistocytes.

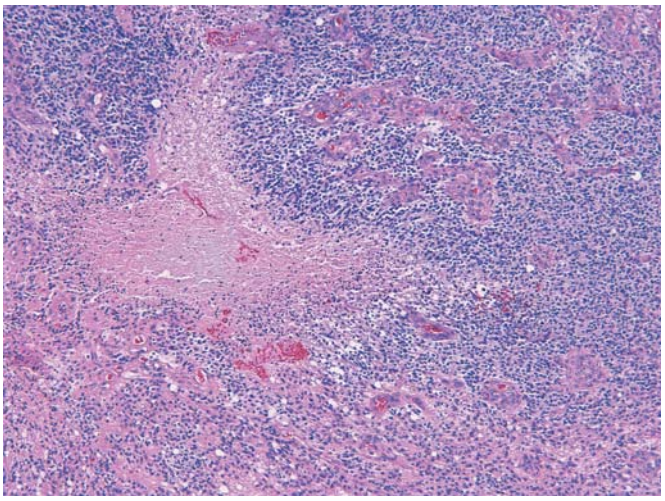

FIGURE 15-16. Anaplastic oligodendroglioma. This WHO grade III tumor displays marked hypercellularity, tumor necrosis, and vascular proliferation accompanied by brisk mitotic activity.

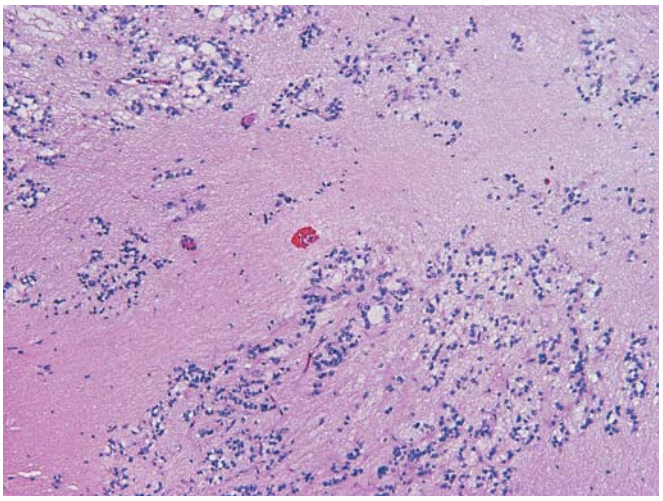

FIGURE 15-17. Subependymoma. In this WHO grade I tumor, cytologically bland cells and associated microcysts in fibrillary matrix are observed.

- **WHO grade III, anaplastic or malignant oligodendroglioma.** In addition to the features described above, this tumor shows diffuse hypercellularity, nuclear atypia, cellular pleomorphism, and brisk mitotic activity. Some cases may display marked cellular pleomorphism and the formation of giant or elongated cells. Tumor necrosis and/or vascular proliferation may be observed (Figure 15-16), but they are not necessary criteria. The features of this tumor overlap with that of a glioblastoma, and some prefer the term glioblastoma with oligodendroglioma component (WHO grade III to IV). Carefully compared, the prognosis of patients with anaplastic oligodendroglioma appears better than for those with glioblastoma.

Ependymoma

Ependymoma arises from ependymal cells lining the cerebrospinal fluid pathways. This tumor occurs in any age group, and is found often in the posterior fossa of children and young adults. The WHO classification recognizes several subtypes, graded on a scale from I to III, as follows:

- **WHO grade I subependymoma.** This group comprises nodular, well-demarcated, and fibrillary ependymal neoplasms on the walls of ventricles and the central canal (spinal cord). Microscopically, subependymomas are paucicellular and fibrillary, with the formation of microcysts and hyalinized vessels. Neoplastic cells are uniform in size and shape, with small round to oval nuclei, and tend to be clustered; they display either vacuolated or eosinophilic cytoplasm (Figure 15-17). Scattered cells with large pleomorphic nuclei of a degenerative nature and occasional mitoses may be seen, but necrosis and vascular proliferation is absent.
- **WHO grade I myxopapillary ependymoma.** This tumor is almost exclusively found in the conus medullaris/cauda equina region of young adults. Radially arranged, uniform, cuboidal or elongated glial cells line the surface of papillae with vascular, hyalinized, or myxoid cores (Figure 15-18). Mucinous vacuoles or microcysts exist between cells. Mitotic activity is low. Local recurrence after resection is uncommon.

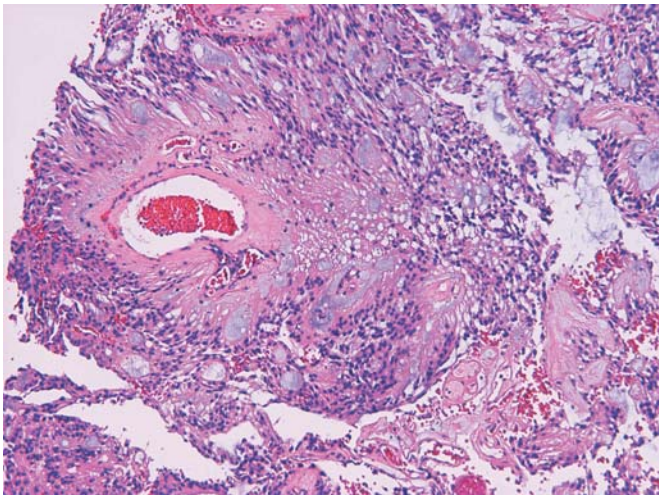

FIGURE 15-18. Myxopapillary ependymoma. This WHO grade I tumor contains mucinous pools. The papillary growth pattern is a hallmark of this tumor.

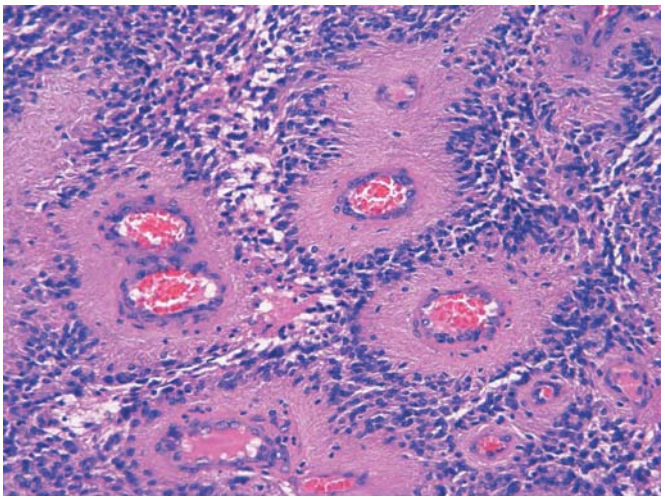

FIGURE 15-19. Ependymoma. Cells forming perivascular pseudorosettes comprise this WHO grade II tumor.

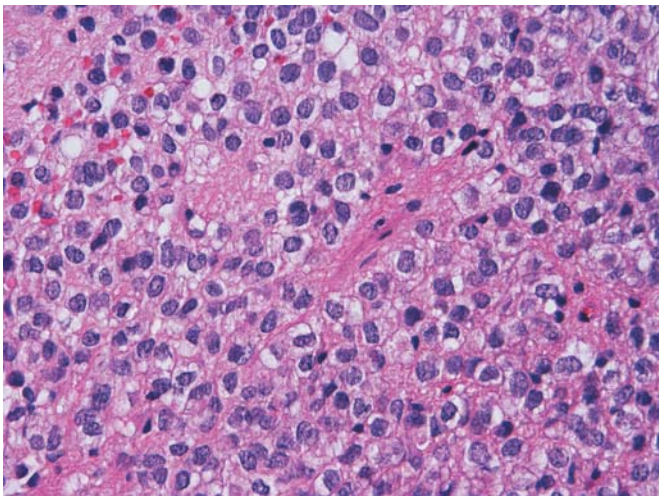

FIGURE 15-21. Clear cell ependymoma. The cells of this WHO grade II tumor have clear cytoplasm.

- **WHO grade II ependymoma.** This often demarcated glial neoplasm shows ependymal differentiation, evidenced by cellular uniformity, varying amounts of fibrillary cytoplasm, and the formation of perivascular pseudorosettes (Figure 15-19) and true ependymal rosettes (also known as ependymal canals) (Figure 15-20). The borders are pushing or, less commonly, infiltrative. In general mitotic activity is low. Cystic change, stromal hyalinization, and calcification may be present. Observed multiple patterns of growth and cytology have given rise to 4 subtypes recognized by WHO: cellular ependymoma, clear cell ependymoma (Figure 15-21), papillary ependymoma, and tanycytic ependymoma. Features of 2 or more of these subtypes may be seen focally in a given case, so a subtype is designated only when a pattern predominates (>50% of the areas examined).
- **WHO grade III (anaplastic or malignant) ependymoma.** In additional to ependymal differentiation, this tumor shows anaplastic features such as hypercellularity, cytologic anaplasia, brisk mitotic activity, pseudopalisaded necrosis, and vascular proliferation (Figure 15-22). However, necrosis without palisading in a posterior fossa ependymoma is not diagnostic of anaplastic ependymoma. Pseudorosettes are inconspicuous, and true rosettes are hardly seen.

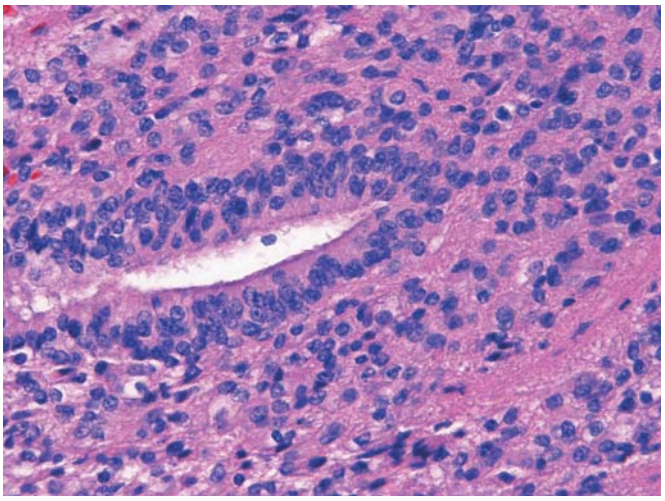

FIGURE 15-20. Ependymoma. This WHO grade II tumor contains an ependymal canal in its center.

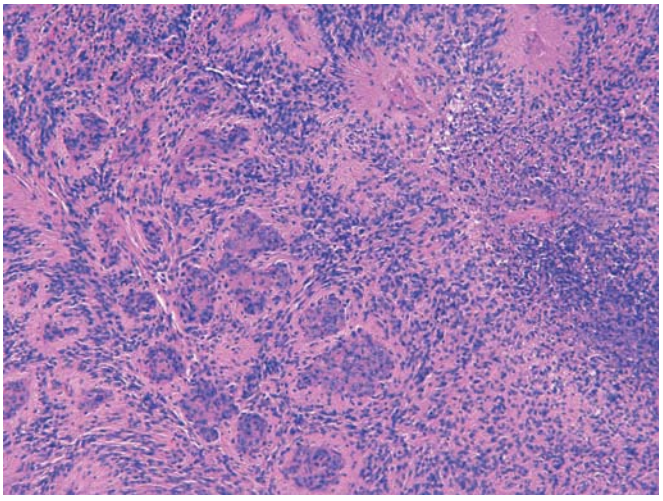

FIGURE 15-22. Anaplastic ependymoma. Necrosis and vascular proliferation are evident in this tumor, as well as brisk mitotic activity and marked cytologic atypia.

Embryonal Tumors, Neuronal Tumors, and Mixed Glioneuronal Tumors

When most constituents in a neuroepithelial neoplasm are poorly differentiated or undifferentiated, it is categorized as a WHO grade IV embryonal tumor or primitive neuroectodermal tumor (PNET). When found in the cerebellum, the pineal gland, and the posterior orbit, PNET is known as medulloblastoma, pineoblastoma, and retinoblastoma, respectively. A neuronal tumor consists of cells with neuronal (ganglionic or neurocytic) differentiation. They include WHO grade I neuronal hamartoma and gangliocytoma, and WHO grade II central (and extraventricular) neurocytoma. Neoplasms containing both mature neuronal and glial components are known as gangliogliomas. Less frequently, a neuroepithelial neoplasm consists of a glial component—usually a diffusely infiltrating astrocytoma—and an embryonal component, without the formation of neurons or neurocytes. These mixed glioneuronal tumors are generally regarded as high-grade neoplasms, of WHO grade III to IV(8–10).

Medulloblastoma

These WHO grade IV embryonal neoplasms typically occur in the cerebellum (especially the vermis) of children and young adults. Like other PNET, medulloblastoma tends to spread through cerebrospinal fluid circulation and may metastasize to extraneural sites. Generally regarded as malignant, medulloblastomas show varying degrees of differentiation in histopathology; a few grading schemes have been proposed, but none have been universally adopted. Four histological types are recognized, as follows:

- **Classic medulloblastoma.** This is the most common form. It consists of diffuse sheets of embryonic cells with round, oval, or carrot-shaped hyperchromatic nuclei, and scant cytoplasm with the possible formation of neuroblastic Homer-Wright rosettes (Figure 15-23) and astrocytic differentiation shown by glial fibrillary acidic protein expression. Pale areas of lower cellularity and containing cells with neuronal and astrocytic differentiation may be observed (Figure 15-24). Neoplastic cells infiltrate the neural parenchyma at interface. Apoptotic bodies and mitotic figures vary in density. Patients with desmoplastic medulloblastomas and cerebellar neuroblastomas may have a better prognosis than those with classic medulloblastomas; those with large cell medulloblastomas have a worse prognosis.
- **Desmoplastic (nodular) medulloblastoma.** This tumor tends to be located in the cerebellar hemisphere, rather than the vermis. It displays biphasic histology and contains many hypocellular, sometimes confluent nodules between reticulin-rich and hypercellular areas (Figure 15-25). Cells in nodules are more differentiated (neuronal, neurocytic, and astrocytic), with uniform, round to oval nuclei of varying sizes embedded in a fibrillary, neuropil-like matrix.
- **Medulloblastoma with extensive nodularity and advanced neuronal differentiation (cerebellar neuroblastoma).** This rare tumor occurs in young children (usually those less than 3 years of age). It displays a strikingly lobular appearance on neuroimaging that corresponds to multiple large nodules on histology. Intranodular neoplastic cells have small, round nuclei and resemble those found in central neurocytomas, accompanied by occasional large neurons.

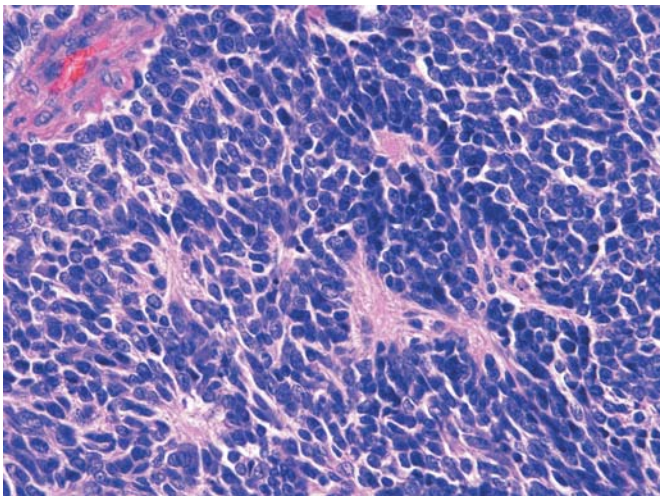

FIGURE 15-23. Medulloblastoma, classic. The tumor cells form Homer-Wright (neuroblastic or true) rosettes.

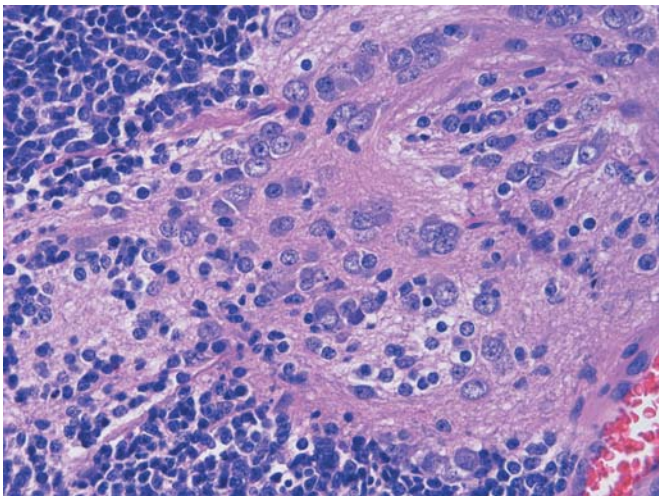

FIGURE 15-24. Medulloblastoma, classic. In addition to undifferentiated cells, the tumor displays signs of neuronal differentiation.

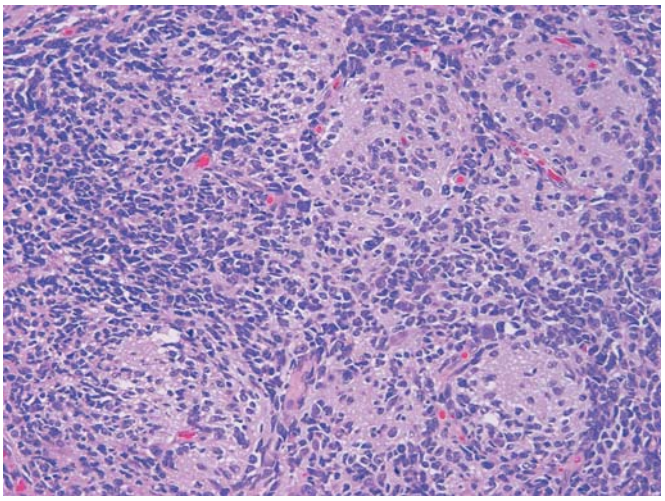

FIGURE 15-25. Medulloblastoma, desmoplastic. The tumor shows obvious nodularity.

- **Large cell (anaplastic) medulloblastoma.** This tumor accounts for 5% to 25% of all medulloblastomas. It consists of cells with large, round, or pleomorphic vesicular nuclei, prominent nucleoli, and more abundant cytoplasm (Figure 15-26). Frequently, there is nuclear molding, cell wrapping, necrosis, and high apoptotic and mitotic activities.

Supratentorial Primitive Neuroepithelial Tumor

This WHO grade IV neoplasm also occurs in children and young adults. In general, their cells are poorly differentiated, but some may display divergent differentiation (e.g., neuroblastic, neuronal, astrocytic, ependymal, oligodendrocytic, muscular, and melanocytic). When both neuroblasts and differentiated neurons predominate, the terms cerebral neuroblastoma and ganglioneuroblastoma (Figure 15-27) may be applied.

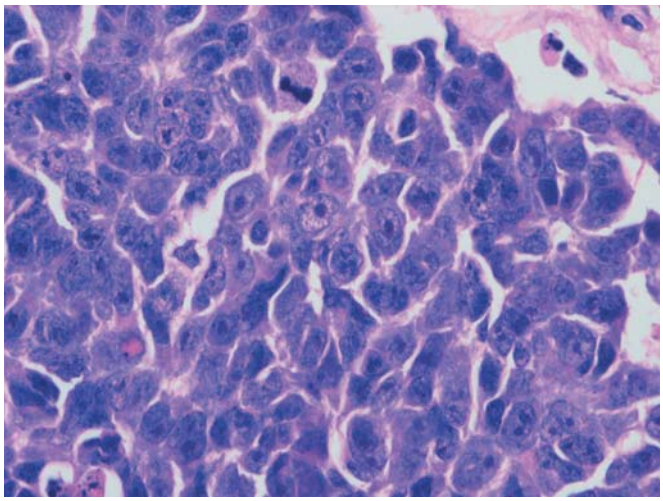

FIGURE 15-26. Medulloblastoma, large cell or anaplastic. The tumor consists of cells with large, round, or pleomorphic vesicular nuclei showing molding or wrapping. The nucleoli are prominent and the cytoplasm more abundant than in classical medulloblastoma.

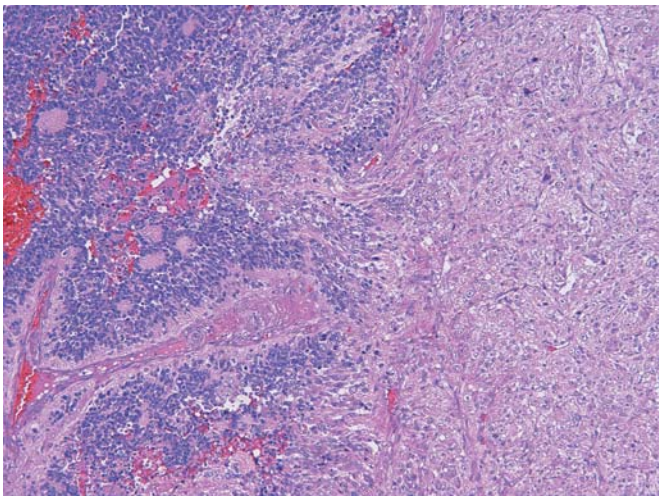

FIGURE 15-27. Ganglioneuroblastoma. The tumor is composed of well-differentiated (right half) and poorly differentiated (left half) areas.

Pineal Parenchymal Tumor

The histopathologic hallmark of pineal parenchymal tumors is the pineocytomatous rosettes—small to medium-size, ill-defined zones of fibrillary processes rimmed by nuclei (Figure 15-28). Pineocytomatous

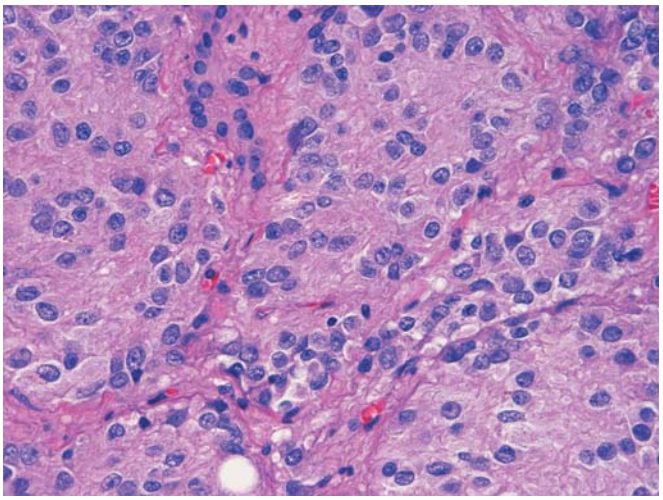

FIGURE 15-28. Pineocytoma. The tumor cells form pineocytomatous rosettes. These structures show vague circular, nuclear arrangements around fibrillary matrix and are larger than Homer-Wright rosettes.

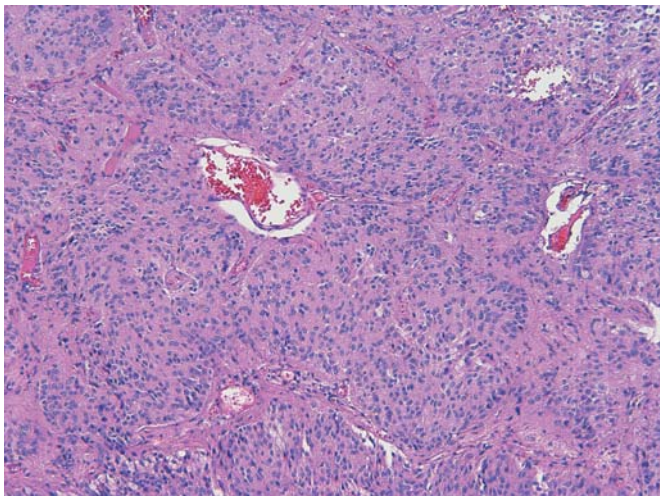

FIGURE 15-29. Pineocytoma. The tumor has a lobular structure, and it is difficult at times to distinguish pineocytoma from the normal pineal gland.

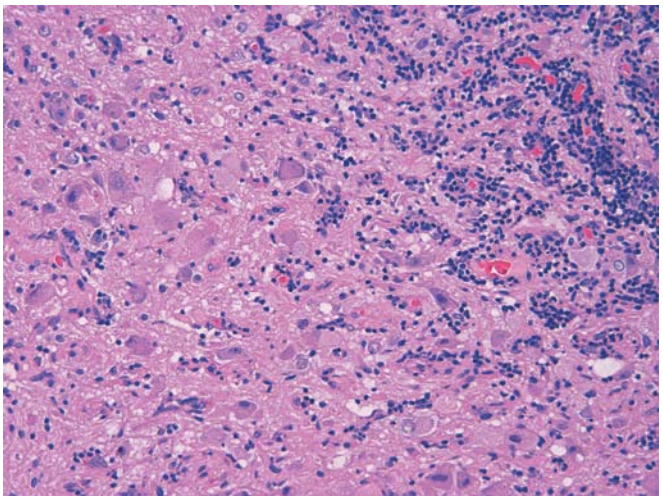

FIGURE 15-30. Gangliocytoma. Large dysplastic ganglion cells and the infiltrates of lymphocytes and plasma cells are typical of these tumors.

rosettes are larger and less regular in shape than Homer-Wright rosettes. These tumors include the following:

- **Pineoblastoma.** This WHO grade IV tumor is a poorly differentiated neoplasm in children showing high-grade features expected of PNET.
- **Pineocytoma.** This is a slow-growing WHO grade II tumor that affects young adults. It consists of sheets or lobules of small, uniform cells resembling normal pineocytes, arranged between small blood vessels (Figure 15-29). Rarely, large or medium-size ganglion cells are found.
- **Pineal parenchymal tumor of intermediate differentiation.** This WHO grade III tumor shows signs of intermediate differentiation and has features that range between those of pineocytomas and pineoblastomas.

Gangliocytoma and Ganglioglioma

Gangliocytoma is a WHO grade I neoplasm of varying cellularity containing numerous differentiated ganglion cells (Figure 15-30). Typically, this tumor contains hyalinized blood vessels with calcospherites and perivascular inflammation. When both dysplastic neurons and neoplastic glia (usually astrocytes) are present, the neoplasm is a ganglioglioma. The glial component in a ganglioglioma may be well-differentiated (WHO grade I or II) (Figure 15-31), anaplastic (WHO grade III anaplastic ganglioglioma) or, rarely, may be indistinguishable from that in a glioblastoma (WHO grade IV).

Central Neurocytoma

This sharply demarcated WHO grade II neoplasm is typically found in young adults. It consists of uniform round cells with neuronal (neurocytic) differentiation in the lateral and third ventricles near the foramen of Monro. Neoplastic neurocytes have small, round to oval nuclei and pale, granular, eosinophilic or clear cytoplasm. It is found between delicate or hyalinized blood vessels and scattered calcospherites. Isolated or small clusters of larger ganglionic cells and small, ill-defined, and neuropil-like fibrillary zones may be present. There are no histological prognosticators, except that a MIB-1 labeling index of >2% to 3% has been associated with a shorter recurrence-free interval.

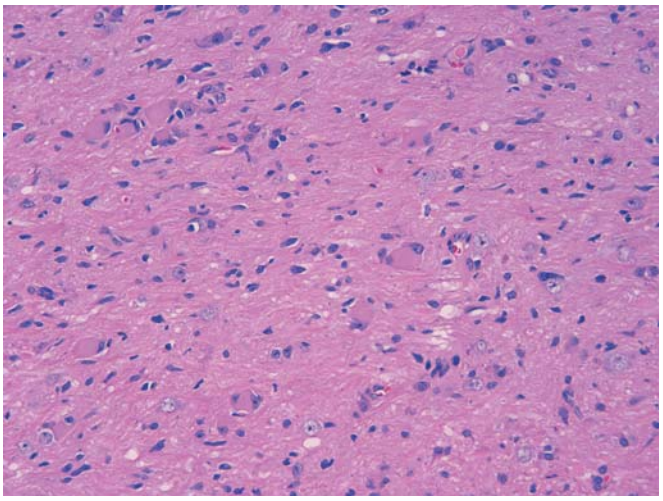

FIGURE 15-31. Ganglioglioma. This WHO grade II tumor contains dysplastic neurons and atypical astrocytes.

Dysembryoplastic Neuroepithelial Tumor (DNET)

This WHO grade I glioneuronal neoplasm occur in children and young adults. It has a supratentorial cortical (especially the temporal lobe) location and is multinodular on gross examination. Histologically, the characteristics include prominent nodular growth, a specific glioneuronal element (small oligodendrocyte-like cells decorating delicate columns of axons arranged perpendicular to the cortical surface), small mucinous cysts containing floating neurons, scattered stellate astrocytes with or without brown granular cytoplasmic pigment, and adjacent cortical dysplasia.

Meningioma

Meningioma is a neoplasm of meningothelial or subarachnoid cap cells found in the leptomeninges. It is assigned a WHO grade of I to III, and is known to display widely variable histopathology. The list of recognized variants of meningiomas continues to change, and at least 13 were described in the WHO monograph devoted to brain tumors (Kleihues and Cavenee, 2000) (Table 15-1). Some variants occur in pure forms (e.g., secretory and clear cell meningiomas), while diagnostic features of others (e.g., chordoid, rhabdoid, and papillary meningiomas) are found only focally. Quantitative criteria for the designation of specific variants have not yet been established.

The risk for local recurrence after surgical resection is increased in WHO grade II atypical meningiomas. WHO grade III malignant or anaplastic meningiomas have the potential of cerebrospinal fluid seeding and distant metastasis. Invasion into the adjacent brain parenchyma has been established as a prognosticator independent of the histologic grade of meningiomas (11, 12), and some consider this finding to be diagnostic of at least atypical meningioma. Brain invasion is evidenced by an irregular rather than smooth pushing border at the interface, with small irregular nests or burrowing tongues of neoplastic meningothelial cells displaced in the parenchyma.

Table 15-1. Meningioma variants.

WHO grade	Meningioma variants
Grade I (Benign meningioma)	Meningothelial or syncytial meningioma Fibrous or fibroblastic meningioma Transitional meningioma Psammomatous meningioma Secretory meningioma Microcystic meningioma Angiomatous meningioma Lymphoplasmacyte-rich meningioma Metaplastic meningioma
Grade II (Atypical meningioma)	Clear cell meningioma Chordoid meningioma
Grade III (Malignant or anaplastic meningioma)	Papillary meningioma Rhabdoid meningioma

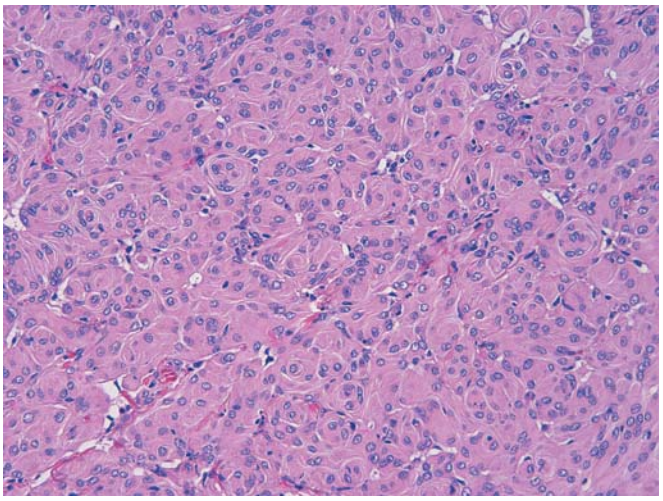

Figure 15-32. Meningothelial meningioma. Tumor cells form whorls.

WHO Grade I Benign Meningioma

This group of tumors includes several variants:

- **Meningothelial or syncytial meningioma.** Tumors of this group consist of neoplastic meningothelial cells with round, oval, or elongated nuclei, smooth nuclear profiles, dispersed chromatin, indistinct small nucleoli, and occasional intranuclear pseudoinclusions. Various architectural patterns and structures may be formed, most commonly whorls (Figure 15-32) and syncytia (Figure 15-33).

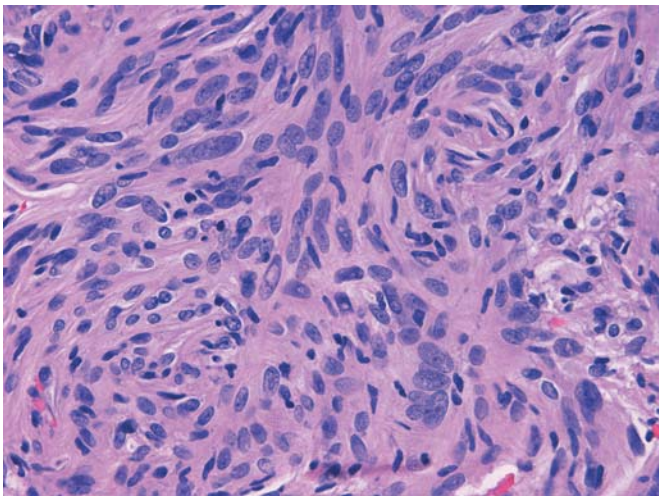

Figure 15-33. Meningothelial meningioma. Streaming neoplastic meningothelial cells display oval nuclei and intranuclear pseudoinclusions in syncytia.

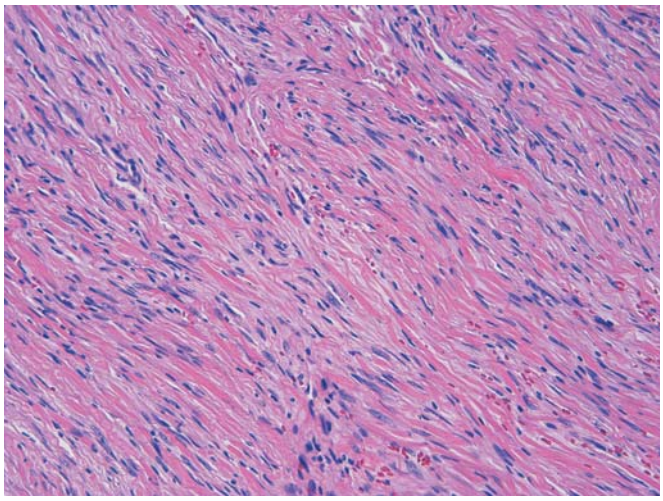

FIGURE 15-34. Fibrous meningioma. Elongated fibroblastic cells surrounded by extracellular matrix comprise this tumor.

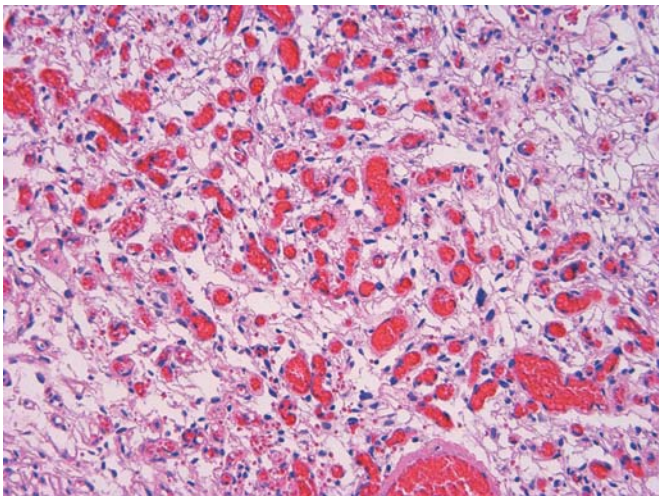

FIGURE 15-36. Angiomatous meningioma. The tumor is highly vascular.

- **Fibrous or fibroblastic variant.** This tumor is composed of slender fibrocyte-like cells between collagen (Figure 15-34).
- **Psammomatous variant.** Psammoma bodies are present in most meningiomas, but if they are prominent, the tumor may be classified as a psammomatous meningioma.
- **Secretory meningioma.** This tumor has plump and epithelioid cells in sheets, forming scattered round vacuolar spaces that contain eosinophilic hyaline globules (pseudopsammoma bodies) (Figure 15-35). Pericytic proliferation around blood vessels may be prominent.
- **Angiomatous meningioma.** Numerous, often hyalinized blood vessels between scarce neoplastic cells characterize this tumor (Figure 15-36); it may be confused with hemangioblastoma or meningeal hemangioma.
- **Microcystic meningioma.** This tumor consists of cells with single or multiple cytoplasmic vacuoles between intercellular microcysts containing mucin or proteinaceous fluid (Figure 15-37). The cytoplasmic vacuoles often indent large hyperchromatic nuclei. Abundant, often hyalinized, blood vessels are present.
- **Lymphoplasmacyte-rich meningioma.** In this rare variant, the tumor typically contains extensive infiltrates of chronic inflammatory cells.
- **Metaplastic meningioma.** This is a rare variant characterized by the formation of bone, cartilage, and/or apparent fat.

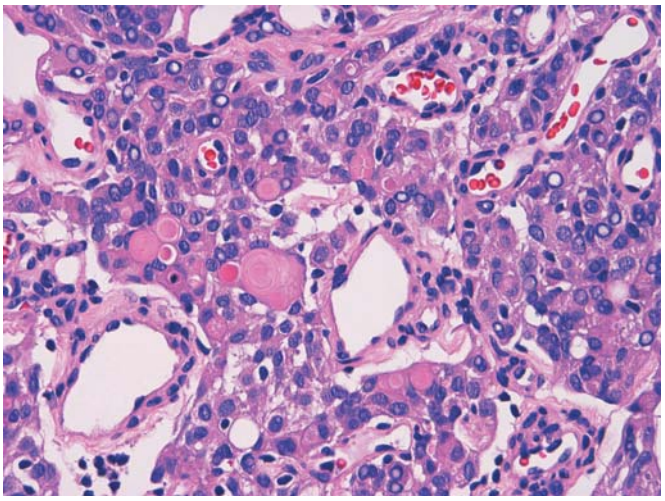

FIGURE 15-35. Secretory meningioma. The tumor contains eosinophilic "pseudopsammoma" bodies.

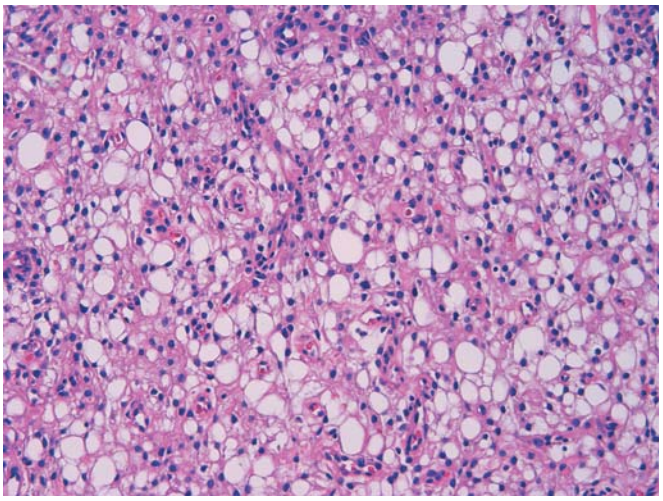

FIGURE 15-37. Microcystic meningioma. Numerous small cystic spaces typify this tumor.

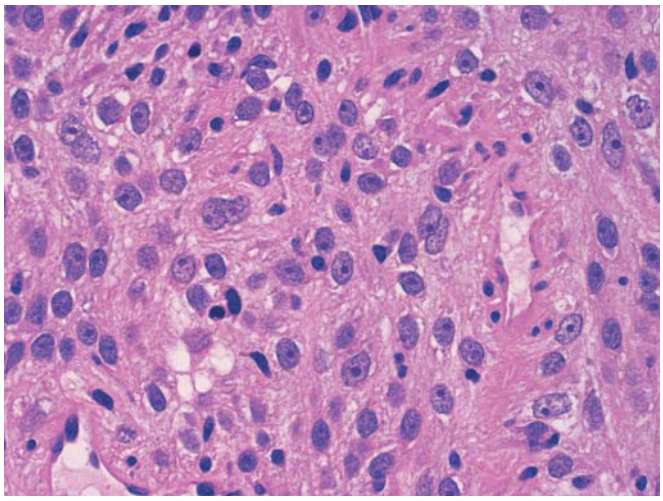

FIGURE 15-38. Atypical meningioma. The tumor cells have prominent nucleoli.

WHO Grade II Atypical Meningioma

According the criteria set by the WHO panel (Kleihues and Cavenee, 2000), a diagnosis of atypical meningioma should be made if the tumor has an average mitotic rate of >4 per 10 hpf, or has 3 or more of the following 5 features: prominent nucleoli (Figure 15-38); tumor necrosis; sheet-like, patternless growth; small cells with high nucleocytoplasmic ratios; and hypercellularity (Figure 15-39). Of these features, only tumor necrosis is objective. Tumor necrosis in meningiomas appears as small or large areas of coagulative necrosis rimmed by a condensed band of cells, and should be distinguished from infarctive necrosis resulting from presurgical embolization. Occasionally, neoplastic meningothelial cells have enlarged, hyperchromatic nuclei, but these changes are degenerative and

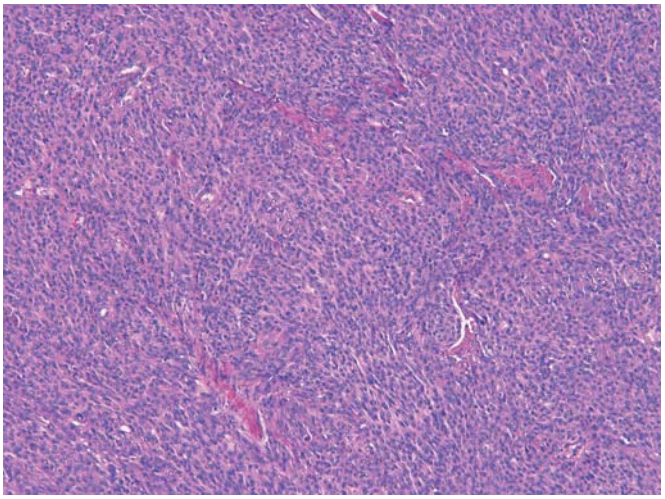

FIGURE 15-39. Atypical meningioma. The tumor appears hypercellular because the small hyperchromatic cells have scant cytoplasm and are compacted into "patternless" sheets.

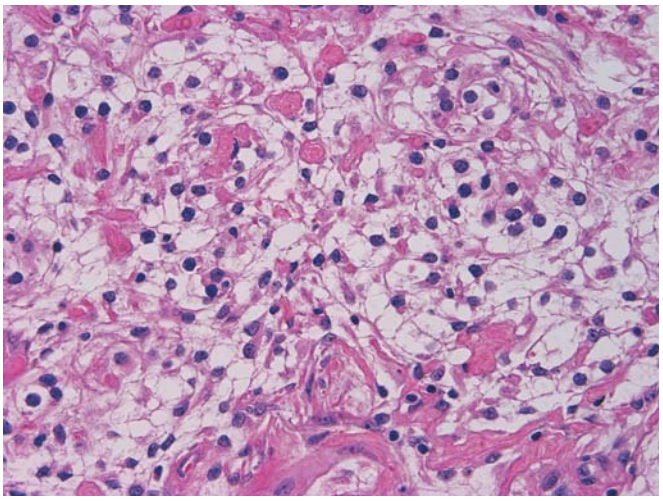

FIGURE 15-40. Clear cell meningioma. The tumor is composed of cells that have clear cytoplasm and small, centrally located nuclei.

are not indicative of true atypia. Two specific variants are designated WHO grade II, due to their atypical clinical behavior:

- **Clear cell meningioma.** This rare neoplasm is composed of clear cells that have a glycogen-rich cytoplasm and central small nuclei (Figure 15-40). Numerous thick collagenous fibers and, sometimes, prominent hyalinization are found in the stroma. Whorls are not apparent, and psammoma bodies are rare. Many are found at the cerebellopontine angle or the cauda equina region in children and young adults. Cerebrospinal fluid seeding of clear cell meningiomas has been reported.
- **Chordoid meningioma.** This tumor is rarely found in a pure form. Typically, it is composed of anastomosing cords of epithelioid neoplastic cells in a myxoid background (Figure 15-41).

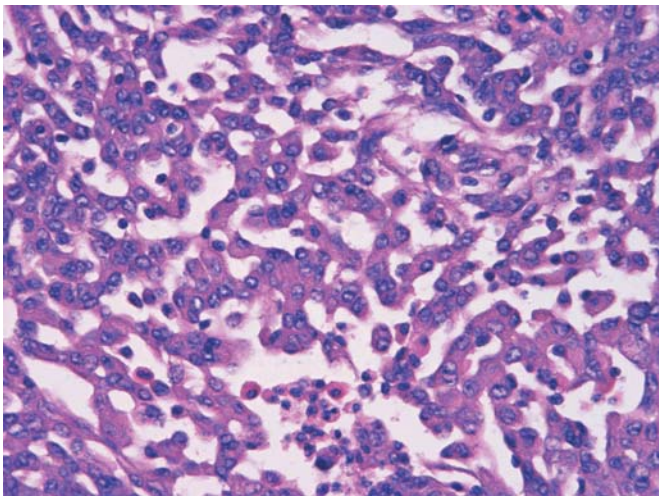

FIGURE 15-41. Chordoid meningioma. The epithelioid tumor cells form inter-anastomosing cords in a loose background.

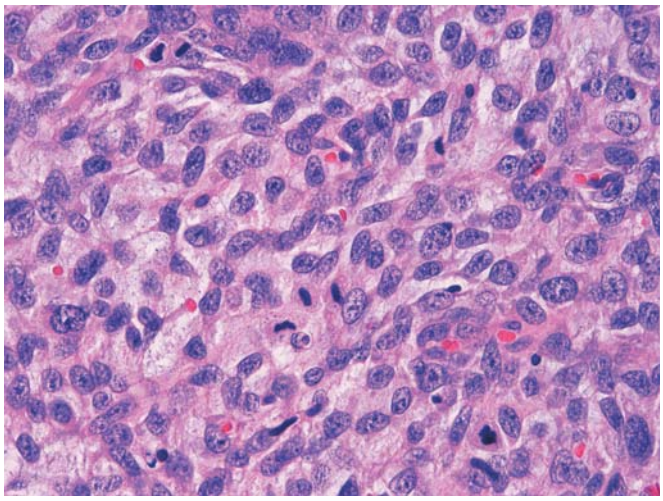

FIGURE 15-42. Meningeal sarcoma. Spindle-shaped tumor cells show marked atypia and brisk mitotic activity.

WHO Grade III, Malignant or Anaplastic Meningioma

This group includes meningothelial neoplasms with a brisk mitotic rate (>20 per 10 hpf) and other atypical features, or dura-based sarcoma without meningothelial or heterologous differentiation (meningeal sarcomas) (Figure 15-42). The following 2 histological variants also are known to behave in a malignant fashion:

- **Papillary meningioma.** This tumor has a predilection for children and young adults. The hallmark of this neoplasm is the formation of perivascular pseudorosettes in discohesive regions of the neoplasm (Figure 15-43). Although neoplastic cells display bland cytology (Figure 15-44), mitoses are readily found.

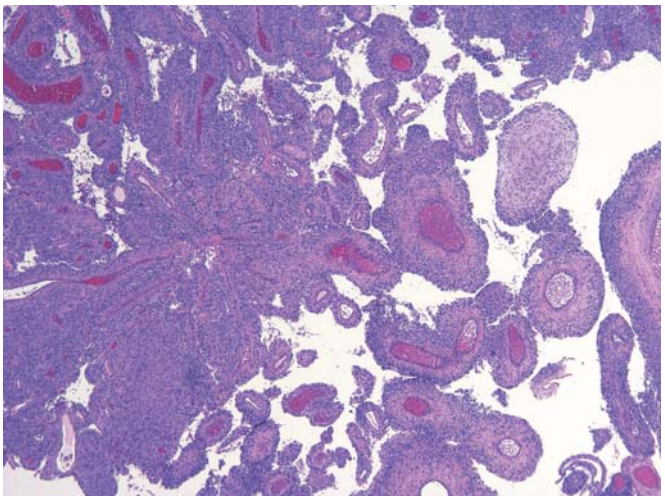

FIGURE 15-43. Papillary meningioma. The tumor cells line the fibrovascular cores of well-formed papillae.

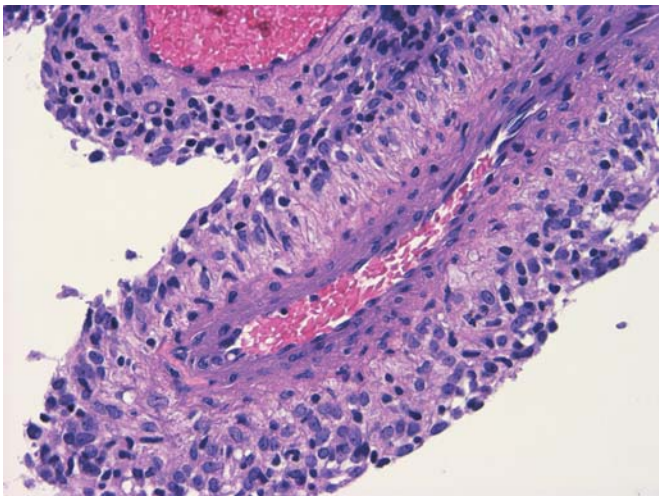

FIGURE 15-44. Papillary meningioma. The papillae are lined by neoplastic cells that still have meningothelial features, such as intranuclear pseudoinclusions (upper left) and whorls (not shown).

- **Rhabdoid meningioma.** This variant is rarely found in a pure form, and meningothelial whorls are seen focally. Rhabdoid cells have large vesicular and eccentric nuclei adjacent to globular cytoplasmic bodies composed of intermediate filaments (Figure 15-45). They are either nested or in massive sheets.

Choroid Plexus Neoplasm

This neoplasm of the choroid plexus epithelium is found in or adjacent to the ventricles, including the cerebellopontine angle. Calcification is common. It can present as low- or high-grade tumors:

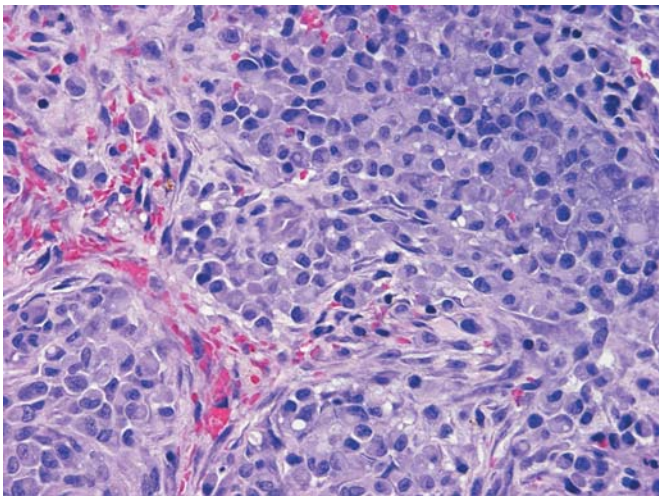

FIGURE 15-45. Rhabdoid meningioma. The tumor cells have a well-developed cytoplasm that contains globular bodies.

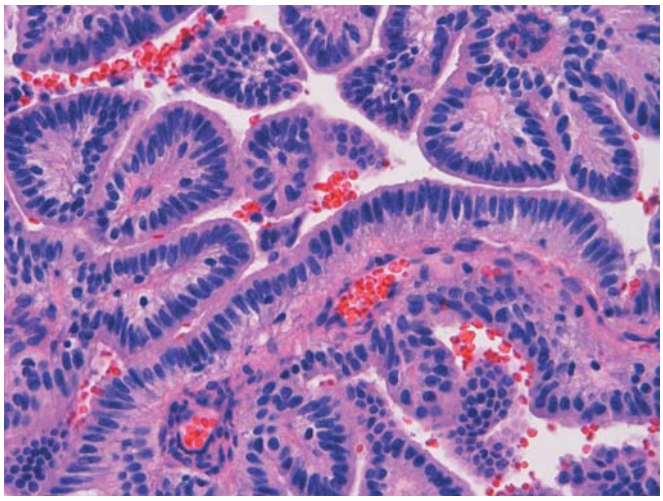

FIGURE 15-46. Choroid plexus papilloma. This WHO grade I tumor is composed of cylindrical cells lining papillary structures.

- **Choroid plexus papilloma.** This is a WHO grade I neoplasm that may be found in patients at all ages. Papillary fronds are lined by a single layer of cuboidal to columnar epithelia over fibrovascular cores. The nuclei of the epithelia are bland, and mitotic activity is low (Figure 15-46). Focal cytoplasmic clearing may be present. Occasionally, small islands of glial tissue are incorporated in the papillary cores, but brain invasion, cytologic anaplasia, and necrosis are not seen.
- **Choroid plexus carcinoma.** This WHO grade III to IV neoplasm is found in young children. Histologically, choroid plexus carcinoma consists of papillary structures and solid hypercellular sheets of pleomorphic epithelial cells with readily identified mitoses, associated tumor necrosis, and brain invasion (Figure 15-47).

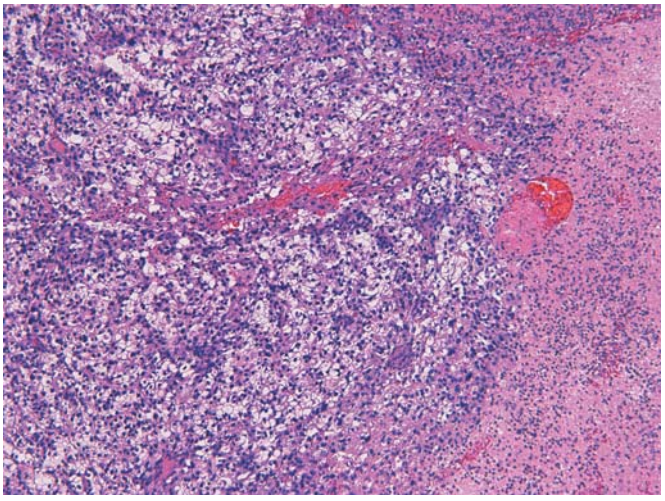

FIGURE 15-47. Choroid plexus carcinoma. This WHO grade III tumor invades the brain parenchyma. It has vacuolated cells and contains foci of necrosis.

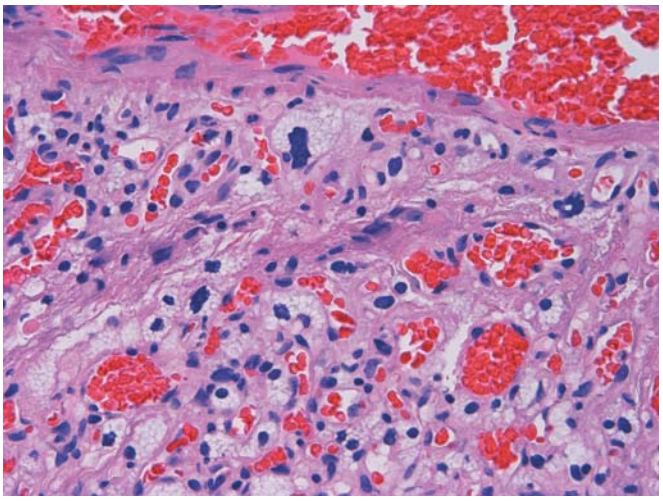

FIGURE 15-48. Hemangioblastoma. This tumor is composed of numerous capillaries filled with blood. The stroma contains clear cells.

Poorly differentiated examples may be difficult to distinguish from an atypical teratoid/rhabdoid tumor.

Hemangioblastoma

This WHO grade I vascular leptomeningeal neoplasm may occur anywhere in the neuraxis, but most commonly present as cystic or solid enhancing masses in the posterior fossa. Up to 25% of the patients with hemangioblastomas have familial (autosomal dominant) von Hippel-Lindau (VHL) disease caused by germ line mutations in the VHL tumor suppressor gene. This tumor consists of abundant capillaries between neoplastic "stromal" cells with round or oval nuclei of varying size, abundant clear or vacuolated, lipidized cytoplasm, and distinctive cellular borders (Figure 15-48). Occasional stromal cells have giant hyperchromatic nuclei indented by cytoplasmic vacuoles. Mitotic activity is low, and necrosis is rarely seen.

Craniopharyngioma

This WHO grade II tumor typically presents in the form of a circumscribed, often cystic mass in the pituitary fossa and the suprasellar region. It consists of neoplastic, stratified squamous epithelia between supporting stroma that may show old hemorrhage. The epithelia line cystic spaces or form anastomosing sheets with no cytologic features of malignancy. Two morphologic variants have been described—papillary and adamantinomatous. The epithelia in the adamantinomatous variant keratinize and form masses of "wet" keratins that tend to calcify

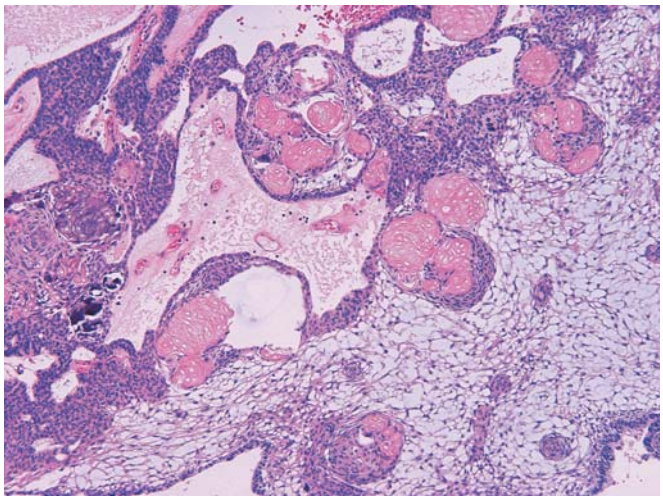

FIGURE 15-49. Craniopharyngioma. Strands and islands of stratified squamous epithelium surrounded by loose stroma are observed.

or even ossify (Figure 15-49). The surrounding gliotic parenchyma often contains prominent Rosenthal fibers.

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