Thyroid Disease

A Case-Based and Practical Guide for Primary Care

Emanuel O. Brams, MD

Humana Press

Thyroid Disease

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Thyroid Disease

A Case-Based and Practical Guide for Primary Care

Emanuel O. Brams, *MD*

University of California School of Medicine, Davis, CA

Foreword by

Steven N. Levine, *MD*

Professor of Medicine
Chief, Section of Endocrinology and Metabolism
Louisiana State University Health Sciences Center
Shreveport, LA

HUMANA PRESS TOTOWA, NEW JERSEY

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

humanapress.com

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American Standards Institute) Permanence of Paper for Printed Library Materials.

Production Editor: Robin B. Weisberg

Cover design by Patricia F. Cleary

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Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN 1-59259-944-3

Library of Congress Cataloging-in-Publication Data

Brams, Emanuel O.
Thyroid disease : a case-based and practical guide for primary care /
Emanuel O. Brams ; foreword by Steven N. Levine.
p. cm. -- (Current clinical practice)
Includes bibliographical references and index.
ISBN 1-58829-534-6 (alk. paper)
1. Thyroid gland--Diseases--Case studies. I. Title. II. Series.
RC655.B69 2005
616.4'4--dc22

2005001925

Series Editor's Introduction

Thyroid Disease: A Case-Based and Practical Guide for Primary Care, by Dr. Emanuel Brams, is a supremely readable cased-based approach to understanding the myriad of disorders that encompass thyroid disease. Using cases derived from his busy practice, Dr. Brams gives us the history and physical examination details of each case, along with test results. Then, through a series of questions similar to that which any good clinician asks while caring for a patient, Dr. Brams explains an optimal approach to diagnosis, treatment, and follow-up of thyroid disease, with an emphasis on the practical and common issues that primary care physicians see in their offices.

This is an important book for primary care physicians because thyroid disease is common in the population we take care of and accounts for 3–5% of primary care visits. It is often cited as an area that primary care physicians find confusing. Dr. Brams clarifies thyroid disease and, through his generous sharing of cases, allows us to join him in making clear diagnoses as well as share in the ambiguity and decisions about approach when the diagnoses and course of treatment are not clear. In this way, the book is honest, and deals directly with the issues of thyroid disease as they are seen by us as physicians, not as we sometimes may wish they were seen if patients presented with the clarity of walking textbooks. Dr. Brams' approach also makes his learning points far more memorable than the long dissertations found in many textbooks.

In summary, *Thyroid Disease: A Case-Based and Practical Guide for Primary Care* is an excellent book on an important topic written for primary care physicians in a style that makes for enjoyable reading that is easily translated into useful lessons for patient care.

Neil S. Skolnik, *MD*
Associate Director
Family Practice Residency Program
Abington Memorial Hospital
Professor of Family and Community Medicine
Temple University School of Medicine
Philadelphia, PA

Foreword

Diseases of the thyroid gland are among the most common problems encountered by primary care physicians each day. Many symptoms of thyroid diseases, such as fatigue, anxiety, and weight gain are quite nonspecific. Thus, both patients and physicians often consider thyroid dysfunction to be the cause of a wide variety of clinical complaints.

In the context of a busy clinical practice, most primary care physicians do not seek a comprehensive textbook filled with chapters on biochemistry and molecular biology. Rather, they benefit most by having access to a book that presents a concise and practical approach to identifying and treating patients with thyroid disease.

Thyroid Disease: A Case-Based and Practical Guide for Primary Care, authored by Dr. Emanuel Brams, is "just what the doctor ordered." Not a traditional multiauthored authoritative text, it is rather a practical manual specifically directed toward primary care physicians and those in training. Dr. Brams brings to his book extensive experience from his clinical practice of endocrinology. Throughout his career he has worked side by side with primary care physicians. From his vast knowledge he has distilled the most important elements of diagnosing and treating thyroid diseases. Dr. Brams writes in a straightforward manner, highlighted by case presentations that clearly illustrate a wide variety of salient clinical points.

Steven N. Levine, *MD*
Professor of Medicine
Chief, Section of Endocrinology and Metabolism
Louisiana State University Health Sciences Center
Shreveport, LA

Preface

I am a thyroid specialist and should think "thyroid" every day, right? Maybe not? A few years ago, our dog, Duffy, a 12-year-old West Highland terrier, seemed to be lying around more than usual. My wife complained that Duffy was not acting right. I told her that the dog was just getting old. When we came back from a vacation, the dog seemed even more lethargic. I told my wife that he was tired after 2 weeks in the kennel. Two days later she called me at the office with a tinge of panic in her voice. She said: "the dog is lying in his bed shivering. I think he is dying." My best advice was to take him to the vet.

The vet examined the dog and told my wife that Duffy was probably hypothyroid. Sure enough, a serum T4 was less than 1. The dog was probably close to myxedema coma. Needless to say, I was a bit embarrassed that I had missed the diagnosis. The good news is that he began to perk up after several weeks of thyroxine therapy. I guess we all have to be reminded now and again to THINK THYROID.

Primary care physicians (PCPs) are faced with a large number of patients every day with nonspecific complaints. Although many of these complaints are related to minor illness, anxiety, and stress at home or at work, some of these patients may have more serious underlying problems such as thyroid disease. The PCP has the very difficult job of sorting out the patients with minor illness from the patients with more serious underlying disease. This is particularly difficult in the thyroid area because most thyroid symptoms are nonspecific. Therefore, many patients with thyroid dysfunction go undiagnosed or misdiagnosed for months or even years. This is unfortunate because good treatment is available for most thyroid problems.

The goal of *Thyroid Disease: A Case-Based and Practical Guide for Primary Care* is to help primary care doctors and other nonendocrinology specialists diagnose and manage patients with thyroid disease in the office. It is very clinical and practical and will, I hope, be helpful to physicians in finding patients with thyroid problems and caring for them. It includes real cases from my endocrinology practice to illustrate the problems and a discussion of how to go about testing, arriving at a diagnosis, initiating treatment, and followup evaluation.

I have had the opportunity to work closely with PCPs as a colleague and endocrine consultant over many years. As a general endocrinologist in a medium-sized city, I have practiced in the "front lines" of patient care medicine. I have had the opportunity to see what type of support and practical clinical advice and education PCPs need and request to help in the care of their patients. This book is an expansion of a case-based approach that I have used for many years in continuing medical education lectures and the writing of a nationally distributed newsletter for PCPs, "Think Thyroid." I used to note the following in my newsletter, and it is worth repeating: These cases are for teaching purposes only. The physician must evaluate each patient individually.

Thyroid Disease: A Case-Based and Practical Guide for Primary Care is divided into two parts. In Part I, I present and discuss cases illustrating the more common thyroid problems seen in practice. A brief discussion of thyroid physiology and testing is also included. Part II covers some more difficult and challenging thyroid problems, and include my views on some controversial issues in the management of the thyroid patient. Chapter 13, discusses four patients who presented diagnostic and therapeutic challenges and were learning experiences for me. Chapter 14 is a discussion of my personal views on treatment of Graves' disease and includes several interesting case vignettes. Chapter 15 reviews a problem that is extremely difficult for the physician to manage, iatrogenic hyperthyroidism.

Emanuel O. Brams, *MD*

Acknowledgments

I dedicate this book to my mentor in endocrinology fellowship, Dr. Robert J. Ryan. Bob taught me to think independently and creatively in the clinic and the laboratory. He helped me to learn the physiology underlying function and pathology of the thyroid gland. This training has served me well in the care of thyroid patients.

I also wish to thank my friend and endocrinology colleague, Dr. J. David Bernard, for his help and encouragement in this and other projects. He read several chapters from this book and offered constructive criticism. Other colleagues—including Drs. Richard Davis, Robert Goldberg, Roland Nyegaard, and Robert Watson—reviewed several chapters for me and their help was appreciated. Dr. John Abele has been my mentor in thyroid fine-needle biopsy over the past 20 years. I also wish to thank all the referring physicians who entrusted me with the care of their patients and the many thyroid patients whom I have had the privilege of caring for over the past 40 years.

Special thanks to Dr. Steven Levine, chairman of endocrinology at Louisiana State University Health Sciences Center, for his help and support.

Emanuel O. Brams

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I Physiology, Testing, and Common Thyroid Disorders

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Introduction

INTRODUCTION

A prominent professional golfer began to note problems with her game. She was becoming shaky and weak and fell in the standings. She thought it was stress related and sought medical help, but the diagnosis of hyperthyroidism was missed for months. Once the diagnosis was made, she received treatment and regained her position in women's golf. The elder President Bush was diagnosed with Graves' disease only after he developed a cardiac arrhythmia. A truck driver was found to have severe hypothyroidism after his eyelids became so swollen that he was a danger on the road. He had probably been hypothyroid for several years. A woman with Graves' disease was so weak by the time she was diagnosed that she had trouble getting up from a chair. She had been ill for 2 yr before her doctor considered hyperthyroidism.

WHY IS THE DIAGNOSIS OF HYPOTHYROIDISM OR HYPERTHYROIDISM OFTEN MISSED FOR MONTHS OR YEARS?

I think the main reason is that the symptoms of thyroid dysfunction are *nonspecific*. Complaints such as shakiness, palpitations, and nervousness—which are common in hyperthyroidism—may be attributed to anxiety. Forgetfulness, confusion, and fatigue—which may be seen in hypothyroidism—may be attributed to old age. (Hypothyroidism is more common in the elderly.) Also, the onset of symptoms of hypothyroidism may be so gradual that the patient becomes accustomed to being cold and forgetful and does not seek help. Many thyroid patients are only aware of how ill they were after they feel better with treatment.

When the thyroid is working in a normal fashion, the individual is unaware of its function. In this sense, the thyroid is different from some other organs, such as the heart or bowel. Even when the heart is working normally, the person may feel it beating in the chest with exercise and note a pulse at the wrist. Everyone

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
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is aware of a bowel movement even when the bowel is functioning normally. We are all aware of our kidneys, brain, eyes, and ears, and can usually tell when something is wrong with them. Thyroid complaints are more nonspecific and are often misdiagnosed or overlooked by the patient or physician.

WHO GETS THYROID DISEASE?

Thyroid disease is very common. It affects about 3% of adults in the United States. It is about eight times more common in women than in men. If people with a thyroid-stimulating hormone (TSH) level between 5 and 10, which suggests mild thyroid dysfunction, are included, hypothyroidism is estimated to occur in 10% of people in the United States. About 25% of the patients in this group have a TSH over 10, which is compatible with clinical hypothyroidism. Thyroid disease is more common in people with other autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, and lupus. It is also more common in the elderly and in people taking certain medications.

SHOULD WE SCREEN FOR THYROID DISEASE?

There is no consensus among experts and organizations regarding screening for thyroid disease in asymptomatic patients. Some groups recommend routine screening of all adults over a certain age. Others recommend testing only those people with suspicious symptoms or certain risk factors (*see* Tables 1 and 2). All agree that the appropriate test is the sensitive TSH.

GENERAL CATEGORIES OF THYROID PROBLEMS

The general categories of thyroid problems are as follows:

- Hypothyroidism: the thyroid is unable to make and secrete adequate amounts of thyroid hormones to maintain a euthyroid state.
- Hyperthyroidism: the thyroid is no longer under normal pituitary–hypothalamic control and produces and secretes excessive amounts of thyroid hormones.
- Thyroid nodules and goiter: the thyroid may be working normally, but it enlarges (goiter) or develops lumps (nodules).

APPROACH TO EVALUATION OF THE THYROID PATIENT

This section discusses the approach that I have used for many years in evaluating patients with possible thyroid disease. Because most of my patients are referred for suspected thyroid disease, it is easier for me to focus in on the problem. It is more difficult for the primary care physician (PCP) who must distinguish possible patients with thyroid problems from the large number of patients seen in the office every day. However, I think this general approach may be utilized by the PCP when thyroid disease is considered in the differential diagnosis.

Table 1
Risk Factors for Hypothyroidism

History
Age >60 years
Hyperthyroidism
Other autoimmune disease
Addison's disease
Pernicious anemia
Diabetes mellitus (type 1)
Subacute thyroiditis (overt or silent)
Head/neck cancer (treated)
Family member with thyroid disease
Medication use
Lithium carbonate
Amiodarone
Iodine (any form)
Routine tests (if previously done)
Hypercholesterolemia
Thyroid tests (if previously done)
Slightly raised serum TSH concentration
Abnormal anti-TPO antibodies

TSH, thyroid-stimulating hormone; TPO, thyroid peroxidase. (From Sawin CT. Thyroid disease in older persons. In: Braverman LE, ed. Diseases of the Thyroid, 2nd ed. Humana Press, Totowa. NJ, 2003.)

Table 2
Risk Factors for Hyperthyroidism

History
Family member with thyroid disease
Known goiter
Cigarette smoker (?)
Current findings
Atrial fibrillation
Goiter
Osteopenia
Congestive heart failure, unexplained
Medication
Amiodarone
Iodine (any form)
Lithium
Routine tests
Radioopaque dye
Thyroid tests
Low serum TSH concentration

TSH, thyroid-stimulating hormone. (*See* Table 1 for source.)

THYROID EVALUATION

NAME:

DATE: **AGE:**

HISTORY:

EYES

NECK MASS

WEIGHT CHANGE

TEMP. INTOLERANCE

MUSCLES

FATIGUE

SKIN CHANGES

HAIR LOSS

BOWELS

NERVOUSNESS

PALPITATIONS

TREMOR

MENSES

NECK RADIATION

THYROID DISEASE

OTHER

PAST HISTORY

FAMILY HISTORY

MEDICATIONS

PHYSICAL EXAMINATION

PULSE BP

EYES

NECK (THYROID DRAWING)

CHEST

HEART

ABDOMEN

EXTREMITIES

NEURO

SKIN

OTHER

IMPRESSION

RECOMMENDATIONS

Fig. 1. Thyroid evaluation form.

As with any patient, the first step is to obtain a good history (Fig. 1). Because most of the symptoms of thyroid dysfunction are nonspecific, the PCP must first think about possible thyroid disease from the presenting complaints. For example, the patient might present with weight loss. The physician might think about hyperthyroidism as a diagnostic possibility along with such entities as infection, neoplasm, and anorexia.

The next step would be to ask some other questions and see if a pattern suggestive of hyperthyroidism emerges. For example, is the weight loss accompanied by increased appetite and food intake? Is the patient's spouse complaining that the house is cold or hot all the time, although the patient thinks the temperature is fine? Does the patient note shakiness when writing a check? Has there been a change in the appearance of the patient's eyes compared with a picture on the driver's license issued 1 or 2 years ago? Does the patient note palpitations when walking up a few stairs or even sitting in a chair? Is the patient unable to lift a child because of weakness of his or her arms?

If the history is suggestive of hyperthyroidism, the physical examination can be focused on findings of hyperthyroidism. Observe the patient. He or she may be squirming in the chair and have rapid speech. Is the pulse rapid or irregular? Does the blood pressure demonstrate a wide pulse pressure? Does the patient stare or have bulging of one or both eyes? Check for diplopia.

The most important part of the examination is palpation of the thyroid gland. It is important to have the patient swallow while examining the neck. I usually give the patient a small cup of water to facilitate swallowing. Because the thyroid gland is attached to the thyroid cartilage, you can feel it move with swallowing. Check for nodules, tenderness, and consistency of the tissue. If the thyroid is enlarged, the odds of thyroid dysfunction as a cause of the complaints increase markedly. A careful cardiac exam may show increased heart tones or irregular rhythm. Ask the patient to hold out both arms and feel the fingertips for the fine buzz or high-frequency tremor of hyperthyroidism. This feels quite different from the gross shakiness of anxiety or neurological disease. To check for proximal muscle weakness, ask the patient to squat down and see if he or she can get up easily. The muscle weakness of hyperthyroidism is usually most pronounced in the proximal muscles. The deep tendon reflexes may show rapid contraction. The skin is often warm, moist, and silky smooth. Also, check the pretibial areas for the raised skin lesions of pretibial myxedema.

If many of the findings noted here are present on history and in the physical examination, the next step is to get some help from the laboratory. We are fortunate to have one blood test that will rule in or out the diagnosis of hyperthyroidism or hypothyroidism in more than 90% of patients. That test is the sensitive TSH, which has been available for more than 15 years and is the TSH test now used by all clinical laboratories (the TSH test is discussed in more detail in Chapter 2). A normal TSH would make thyroid dysfunction very unlikely. In hyperthyroidism, the TSH is suppressed and often unmeasureable. If the TSH is suppressed, a serum-free thyroxine (T_4) should be ordered to confirm the diagnosis. The TSH can occasionally be low because of hypopituitarism, but in hypopituitarism the T_4 will also be low. If the TSH is low and the T_4 is elevated,

the diagnosis of hyperthyroidism is confirmed, and one can proceed to further evaluation to determine the etiology and appropriate treatment.

A similar approach can be used in evaluating a patient for hypothyroidism. In this case, the patient may have symptoms of a sluggish metabolism, such as fatigue, cold intolerance, and constipation. The thyroid may or may not be enlarged. The test results will be the reverse of those in hyperthyroidism. The TSH will be elevated and the serum-free T_4 will be low. The thyroid peroxidase antibody level will often be elevated, which supports a diagnosis of Hashimoto's thyroiditis, the most common cause of hypothyroidism

Thyroid nodules and goiter may be present in a patient with normal or abnormal thyroid function. Thus, a TSH test should be done to check for hyperthyroidism or hypothyroidism. The first-line test for evaluation of thyroid nodules is not a nuclear scan or ultrasound. It is a fine-needle aspiration biopsy. A fine-needle aspiration biopsy will give you the answer to the question you and the patient are asking in the majority of cases: is it cancer or a benign problem? Thyroid nuclear scan is usually not needed but may be helpful in specific patients. Thyroid nodules and cancer are discussed in more detail in Chapters 11 and 12.

2
Thyroid Testing and Imaging

INTRODUCTION

This chapter reviews the most helpful tests for evaluating the thyroid patient. It also covers common thyroid imaging techniques. A brief discussion of thyroid physiology is included to help the reader better understand and evaluate thyroid test results.

THYROID PHYSIOLOGY

This brief discussion of thyroid–pituitary physiology will help the reader interpret thyroid test results. The thyroid gland produces the thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4) under the control of the pituitary gland's secretion of thyroid-stimulating hormone (TSH). TSH secretion is also controlled by thyroid-releasing hormone (TRH) from the hypothalamus. A classic endocrine feedback loop (Fig. 1) functions to keep thyroid hormone levels normal in a patient without thyroid or pituitary disease. Thus, a small increase in thyroid hormones in the blood is detected by the pituitary gland (and hypothalamus), and secretion of TSH is decreased. When thyroid hormone levels fall, pituitary TSH secretion rises. The thyroid synthesizes and secretes both T_4 and T_3. However, much of the T_4 that is secreted is deiodinated to T_3 in the liver and other peripheral tissues. T_3 is the active hormone at the level of the peripheral cell nuclei and at the pituitary and hypothalamic level.

When the thyroid is unable to produce adequate thyroid hormones (hypothyroidism) because of a disease such as Hashimoto's thyroiditis, the pituitary gland senses the fall of thyroid levels in the blood and TSH secretion increases (Fig. 2). In contrast, when the thyroid produces excessive thyroid hormones (hyperthyroidism), as in Graves' disease, the TSH level falls below the normal range (Fig. 3). This feedback mechanism is the basis for biochemical testing of thyroid function.

LABORATORY EVALUATION OF THYROID FUNCTION

Thyroid testing has evolved over the past half century from the old basal metabolism test (BMR) to the current high-tech and very precise assays of

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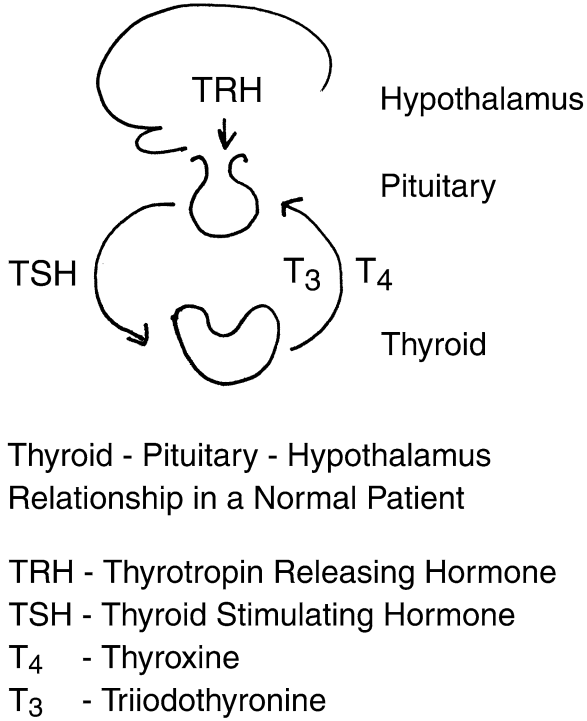

Fig. 1. Thyroid–pituitary–hypothalamus relationship in a normal patient.
TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine.

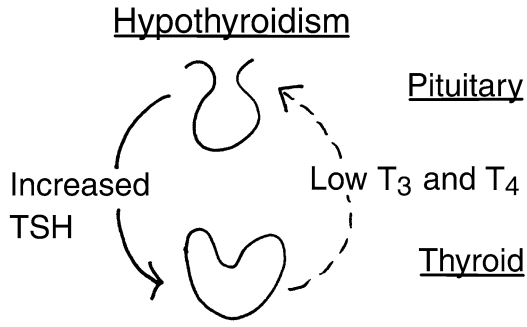

Fig. 2. Hypothyroidism.

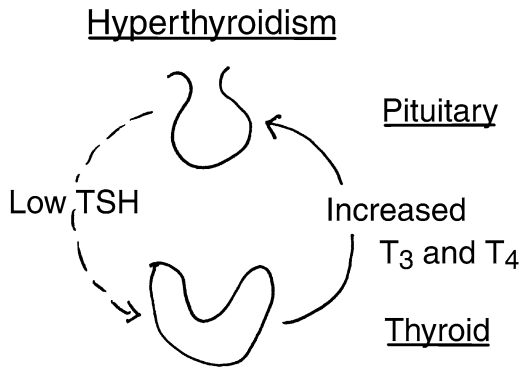

Fig. 3. Hyperthyroidism.

TSH, T_4, and T_3, as well as measurement of thyroid-binding proteins and antithyroid antibodies. Nuclear medicine tests, such as the radioiodine uptake (RAIU) and thyroid scan, which date back more than 50 years, are still useful. Fine-needle aspiration biopsy (FNAB), which has been available in the United States for more than 20 years, has become the first-line test in evaluation of thyroid nodules. Thyroid ultrasound is useful in specific situations in evaluating thyroid nodules. We have come a long way in evaluating the thyroid from the days of the BMR and the protein-bound iodine (PBI). This chapter discusses the most efficient and cost-effective use of these and other tests.

Thyroid-Stimulating Hormone

The TSH assay was one of the tests developed after Berson and Yalow developed the radioimmunoassay (RIA) technique to measure insulin for which they won the Nobel Prize®. It measures the pituitary hormone (TSH) that stimulates the thyroid to produce and secrete T_4 and T_3. However, the RIA measurement of TSH was not sensitive enough to separate a low-normal TSH from a low TSH. It was used on the other end of the scale to distinguish a normal from an elevated level. Thus, the test could be used to diagnose hypothyroidism (high TSH), but it was not useful in diagnosing hyperthyroidism. In about 1985, a new method for measuring TSH was developed. Immunoradiometric assay (IRMA) was 10 times as sensitive as RIA and could distinguish between a low-normal and a truly low TSH. Patients with hyperthyroidism were, as expected, found to have very low TSH levels. Now, with a single test one can diagnose both hypothyroidism and hyperthyroidism in most cases. This test was known as a *second-generation TSH* or sensitive TSH and was gradually adopted by clinical labs. Several years later, an even more sensitive TSH test, known as

third-generation TSH by immunochemiluminescent assay (ICMA), became available and has been adopted by many clinical labs.

When Should You Order TSH?

TSH has replaced T_4 as the first-line test in evaluation of thyroid function. It should be ordered when hypothyroidism or hyperthyroidism is suspected. It is also the best test for screening abnormal thyroid function. A normal TSH will, in most cases, rule out thyroid function abnormalities.

Evaluation of TSH Results

The normal range for TSH varies a bit between clinical laboratories, but is usually detailed on the lab report as between approx 0.4 and 5.5. Some researchers believe that the upper-normal level of around 5 is too high. A new "reference range" of 0.4 to 2.5 has been delineated, although this is not yet quoted as the "normal" range. The new reference range is still controversial (this issue is discussed further in Chapter 7). Most patients with overt hypothyroidism have a TSH of more than 10. Patients with TSH levels between 5.5 (or perhaps 2.5) and 10, with no findings of hypothyroidism and a normal T_4, are diagnosed as having *subclinical hypothyroidism*. Treatment of these patients is controversial and is discussed in more detail later. Most patients with clinical hyperthyroidism have a TSH level that is very low, often unmeasureable by second- or third-generation TSH tests. Patients with a TSH below 0.4, normal T_3 and T_4, and no clinical findings of hyperthyroidism are diagnosed as having *subclinical hyperthyroidism*.

When Are Other Thyroid Tests Needed?

If the patient has clinical findings of hypothyroidism or hyperthyroidism, a T_4 measurement, preferably a free thyroxine (FT_4), should be added. The combination of a low TSH and elevated FT_4 confirms a clinical diagnosis of hyperthyroidism. A low TSH may rarely indicate secondary hypothyroidism owing to hypopituitarism, but in this case, the FT_4 will also be low. A high TSH in combination with a low FT_4 will confirm a diagnosis of hypothyroidism. A high TSH may very rarely reflect a TSH-secreting pituitary tumor with hyperthyroidism, but in this case the FT_4 will also be elevated. The combination of a TSH and FT_4 will provide a diagnosis in most cases. Figure 4 provides a suggested algorithm for thyroid evaluation. Of course, the approach may vary in the individual patient.

Thyroxine

Like the TSH, the T_4 test has evolved over the past 50 years. Because T_4 has four iodine atoms per molecule, early tests relied on the measurement of iodine to estimate T_4 levels. Because more than 99% of T_4 is bound to protein in the blood, the PBI was developed to separate this fraction from the inorganic iodine in plasma. Inorganic iodine levels vary widely depending on iodine

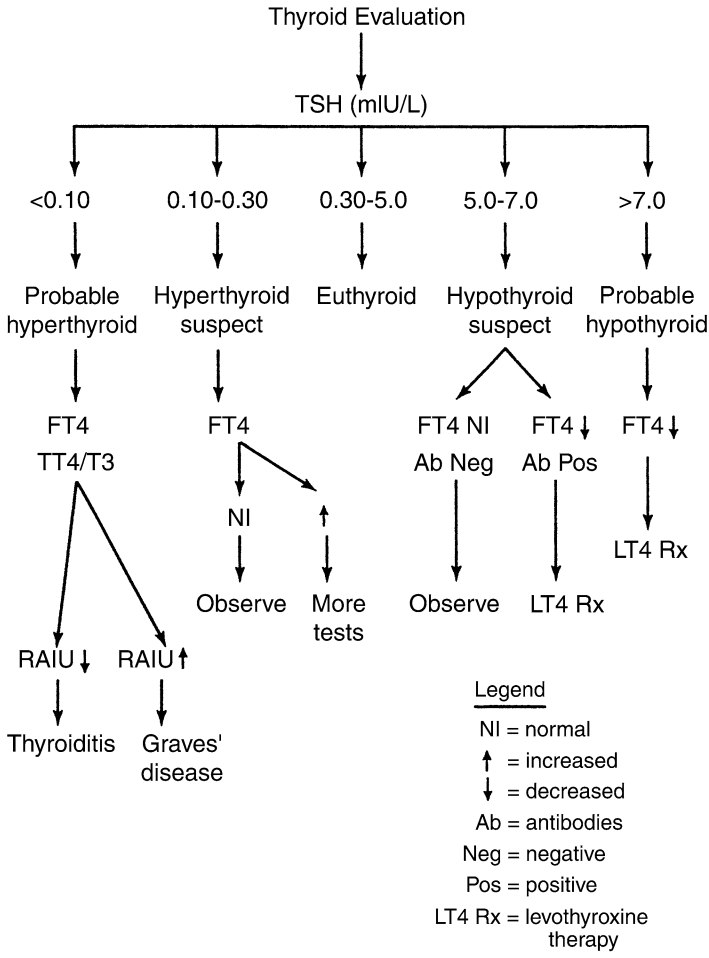

Fig. 4. Suggested algorithm for evaluation and management of thyroid disease when TSH is the initial diagnostic test. (From Kane LA, Gharib H. Thyroid testing: a clinical approach. In: Braverman LE, ed. Diseases of the Thyroid, 2nd ed. Humana Press, Totowa, NJ, 2003.)

intake. One major problem with this chemical test was the effect of large amounts of inorganic iodine, such as those found in cough syrups and cold medicines, in falsely elevating the PBI level. However, for a number of years, this was the best test available, and it was widely used. Modifications of this test based on iodine measurement were developed, but it could still be affected by inorganic iodine. A major improvement in T_4 measurement came with the RIA method. T_4 by RIA was not affected by inorganic iodine and was therefore more accurate. However, this method still measured total T_4. Because more than 99% of T_4 is protein bound and inactive, this test could be falsely affected

by thyroid-binding protein (TBP) changes, as in pregnancy and in patients taking estrogen or birth control pills, which increase binding proteins.

The best current tests measure the free or active portion of T_4 either directly or indirectly. In most cases, these tests are not affected by changes in TBPs and give a true estimate of the clinically important portion of T_4.

When Should You Order a T_4?

An FT_4 should usually be added to a TSH in any patient with clinical thyroid disease to confirm the diagnosis as just discussed. In most cases, a measured, FT_4 is best, although an estimate of T_4 can be obtained by ordering an FT_4 index. This is a calculated FT_4 based on a total T_4 measurement and a so-called T_3 uptake. The T_3 uptake has nothing to do with serum T_3 level, and is simply a laboratory's way of estimating TBPs.

How Do You Interpret the Result?

An elevated FT_4 along with a low TSH is usually diagnostic of hyperthyroidism. A low FT_4 along with an elevated TSH is usually diagnostic of hypothyroidism.

Triiodothyronine

T_3, the other active thyroid hormone, was discovered more than 40 yr ago. Assays were developed for total T_3 and later for free triiodothyronine (FT_3). The total T_3, like the total T_4, may be affected by pregnancy and estrogens. Measurement of the free or active portion of the hormone by a good assay is usually more accurate.

When Should You Order a T_3?

The T_3 is useful in cases where the diagnosis is not clear after review of the TSH and T_4 results. An occasional patient with hyperthyroidism may have a low TSH, normal T_4, and elevated T_3, so-called T_3 toxicosis. It may also be useful in some patients who are undergoing treatment for thyroid dysfunction, and in acutely ill patients with so-called nonthyroidal illness. Nonthyroidal illness is discussed later in this chapter.

How Should You Interpret the Result?

An elevated FT_3, in combination with a low TSH, confirms a diagnosis of hyperthyroidism even in the presence of a normal FT_4.

Radioactive Iodine Uptake

The RAIU test measures the percentage of an orally administered dose of a radioactive form of iodide (usually iodine 123), which is taken up by the thyroid. The measurement is made with an external radiation detector at 4 or 6 and 24 h after administration of the tracer. The test has been available for more than

50 yr and was out of favor for a time after the improved serum tests became available. However, it has become useful again in the differential diagnosis of the etiology of hyperthyroidism.

How Should You Interpret the Result?

An elevated RAIU in the presence of clinical evidence for hyperthyroidism confirms a diagnosis of Graves' disease. A depressed (usually very low) uptake is compatible with hyperthyroidism resulting from thyroiditis.

Thyroid Antibodies

The etiology of the majority of cases of hyperthyroidism is Graves' disease, an autoimmune disease. Also, the large majority of cases of hypothyroidism are caused by Hashimoto's thyroiditis, another autoimmune disease. Thus, it is useful to measure thyroid antibodies in some patients. A brief discussion of several types of thyroid antibodies follows.

Thyroid Microsomal and Peroxidase Antibodies

A test for antithyroid microsomal antibodies has been available for many years. This test measures a cellular antibody that is often present in the blood of patients with Hashimoto's thyroiditis and may also be present in Graves' disease. More recently, a test for antibodies against thyroid peroxidase (TPO) has been developed. This enzyme is involved in the synthesis of T_4 in the thyroid cell. The TPO antibody test is an improvement over the microsomal antibody test and may also be positive in Hashimoto's thyroiditis and Graves' disease.

When Should You Order the TPO Antibody Test?

The TPO antibody test is useful in evaluating patients with hypothyroidism and diagnosing autoimmune thyroid disease. It is particularly useful in patients with subclinical hypothyroidism with mild TSH elevation because a positive test will confirm underlying thyroid disease. Because Hashimoto's thyroiditis often runs in families, it may be helpful to perform a TPO antibody test in relatives of patients with this diagnosis.

How Do You Evaluate the Result?

Most patients with Hashimoto's thyroiditis will have moderately or markedly elevated TPO levels, rather than borderline elevations. TPO elevation may help make the decision to treat mild or subclinical hypothyroidism, because patients with positive antibodies tend to progress from subclinical to clinical hypothyroidism over time.

TSH Receptor Antibodies

Antibodies against the TSH receptor on thyroid cells, such as thyroid-stimulating immunoglobulin (TSI), stimulate increased thyroid function and thyroid

hormone production resulting in hyperthyroidism. The TSI is often, but not always, positive in Graves' disease. In Graves' disease, the thyroid is no longer under the normal feedback control of pituitary TSH. Excessive stimulation by TSI results in hyperthyroidism.

When Should You Order a TSI Test?

The TSI may be useful in difficult or confusing cases of hyperthyroidism where the diagnosis is not clear. However, it is not needed in making the diagnosis of Graves' disease in most patients. Also, a negative test does not rule out Graves' disease.

THYROID IMAGING

Nuclear Thyroid Scan

This scan is often ordered along with the RAIU test. It has been used mainly in the diagnosis of thyroid nodules. The scan is done after administration of a radioactive tracer, either iodine 123 or technecium 99m. These tracers are concentrated in functioning thyroid tissue and can be imaged with a γ-camera. In a patient with a thyroid nodule, the report will determine whether the nodule is functioning (warm or hot) or nonfunctioning (cold). Functioning nodules are rarely cancerous, whereas nonfunctioning nodules may harbor a cancer. The problem with this test is that only about 5 to 10% of cold nodules are cancerous; the rest are benign. Thus, this test is sensitive but nonspecific.

When Should You Order a Nuclear Thyroid Scan?

The first-line test in diagnosis of thyroid nodules is FNAB. However, when FNAB results indicate the possibility of cancer but are not definite (follicular neoplasm), the finding of a hot nodule on a nuclear scan would make cancer very unlikely. Only about 10% of nodules are hot on scan. A cold nodule is not specific for cancer, and surgery might be needed to make a diagnosis. A nuclear scan may also be helpful in diagnosis of hyperthyroidism owing to a toxic nodule or toxic nodular goiter.

Thyroid Ultrasound

Thyroid ultrasound is often used in the evaluation of thyroid nodules. It will show whether a nodule is solid, cystic, or complex (having both solid and cystic components). The rationale for this test is that cancers are usually solid and most cysts are benign. The problem is that many nodules are complex and cystic carcinomas are occasionally seen. Thus, FNAB is still the most useful and specific study in evaluating thyroid nodules. Thyroid ultrasound is being used more frequently in guiding FNA and may also be used in accurately measuring the size of nodules and following them.

Fine-Needle Aspiration Biopsy

FNAB has been used in the United States in the evaluation of thyroid nodules for about 25 years. FNAB has become the first-line test in evaluation of thyroid nodules. The test is quite accurate in differentiating thyroid cancer (surgical) from benign thyroid nodules (usually nonsurgical) when performed by an experienced biopsier and interpreted by a cytopathologist experienced in this technique. Because only about 5% of nodules are cancerous and thyroid nodules are common, it is extremely useful and cost-effective to separate the patients needing surgery from the rest. In most large series, about 80% of diagnostic biopsies are benign, 5% are cancerous, and 15% are suspicious (follicular neoplasm). In the suspicious group, about 15% are cancerous and 85% are benign adenomas, but surgery is required to make the diagnosis. The false-negative rate is 2 to 5% when performed by an experienced biopsier and interpreted by an expert cytopathologist. Quantity not sufficient or nondiagnostic biopsies are in the range of 5 to 20%, depending on the experience of the biopsier and pathologist. If the nodule falls into the suspicious group, a nuclear scan may be helpful because hot nodules are rarely cancerous.

When Should FNAB Be Performed?

FNAB should be the first test performed after discovery of a thyroid nodule in most cases. It is sensitive and specific and is usually the best test to answer the critical question in the patient's mind: is it cancer?

Thyroid Function Tests in Nonthyroidal Illness

The previous discussion applies to thyroid testing in the outpatient setting where most thyroid testing is ordered. However, thyroid function tests are less reliable in seriously ill patients in the hospital, especially those in the intensive or coronary care units. The term "nonthyroidal illness" refers to patients who have abnormal thyroid tests but do not have thyroid disease or who may have transient thyroid disease secondary to the acute illness. This section attempts to briefly summarize this rather complex subject.

Thyroid tests are often ordered in acutely ill patients because of such findings as atrial fibrillation which suggests the possibility of hyperthyroidism, or lethargy and confusion which may in turn suggest hypothyroidism. Although the TSH alone is adequate to screen for thyroid disease in most outpatients, it is not sufficient in the intensive care unit. The TSH in this setting may be low for a number of reasons unrelated to thyroid disease, including drugs such as dopamine and steroids that are frequently used in acutely ill patients. The general recommendation is that thyroid tests should not be ordered in seriously ill patients unless there is a clinical reason, such as goiter or thyroid eye findings, to suspect thyroid disease, or if there is a history suggestive of thyroid disease.

If thyroid tests are indicated, a panel to include TSH, T_4 or FT_4 and T_3 or FT_3 should be ordered. The TSH should be done by third-generation technique that will measure TSH down to about 0.01. An undetectable TSH by this method along with an elevated T_3 would suggest hyperthyroidism. The findings in nonthyroidal illness might show a low but detectable TSH along with a low or low-normal T_3. If possible, FT_3 and T_4 should be measured, rather than total T_3 and T_4 to avoid the effect of abnormalities in TBP.

TBP abnormalities are often seen in seriously ill patients. The thyroid hormones T_3 and T_4 are bound to thyroid-binding globulin, thyroid-binding prealbumin (or transthyretin) and albumin. Low levels of TBP are often seen in sick patients and will result in a decrease in total T_3 and T_4. Patients who are on estrogens or who have liver disease may have elevated TBP and resulting increase in total T_3 and T_4. Also, drugs such as androgens and nicotinic acid may decrease TBP and result in low total T_3 and T_4. In patients on these drugs, the free hormone levels will usually be unaffected.

A complete discussion of nonthyroidal illness is beyond the scope of this book. However, the following points should be helpful:

- Remember that thyroid tests are more difficult to interpret in seriously ill patients in the hospital than in the outpatient setting.
- In general, do not order thyroid tests on hospital patients unless there is reason to suspect thyroid problems clinically.
- Order a complete panel rather than just a TSH in initial thyroid evaluation of sick hospital patients.
- Be aware that a low TSH may be secondary to the acute illness or medications, such as dopamine or steroids, rather than hyperthyroidism.
- Treatment with thyroid hormone is not helpful and may be harmful in patients with nonthyroidal illness who have abnormal thyroid tests but do not have hypothyroidism.

SUMMARY

Thyroid testing has come a long way in the past 50 years. The tests discussed here should help you sort out most thyroid problems. TSH is now the first-line test in evaluating patients suspected of having thyroid dysfunction and in thyroid screening. FNAB is the first-line test in evaluating most thyroid nodules. The other tests reviewed in this chapter are useful in specific patients. The problem of nonthyroidal illness in acutely ill patients is often difficult to sort out, but the points listed here should be helpful.

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3
Graves' Disease

INTRODUCTION

Graves' disease is the most common cause of hyperthyroidism. It is an autoimmune disease. The body produces stimulating antibodies against the thyroid-stimulating hormone (TSH) receptors on the thyroid gland. This results in stimulation of the thyroid to produce excessive amounts of the two thyroid hormones, triiodothyroniine (T_3) and thyroxine (T_4). The thyroid is no longer under the normal feedback control of pituitary TSH. Increased levels of T_3 and T_4 circulate in the bloodstream and affect the function of most organ systems in the body. The active hormone at the level of the cell nucleus is T_3. Although both hormones are secreted by the thyroid, much of the secreted T_4 is converted to T_3 in peripheral tissues.

The effect of the excessive levels of thyroid hormones at the cellular level results in clinical symptoms experienced by the patient. The patient commonly notes palpitations, heat intolerance, sweating, shakiness, muscle weakness, nervousness, irritability, hair loss, and fatigue resulting from the revved up metabolism. These symptoms are nonspecific and may suggest an etiology other than thyroid disease to both patient and physician. Thus, the patient may wait weeks or months before seeking medical help. Then the physician may diagnose stress or panic disorder and prescribe a tranquilizer. Again, weeks or months may go by before the physician thinks about hyperthyroidism. Once the doctor considers the possibility of hyperthyroidism, it is relatively easy to verify the diagnosis with a TSH test. The following case discussions illustrate a variety of clinical presentations, physical findings, and an approach to differential diagnosis and treatment.

CASE 1

A 43-year-old woman was referred by her family physician because of recent onset of palpitations and rapid heart rate. She had been working as an auto saleswoman. She tried to minimize her symptoms, but her mother, who lived with her, revealed that her daughter liked the house much cooler than she

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
By: E. O. Brams © Humana Press Inc., Totowa, NJ

did. The patient claimed that the heat intolerance was intermittent. She also admitted to diarrhea, nervousness, and a "hyper" feeling recently. She had gained 10 lb over the previous 9 months since she quit smoking. TSH was 0.1 (0.4–4.5). She denied any family history of thyroid disease, but her mother recalled that a cousin of the patient had Graves' disease and was treated with thyroid surgery. The patient's only medication was a β-blocker prescribed recently by her family doctor.

Physical examination revealed a pulse of 120. Bilateral lid lag was present, but there was no proptosis and eye movements were normal. The thyroid was diffusely enlarged to twice the normal size. The heart showed a regular rhythm at 120 beats per minute. There was no tremor or muscle weakness.

What Is Your Diagnosis at This Point?

The patient is clinically hyperthyroid, as confirmed by the low TSH. Although Graves' disease is the most likely diagnosis, the differential diagnosis includes autoimmune (silent) thyroiditis and subacute thyroiditis with hyperthyroidism.

Additional Testing

A radioactive iodine uptake (RAIU) was ordered to establish the correct diagnosis.

The test results were as follows:

- RAIU: 6 hour—45% (4–12%); 24 hour—53% (7–24%).

Final Diagnosis

The elevated RAIU confirms a diagnosis of Graves' disease.

Treatment Options

Treatment options discussed with the patient included radioactive iodine (RAI), antithyroid drugs, and surgery. RAI was recommended, and the patient agreed to treatment. The side effect of permanent hypothyroidism and the possibility of thyroid eye problems were discussed.

Clinical Course

Over the next 2 months, the palpitations, heat intolerance, and shakiness completely disappeared and the patient gained 5 lb. The thyroid gland was no longer palpable. TSH at 2 months posttreatment was low-normal at 0.54. One month later, she complained of cold intolerance and puffiness. TSH was over 80. She was started on an estimated full replacement dose of T_4 for her post-RAI hypothyroidism. On follow-up about 6 weeks later, the hypothyroid symptoms were gone and her TSH was 1.7. Now that she was feeling well, she was more aware of how ill she had been prior to treatment. She was continued on T_4 and placed on yearly recall.

Case Discussion

This case demonstrates the most common presentation of hyperthyroidism with symptoms of hypermetabolism, such as palpitations, heat intolerance, and nervousness. Although most hyperthyroid patients lose weight, some gain weight, as did this patient, because the appetite and food intake are markedly increased. The significant finding on the physical exam was the enlarged thyroid. She did not have typical eye findings of Graves' disease such as proptosis and eye muscle involvement. The lid lag noted is an adrenergic effect and may be present in any type of hyperthyroidism.

The low TSH confirmed the diagnosis of hyperthyroidism. The RAIU was needed to differentiate Graves' disease (high RAIU) from thyroiditis with hyperthyroidism (very low RAIU). The very high RAIU confirmed the diagnosis of Graves' disease, and RAI therapy was very effective in curing the hyperthyroidism. The patient developed the usual post-RAI therapy hypothyroidism and has done well for several years on replacement T_4.

What Can We Learn From This Case?

- This patient was a hard-driving salesperson and assumed that her palpitations and nervousness (nonspecific complaints) were caused by stress. She tried to minimize her symptoms. Only after treatment was she aware of how ill she had been. Her mother's observations of the patient and information on family history were helpful.
- An RAIU should be performed in most patients with hyperthyroidism to differentiate Graves' disease from other causes of hyperthyroidism. The RAIU is usually elevated in patients with Graves' disease and very low in patients with thyroiditis with hyperthyroidism. Of course, this test should not be done in pregnant women.
- RAI therapy is the most common treatment for Graves' disease in the United States. It is safe and effective, usually resulting in a cure after one treatment. Some patients with very large thyroids or severe disease may require additional treatments. Hypothyroidism is the expected result and is easily controlled with T_4 in most patients. There is ongoing debate as to whether RAI therapy may have an adverse effect on Graves' ophthalmopathy (*see* Chapter 5), but most thyroidologists feel that the advantages of this treatment in appropriate patients outweighs the disadvantages.

CASE 2

A 70-year-old man was referred by his family doctor for thyroid evaluation and treatment. When I came into the examining room, he was pacing around. He seemed shaky and his speech was rapid. Attempts to elicit a history met with limited success. He talked constantly and did not answer my questions at first. I persisted and got some responses, but they were vague and rambling. He recalled having thyroid surgery years ago. After repeated questioning, he eventually

admitted to a 20-lb weight loss over the past year. He was hot and had occasional palpitations. He thought he might be having trouble remembering things. He denied shakiness or muscle weakness. Thyroid testing 3 months before this visit included a TSH of less than 0.03, FT_4 of 1.86 (0.8–1.5). The RAIU was within normal limits. The scan was compatible with subtotal thyroidectomy in the past.

Physical examination revealed a hyperactive man with rapid speech who had trouble remembering things. His pulse was 96 and irregular, blood pressure (BP) was 150/78. Examination of the eyes revealed bilateral proptosis, more marked in the left eye. Thyroid examination showed a well-healed thyroidectomy scar and no palpable thyroid. The cardiac rhythm was irregular at 96, compatible with atrial fibrillation. There was a fine tremor of his outstretched upper extremities. The skin was warm.

What Would You Do Next?

- Obtain further history from the referring doctor.
- Order TSH, FT_4, and T_3.

Results

The referring doctor revelaed that the patient had been diagnosed with Graves' disease 14 years previously with RAIU of 75% and a very large thyroid. He underwent thyroidectomy at that time.

The patient's TSH is less than 0.03, FT_4 is 1.61 (0.76–1.79), total T_3 is 168 (60–181).

What Is Your Diagnosis?

The findings on history and physical examination and the very low TSH confirmed the diagnosis of hyperthyroidism secondary to Graves' disease. The diagnosis is recurrent hyperthyroidism after subtotal thyroidectomy for Graves' disease many years ago. This man had probably been hyperthyroid for months or years. He had significant morbidity, including atrial fibrillation and mental changes.

How Would You Treat This Patient?

The patient was given RAI. Over the next several months, his cardiac rhythm converted spontaneously to sinus, his mentation improved, and his shakiness cleared. He became hypothyroid about 3 months after treatment and was placed on T_4. When last seen, he was clinically well.

What Can We Learn From This Case?

- Hyperthyroidism in the elderly may present with nonspecific complaints. Common presenting complaints are atrial fibrillation, mental confusion, and hyperactivity.

- Hyperthyroidism may recur years after surgery.
- This patient demonstrates the importance of follow-up in all patients treated for Graves' disease. This man could have been treated sooner and had less morbidity if he had been followed at least annually with TSH testing.

CASE 3

A 67-year-old woman was referred because of eye problems and abnormal thyroid tests. She was seen by an optometrist about 6 months previously because of double vision. She then saw an ophthalmologist 4 months later and was told she had thyroid disease. Prism glasses were prescribed and corrected the diplopia. The patient's daughter, who accompanied her, had noted a change in the appearance of the patient's eyes for several months. The patient complained of recent weight loss of about 20 lb and muscle weakness. She had recently noted palpitations, shakiness, nervousness, and frequent bowel movements. She had noted a rapid pulse. Recent thyroid tests showed a TSH of 0.03 and an upper-normal total T_4 of 10.7. Significant past history revealed surgery for pheochromocytoma 20 years previously. Family history was negative for thyroid disease. The patient had been recently started on propranolol.

Physical examination revealed a pulse of 60 and BP of 130/64. Eye examination showed a widened right palpebral fissure. The left eye showed lid droop. Without glasses, the patient had diplopia in all fields of gaze. The left eye did not elevate as well as the right. The thyroid was enlarged to about 1.5 times normal. The heart showed a regular rhythm at 60 and there was no tremor. Pretibial myxedema was not present.

What Is Your Diagnosis?

The patient is hyperthyroid and has thyroid eye findings. The diagnosis is Graves' disease.

What Next?

Serum thyroid levels were ordered including TSH, FT_4, and total T_3. RAIU and thyroid scan were also ordered. Graves' disease and options for treatment were discussed with the patient.

Test Results

- TSH less than 0.03, FT_4 3.08 (0.75–2), total T_3 222 (70–180).
- Thyroid uptake: 6 hour, 18.4 % (4–12); 24 hour, 40.9% (7–24).
- Thyroid scan: no nodules, compatible with Graves' disease.

How Would You Treat This Patient?

The diagnosis of Graves' disease was confirmed by the above test results. Graves' disease was discussed with the patient and her daughter, a radiology

technician, at length in the office. The options for treatment including RAI, antithyroid drugs (ATDs), and surgery were reviewed. Orbital radiation was also considered for the ophthalmopathy. After phone consultation with a thyroid eye specialist at the university, RAI therapy was recommended to control the hyperthyroidism and possible orbital radiation later. After a long discussion in the office, the patient and her daughter were comfortable with this approach. She was given 10 mCi of iodine 131. Propranolol was continued as symptomatic therapy for the palpitations.

Clinical Course

The patient's hyperthyroid symptoms cleared up over the next 2 months, but her diplopia persisted. At 2 months posttreatment, the FT_4 and total T_3 were normal. The TSH was still suppressed at 0.03. At 3 mo posttreatment, she was hypothyroid with a TSH of 20 and FT_4 0.50. Her diplopia was stable and corrected with prism glasses. She was started on 0.075 mg daily of T_4. One month later, she was clinically euthyroid and had minimal eye complaints with her glasses. She was euthyroid on evaluation 3 mo later and was placed on yearly follow-up.

Case Summary and Discussion

- This patient's presenting complaint was double vision and she was first seen by eye doctors. Fortunately, the second eye doctor recognized thyroid eye disease, and she was referred appropriately. However, she was symptomatic for at least 6 months before she was seen and treated for her Graves' disease.
- This woman had the combination of hyperthyroidism, thyroid ophthalmopathy, and goiter, which were originally described by Dr. Graves and are diagnostic of Graves' disease. Many patients with Graves' disease do not have eye problems and this may delay diagnosis, as noted previously. In the absence of thyroid eye signs, other causes of hyperthyroidism, such as silent thyroiditis, must be considered.
- RAI treatment was effective in curing the hyperthyroidism and the eye problem remained stable. Thyroid eye problems are unpredictable but often stabilize when the hyperthyroidism is controlled. Some studies suggest a higher incidence of progressive ophthalmopathy after RAI than with ATD (*see* Chapter 5). In this older woman, the rapid cure of the hyperthyroidism with RAI probably outweighed the small risk.
- The patient developed the usual post-RAI hypothyroidism, which was well controlled with T_4. She requires yearly follow-up with TSH level to be sure she is taking her T_4 and the dose is correct.

CASE 4

The patient is a 45-year-old woman who was referred for evaluation and treatment of hyperthyroidism. She was generally well until approx 2 months

prior to this visit. During the previous 2 months, she had noted palpitations, shakiness, muscle weakness, heat intolerance, and sweating. She had been extremely nervous and fatigued with frequent crying spells. Her appetite and food intake had increased, yet she had lost 18 lb. She had no menstrual period for 3 months, although her menses had previously been regular. Past history was negative, except for an appendectomy. Family history was positive for thyroid disease in the patient's mother.

Physical examination revealed a middle-aged appearing woman in moderate distress with palpitations and obvious shaking. Her pulse was 110, BP was 140/50. An eye examination showed bilateral stare and lid lag, but no proptosis, and eye movements were normal. The thyroid gland was diffusely enlarged to at least twice normal size without nodules or tenderness. The heart showed a regular rhythm at 110 beats per minute with increased heart tones but no murmur or rub. There was marked fine tremor of the outstretched upper extremities. She showed evidence of muscle weakness and was unable to get up from a squatting position without using her arms.

Working Diagnosis

Hyperthyroidism.

What Tests Would You Order?

The following tests results were obtained:

- TSH less than 0.03 (0.47–6.90).
- Total T_4: 23 (4.5–12).
- RAIU: 6 hour, 69.5% (4–12); 24 hour, 73% (7–24).
- Thyroid scan: no nodules.

Diagnosis

The diagnosis of severe hyperthyroidism is clear from the findings on history and physical examination and the markedly elevated T_4 with suppressed TSH. The diagnosis of Graves' disease as the etiology of the hyperthyroidism is confirmed by the elevated RAIU.

Treatment

The patient required both symptomatic treatment for her tachycardia and shakiness and definitive treatment for the underlying Graves' disease. She was given a β-blocker as symptomatic treatment. The options for treatment of her underlying Graves' disease were discussed with her at length including ATD, RAI, and surgery. RAI was recommended and the side effect of permanent hypothyroidism, which would require T_4 for life, was outlined. It was explained that RAI therapy would likely result in a cure, whereas an ATD

would probably only control the disease with likely relapse when the drug was stopped. At that point, RAI would be needed. Surgery seemed the least desirable option. She was agreeable and RAI was administered after a negative pregnancy test was obtained in view of her amenorrhea.

Clinical Course

At 1 month post-RAI treatment, the patient was less hot and irritable, and her shakiness had decreased. She had her first menstrual period in 4 months. Her thyroid had decreased in size and tremor was decreased. At 3 months post-treatment, she had gained 7 lb, and most of her hyperthyroid symptoms were markedly improved or no longer evident. On examination, the eyes appeared normal and the thyroid was smaller. Her FT_4 was 2.09 (0.76–1.79) and TSH was still suppressed at less than 0.03.

At 4 months post-RAI, she complained of a weight gain of 12 lb, and she was now cold. She noted muscle aches and constipation and felt sluggish. Her vision was a little blurry. On physical examination, there were no thyroid eye signs. The thyroid gland was no longer palpably enlarged. The deep tendon reflexes demonstrated slow relaxation compatible with "hung up" reflexes. TSH was 52 (0.4–5), FT_4 0.21(0.8–1.8). She was clearly clinically hypothyroid and laboratory studies confirmed this diagnosis. She was started on 0.1 mg of T_4 daily. T_4 dosage was titrated upward over the next several months based on TSH levels. Her TSH slowly decreased and finally became normal on 0.175 mg of T_4 daily. She was advised to continue on this dosage with follow-up in 1 yr. A year later she was feeling well and examination was normal, but her TSH was up to 8.3 (0.4–5). She admitted that she had been missing a few thyroid pills. She was counseled on the importance of taking her medication daily and continued on the same dosage. Three months later, her TSH was low-normal at 1.33. She was again placed on annual follow-up.

Case Summary

This patient presented with the rapid onset of most of the symptoms of severe hyperthyroidism, including heat intolerance, sweating, palpitations, shakiness, nervousness, weight loss, fatigue, and significant muscle weakness. Physical findings were also prominent, including adrenergic eye findings of stare and lid lag, a large thyroid, tachycardia, and wide pulse pressure. She was obviously shaky and had severe proximal muscle weakness. However, she did not have the proptosis and eye muscle involvement of infiltrative Graves' ophthalmopathy.

Laboratory findings included an extremely high T_4 and very low TSH. The thyroid uptake of RAI was extremely rapid as evidenced by the very high level even at 6 hours. These findings were consistent with the clinical picture of severe hyperthyroidism.

This patient required symptomatic treatment with a β-blocker to slow her heart and decrease her shakiness. Definitive treatment for the underlying Graves' disease was pursued with RAI.

What Can We Learn From This Case?

- This case demonstrates that Graves' disease can have an abrupt onset with severe symptoms in some patients. The stare and lid lag demonstrated by this patient were due to increased adrenergic tone rather than evidence of true thyroid ophthalmopathy.
- Patients with infiltrative thyroid ophthalmopathy will usually present with true proptosis, which can be confirmed by eye measurements and may have diplopia, periorbital edema, redness, and tearing. It is important to distinguish true Graves ophthalmopathy from adrenergic eye findings because the latter can be seen in non-Graves' hyperthyroidism and do not confirm a diagnosis of Graves' disease.
- Although the severity of the hyperthyroidism made Graves' disease the most likely etiology, an elevated RAIU helped to confirm the diagnosis in the absence of true Graves' opthalmopathy. The uptake was also needed to plan RAI dosage.
- In view of the severity of this patient's hyperthyroidism, one might have considered giving an ATD for several weeks prior to RAI therapy to "cool down" the hyperthyroidism. I might have pursued that approach if the patient had heart disease or was elderly. Occasional patients may have an exacerbation of hyperthyroidism briefly after RAI therapy.
- The physician must counsel the patient that thyroid eye problems, such as bulging and double vision, are unpredictable and can occur or worsen after treatment. Evidence is conflicting, but some studies suggest a higher incidence of thyroid eye problems after RAI than after ATDs or surgery. The advantage of cure from RAI must be balanced against this possible risk. My view and the view of most thyroidologists in the United States is that the advantages of RAI outweigh this risk in the majority of Graves' patients.
- Pregnancy and nursing are the only real contraindications to RAI therapy. A pregnancy test should be ordered prior to treatment in most premenopausal women.

SUMMARY

The cases in this chapter demonstrate several different ways in which Graves' disease can present to the primary care physician (PCP). The first case, a middle-aged woman, presented to her PCP with typical symptoms of hyperthyroidism but without eye findings. In the absence of ophthalmopathy, it would be easy for the physician to attribute her nonspecific complaints of palpitations, heat intolerance, and diarrhea to stress and prescribe a tranquillizer. Even the patient tried to minimize her symptoms and only went to her doctor at the urging of her mother. Fortunately, the patient's PCP thought about hyper-

thyroidism, performed a careful examination of the neck, and ordered a TSH. After the low TSH was found, the patient was on the road to appropriate diagnosis and treatment. Only after she was well did she realize how bad she had felt before treatment. She was very grateful.

The second case, an elderly man, presented to his PCP with atrial fibrillation and confusion. This case demonstrates the more subtle presentation of hyperthyroidism in older patients. Again, the presenting complaints could easily be attributed to other causes, such as underlying cardiac or neurological disease. This case was especially difficult for the PCP because the patient could not give a good history. A good physical examination revealed proptosis and a thyroidectomy scar. There was no palpable thyromegaly. The physical findings led to thyroid testing and appropriate diagnosis and treatment. It was very satisfying to me to see this man regain normal mental status and convert his cardiac arrhythmia spontaneously.

The third case, an older woman, presented to an eye doctor because of diplopia. The optometrist did not think about thyroid disease and prescribed prism glasses. Fortunately for the patient, the second eye doctor thought about Graves' disease, took a more complete history, and ordered some thyroid testing. Diagnosis and treatment were delayed several months.

The fourth case demonstrates yet another presentation of Graves' disease, with abrupt onset and severe signs and symptoms. The diagnosis was more evident in this case because of the florid presentation. The PCP ordered the appropriate tests. Therapy was more challenging because the patient was quite ill. However, the end result of treatment was satisfying to the physicians and the patient.

These cases demonstrate a variety of ways in which hyperthyroidism may present and the difficult job of the PCP or specialist in making the correct diagnosis. As in most areas of medicine, the first step is a good history and physical examination. The good news is that we now have excellent testing and good treatment once the physician "thinks thyroid."

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4
Other Causes of Hyperthyroidism

This chapter explores several causes of hyperthyroidism and the approach to diagnosis and treatment. Although the majority of patients with hyperthyroidism have Graves' disease, some do not. When a patient presents with hyperthyroidism and ophthalmopathy, the diagnosis of Graves' disease is usually evident. However, many Graves' patients do not have typical eye findings, such as proptosis and eye muscle dysfunction. In patients who present with hyperthyroid findings without ophthalmopathy, additional evaluation is often needed to establish the correct diagnosis. Entities such as silent thyroiditis, toxic nodular goiter, subacute thyroiditis, and toxic nodules must be considered in the differential diagnosis. The case discussions in this chapter will help you sort out these patients in the office and make the correct diagnosis. Finding the correct cause of the hyperthyroidism is critical to recommending appropriate treatment.

CASE 1

This 34-year-old woman was referred by her family physician regarding a thyroid nodule and possible hyperthyroidism. She told me she had noted a lump in the left side of her neck 2 or 3 weeks previously. She denied pain in the area, but she had noted a slight pressure sensation. On questioning, she admitted to the recent onset of heat intolerance and intermittent palpitations. She felt "hyper" at times, but denied tremor. She was about 1 year postpartum with her second child and had suffered a miscarriage 6 weeks prior to this visit. She had not had a period since her dilation and curettage and thought she might be pregnant again. She had a strong family history of thyroid disease, including hyperthyroidism in her mother and a cousin. Her grandmother and an aunt had surgery for goiter. She was on no medications.

Laboratory studies that accompanied her included a thyroid-stimulating hormone (TSH) of less than 0.1, total thyroxine (T_4) of 10.1 (4–12), and cholesterol of 107.

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Physical examination revealed a young woman in no acute distress. The pulse was 100, blood pressure (BP) was 110/64. There were no thyroid eye signs. A 3 × 4 cm firm, nontender nodule was palpable in the left lobe of the thyroid gland. The skin was warm and moist. Physical examination was otherwise negative.

What Is Your Working Diagnosis?

The diagnosis is hyperthyroidism, probably secondary to a toxic nodule.

What Additional Tests Would You Order?

The following test results were obtained:

- TSH (third generation): less than 0.005.
- Free thyroxine (FT_4): 1.9 (0.8–1.5).
- Free triiodothyronine (FT_3): 701 (230–420).
- Human chorionic gonadotropin: negative.

What Next?

Because she was not pregnant, a thyroid uptake and scan were performed. The uptake was 11.8% at 6 hours (4–12) and 16.1% (7–24) at 24 hours.

Thyroid scan showed a "hot nodule" in the left lobe with only faint visualization of the right lobe.

Final Diagnosis

Hyperthyroidism secondary to a toxic nodule.

Treatment

Options for treatment were discussed at length with the patient, including radioactive iodine (RAI), thyroidectomy, and antithyroid drugs (ATDs). She was told that ATDs were the least desirable option. Her hyperthyroidism could be controlled with pills, but the hot nodule would never be cured, and the pills have some risk of side effects. The hyperthyroidism could be cured by either RAI or surgery. RAI was recommended as a simpler and safer option. It was explained to the patient that she might end up with an underactive thyroid after RAI and would have to take a thyroid pill once a day for life.

The patient had several questions. Her main question concerned whether the lump could possibly be cancerous, which was what she had been worrying about all along. She was reassured that the type of nodule she had is almost never cancer. Radiation precautions after treatment were discussed because she had young children at home. After she left the office, she called to ask more questions about radiation dangers to her or her family. After further reassurance that this was a safe treatment that had been used for more than 50 years, she decided to go ahead. A repeat pregnancy test was done because she had not had

a period for 2 months. The pregnancy test was negative and she was treated with a dose of RAI calculated to ablate the nodule.

Clinical Course

The patient was seen 6 weeks after treatment. Her palpitations and heat intolerance were gone. The nodule had decreased in size to about 2 cm. She appeared clinically euthyroid. Her TSH was still suppressed at less than 0.1, but the FT_4 was down to 0.9 (0.8–1.5).

At 3 months posttreatment, she complained of cold intolerance, facial puffiness, dry skin, and constipation. On examination, her face appeared puffy and she had gained 4 lb. The nodule was still palpable at about 2 cm, approximately half its original size. Her TSH was 13.6 (0.4–5.5), FT_4 0.5.

The patient clearly had post-RAI hypothyroidism and began treatment replacement with 0.1 mg of T_4 daily. Two months later, most of her hypothyroid symptoms were gone and her TSH was normal at 1.4. She was having some mild loss of scalp hair. The nodule was no longer palpable. She continued taking 0.1 mg of T_4 daily and was advised to return in 1 year.

Case Summary

This young woman presented with a thyroid nodule and clinical findings of hyperthyroidism. The laboratory studies confirmed the diagnosis of hyperthyroidism. The thyroid nuclear scan demonstrated the presence of a hot nodule as the cause for her hyperthyroidism. The opposite lobe was suppressed and not visualized. RAI therapy cured her hyperthyroidism and the nodule decreased in size. She developed post-RAI hypothyroidism, which was easily controlled on T_4. She remained well and required only yearly follow-up to check her neck for nodules, be sure she was taking her T_4, and adjust dosage as needed based on TSH testing.

What Can We Learn From This Case?

- All hyperthyroidism is not Graves' disease. Although Graves' disease is the most common cause of hyperthyroidism, it is important to consider other causes before recommending treatment.
- When a patient presents with a thyroid nodule and hyperthyroidism, a nuclear thyroid scan should be the first step in evaluating the nodule rather than fine-needle biopsy (FNAB). If the nodule is "hot" on scan, FNAB is usually not needed and may be misleading. Because these hot nodules are usually adenomas, they may be reported as suspicious on FNAB and lead to unnecessary surgery. Hot nodules are almost never cancers.
- Once the diagnosis of hyperthyroidism owing to a hot nodule is confirmed, treatment options should be discussed with the patient as outlined in the treatment section. I prefer RAI to surgery for most patients because it is simpler and safer. Although this patient developed post-RAI hypothyroidism, many

patients do not because the opposite lobe is often suppressed by the autonomous hyperfunctioning nodule and may not take up much RAI.
- This case demonstrates the usefulness of serum T_3 or FT_3 in confirming the degree of hyperthyroidism when the T_4 is only borderline elevated or normal. If the T_3 and T_4 were normal with only a suppressed TSH and the patient was not symptomatically hyperthyroid, one could consider following the patient without treatment as an option. If that option were selected, a bone density test should be done to be sure the patient did not have osteoporosis. Even subclinical hyperthyroidism may have a negative effect on bone over time.
- It is important to spend as much time as necessary talking to the patient and answering all questions and concerns in order to ensure the best treatment.
- Annual follow-up is important as outlined previously.

CASE 2

This 49-year-old man was referred because of neck pain. He was obviously ill and in a lot of pain. He gave a history of a flu-like episode 2 months previously. One month previously, he noted severe pain in his lower anterior neck area. The pain increased with swallowing, coughing, or sneezing. He also noted night sweats, chills, and low-grade fever. Other complaints included arthralgias, myalgias, fatigue, slow thinking, and insomnia. He had been very tired at work. His physician treated him with an antibiotic and sent him home. His weight had remained stable and he had been eating normally despite the dysphagia. He denied any palpitations, and was taking a β-blocker for shakiness.

Physical examination revealed a middle-aged man who appeared acutely ill. His pulse was 60, BP was 130/78. There were no thyroid eye signs. The thyroid gland was enlarged bilaterally to twice normal size. Both lobes were 4+ tender. TSH was 0.1, total T_4 was upper-normal at 11.4.

Test Results

- Sedimentation rate: 105.
- Complete blood count: normal.
- Thyroid peroxidase (TPO) antibody test: negative.
- RAI uptake (RAIU): 6 hour, 3.6% (4–12); 24 hour, 2.7% (7–24).

What Is Your Diagnosis?

Subacute thyroiditis with mild hyperthyroidism. The painful, tender thyroid along with a low RAIU and very high sedimentation rate are typical of this disease.

Treatment

Subacute thyroiditis is a self-limited disease. Therefore, treatment is symptomatic. Options for treatment of the pain include salicylates, nonsteroidal anti-

inflammatory drugs, and steroids. The decision to use steroids is usually based on the severity of symptoms, especially pain that interferes with eating or keeps the patient awake. The patient elected to try nonsteroidals and was treated with 375 mg of naproxen three times daily. The patient did not want steroids because he thought he might have another underlying nonthyroidal infection.

He returned to the office 10 days later. He was still quite ill with neck pain and night sweats. He was convinced to begin taking prednisone. He was started on 60 mg/day and his symptoms cleared in 48 hours. Response to prednisone in this disease is quite dramatic. When seen several days later, his thyroid gland was smaller and no longer tender. However, he now noted palpitations, shakiness, and heat intolerance. His FT_4 was elevated to 2.6 (0.8–1.8) and TSH was less than 0.1. The dosage of the β-blocker was increased as symptomatic treatment for his mild hyperthyroidism, and his prednisone was gradually tapered over the next 2 weeks to 10 mg daily. At that point, he was asymptomatic except for slight pain in the right thyroid area. On examination, his thyroid had further decreased in size and was only 1+ tender on the right. He was advised to stay on 10 mg of prednisone daily for another week and then taper to 5 mg if he was asymptomatic. His FT_4 was 1, TSH was less than 0.1.

When seen 1 mo later, he had been off prednisone for 1 week. He was feeling generally well and had no neck pain or hyperthyroid symptoms. His FT_4 was 1.1, TSH was 0.2, and sedimentation rate was 46. Physical examination showed a slightly enlarged thyroid that was not tender.

Case Discussion

The diagnosis was subacute thyroiditis. The differential diagnosis included acute thyroiditis (bacterial) and painful autoimmune (silent) thyroiditis with hyperthyroidism. The long course, low-grade fever, and normal white blood cell count made bacterial thyroiditis unlikely. The negative antibody level was evidence against autoimmune disease.

What Can We Learn From This Case?

- Subacute thyroiditis is a clinical diagnosis based mainly on history and physical examination of the thyroid and confirmed by a few laboratory tests. This patient was treated inappropriately with an antibiotic for several weeks. A good thyroid examination with the finding of an enlarged, tender thyroid might have led to much earlier diagnosis and treatment and spared the patient a lot of misery.
- A high sedimentation rate and laboratory findings of hyperthyroidism are commonly seen in this disease. The tip-off that this is not Graves' disease is the low RAIU. The hyperthyroidism in this disease is not the result of an overactive thyroid. It is caused by leakage of preformed hormone from an inflamed and damaged thyroid.

- Steroid therapy can dramatically control symptoms in subacute thyroiditis but will not affect the course of the disease. It should be used if pain and other symptoms are severe and disabling. A high dose is needed and it should be tapered slowly to avoid flareup. In mild cases, nonsteroidals may be adequate to control symptoms.

CASE 3

This 49-year-old woman was referred with a 2-month history of pain in the jaw and ear and tightness in her lower neck with swallowing. She had noted fatigue, heat intolerance, sweating, palpitations, and shakiness for 2 mo, along with slight hair loss. She had no past or family history of thyroid disease. TSH was less than 0.1 (0.4–5), FT_4 was 2.6 (0.8–1.8).

Physical examination revealed a pulse of 84 and BP of 116/72. The eyes showed a slight stare. The thyroid gland was enlarged to twice normal size. The left lobe was larger than the right and 2+ tender. There was no tremor and muscle power was good. Reflexes were normal.

What Would You Do Next?

The patient was given propranolol for the shakiness and palpitations. Tests were ordered. She returned 1 wk later. She was feeling better and did not take the propranolol. On examination, the thyroid was still bilaterally enlarged but no longer tender.

Laboratory Results

- Sedimentation rate: 88.
- TPO antibody: 69.8 (<2).
- RAIU: 6 hour, 2%; 24 hour, 0.7%.

What Is Your Diagnosis?

Silent (autoimmune) thyroiditis with hyperthyroidism.

Treatment

The patient did not require the prescribed β-blocker for her hyperthyroid complaints. Her neck and jaw pain and thyroid tenderness cleared spontaneously without treatment.

Clinical Course

The patient returned 6 weeks later. She had no complaints.

Physical examination was normal except for slight thyroid enlargement on the left. The thyroid had decreased in size and was not tender. The TSH was 29 (0.4–5), FT_4 was 0.3 (0.8–1.8).

What Is Your Diagnosis? What Would You Do Next?

The patient was now hypothyroid by testing but asymptomatic. I elected to follow her without treatment. Hypothyroidism in this setting is often transient.

She returned 6 weeks later. She complained that she was tired and cold. Her eyes felt gritty. Examination was unchanged from the previous visit. TSH was 6, FT_4 was 0.8.

What Next?

Because the TSH and FT_4 were now close to normal, I elected to follow her without treatment.

She returned 2 months later. She had no complaints. Examination was negative, and TSH was normal at 3.8.

How Would You Counsel the Patient? Follow-Up?

The patient was advised that her thyroid function was now normal. No treatment was needed at this point. She was advised that hypothyroidism or hyperthyroidism could recur, and she was told what to look for. She was asked to return for follow-up in 1 year or as needed.

Case Summary

This woman presented with neck and jaw pain and symptoms of hyperthyroidism. Her workup showed a low TSH and elevated free T_4 compatible with hyperthyroidism. The positive TPO antibody suggested an autoimmune etiology. The very low RAIU confirmed a diagnosis of autoimmune thyroiditis with hyperthyroidism. She was observed and did not require treatment. She converted from hyperthyroidism to hypothyroidism, and then spontaneously returned to normal thyroid function. Her neck pain resolved spontaneously.

What Can We Learn From This Case?

- Although autoimmune thyroiditis with hyperthyroidism usually presents without pain and has been called "painless thyroiditis," it can occasionally present with a painful, tender thyroid. Thyroid pain may radiate to the jaw as it did in this patient.
- The very low RAIU is the critical test result that distinguishes this type of hyperthyoidism from Graves' disease.
- The hyperthyroidism cleared spontaneously followed by transient hypothyroidism, and then a spontaneous return to a euthyroid state. Many patients will follow this pattern, although some will go directly from hyperthyroidism to euthyroidism, and others will develop permanent hypothyroidism.
- Follow-up is important because some patients will develop recurrent hyperthyroidism or hypothyroidism. The patient should be counseled to call if symptoms of hyperthyroidism or hypothyroidism occur. Otherwise, yearly follow-up with a TSH level and neck examination is adequate.

CASE 4

A 40-year-old woman was referred for thyroid evaluation. She had lost 15 lb over the previous month and complained of palpitations. She had been hot, shaky, and noted hair loss. She denied any history of thyroid problems. Her TSH was less than 0.03.

Physical examination revealed a pulse of 80 and BP was 104/72. When I entered the room, she was moving restlessly in the chair. There were no thyroid eye signs. The thyroid gland was diffusely enlarged to about twice normal size and not tender. Slight tremor of her outstretched upper extremities was present.

What Is Your Differential Diagnosis?

This woman was hyperthyroid on history and physical examination. The low TSH confirmed the diagnosis. The differential diagnosis was between Graves' disease and hyperthyroidism secondary to thyroiditis.

Additional Workup

The following test results were obtained:

- FT_4: 2.84 (0.75–2).
- TPO antibody: 241.5 (<2).
- Sedimentation rate: 4.
- RAIU at 24 hours: less than 1%.

What Is Your Diagnosis?

Autoimmune (silent) thyroiditis with hyperthyroidism.

How Would You Manage This Patient?

Treatment of the hyperthyroidism in this case is symptomatic because the hyperthyroidism is usually self-limited. The patient was started on propranolol and the shakiness and palpitations improved. During the next 2 months, her symptoms cleared and her thyroid gland decreased in size. Her TSH at that point was 3.33 (0.4–5), and the FT_4 was 1.17 (0.8–1.8).

The patient was seen 3 months later. She was asymptomatic on no medication. Symptoms of hyperthyroidism and hypothyroidism were discussed and it was agreed that she would call if she developed any of these complaints. Otherwise she would be re-evaluated in 1 year.

Case Discussion

This woman has autoimmune thyroiditis with hyperthyroidism rather than Graves' disease. The low RAIU is the differential test. The high TPO antibody level, normal sedimentation rate, and absence of pain point toward autoimmune (silent) thyroiditis with hyperthyroidism rather than subacute thyroiditis.

What Can We Learn From This Case?

- Think about hyperthyroidism in patients with weight loss and palpitations and look for thyroid enlargement to confirm your suspicion. Then obtain a TSH.
- If the TSH confirms hyperthyroidism, order an RAIU to differentiate Graves' disease (high uptake) from thyroiditis with hyperthyroidism (low uptake).
- It is important to differentiate thyroiditis from Graves' disease because the hyperthyroidism of thyroiditis may be treated symptomatically and followed. Graves' disease requires more aggressive therapy.
- Follow-up is important in this patient because hypothyroidism may occur over time.

CASE 5

An 80-year-old woman was referred for thyroid evaluation because of a low TSH. She had been seen in gastrointestinal consultation because of diarrhea with four to seven bowel movements a day. She had also been shaky for several years. She denied palpitations, heat intolerance, or muscle weakness. She had been noted to have a goiter at about age 60 years and was treated briefly with thyroid medication. There was a family history of goiter in her mother and two sons.

Physical examination revealed an alert but tremulous elderly woman. Pulse was 72 and BP was 132/62. There were no thyroid eye signs. The thyroid gland was markedly enlarged to at least three times the normal size and was multinodular. The heart showed a regular rhythm. Gross tremor of the upper extremities was present.

Laboratory data that accompanied the patient included a TSH of less than 0.05 (0.4–5), FT_4 of 1.46 (0.8–1.8). The RAIU was high-normal at 10% at 6 hours, and 21% at 24 hours. The thyroid nuclear scan showed irregular uptake with multiple hot nodules bilaterally.

Would You Order Any Other Tests?

A total T_3 and repeat FT_4 were ordered. Both tests were upper-normal.

What Is Your Diagnosis?

Toxic nodular goiter with mild clinical hyperthyroidism

How Would You Treat This Patient?

Treatment options were discussed with the patient. She was clinically hyperthyroid. RAI therapy was advised as the best approach for cure. She was treated with 30 mCi of I131.

Clinical Course

Four months after treatment, the patient noted a 4-lb weight gain and her thyroid was smaller. Her TSH was normal at 2.37, FT_4 was 0.89. At 6 months,

she noted increased energy and muscle strength, and the frequency of bowel movements had decreased. TSH and FT_4 remained normal. Her thyroid had decreased further in size. She was seen 6 months later and felt generally well. Her TSH was low-normal at 0.97. When seen 1 year later, her bowel movements were completely normal. The thyroid remained mildly enlarged and irregular. TSH remained normal at 1.45 without thyroid replacement.

Case Summary

This elderly woman presented with diarrhea and a large goiter. She was found to have a low TSH. The FT_4 and FT_3 levels and the RAIU were upper-normal. The nuclear thyroid scan showed multiple hot nodules. She was felt to be clinically hyperthyroid because of toxic nodular goiter and was treated with RAI. Her diarrhea gradually cleared and she felt generally better. The goiter decreased in size. She remained euthyroid without need for thyroid replacement.

What Can We Learn From This Case?

- Hyperthyroidism in the elderly can present with subtle nonspecific complaints.
- Patients with long-standing goiter can develop autonomous nodules resulting in toxic nodular goiter.
- The patient's age, symptoms, and low TSH led to treatment despite normal T_3 and T_4 levels.
- The patient's response to treatment confirmed the initial impression that she was clinically hyperthyroid.
- Patients with toxic nodular goiter may not develop hypothyroidism after RAI treatment as do most patients with Graves' disease. However, annual follow-up is important because late hypothyroidism may occur.

SUMMARY

The cases in this chapter demonstrate etiologies of hyperthyroidism other than Graves' disease. The first patient presented with a thyroid nodule. On evaluation, she had symptoms of hyperthyroidism and a palpable thyroid nodule. Workup confirmed a toxic nodule with hyperthyroidism. RAI therapy was effective in treating the problem.

Case 2 was a man who was acutely ill with systemic symptoms and a painful thyroid. Workup confirmed a diagnosis of subacute thyroiditis with hyperthyroidism. He required treatment with high-dose prednisone for control of the neck pain and other symptoms. It was possible to taper the prednisone as his disease went in to remission. He became spontaneously euthyroid and did not require any long-term treatment.

Case 3 was a patient with a painful, tender thyroid and mild hyperthyroidism. The diagnosis of autoimmune thyroiditis with hyperthyroidism was

confirmed by the low RAIU. Because this is a self-limited disease, the patient was followed and did not require symptomatic therapy. She developed transient hypothyroidism and eventually became euthyroid. This case was unusual in that most cases of "silent" autoimmune thyroiditis are painless.

Case 4 was a case of silent thyroiditis with more severe hyperthyroidism, which was painless and resolved spontaneously with only symptomatic treatment.

Case 5 was an elderly woman with a long history of goiter who developed hyperthyroidism secondary to toxic multinodular goiter. She presented with diarrhea and had only subtle hyperthyroid symptoms. The gastroenterologist who saw her for the diarrhea thought about hyperthyroidism and ordered a TSH. After the diagnosis was established, she was cured with RAI therapy.

The cases discussed in this chapter demonstrate the importance of making the correct diagnosis regarding etiology of hyperthyroidism. Some problems require more aggressive treatment, such as RAI therapy, whereas others can be observed or treated symptomatically and resolve spontaneously.

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5
Thyroid Ophthalmopathy

INTRODUCTION

Thyroid ophthalmopathy is a part of the presentation of Graves' disease in many, but not all, patients and can also occur or worsen after treatment. It has an autoimmune etiology. Clinical findings may include proptosis, diplopia, periorbital edema, conjunctival injection, chemosis, dry and painful eyes, and occasionally loss of vision. In most cases, thyroid eye findings are mild and stabilize after treatment. However, some patients develop severe proptosis, eye muscle problems, and even optic nerve compression, and require aggressive treatment. The cases discussed in this chapter demonstrate some of these problems and an approach to management.

CASE 1

A 61-year-old farmer was referred by his internist for thyroid evaluation. He had noticed eye problems over the previous 8 mo. His first complaint was itching in his right eye. Several months later he began to note watering in both eyes, but more severe in the right eye. One month later he noted his right eye starting to bulge. Several weeks later, his left eye appeared larger. He complained of dryness and soreness in both eyes but no real pain. He developed conjunctival redness and lid edema, which he treated with eye drops. He denied diplopia or pain on eye movement. After careful questioning, it was found that he had no symptoms of hyperthyroidism. Total thyroxine (T_4) was 10.4 (5–12.5), total triiodothyronine (T_3) 192 (80–200), and thyroid-stimulating hormone (TSH) 0.3 (0.6–4.6).

On examination, the pulse was 72, blood pressure (BP) was 120/90. Positive physical findings were limited to the eyes. There was bilateral conjunctival injection and mild lid edema. The right eye showed definite proptosis and the left eye was slightly prominent. The extraocular movements were normal and there was no diplopia. Exophthalmometry measurements were increased at 25 mm in the right eye and 22 mm in the left eye. His vision was evaluated by an ophthalmologist and found to be normal. The thyroid gland was not palpably

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enlarged and there were no physical findings of hyperthyroidism. Pretibial myxedema was not present.

What Is Your Diagnosis?

Probable Graves' disease with ophthalmopathy.

Additonal Testing

A thyroid uptake and scan, and repeat serum thyroid levels were ordered.

Test Results

- TSH less than 0.05 (0.4–5), free thyroxine (FT_4) 1.3 (0.68–1.8), total T_3 130 (80–200).
- Radioactive iodine uptake (RAIU): 6 hour, 12% (4–12); 24 hour, 17% (7–24).
- Thyroid scan: mild thyromegaly.
- Computed tomography (CT) scan of the orbits: thickening of extraocular muscles.

What Is Your Diagnosis?

Graves' disease with severe ophthalmopathy and mild or subclinical hyperthyroidism.

Treatment

The patient was started on 40 mg of prednisone per day. He was then treated with RAI after consultation with a thyroidologist. My question was whether to treat the mild hyperthyroidism or the eye problem first. We agreed that treatment of the hyperthyroidism with the patient on steroids should be the initial approach. He was given 17 mCi of iodine 131 (I-131). Over the next several months, his TSH came into the normal range. He then developed symptoms of hypothyroidism with an elevated TSH and was treated with T_4 to normalize TSH.

Six months after RAI therapy, he was euthyroid on T_4. His eye findings were essentially unchanged with persistent proptosis, tearing, and conjunctival injection. His vision remained normal. Ophthalmology consultation was obtained. Only local treatment was recommended. However, the patient continued to complain bitterly about his eyes and saw another ophthalmologist. Radiation to the orbits was performed. He returned about 8 months later. There was very little change in eye findings. His TSH was mildly elevated at 7.5 and T_4 dosage was adjusted. His vision remained good. He continued to complain about the appearance of his eyes, irritation, and tearing. He had consulted several other eye doctors and eyelid surgery was recommended by one. He was now about 4 years post-RAI therapy for Graves' disease.

Several months later, he was diagnosed with prostate cancer. He received radiation treatment to the prostate. He remained euthyroid on T_4. He died about 6 months later from complications of prostate cancer.

Case Summary

A 61-year-old man presented initially with Graves' disease, which manifested mainly in his eyes. He had bilateral proptosis and irritation of the eyes, but his vision was normal. He was mildly hyperthyroid as evidenced by a very low TSH with normal T_4. His hyperthyroidism was cured with I-131, but there was very little change in his eyes. The recommendation of an ophthalmologist expert in Graves' ophthalmopathy was to treat him symptomatically with local therapy and avoid radiation and surgery because his eyes were stable and his vision good. However, he continued to seek other opinions and was treated with radiation to the orbits and considered for eyelid surgery. His eyes remained unchanged for more than 5 years. He then developed prostate cancer and died.

What Can We Learn From This Case?

- Graves' disease can present with eye findings and minimal or absent findings of hyperthyroidism.
- This patient had bilateral eye disease. If the proptosis had been unilateral, the differential diagnosis would have included retro-oribital neoplasm.
- This patient was relatively fortunate that he did not have diplopia or decreased vision owing to optic nerve compression.
- The eye findings remained stable over 5 years and were not improved by radiation or steroids.
- Aggressive therapy, such as orbital radiation and orbital decompression surgery, may be needed if the disease is progressive and affects vision. However, a conservative approach is reasonable when symptoms are relatively minor or mainly cosmetic and the chance of improvement is small.

CASE 2

A 59-year-old man was referred for thyroid evaluation because of diplopia and possible Graves' disease. He began to note double vision while driving about 6 months earlier. The diplopia worsened and he began to note problems with reading and television viewing. He also noted mild redness of the eyes, increased tearing, and swollen eyelids. He was evaluated by a local ophthalmologist and then referred to a university eye clinic. His vision in each eye was good and he had no proptosis. He was treated with a patch over one eye to control the diplopia. He had no symptoms of hyperthyroidism. He smoked more than one pack of cigarettes daily. Recent thyroid studies revealed a TSH of 0.1 and total T_4 of 7.9.

Physical examination revealed a pleasant man appearing to be middle-aged with an eye patch over his left eye. On removal of the patch, he noted diplopia in all fields of gaze. He had difficulty elevating his eyes above the midpoint. There was mild lid edema and conjunctival injection. Exopthalmometry measurements were normal and equal. The thyroid gland was just palpable and there

were no nodules. There was mild tremor of the outstretched upper extremities. His pulse was 84, BP 120/64.

What Is Your Working Diagnosis?

Graves' disease with ophthalmopathy and mild hyperthyroidism.

What Additional Studies Would You Order?

The following test results were obtained:

- RAIU: 6 hour, 19% (4–12); 24 hour, 33% (7–24).
- Thyroid nuclear scan: most of the tracer is localized in the right lobe, which appears larger than the left.
- Third-generation TSH: 0.02 (0.4–5).
- Free T_3: 867 (210–440).
- FT_4: 2.8 (0.76–1.8).
- CT scan of the orbits: slight enlargement of the left inferior and medial rectus muscles; otherwise normal.

What Is Your Diagnosis at This Point?

Graves' disease with hyperthyroidism and ophthalmopathy.

How Would You Proceed From Here?

A thyroid ultrasound was ordered in view of the nuclear scan findings. The ultrasound confirmed enlargement of the right lobe but showed no nodules. After discussion with the patient's ophthalmologist, I elected to cover him with high-dose prednisone and proceed with RAI therapy for his hyperthyroidism. The tentative plan was to treat his eye muscle problem surgically after he became euthyroid. He was urged to stop smoking in view of the known association between smoking and thyroid eye problems.

Clinical Course

The case was discussed at length with the patient and his wife. He complained bitterly about his vision and wanted something done immediately. I had several long discussions with him and his wife and tried to reassure them that good treatment was available but it would take some time for him to get better. He finally agreed to RAI treatment. He slowly became clinically and biochemically euthyroid. He was treated with radiation to the orbits on referral by his local ophthalmologist. The prednisone dose was tapered over several months and then discontinued. His FT_4 level became normal after about 3 months, but his TSH level remained low. We were considering repeat RAI therapy when his TSH finally rose to 0.52, with a normal FT_4 of 0.93 at 6 months post-RAI treatment. He remained euthyroid without T_4 replacement, but his diplopia remained unchanged. He underwent eye muscle surgery approx 8 months after

RAI therapy. His diplopia was almost completely corrected by the surgery and he remained clinically euthyroid. His TSH at 11 months post-RAI treatment was normal at 1.25 without thyroid replacement. At that point, his health insurance changed and he was referred to another endocrinologist.

Case Summary

This 59-year-old man developed Graves' disease with hyperthyroidism and ophthalmopathy with severe diplopia. His treatment was complicated and involved consultation with several specialists and coordination of care by his primary care physician (PCP). He became very emotional about his vision and required frequent reassurance by all physicians involved. After extensive consultation between all his physicians, a treatment plan was developed. This included RAI treatment to cure his hyperthyroidism while treating his ophthalmopathy with high-dose prednisone and radiation to the orbits. After he became euthyroid, his diplopia was corrected with eye muscle surgery. Although the treatment took many months, the end result was quite good.

What Can We Learn From This Case?

- Graves' disease can present with only eye complaints, such as diplopia and proptosis.
- Abnormal thyroid function tests, when present, support the diagnosis of Graves' disease as a cause for the eye problem.
- Problems with vision can create a lot of anxiety in the patient and require emotional support during prolonged treatment.
- Curing the hyperthyroidism may stabilize the ophthalmopathy and allow further treatment of the eye complaints.
- This patient received three major treatments for thyroid ophthalmopathy, namely steroids, orbital radiation, and eye muscle surgery. Fortunately, he did not have severe proptosis or loss of vision.
- Although the treatment was prolonged, the end result was good and the patient was well satisfied.

CASE 3

A 52-year-old man was referred by his PCP for thyroid evaluation. Over the previous 6 months, he had lost 20 lb despite a very good appetite and increased food intake. He complained of heat intolerance, fatigue, increased frequency of bowel movements, and tremor of the hands. He had noted some tearing of the eyes but vision was good. The patient was a nonsmoker and was on no medications. He had a family history of thyroid disease in his mother, who was on medication. Test results from his PCP included a total T_4 of 19.6 (5–12) and TSH less than 0.05.

Physical examination revealed a thin, middle-aged man with rapid speech. Pulse was 80, BP 100/58. Proptosis of the right eye was noted and confirmed

by exophthalmometry (right eye 22 mm, left eye 18 mm). Eye movements appeared normal and without diplopia. Bilateral lid lag was present. The thyroid gland was enlarged to approx 1.5 times normal. Cardiac findings were normal. There was mild fine tremor of the outstretched upper extremities. Muscle wasting was noted in the shoulder girdle musculature. The skin was warm, velvety smooth, and moist.

What Is Your Working Diagnosis?

Graves' disease with hyperthyroidism and mild ophthalmopathy.

Additional Testing

RAIU: 6 hour, 22% (4–12); 24 hour, 36% (7–24).

How Would You Treat This Patient?

The elevated RAIU and ophthalmopathy confirmed the diagnosis of Graves' disease. The options for treatment, including RAI, antithyroid drugs (ATDs), and thyroidectomy, were discussed with the patient and his wife. RAI therapy was recommended and the patient agreed to the treatment. The possibility of increased thyroid eye problems after treatment was discussed. The patient was given 12 mCi of I-131.

Clinical Course

At 2 months post-RAI therapy, the patient had gained 4 lb, noted increased energy, and a decrease in the frequency of bowel movements. On examination, right proptosis persisted unchanged, the thyroid gland was smaller, and there was no tremor. The FT_4 was normal at 1.55, TSH still suppressed at less than 0.05. At approx 3 months post-RAI therapy, the patient complained that he was cold. His FT_4 was edging low at 0.69 and the TSH was now normal at 0.69. Three weeks later, he was still cold and now noted leg cramps. On examination, the proptosis was no longer evident and the thyroid gland was barely palpable. FT_4 was low at 0.51, TSH was elevated to 26.20. He was clinically hypothyroid and was started on 0.1 mg of T_4 daily. Six weeks later, his cold intolerance was gone and he felt well, except for rare leg cramps. His eyes appeared normal and his thyroid gland was just palpable. TSH was still elevated at 12 and FT_4 was normal at 1.20. His T_4 dosage was increased to 0.112 mg daily. He was now about 6 months posttreatment.

Six weeks later, he still complained of occasional muscle cramps in his legs. His TSH was 12 and his FT_4 1.24. T_4 dosage was again increased to 0.125 mg daily. Three months later (now about 10 mo posttreatment) the patient complained of being easily fatigued and leg cramps. Examination was normal. TSH was further increased to 23. The patient said he was taking his thyroid medica-

tion daily. He was on no other prescription medications or over-the-counter drugs that might interfere with T_4 absorption. T_4 dosage was increased to 0.15 mg daily. Six weeks later, he was feeling better, but TSH was still elevated at 12. His T_4 dosage was further increased to 0.175 mg daily. Three months later, and now more than 1 yr posttreatment, the patient was feeling well, and his TSH was normal at 3.9. The right eye was slightly prominent but he had no eye complaints. He was continued on 0.175 mg of T_4 daily and placed on annual follow-up.

Case Summary

This patient presented with symptoms of hyperthyroidism, a small goiter, and mild thyroid ophthalmopathy. Laboratory tests confirmed the diagnosis of Graves' disease, and he was treated with RAI. After several months, he became euthyroid and his eye findings improved. He then developed symptoms and laboratory findings of hypothyroidism and was treated with T_4. His T_4 dosage was titrated based on symptoms and TSH level, and he improved slowly. He eventually became euthyroid and asymptomatic on a higher T_4 dosage than would have been expected for his weight.

What Can We Learn From This Case?

- Mild eye involvement, as in this case, is much more common in Graves' disease than the severe ophthalmopathy present in the previous two cases.
- Although ophthalmopathy may occasionally worsen after RAI treatment of Graves' disease, according to some studies, it will more commonly stabilize once the hyperthyroidism is controlled.
- This patient had significant muscle wasting, which typically improves more slowly than some other findings of hyperthyroidism.
- The predicted T_4 dosage for this 70-kg man was in the range of 0.112 mg daily based on the formula of 1.6 mg/kg. He required a much larger dose than predicted. Although the predicted dose may give you a ballpark number for a group of patients, each patient must be titrated based on clinical response and TSH level.

CASE 4

A 38-year-old woman was referred by her PCP for thyroid evaluation. She had noted shakiness, palpitations, and heat intolerance over the previous 9 months. Two months earlier, she was seen by an ophthalmologist because of lid retraction and redness of her right eye. Her weight had been stable and muscle strength normal. Her vision remained good. Thyroid tests obtained by the eye doctor included a TSH of less than 0.1 and total T_4 14.2 (4.5–12).

Physical examination revealed a woman who appeared anxious, with a pulse of 112 and BP 140/82. The right eye appeared more prominent than the left,

with conjunctival injection and lid lag present on the right. The thyroid gland was bilaterally enlarged to about twice normal size, nontender, and without nodules. There was 2+ tremor of the outstretched upper extremities.

What Is Your Diagnosis?

The diagnosis is Graves' disease with hyperthyroidism and mild ophthalmopathy.

Additonal Studies and Treatment

Treatment options discussed with the patient included RAI therapy, ATDs, and surgery. The advantages and side effects of these modalities were discussed in detail with the patient and RAI therapy was recommended. She was agreeable. A thyroid uptake and scan was performed to confirm the diagnosis and plan RAI dosage. The uptake was 17% at 6 hours (4–12), and 28% at 24 hours (7–24). She was treated with 14 mCi of RAI.

Clinical Course

Two months posttreatment, she had gained 6 lb and the heat intolerance and shakiness were gone. In retrospect, she realized that she had noted palpitations prior to treatment and the palpitations were also gone. Examination revealed a pulse of 72, BP of 110/70. There was a slight stare and minimal proptosis of the right eye. The thyroid gland had decreased in size and was now barely palpable. Thyroid tests showed a TSH of less than 0.1, FT_4 now borderline low at 0.7.

Three months posttreatment, she had gained another 5 lb and complained of leg cramps and heavy menses. Examination of the eyes showed puffy eyelids and minimal right proptosis. The thyroid gland was no longer palpable. Examination was otherwise normal. The TSH was 72 (0.4–5) and FT_4 was 0.5 (0.8–1.8). She was started on 0.1 mg of T_4 daily. One month later, her leg cramps were gone, she had more energy, and TSH was normal at 0.7. She was continued on T_4.

Approximately 6 months post-RAI treatment, she returned to her eye doctor complaining of puffy eyelids and mild double vision on upward gaze. The diplopia was not interfering with her daily function in driving or teaching. She remained clinically euthyroid on T_4, and her eye findings remained unchanged over the next 2 years. She required no treatment for her eye complaints. Three years after RAI treatment, she was clinically euthyroid and had no eye complaints except for minimal lid swelling. Diplopia could no longer be elicited on examination. She was continued on T_4 and placed on annual follow-up.

Case Summary

This young woman developed symptoms of hyperthyroidism, but the diagnosis of Graves' disease was made only after she developed eye complaints. Her hyperthyroidism was cured with RAI and she was maintained on T_4 for post-RAI

hypothyroidism. She developed mild progression of her ophthalmopathy after treatment, but required no treatment for this problem. The eye findings gradually improved, and she had only minimal findings 3 years after RAI treatment.

What Can We Learn From This Case?

- Graves' disease was missed for months despite hyperthyroid complaints and was finally diagnosed by an astute eye doctor.
- RAI therapy was effective in curing the hyperthyroidism. It is not possible to know whether the mild progression of ophthalmopathy after treatment was to the result of the RAI or simply the natural course of her disease. Some recent studies suggest that progression of thyroid eye problems is more common after RAI than after surgery or ATDs, but this is controversial. Any progression is most often mild, as in this case. However, some thyroidologists, in the light of recent studies, recommend that RAI therapy be avoided in patients who present with moderate or severe ophthalmopathy. This recommendation is also controversial.
- My observation—and the opinion of many thyroidologists—is that the advantage of curing the hyperthyroidism with RAI outweighs the risk in the majority of patients.
- In light of recent studies, the patient should be fully informed about the possible risk of progression of ophthalmopathy after RAI therapy.

SUMMARY

This chapter focuses on the eye problems of Graves' disease. Case 1 is a man who presented in 1989 with severe Graves' ophthalmopathy and minimal hyperthyroidism. He exhibited mainly proptosis and his vision was good. At that time, studies were conflicting regarding the effect of RAI therapy on thyroid eye disease. Some studies suggested improvement after treatment, some suggested worsening, and some suggested no effect. More recent studies suggest a small increase in risk of occurrence or progression of ophthalmopathy after RAI therapy in comparison with ATD therapy or surgery. Progression is usually mild and often transient. Eye problems after treatment are more common if ophthalmopathy is present prior to treatment. However, steroid treatment seems to protect against progression after RAI therapy. This patient received prednisone for several months in an attempt to treat the ophthalmopathy, and also to protect against progression after RAI. He became euthyroid after RAI therapy, but his eyes remained unchanged. He continued to complain about his eyes and received orbital radiation without success. He was considering eyelid surgery when he developed prostate cancer and died.

Case 2 is a man who was seen in 1995 with Graves' disease presenting with severe eye muscle involvement and diplopia from his ophthalmopathy. He was clearly hyperthyroid by laboratory testing although he denied hyperthyroid symptoms. He was a heavy smoker. As in Case 1, the plan was to treat him with RAI to cure his hyperthyroidism while adding prednisone to cover the RAI

treatment, and also to see if we could improve his eye disease. Recent studies have shown that smoking and a high T_3 level increase the risk of progression of thyroid eye disease after RAI therapy. This patient was encouraged to stop smoking. He became euthyroid after RAI, but his eye problem persisted unchanged. He required eye muscle surgery to correct the diplopia. He did not develop the common post-RAI hypothyroidism, but monitoring was required because hypothyroidism could occur in the future.

Case 3 is a man who presented with severe symptoms of hyperthyroidism and mild ophthalmopathy. His hyperthyroidism was cured with RAI. He developed the usual post-RAI hypothyroidism, which was corrected with replacement T_4. His severe muscle involvement from Graves' disease slowly cleared over the course of several months. His mild ophthalmopathy remained stable to mildly improved, and was asymptomatic. He was maintained on T_4 and followed annually. In view of more recent studies, one might have considered increasing his T_4 dosage to lower the TSH below 2.5 if he had persistent hypothyroid symptoms.

Case 4 is a young woman who had hyperthyroid symptoms for several months and finally presented to an ophthalmologist because of eye complaints of lid retraction and redness in the right eye. When seen, she was clinically hyperthyroid with mild Graves' ophthalmopathy. She was treated with RAI. She noted mild worsening of her eye complaints several months after treatment. She required no treatment for the eye complaints because they were not interfering with her daily activities. Her eye complaints gradually improved and were no longer evident at 3 years post-RAI treatment, except for minimal lid swelling. She was followed annually and remained asymptomatic on replacement T_4.

COMMENT

The cases discussed in this chapter represent a spectrum of thyroid ophthalmopathy from very mild to severe. All of these patients were treated with RAI. Only case 4 showed worsening of eye complaints after RAI treatment, and the worsening was mild and transient. This is consistent with recent studies which suggest that progression of thyroid ophthalmopathy is more common after RAI therapy than after other modes of treatment of Graves' disease. However, progression tends to occur in only a small minority of patients treated with RAI and is most commonly mild and often transient. Most thyroidologists in the United States, including myself, feel that the advantages of RAI therapy in most patients should be weighed against the small risk. In most cases, I think RAI is still the treatment of choice. Concurrent steroid therapy and alternate means of treatment of the hyperthyroidism may be considered in patients with severe ophthalmopathy.

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6
Hypothyroidism

INTRODUCTION

Hypothyroidism is the clinical picture that one sees when the thyroid is unable to produce enough thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), to keep blood levels normal and to satisfy the needs of peripheral tissues. Most patients have primary hypothyroidism, a result of disease in the thyroid that destroys its ability to produce adequate thyroid hormones. Hypothyroidism is occasionally secondary, caused by disease in the pituitary gland or hypothalamus resulting in inadequate production of thyroid-stimulating hormone (TSH). This chapter discusses primary hypothyroidism. The clinical presentation of hypothyroidism is variable, but often includes symptoms such as cold intolerance, fatigue, constipation, hair loss, dry skin, and other symptoms of a sluggish metabolism. As previously discussed, these symptoms are nonspecific and the diagnosis is often missed for months or even years. The clinical picture varies from mild symptoms early in the disease to very severe symptoms, such as confusion, lethargy, and even coma in the later stages. Physical findings may include goiter, slow speech and thinking, very dry skin, and slow relaxation of deep tendon reflexes ("hung up" reflexes). As the patient's mentation slows in more severe disease, the patient is often unaware of how bad things are. This is partially the result of the slow and insidious onset of this disease in many people. Also, the nonspecific nature of the symptoms leads the physician to consider other diagnoses, such as depression, before a thyroid etiology is considered. Once the doctor thinks about a thyroid problem, the diagnosis is easy to make with a TSH test. The following case discussions illustrate varying presentations of hypothyroidism and an approach to diagnosis and treatment.

CASE 1

A 42-year-old woman was referred by her gynecologist for evaluation and treatment of severe hypothyroidism. She complained of a 10-lb weight gain over the previous 4 mo. She also complained of cold intolerance, irregular menses, constipation, and dry skin. She had been working full time in a med-

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
By: E. O. Brams © Humana Press Inc., Totowa, NJ

ical office and noted that she tired more easily. Family history was negative for thyroid disease. She was on no medications.

Laboratory studies included a total T_4 of less than 2.5 (4–12), TSH 140 (0.4–4.5), and negative antimicrosomal thyroid antibodies.

Physical examination revealed a pulse of 72 and blood pressure (BP) of 120/82. There were no thyroid eye signs. The thyroid was diffusely enlarged to about twice normal size and nontender. Examination was otherwise normal.

What Is Your Diagnosis?

The diagnosis is severe primary hypothyroidism.

Additional Tests and Treatment

No additional tests are needed because the diagnosis is clear from the clinical and laboratory findings. The patient was started on 0.05 mg of T_4 daily.

Clinical Course

One month later, the patient noted a decrease in fatigue and cold intolerance. However, she now complained of hair loss and muscle aches. Her total T_4 was now low-normal at 6.5, TSH was 44. The thyroid remained enlarged. T_4 dosage was increased to 0.075 mg daily. One month later, most of her hypothyroid complaints had improved except for the hair loss. She now complained of problems with memory and thinking. Her TSH was normal at 1.8 and her free thyroxine (FT_4) was 1.2 (0.8–1.8). On examination, the thyroid had decreased in size to approx 1.5 times normal. She was continued on 0.075 mg of T_4 daily. Three months later, she was feeling generally well and her menses had returned. Her thyroid was only mildly enlarged. TSH was low-normal at 1.2. She was continued on 0.075 mg of T_4 daily, and advised to return for yearly follow-up.

Case Summary

This patient presented with clinical findings of severe hypothyroidism, or myxedema with goiter. The markedly elevated TSH and very low T_4 confirmed the diagnosis of primary hypothyroidism. In view of the severity of the hypothyroidism, I elected to start her on less than an estimated full replacement dose and titrate dosage based on TSH level and clinical response. Over several months, her symptoms cleared and the goiter decreased in size. She was followed on an annual basis and has continued to do well.

What Can We Learn From This Case?

- Although the patient had only begun to notice symptoms of hypothyroidism a few months before she came in, the severity of her disease suggested that she had been hypothyroid for much longer.

- Hashimoto's thyroiditis is the most likely etiology of hypothyroidism and goiter. The antibodies are often positive but may be negative, as in this case. A biopsy probably would have shown findings of Hashimoto's thyroiditis.
- Most young patients without heart disease can be started on a full replacement dose of T_4 in the range of 1.6 µg/kg of body weight. However, I elected to start this woman on less than full replacement because of the severity of her hypothyroidism, and then titrate the dose based on clinical findings and TSH levels.
- Hashimoto's thyroiditis is often familial. Although this patient had no family history of thyroid disease when I first saw her, her teenage daughter presented less than 1 yr later with abnormal thyroid function, goiter, and positive thyroid antibodies (*see* Chapter 10).

CASE 2

A 22-year-old man was referred by his family doctor because of a TSH of less than 0.1 on a routine panel. He was working 50 hours a week and said he felt pretty well. However, on questioning he admitted to increasing fatigue and a 35-lb weight gain over the past year or so. His skin was dry and he had started wearing a sweater in the office during the summer when everyone else was in shirtsleeves. His mother, who accompanied him, had noted that his face was puffy and he looked different. He had no palpitations or shakiness.

While taking the history, I observed that his face was puffy and his speech was slow. He looked lethargic, although he said he felt fine. On examination, his pulse was 68 and his BP was 90/70. He seemed unaware of his strikingly slow speech. The thyroid gland was borderline enlarged. The skin was very dry. The genitalia were normal adult male. He had normal facial hair and temporal recession of the hair line.

The tests that accompanied him included a cholesterol of 439, thyroid microsomal antibodies of 388 (normal <1), and TSH less than 0.1

What Problem Do You See Here?

The low TSH suggests hyperthyroidism, but the patient appears severely hypothyroid.

The following test results were obtained:

- TSH: 988 (at a different lab).
- FT_4: less than 0.1 (0.8–1.8).
- Testosterone: 105 (263–1593).
- Leuteinizing hormone, follicle-stimulating hormone, and cortisol: normal.
- TSH repeat at initial lab: 1178.
- Chest x-ray: normal.

What Is Your Diagnosis Now?

Severe primary hypothyroidism secondary to Hashimoto's thyroiditis.

How Do You Explain the Initial TSH?

The initial TSH of less than 0.1 was clearly a laboratory error.

How Would You Treat This Patient?

The patient was started on T_4. Six weeks later, he was less cold and sleepy and his skin was less dry. His reflexes remained slow. His TSH was 415, FT_4 was 0.46 (0.76–1.79). The T_4 dose was slowly increased to a maintenance dose of 0.15 mg daily. His TSH gradually returned to normal. His fatigue, cold intolerance, and dry skin completely resolved. His testosterone became normal at 574. When last seen, he felt fine and his TSH was normal at 2.93. In retrospect, he realized that he had been ill for a long time.

Case Discussion

This patient was clearly hypothyroid on history and physical examination. Thus, the initial low TSH of less than 0.1 was puzzling. If the TSH were correct, one would have had to consider hypopituitarism with secondary hypothyroidism. The next step would have been to order an FT_4, repeat TSH and some tests of pituitary function to solve the problem. Once the diagnosis of severe primary hypothyroidism or myxedema was established, T_4 treatment was very effective.

What Can We Learn From This Case?

- **Watch out for laboratory error.** A good history and physical examination is critical. It was clear on history and physical examination that this man did not have hyperthyroidism as the TSH suggested. However, secondary hypothyroidism owing to hypopituitarism could have given this clinical picture with a low TSH.
- Patients with severe hypothyroidism or myxedema may not complain much because the onset is slow and insidious. Only after they feel better with treatment do they realize how ill they had been. This patient later realized that he had suffered from symptoms, such as fatigue and cold intolerance, for at least 2 years.
- In severe hypothyroidism or in older patients, consider starting with a lower dose of T_4 and follow with T_4 and TSH every 4 to 6 weeks. The T_4 will change faster than the TSH as the patient improves. Alternatively, if the patient is young and healthy, many thyroidologists would start with an estimated full replacement dose of T_4 resulting in faster return to a euthyroid state.
- Monitor tests and adjust T_4 dosage. Use the TSH as your guide to a maintenance dose.

CASE 3

This 48-year-old truck driver was referred to me by his primary care physician for thyroid evaluation. He told me he had been well until approx 2 years ago. Over the past 2 years, he had noted fatigue, increased cold intolerance, swelling of his face and arms and, to a lesser extent, his legs, and severe dryness and scaling of his skin. Other complaints included splitting of fingernails, lack of energy, dizziness, increased urination, pleuritic chest pain, yellow skin color, and muscle cramping. He denied any change in memory or thinking. He had been driving his truck until recently. However, he now realizes that he should not have been driving the truck because his eyes were almost swollen shut. Recent laboratory studies included a T_4 of 0.1 (4–12), cholesterol of 534, creatine phosphokinase of 3594, lactic dehydrogenase (LDH) of 558, serum glutamic oxaloacetic transaminase (SGOT) of 111, and TSH of 189.

He had been started on 0.2 mg of T_4 by his doctor approx 6 weeks before. He complained of increased muscle aching, headache, sore throat, and hoarseness on the T_4. However, he had more energy and his skin was less dry and starting to peel. The edema had gradually cleared. The muscle cramping was gone, but he complained bitterly of severe muscle aching and soreness that was worse at night. The easy bruising he had noted was better. He had lost 15 lb in 6 weeks. He had a history of low BP, but no syncopal episodes. His studies after 1 mo on thyroid included a T_4 of 10.8, LDH of 172, cholesterol of 154, and SGOT of 30.

The history revealed no serious health problems. The family history revealed probable thyroid disease in his father. He had been switched to desiccated (Armour) thyroid, 1 grain daily, about 1 wk before being seen.

Physical examination revealed a pulse of 84 and BP of 125/90 sitting and 118/90 standing. He had no significant facial edema and no thyromegaly. There was 1+ edema of the lower legs. The skin was dry. Reflexes were normal. Examination was otherwise negative.

What Is Your Diagnosis?

Severe primary hypothyroidism or myxedema.

Treatment

I switched the patient from desiccated thyroid to 0.1 mg of T_4 a day. One month later, he was feeling better. His muscle aching was almost gone and he was no longer cold. The edema was gone. His family doctor also placed him on a diuretic. FT_4 was 1 (0.8–1.8) and TSH was 0.17 (0.4–5). Cholesterol was 246, SGOT was 19, and LDH was 132. Three months later, he told me he felt the best he had in several years. The TSH was 20.2, FT_4 0.8. His T_4 dose was increased to 0.125 mg/day. Several months later, his TSH was normal at 2.15

and he felt well. He was continued on 0.125 mg of T_4 a day and asked to return in 1 year. The following year, he had gained weight and his TSH was 6.58. T_4 dose was increased to 0.15 mg/day. He has remained on that dosage for the past several years with yearly check-ups.

Case Discussion

This patient had severe hypothyroidism or myxedema. It had likely been coming on for much longer than 2 years, judging by his clinical presentation. He had developed morbidity to the extent that he could no longer work as a truck driver, yet he went to see his family doctor for a physical to obtain a commercial driver's license rather than for his complaints. Fortunately, his doctor thought about hypothyroidism and ordered the thyroid tests. His panel also showed the marked increases in cholesterol and muscle enzymes often seen in severe myxedema, which would explain his severe muscle complaints. The history of low BP and the severity of his myxedema made me think about hypopituitarism secondary to pituitary myxedema.

Cortisol level and thyroid antibody tests were ordered. His antimicrosomal antibody level was more than 700, and his cortisol levels were normal. The high antimicrosomal antibody level was compatible with Hashimoto's thyroiditis as a cause of his hypothyroidism.

What Can We Learn From This Case?

- This patient presented with severe, long-standing hypothyroidism or myxedema. He ignored his symptoms and did not seek medical help earlier because of the slow, insidious onset and progression of the disease. He did not realize how bad things were. Also, he continued to work as a truck driver despite poor vision resulting from periorbital edema. Fortunately, he did not have a serious accident.
- This man finally received medical help because he went to his doctor for a routine physical for his truck driver's license. Fortunately, the primary care physician (PCP) recognized the problem and obtained the appropriate tests and initiated treatment.
- This patient only realized how sick he had been in retrospect after he felt better with treatment. This finding is quite common in hypothyroidism, as discussed in the other cases.
- Elevated enzyme levels and cholesterol may be seen in severe hypothyroidism or myxedema. These findings may lead to a search for liver or muscle disease if the physician does not "think thyroid." These abnormal tests usually revert to normal after the hypothyroidism is corrected as they did in this case.

SUMMARY

The cases discussed in this chapter demonstrate a variety of presentations of hypothyroidism. The first case presents a middle-aged woman who was medically knowledgeable but waited months before telling her boss, a gynecologist,

that she was not feeling well. She had obviously been hypothyroid for a long time, but the onset and progression had been so gradual that she ignored the symptoms until they became so severe that she had trouble getting through the day at work. Her T_4 was so low that it was unmeasureable by the clinical lab. She had a goiter and probably also had Hashimoto's thyroiditis, although the microsomal antibodies were not elevated.

The second case is interesting from several points of view. The most important point is that the patient was referred for hyperthyroidism because of a lab error. This demonstrates the obvious but sometimes overlooked importance of a good history and physical examination. It was obvious on history and physical examination that this patient was hypothyroid rather than hyperthyroid. This patient was highly motivated and continued to work long hours despite fatigue and other hypothyroid symptoms. It was only after treatment that he realized how bad he had felt over the previous couple of years.

The third case describes a truck driver who continued to work despite increasing symptoms of hypothyroidism including periorbital edema. He obviously should not have been driving a truck when his eyelids were so swollen that he could hardly see. He came to see his PCP for an examination for his truck drivers' license. Fortunately, his PCP thought about thyroid disease and ordered the appropriate tests. His hypothyroidism was so severe that his muscle enzyme tests and lipids were markedly elevated. Again, it was only after treatment that he realized how bad he had been feeling for at least several years.

It would have been much better for all these patients if their hypothyroidism had been diagnosed earlier. However, complaints at that stage would have been milder, and the patient or physician would have had to "think thyroid" in order to make the diagnosis.

A BRIEF COMMENT ON THE TREATMENT OF HYPOTHYROIDISM WITH T_3

The generally accepted treatment for hypothyroidism is T_4. However, there has been a lot of discussion in recent years about adding T_3 to T_4 in patients who do not feel well on T_4 alone despite a normal TSH level. T_3 is the active hormone at the nuclear receptor. It has been well established that a portion of T_4 is converted to T_3 in the liver and other tissues. Most of the trials of combined therapy with T_3 and T_4 have not shown an improvement in patients treated with combined therapy over T_4 therapy alone. However, some physicians feel that a trial of combined therapy may be reasonable in occasional hypothyroid patients who are not feeling well on T_4 alone. Generally, the approach is to decrease the T_4 dosage and add a small dose of T_3 (5–12.5 mg), with the goal of keeping TSH in the low-normal range. If it is used, the T_3 dose should be kept low, and T_3 should probably be avoided in patients with heart disease.

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7
Subclinical Thyroid Disease

INTRODUCTION

Subclinical thyroid disease is currently a hot topic. The concept of subclinical hypothyroidism and hyperthyroidism has developed over the past 20 years or so since the advent of "sensitive" thyroid-stimulating hormone (TSH) testing. The development of the second-generation or sensitive TSH in the mid-1980s allowed for the use of TSH testing to screen for or diagnose both hypothyroidism and hyperthyroidism. This issue is discussed in more detail in Chapter 2.

Subclinical hypothyroidism is defined as a TSH above the upper limit of the reference range with a normal free thyroxine (FT_4) in a patient with no symptoms or signs of hypothyroidism. Other causes of an elevated TSH, such as recent change in thyroid hormone replacement dosage, acute illness, and the recovery phase of thyroiditis, must be ruled out. Subclinical hyperthyoidism is defined as a TSH below the lower limit of the reference range with a normal FT_4 and free triiodothyronine (FT_3) in a patient with no hyperthyroid signs or symptoms. Other causes of low TSH, such as euthyroid sick syndrome (nonthyroidal illness), T_4 overtreatment, and persistent low TSH after recent treatment of hyperthyroidism with radioactive iodine (RAI), must be considered.

Symptoms of thyroid dysfunction are often vague or nonspecific, and physicians frequently order thyroid testing in evaluating patients with symptoms, such as fatigue, weight loss, and palpitations. Laboratory findings of subclinical thyroid disease are common. I often get calls from primary care physicians (PCPs) regarding interpretation of these test results. The following case discussions illustrate some of these vexing problems.

CASE 1

A 23-year-old woman was seen regarding possible hyperthyroidism and type 1 diabetes. She had no symptoms of hyperthyroidism except for rare palpitations. She had been gaining weight and admitted to overeating at times. She had a low TSH and elevated radioactive iodine uptake (RAIU) in the past.

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Physical examination was normal except for a borderline enlarged thyroid gland. Her TSH was 0.007 (0.4–5) and her FT_4 was 1.3 (0.8–1.8).

What Other Tests Would You Order?

The following test results were obtained:

- Free T_3: 2.97.
- TSH: 0.027.
- FT_4: 1.11 (normal FT_3 and FT_4 with low TSH).

What Is Your Diagnosis?

Subclinical hyperthyroidism in a patient with insulin-dependent diabetes. The elevated RAIU in the past suggested that she had underlying Graves' disease.

Treatment Options

Options for treatment were discussed with the patient. She could have been treated with a low dose of an antithyroid drug (ATD) or she could have been simply followed because she was asymptomatic. She elected to be followed without treatment.

Follow-Up

The patient returned 4 months later. She still had no symptoms of hyperthyroidism. Physical examination was unchanged. Her diabetic control was good. Her TSH was 0.09. FT_4 and FT_3 were still normal.

Diagnosis

The diagnosis remained subclinical hyperthyroidism in view of the low TSH and normal FT_3 and FT_4 with no symptoms of hyperthyroidism.

Treatment

Again, options for treatment as described in the Treatment Options section, were discussed. She elected follow-up without medication. She was advised to call if she developed symptoms of hyperthyroidism, and we discussed the things to look for. Otherwise, it was agreed that she would return in approx 3 months with repeat TSH, FT_4, and FT_3 and a dual-energy x-ray absorptiometry (DEXA) bone density test.

Case Summary

This young woman had subclinical hyperthyroidism, which was probably secondary to underlying Graves' disease along with type 1 diabetes. The fact that she had type 1 diabetes, an autoimmune disease, increased the odds that she also had Graves' disease, also an autoimmune disease. The incidence of Graves' disease is higher in patients with another autoimmune disease. Because

she had subclinical hyperthyroidism and felt well, she declined treatment and agreed to be followed. Because she elected follow-up without treatment, a DEXA test was ordered. A low bone density might be a further indication to treat her because even subclinical hyperthyroidism may cause a decrease in bone density.

What Can We Learn From This Case?

- This patient has subclinical hyperthyroidism as defined by a low TSH with normal T_3 and T_4 levels in an asymptomatic patient.
- Because she is a type 1 diabetic, it is more likely that her hyperthyroidism is the result of underlying Graves' disease. Both are autoimmune diseases.
- The treatment of subclinical hyperthyroidism is controversial. There is very little evidence for or against treatment. The current guidelines recommend more serious consideration of treatment when the TSH is below 0.1, if the patient is more than 60 years old, or has heart disease or osteopenia. This woman is young, has no history of heart disease, and will be evaluated for osteopenia with a DEXA test. Patient preference against treatment is an important consideration in this case because indications for treatment are not strong. If the bone density is low, treatment should be reconsidered.

CASE 2

A 52-year-old woman was seen for thyroid evaluation. She had been evaluated by another endocrinologist 1 year previously. At that time, she complained of dysphagia. She had no symptoms of hyperthyroidism, but her thyroid gland was enlarged to about twice the normal size and multinodular. Previous thyroid evaluation revealed a low TSH of 0.008 with normal FT_4 and total T_3. Thyroid ultrasound revealed multiple solid nodules in both lobes. A computed tomography (CT) scan, performed because of the dysphagia, was negative except for small nodules in the thyroid.

When seen, she no longer complained of dysphagia. She had no symptoms of hyperthyroidism. There was no history of radiation to the neck. Physical examination revealed a pulse of 64, blood pressure (BP) was 150/82. There were no thyroid eye signs. The thyroid gland was bilaterally enlarged and compatible with a multinodular goiter (MTNG). The examination was otherwise normal.

What Would You Do Next?

The following tests results were obtained:

- TSH: 0.016, FT_4 1.8 (0.8–1.8), FT_3 4.87 (1.8–4.6).
- RAIU: 4 hour, 7% (4–12); 24 hour, 15% (7–24).
- Thyroid scan: no definite hot or cold nodules, compatible with MTNG. No change since previous scan.
- Bone density: normal.

Review of History

Because the patient now had a borderline elevated FT_3 along with an upper-normal FT_4 and TSH less than 0.1, she might well have clinical rather than subclinical hyperthyroidism. She now admitted that she had been having palpitations prior to initiation of a β-blocker. She also admitted to intermittent episodes of shakiness and nervousness.

Diagnosis

MTNG with probable mild hyperthyroidism.

Treatment

Options for treatment, including RAI therapy, careful follow-up without treatment, and an ATD were discussed with the patient. Because her bone density was good and she had very few symptoms of hyperthyroidism, she chose follow-up without treatment at this point. She was asked to call if she developed further hyperthyroid symptoms. Otherwise, it was agreed to repeat TSH, FT_3, and FT_4 in 3 months.

Case Summary

This middle-aged woman had a history of MTNG with subclinical hyperthyroidism, which was progressing toward clinical hyperthyroidism. The FT_3 was now borderline elevated with low TSH and upper-normal FT_4. On careful questioning, she admitted to some possible symptoms of hyperthyroidism. After careful review of treatment options, she elected follow-up without treatment at this point. It is likely that she will progress further and require treatment in the future.

What Can We Learn From This Case?

- Patients with MTNG may progress to subclinical or clinical hyperthyroidism.
- The decision of whether to treat is difficult, and the physician must carefully review all the data in order to make the best recommendation.
- Patient input regarding treatment is important, and the case should be carefully reviewed with the patient, including all treatment options.
- If the patient decides against treatment, careful follow-up is essential.

CASE 3

The patient is a 79-year-old man who was referred to another endocrinologist previously because of thyroid nodules noted on a carotid ultrasound. Thyroid testing at that time revealed a TSH of less than 0.005 and FT_4 of 1.8. Thyroid ultrasound showed a 1-cm solid nodule on the right and several less-than-1-cm cystic nodules bilaterally with no change over the previous year. On careful questioning, it was determined that the patient had no symptoms of hyperthyroidism. Attempted fine-needle aspiration biopsy (FNAB) of the solid

nodule 1 year ago was reported as not adequate for diagnosis. Past history was significant for severe heart disease with arrhythmias and the patient had been on amiodarone in the past. He had a pacemaker in place. A TSH done 4 months ago was 0.208 with normal FT_4 and FT_3.

Physical examination revealed a pulse of 80 and BP of 100/50. No thyromegaly or nodularity was present. The heart showed an irregular rhythm. Examination was otherwise normal.

Additional Workup

The following tests results were obtained:

- TSH less than 0.005, FT_4 1.5, FT_3 3.22.
- RAIU: 4 hour, 6.2%; 24 hour, 20.1% (normal for the laboratory).
- Thyroid scan: normal.

What Is Your Diagnosis?

Subclinical hyperthyroidism.

How Would You Treat This Patient?

Treatment options were reviewed with the patient. These included RAI therapy, an ATD, and follow-up without treatment. Careful follow-up without treatment at that point was the decided action.

Case Summary

This elderly man had findings of subclinical hyperthyroidism. He had been followed for 1 year with very little change in thyroid findings. However, he had severe heart disease with arrhythmias and a pacemaker in place. Because he had no symptoms of hyperthyroidism and normal FT_3 and FT_4, he was closely followed without treatment.

What Can We Learn From This Case?

- Subclinical thyroid disease is more common in older patients.
- The history of amiodarone therapy complicates this case. The thyroid findings may be secondary to amiodarone even though he is not currently taking it.
- On review of this case for this book and in view of more recent guidelines, I would now recommend treatment in view of his age, cardiac disease, and TSH below 0.1.
- Treatment choices would be either RAI or an ATD. My choice would be RAI in view of his age and cardiac disease because this would likely result in a cure. His RAIU is high enough to use RAI therapy despite the amiodarone history.
- Interestingly, when I returned to do another locum at this clinic several months later, I found that this patient had been referred for RAI treatment. The radiation oncologist elected not to treat him because he had no hyperthyroid symptoms and the FT_4 was only mildly elevated at 1.88 with a normal total T_3 of 1.6.

CASE 4

A 59-year-old woman was referred by her PCP because of the finding of a thyroid nodule on routine examination. She went to see her doctor for a routine physical and had no complaints. Careful review of the patient's history revealed no symptoms of thyroid dysfunction. The thyroid studies that were sent over with her included a TSH of 9.4 and a total T_4 of 5.4 (4.5–12). A thyroid nuclear scan was reported to show a hot nodule in the right lobe. There was no history of radiation treatment to the neck area. She had a past history of paroxysmal atrial tachycardia (PAT). Her daughter had thyroid disease.

Physical examination revealed a pulse of 60 and BP of 110/70. The thyroid gland was bilaterally enlarged and multinodular. A more discrete nodule in the left lobe measured 2 × 3 cm. There were no palpable cervical nodes. The remainder of the examination was negative.

What Is Your Diagnosis?

I reviewed the original scan pictures and disagreed with the report of a hot nodule. The scan showed hot and cold areas compatible with a MTNG or Hashimoto's thyroiditis. Neoplasm was also considered. The laboratory and clinical findings were compatible with subclinical hypothyroidism.

Would You Order Additional Studies?

A thyroid microsomal antibody level was ordered and was markedly elevated to more than 700 U/mL.

Working Diagnosis

Subclinical hypothyroidism and MTNG secondary to Hashimoto's thyroiditis.

Treatment

The patient was started on 0.1 mg of T_4 daily.

Clinical Course

The patient was seen about 1 month later. The thyroid gland was smaller, with the nodule on the left now measuring 1 × 2 cm. However, the patient had several episodes of PAT since starting on T_4. Her TSH was now 0.18, and her total T_4 was 12.8. The T_4 dosage was decreased to 0.075 mg daily. Three months later, the thyroid nodules had decreased further in size. The patient felt well except for a little inner shakiness since taking T_4. Her total T_4 was 10.4, and her TSH was less than 0.05. The T_4 dose was reduced further to 0.05 mg daily. Three months later, she felt well and denied any palpitations or shakiness. Her thyroid findings were unchanged. TSH was 5.74, and her T_4 was 7.4. She was followed on an annual basis and maintained on low-dose T_4. She continued

to have occasional episodes of PAT. Several years later, the thyroid was no longer palpably enlarged. She continued to run borderline high TSH levels, but she felt well. I attempted to edge up her T_4 dosage, but she did not want to increase it because of concern about PAT.

Case Summary

This middle-aged woman presented with a nodular goiter and laboratory findings of subclinical hypothyroidism. Her thyroid microsomal antibody level was markedly elevated. The clinical and laboratory findings were compatible with Hashimoto's thyroiditis with goiter and subclinical hypothyroidism. She was treated with T_4 as suppressive therapy in an attempt to shrink her nodular goiter and also treat her subclinical hypothyroidism. Her treatment was complicated by PAT, and she was unable to tolerate a suppressive dose of T_4. However, her goiter decreased in size, and she felt generally well on low-dose T_4 with only minimally elevated TSH levels.

What Can We Learn From This Case?

- Hashimoto's thyroiditis can present with a nodular thyroid, although it is more commonly seen with diffuse thyromegaly.
- It is useful for the clinician to review the scan pictures and correlate them with findings on physical examination. In this case, the report by the radiologist was misleading.
- Because the clinical findings suggested benign disease, a trial of suppressive T_4 was reasonable, and the patient responded with decrease in thyroid size. If the nodules had enlarged, FNAB to rule out neoplasm would have been needed.
- If the patient had presented with only subclinical hypothyroidism and no thyromegaly, the decision to treat with T_4 would have been more difficult, especially in view of the PAT. However, the markedly positive thyroid antibodies made it likely that she would progress to overt hypothyroidism over time. If treatment were not pursued, close follow-up would be important.

SUMMARY

Three cases of subclinical hyperthyroidism and one case of subclinical hypothyroidism are discussed in this chapter. By definition, subclinical thyroid dysfunction includes patients with abnormal TSH levels, normal thyroid hormone levels, and no symptoms of thyroid disease. The decision to treat or simply follow these patients is difficult and is usually made in conjunction with the patient after careful review of all findings. The cases discussed here should help the physician in coming to the best decision in each patient.

The first patient is a young woman with type 1 diabetes and probable subclinical Graves' disease. Both are autoimmune diseases, and the incidence of

Graves' disease is higher in patients with type 1 diabetes. Because the patient is young and without heart disease or osteoporosis, we agreed that she could be followed without treatment.

The second case discussion involves a middle-aged woman with an MTNG and borderline high T_3. She may be edging into clinical hyperthyroidism. I would have been comfortable treating this patient, but she elected to be followed without treatment. She agreed to close follow-up and is aware that she will probably need treatment in the future. RAI will probably be the best treatment modality.

The third patient is an elderly man with subclinical hyperthyroidism complicated by heart disease, cardiac arrhythmias, and an implanted pacemaker. He also has a history of amiodarone therapy, which can cause thyroid dysfunction. His thyroid status had been stable for more than 1 year, and I elected to continue to follow him. In reviewing the case and in view of current guidelines, I think I would recommend treatment.

The last case describes a middle-aged woman with an MTNG and subclinical hypothyroidism. The underlying disease is autoimmune (Hashimoto's) thyroiditis. Treatment with T_4 was pursued in an attempt to suppress TSH and shrink her goiter. She was unable to tolerate a suppressive dose of T_4, but she did well and her goiter decreased on a lower dose.

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8
Hashimoto's Thyroiditis

INTRODUCTION

Hashimoto's thyroiditis or chronic autoimmune thyroiditis is the most common cause of hypothyroidism in the United States and a common cause of goiter. It was described by Dr. Hashimoto in 1912 as a lymphocytic infiltration of the thyroid gland with goiter. It has since been well established as an autoimmune disease and circulating antibodies against the thyroid (microsomal or peroxidase and thyroglobulin antibodies) can be found in the majority of cases. Like most thyroid diseases, it is much more common in women than in men, with a sex ratio of 6 or 7 to 1. It can present with goiter alone, goiter and hypothyroidism, or occasionally with transient hyperthyroidism followed by hypothyroidism. Subclinical hypothyroidism is seen in some cases. The goiter is most often diffuse, but Hashimoto's thyroiditis may present with multinodular goiter (MTNG) or a single nodule. The case discussions in this chapter illustrate varying presentations of the disease and an approach to diagnosis and treatment.

Case 1

A 36-year-old woman was referred regarding a goiter. She had a history of right-sided thyroid enlargement at age 20 years and was treated with thyroid medication for approx 1 year. She thought that the swelling went down, and she stopped the medicine. She took medication again 6 years later for right-sided swelling with a similar result. Recently, she had noted recurrence of the right-sided swelling. She had no symptoms of hyperthyroidism or hypothyroidism and no history of radiation treatment to the neck.

Physical examination revealed a pulse of 72 and blood pressure (BP) 112/60. There were no thyroid eye signs. The thyroid gland was bilaterally enlarged to about twice the normal size with the right lobe larger than the left. It was diffusely irregular or bosselated and nontender. The examination was otherwise negative.

What Is the Most Likely Diagnosis?

Hashimoto's thyroiditis with goiter and possible hypothyroidism.

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What Tests Would You Order?

The following test results were obtained:

- Thyroid-stimulating hormone (TSH): 11(0.4–5), FT_4 0.75 (0.76–1.79).
- Antithyroid microsomal antibody: 697 (<25).

Final Diagnosis?

Hashimoto's thyroiditis with goiter and mild or subclinical hypothyroidism.

Treatment

The patient was started on 0.1 mg of thyroxine (T_4) daily as treatment for the goiter and hypothyroidism. She was seen 2 months later. The goiter had decreased in size. TSH was 0.24. The T_4 dosage was decreased to 0.088 mg daily. Although she was asked to return in 3 months, she did not do so.

Case Summary

This young woman had a long history of goiter, which had previously decreased in size on T_4. The goiter had recently recurred. She had no symptoms of hypothyroidism. Her laboratory studies were compatible with mild or subclinical hypothyroidism and Hashimoto's thyroiditis. Her goiter decreased in size on T_4. She was lost to follow-up.

What Can We Learn From This Case?

- This patient illustrates a common initial presentation of Hashimoto's thyroiditis. The patient had a goiter and borderline or subclinical hypothyroidism.
- The goiter of Hashimoto's disease will often shrink on T_4 therapy, as in this patient.
- The decision to treat this patient again with T_4 was based on the fact that she had responded in the past and that her subclinical hypothyroidism might progress to overt hypothyroidism.
- Patients with Hashimoto's thyroiditis and subclinical hypothyroidism progress to overt hypothyroidism at a rate of about 5% a year in some studies. If it is elected not to treat the patient, she should be followed at least annually.

CASE 2

A 74-year-old woman was referred for evaluation of a goiter. The right lobe had been noted by her primary care physician (PCP) to be enlarging recently. History was obtained using the patient's daughter as interpreter because the patient spoke only Spanish. A goiter had been noted by a physician approx 2 years before. At that time, she was being evaluated for paroxysmal atrial fibrillation (PAT). The patient had a history of intermittent palpitations and shakiness, cold intolerance, and loss of scalp hair. She was mildly constipated. There was no history of radiation to the neck, and no family history of thyroid disease.

Physical examination revealed an alert elderly woman in no distress. There were no thyroid eye signs. The thyroid gland was bilaterally enlarged to three times the normal size and was multinodular. The heart showed an irregular rhythm at 108, which was compatible with atrial fibrillation. Examination was otherwise negative.

Laboratory data from her doctor included a TSH of 1.78, total T_4 of 5.7, and total triiodothyronine (T_3) of 88, all within normal limits. TSH 1 yr before was borderline elevated at 5.7.

What Is Your Differential Diagnosis?

The differential diagnosis includes benign MTNG, Hashimoto's thyroiditis, and neoplasm. The patient is clinically euthyroid and has atrial fibrillation.

What Additional Workup Would You Order?

Thyroid antibodies, thyroid uptake and scan, and repeat TSH were ordered. The uptake was normal and the scan showed multiple "hot" and "cold" nodules bilaterally. TSH was borderline high at 5.78. The antimicrosomal thyroid antibody was markedly elevated at 373 (normal <25).

What Is Your Diagnosis?

Hashimoto's thyroiditis with MTNG and possible subclinical hypothyroidism.

What Next? Further Testing? Treatment?

This patient presents a complex problem. Neoplasm is still a possibility, although the patient does not have a dominant nodule and the elevated antibodies are compatible with Hashimoto's thyroiditis. Fine-needle aspiration biopsy (FNAB) might be considered. Treatment with T_4 might be considered to treat the borderline-elevated TSH and possibly shrink the goiter. Another option would be to follow the patient without further testing or treatment to see if the thyroid enlarges further or if she develops more evidence of hypothyroidism.

I elected to follow her without further testing or treatment. The risk of neoplasm was small in view of the lack of a dominant "cold" nodule and the high antibody level. She was not clinically hypothyroid. T_4 therapy would carry some risk of precipitating hyperthyroidism in this elderly woman with atrial fibrillation in view of the "hot" nodules on scan, which might be autonomous. When seen several months later, her thyroid examination was unchanged and the TSH was 3.70. The plan was to follow her without treatment. Unfortunately, she did not return for follow-up as advised.

Case Summary

This elderly woman presented with a large MTNG and borderline elevated TSH. Thyroid nuclear scan revealed an MTNG with both "hot" and "cold" nodules, but

no dominant nodule. The antithyroid microsomal antibody level was markedly elevated and compatible with Hashimoto's thyroiditis. I elected to follow her without treatment. If the goiter enlarged further or a dominant nodule appeared, FNAB would be performed. Unfortunately, she did not return as advised.

What Can We Learn From This Case?

- Hashimoto's thyroiditis may present as an MTNG, although diffuse thyromegaly is more common.
- The nuclear scan showed some "hot" nodules, suggesting autonomous thyroid function. In view of her age and atrial fibrillation, this patient should be followed for possible development of hyperthyroidism from these possibly autonomous nodules.
- Treatment with T_4 could precipitate hyperthyroidism by adding exogenous thyroid hormone to that produced by the probably autonomous and nonsuppressible nodules noted on scan.
- The risk of malignancy in this patient was low in view of the scan findings, elevated antibody level, and lack of a dominant nodule. Therefore, biopsy was not pursued. FNAB would be indicated if the thyroid enlarged further.

CASE 3

A 24-year-old woman was referred by her PCP for evaluation of a goiter. She had a history of thyroid disease since childhood. At age 8 years, she had surgery to remove a thyroglosssal duct cyst. At age 13 years, she was diagnosed with Hashimoto's thyroiditis. She was placed on T_4 and took it erratically for 2 years and then discontinued it on her own. She had no further thyroid complaints until 1 to 2 months ago when she noted neck swelling without pain or tenderness. She had recently noted fatigue, cold intolerance, hair loss, and a 10-lb weight gain. A recent total T_4 level ordered by her doctor was low at 3.7. Thyroid microsomal antibody was negative. Family history revealed that the patient's mother and grandmother had both undergone thyroid surgery.

Physical examination revealed a young woman with facial puffiness. Pulse was 80 and blood pressure (BP) was 115/78. There were no thyroid eye signs. The thyroid gland was markedly enlarged to about three times the normal size. The left lobe was larger than the right and the isthmus was also palpably enlarged. There were no palpable cervical nodes. The examination was otherwise negative.

What Is Your Diagnosis at This Point?

My diagnosis was probable Hashimoto's thyroiditis with goiter and hypothyroidism.

What Additional Testing Would You Do?

In view of the negative antibody level and enlarging goiter, I performed an FNAB in the office. A TSH was also ordered.

Results

The biopsy was reported as Hashimoto's thyroiditis, and the TSH was 267 (0.4–5).

How Would You Treat This Patient?

The patient was started on 0.1 mg of T_4 daily.

Clinical Course

On evaluation 6 weeks later, the patient reported a 5-lb weight loss, and improvement in fatigue and cold intolerance. Her thyroid gland had decreased in size to about twice the normal size. TSH was still elevated at 16. T_4 dose was increased to 0.125 mg daily. She did not return for her 3-month appointment and was finally seen several months later. The thyroid gland was now only borderline enlarged. TSH was normal. She was placed on yearly follow-up.

The patient finally returned 3 years later. She had been off T_4 for several months. She complained of fatigue, cold intolerance, and hair loss. Physical examination revealed the thyroid to be markedly enlarged to about three times the normal size and mildly irregular, but without discrete nodules. TSH was 12. I had a long talk with the patient about the need for her to take the thyroid medication regularly. She was started on 0.1 mg of T_4 daily. Two months later, her TSH was normal at 1.8. She was seen annually. Mild thyroid enlargement persisted. Her TSH remained normal.

What Can We Learn From This Case?

- Hashimoto's thyroiditis may present in childhood.
- The initial clinical finding may be goiter. Hypothyroidism may develop over time.
- The disease often runs in families, as in this case.
- T_4 therapy is useful for shrinking the goiter and also for treating hypothyroidism when present.
- Compliance is a problem as with any long-term medication. It is important to emphasize to the patient that T_4 is a lifetime medication and should not be discontinued.
- Regular follow-up is important to monitor compliance and adjust T_4 dosage based on clinical findings and TSH level.

CASE 4

A 38-year-old woman was referred by her PCP because of a goiter. The patient described an enlarging mass in her neck over at least the past year. She was not sure whether it was continuing to enlarge. She denied dysphagia, but noted pressure sensation in her neck when she was lying on her right side. She had no neck pain and no symptoms of hyperthyroidism or hypothyroidism. Family history was negative for thyroid disease. Laboratory studies included a TSH of 3.1 and elevated antithyroglobulin antibodies of 84 (normal <1).

Physical examination revealed an obese woman, with a pulse of 104 and BP of 130/66. There were no thyroid eye signs. The thyroid gland was massively enlarged bilaterally to at least four times the normal size. It was firm and nontender. The right lobe was multinodular. There were no palpable cervical nodes. Physical examination was otherwise negative.

What Is Your Differential Diagnosis?

The most likely diagnosis was Hashimoto's thyroiditis with massive goiter, but neoplasm, such as lymphoma, must be ruled out. She was clinically euthyroid but had compression symptoms from the large mass.

What Would You Do Next?

FNAB was performed it and confirmed a diagnosis of Hashimoto's thyroiditis.

How Would You Treat This Patient?

I started the patient on suppressive therapy with T_4 in an attempt to shrink the goiter. The goiter decreased slightly in size, but the patient began having choking episodes. The patient was referred for thyroidectomy in view of the severe compression symptoms. At surgery, both lobes were rock hard and multinodular. Pathology confirmed the diagnosis of Hashimoto's thyroiditis. The choking was no longer a problem after surgery. The patient was treated with replacement T_4 and did well.

Case Summary

This woman presented with a huge MTNG. FNAB diagnosis was Hashimoto's thyroiditis. The goiter did not respond well to suppression with T_4. She was sent to surgery because of compression symptoms. Total thyroidectomy confirmed the diagnosis of Hashimoto's thyroiditis and cured her choking symptoms. She did well on replacement T_4.

What Can We Learn From This Case?

- Hashimoto's thyroiditis can present as a large MTNG in a euthyroid patient.
- In this situation, it is important to rule out lymphoma or other neoplasm.
- The huge gland was compressing the trachea and causing choking symptoms.
- Although the mass was benign, surgery was indicated to relieve the compression symptoms.
- In this case, the choking was felt to be the result of the very large mass. However, some patients with goiter complain of choking that is not caused by the goiter and may not be relieved by surgery.

SUMMARY

The cases discussed in this chapter illustrate the varying presentations of Hashimoto's thyroiditis. Case 1 illustrates a common presentation of this dis-

ease with a small goiter and mild or subclinical hypothyroidism. The patient responded well to T_4 therapy with decrease in the size of her goiter. She will require treatment indefinitely.

Case 2 illustrates another presentation of this disease in an elderly woman with MTNG and mild or subclinical hypothyroidism. Workup was compatible with Hashimoto's thyroiditis in a multinodular thyroid gland with areas of possible autonomous function on nuclear scan. The TSH was compatible with mild subclinical hypothyroidism. The risk of neoplasm appeared low and I elected to follow her without treatment.

Case 3 is a young woman who developed goiter in childhood and was found to have Hashimoto's thyroiditis. She had been on and off T_4 over the years and presented with a large goiter and hypothyroidism. T_4 treatment corrected the hypothyroidism and decreased the size of the goiter. However, she did not follow-up or take her medicine as advised and presented several years later with similar findings of a large goiter and hypothyroidism.

Case 4 is a young woman who presented with a huge goiter with tracheal compression symptoms and was clinically euthyroid. FNAB was performed because of concern about possible neoplasm. Biopsy confirmed the diagnosis of Hashimoto's thyroiditis. A trial of TSH suppression with T_4 was unsuccessful, and she required surgery to relieve the tracheal compression.

All of these patients presented to a PCP with goiter. The thyroid enlargement was either noted initially by the patient or the physician. Hashimoto's thyroiditis was a diagnostic possibility in all of these patients, but other diagnoses, such as neoplasm, were considered in some. TSH level and thyroid antibodies were helpful in establishing a diagnosis. FNAB and nuclear scanning were useful in selected cases. Initial treatment for the goiter and hypothyroidism when present was T_4. Thyroidectomy was required to relieve compression symptoms in one case.

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Thyroid Disease in Pregnancy and Postpartum

INTRODUCTION

This chapter discusses cases of pregnancy complicated by thyroid disease and thyroid test abnormalities, as well as thyroid problems after delivery. Thyroid diagnosis and treatment during pregnancy is more complex because there are two patients with whom to be concerned—the mother and the fetus. Diagnosis is more difficult because thyroid tests may be harder to interpret in this setting. Also, tests using radiation, such as the thyroid uptake and scan, cannot be safely performed on pregnant women. Treatment is more difficult because of concern about the effect of thyroid disease and medication on the fetus. Radioactive iodine (RAI) treatment is contraindicated during pregnancy.

Thyroid problems are also common in the months after delivery, and they are often missed. Following delivery, women may develop nonspecific symptoms, such as fatigue, depression, nervousness, and palpitations. These complaints may be the result of the stress of caring for a new infant and the major lifestyle changes that result. However, they may also result from thyroid dysfunction.

Postpartum hypothyroidism or hyperthyroidism occurs in up to 20% of women. It is often transient, but awareness and possible treatment may make a big difference to the patient. Often, the physician will feel that the complaints are the result of emotional problems, and the patient will either reject this diagnosis or feel unhappy about it. The diagnosis of an underlying and probably temporary thyroid disorder will relieve a lot of the patient's stress even if treatment is not indicated. This chapter discusses several cases that demonstrate the types of thyroid problems that are seen in pregnancy and the postpartum period.

CASE 1

A 32-year-old woman was referred because of abnormal thyroid function tests. Her thyroid-stimulating hormone (TSH) was less than 0.03, total thyroxine (T_4) was 20 (4–12), and total triiodothyronine (T_3) was 274 (70–180). She was 16 weeks pregnant and had severe hyperemesis gravidarum with a 19-lb weight loss. She had noted shakiness and intermittent palpitations.

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Physical examination revealed an acutely ill young woman who was weak and shaky. Pulse was 100 and blood pressure (BP) was 80/44. Her buccal mucosa was dry and her eyes were sunken. The thyroid was enlarged to about 1.5 times the normal size. She had no thyroid eye signs.

The following laboratory results were obtained:

- Free thyroxine (FT_4):1.48 (0.8–1.8).
- Free triiodothyronine (FT_3): 515 (210–440).
- Antithyroid peroxidase antibody was negative.
- Thyroid-stimulating immunoglobulin (TSI) was normal.

What Is Your Diagnosis?

The patient is clearly thyrotoxic. The differential diagnosis includes Graves' disease and thyrotoxicosis of hyperemesis gravidarum. This is often a very difficult differential to make (*see* Case Discussion section). In this case, my working diagnosis was Graves' disease.

How Would You Manage This Patient?

The patient was started on 100 mg of propylthiouracil (PTU) every 8 hours, and given parenteral hyperalimentation. One week later, she was seen by her obstetrician for jaundice and referred to a gastroenterologist. I was concerned that the jaundice might be a side effect of the PTU. Fortunately, she had not started the PTU yet because it was pending approval by Medicaid. The gastrointestinal consultant diagnosed fatty liver of pregnancy. The Medicaid approval came through and she started the PTU.

Clinical Course

The patient gained weight, her pulse slowed to 70 to 80, and the tremor cleared. Follow-up FT_3 and FT_4 were normal, although the TSH remained low. The PTU dose was gradually decreased to 50 mg twice daily. A TSI at 8 months of pregnancy was normal. She delivered a normal full-term infant.

Postpartum

The baby's total T_4 at 1 d was 24.1 (upper-normal for that age). At 1 week, the baby's total T_4 was 13.6, TSH was 1. The mother became clinically hyperthyroid and required an increase in PTU to 150 mg every 8 hours. She was continued on PTU for several months while awaiting Medicaid approval for RAI therapy. Eventually, she was treated with RAI and developed the usual post-RAI hypothyroidism. She is now euthyroid on replacement T_4. The baby is doing well.

Case Discussion

This challenging case demonstrates the difficulty in diagnosis of the etiology of hyperthyroidism in a pregnant woman. Making the correct diagnosis is obvi-

ously critical to appropriate treatment. The differential diagnosis is usually between transient hyperthyroidism of hyperemesis gravidarum (THHG) and Graves' disease. THHG is caused by inappropriate secretion of human chorionic gonadotropin (HCG). HCG and TSH have the same α-subunit and different β-subunits. HCG is a mild thyroid stimulator, and high levels may produce hyperthyroidism. Graves' disease is, of course, an autoimmune disease and is caused by immunoglobulins that stimulate the TSH receptors on thyroid cells. Hyperthyroidism is the second most common endocrine disease in pregnancy (diabetes is the first) and occurs in 1 in 500 pregnancies.

Graves' disease is the more serious problem, and requires aggressive therapy to avoid complications in mother and child. THHG is usually a self-limited disease and may only require symptomatic therapy or observation. In the absence of Graves' disease ophthalmopathy, the differential diagnosis is often difficult. Some clinical clues that point to Graves' disease include a history of hyperthyroid symptoms prior to pregnancy, the presence of goiter, and exophthalmos and positive antibodies. In THHG, the severity of the hyperthyroidism is usually related to the severity of the vomiting, and the hyperthyroidism will usually spontaneously clear by the fourth or fifth month of pregnancy. A suppressed TSH may also be seen in normal pregnancy without thyroid disease, but in this case the patient will not have hyperthyroid symptoms, and the T_3 and T_4 will be normal.

This patient had severe hyperemesis and could well have had THHG. However, she had a goiter, and I made a working diagnosis of Graves' disease. Antithyroid drugs (ATDs) are the treatment of choice in the pregnant Graves' patient. She was started on PTU in a moderate dose, and the dose was tapered as she improved. It is important not to over treat and cause hypothyroidism, because hypothyroidism in the mother may produce goiter and hypothyroidism in the fetus. The ATD dose should be adjusted to keep the FT_4 in the upper normal range. Graves' disease, like other autoimmune diseases, tends to improve during pregnancy, and the ATD can often be decreased and even discontinued in the latter part of pregnancy.

This patient delivered a normal infant. The baby was euthyroid and had no goiter. A TSI at 8 months of pregnancy was normal. The TSI should be measured in the last trimester. A significantly elevated TSI should alert the physician to the possibility of neonatal hyperthyroidism in the newborn. This is a serious problem that requires expert help from the endocrinologist and pediatrician.

My working diagnosis of Graves' disease in the mother proved correct in this patient. The Graves' disease persisted through pregnancy and became more severe after delivery. She required definitive therapy with RAI and has done well on replacement T_4. If she becomes pregnant again, a TSI should be done in early pregnancy. A significantly elevated TSI will alert the physician to the pos-

sibility of neonatal hyperthyroidism. The mother's thyroid function should be monitored during pregnancy and the T_4 dosage adjusted to maintain a euthyroid state.

What Can We Learn From This Case?

- Consider hyperthyroidism in pregnancy, especially if the patient has a resting pulse over 100 and fails to gain weight despite good intake. Obtain FT_4 and TSH.
- Try to make differential diagnosis between Graves' disease and the less serious THHG.
- Be aware that a suppressed TSH alone without symptoms and other findings of hyperthyroidism is common in normal pregnancies and requires no medication.
- Look for thyroid ophthalmopathy and goiter as signs that may point to Graves' disease.
- In difficult cases, thyroid peroxidase (TPO) antibody and TSI testing may be helpful.
- If Graves' disease is diagnosed, treatment with PTU or methimazole may be needed. Close monitoring is required to prevent maternal hypothyroidism from medication, which can result in fetal goiter and fetal hypothyroidism.
- In pregnant women with Graves' disease, a TSI should be obtained in the last trimester. A signifigantly elevated TSI indicates that fetal or neonatal hyperthyroidism may occur.
- If treatment with an ATD is needed, keep FT_4 in upper third of the normal range, and try to decrease the dosage as pregnancy progresses. It may be possible to discontinue the drug in the last trimester.
- Be aware that autoimmune diseases, such as Graves' disease, tend to improve in the last half of pregnancy and may flare up after delivery. Flare-ups can also occur in the first trimester.
- TSI should be monitored in the last trimester in all Graves' disease patients, even those who have been treated prior to pregnancy and are euthyroid. TSI crosses the placental barrier and may cause fetal or neonatal hyperthyroidism.
- Think of hyperthyroidism in the fetus of a Graves' disease mother if fetal tachycardia, growth retardation, or goiter on ultrasound are seen.

CASE 2

A 30-year-old woman was referred for thyroid evaluation. She was 12 weeks pregnant with her second child. She had noted fatigue, moodiness, and heat intolerance over the previous 2 months. She had constant nausea from morning sickness, but no vomiting. She had lost 5 lb over the previous 2 weeks and complained of headaches. She denied palpitations or tremor. She noted no change in the appearance of her eyes or in her vision. She had one child age 7 years and had no thyroid problems with that pregnancy or postpartum. However, she was found to have a goiter 4 years previously and was treated with T_4 for 3 months. The past several days she had felt better, less tired, but still moody. There was no family history of thyroid disease.

Physical examination revealed a pulse of 72 and BP of 110/70. The eyes showed bilateral stare without proptosis or lid lag and the extraocular movements appeared normal. The thyroid was bilaterally enlarged to about twice the normal size, firm, and without nodules. The examination was otherwise normal.

The following test results were obtained:

- TSH less than 0.03; FT_4 1.17 (0.7–1.5); sedimentation rate, 18.
- TPO antibody, FT_3, and TSI were normal.

What Is Your Differential Diagnosis?

The differential diagnosis includes Graves' disease, THHG, and low TSH of pregnancy. This patient could have THHG, however, the goiter and previous history of thyroid disease make Graves' disease a more likely diagnosis. Suppressed TSH with normal T_4 is also a common finding in normal pregnancies, but these patients do not usually have a goiter or other evidence of thyroid disease. I saw this patient on a short locum assignment and was not able to follow her further. She probably had Graves' disease.

CASE 3

A 26-year-old woman was referred because of a TSH of 0.14, total T_4 of 9.7 (4.5–12), and thyroid microsomal antibody elevated to 15 (<1). She was 6 months postpartum and had complained to her doctor that she could not lose the weight she had gained during pregnancy. She reported that she has been warmer than others at work. She felt otherwise well. Her only medication was a birth control pill.

On physical examination, the pulse was 68, BP was 124/72. There were no thyroid eye signs. The thyroid gland was diffusely enlarged to twice the normal size and rubbery in consistency. Examination was otherwise normal.

What Is Your Diagnosis?

The most likely diagnosis is postpartum thyroiditis (PPT) with mild or subclinical hyperthyroidism. Early Graves' disease should be considered in the differential diagnosis.

Additional Testing? Treatment?

No additional testing or treatment is indicated at this point. Close follow-up is important.

Clinical Course

The patient returned 1 month later. She was no longer hot and felt well. Physical examination revealed that her thyroid had decreased in size to about 1.5 times the normal size. The TSH was now elevated to 46, FT_4 was 0.24 (0.75–2).

What's Going On?

The patient has switched from borderline hyperthyroid to biochemically hypothyroid. In view of the degree of TSH and FT_4 abnormality, she was started on T_4. She returned 2 months later and reported a 6-lb weight loss. Her TSH was 1.42.

Final Diagnosis? Treatment Plan?

The final diagnosis is PPT.

Treatment Plan

Options for treatment include continuing T_4 or discontinuing T_4 with close follow-up to see if her thyroid has recovered. The majority of patients with PPT recover, whereas some go on to permanent hypothyroidism. Because she planned another pregnancy, I elected to continue therapy rather than risk hypothyroidism during pregnancy.

Case Summary

This 26-year-old woman presented 6 mo postpartum with mild heat intolerance and an enlarged thyroid gland. Her TSH was low with a normal T_4 and thyroid microsomal antibody was positive. The diagnosis was subclinical hyperthyroidism due to PPT. She then converted to hypothyroidism and was treated with T_4. Because she planned another pregnancy, the T_4 was continued to ensure a euthyroid state.

What Can We Learn From This Case?

- Consider thyroid disease in the postpartum period when the patient has vague complaints.
- Once the physician thinks about thyroid disease in this setting, the diagnosis can be easily ruled in or out with a TSH and FT_4.
- Postpartum thyroid dysfunction can present as either hyperthyroidism or hypothyroidism and can progress from one to the other.
- PPT is an autoimmune disease. The patient will return to a euthyroid state spontaneously in the majority of cases.
- Short-term treatment may be needed to relieve symptoms in some patients, whereas others can be followed without treatment.
- Whereas the majority of patients will return spontaneously to a euthyroid state, about 25% of patients will become permanently hypothyroid.
- Look for thyroid dysfunction in subsequent pregnancies.

CASE 4

A 28-year-old woman was referred because of heat intolerance and abnormal thyroid function tests. She had delivered twins 10 wk previously. Thyroid testing at 6 weeks postpartum revealed a TSH of 0.05, FT_4 of 2.45 (0.8–1.8), and FT_3 of

6.5 (2.3–4.2). The patient developed PPT after the birth of her first child approx 2 years previously. Approximately 5 months after her first delivery, she noted palpitations, nervousness, insomnia, and fatigue. Her thyroid was noted to be enlarged. Thyroid studies at that time revealed a TSH of less than 0.06 and total T_4 of 10 (4.5–12). Over the next several weeks, these symptoms cleared and she noted the onset of severe fatigue. Repeat studies showed a TSH of 98, FT_4 of 0.39, and radioactive iodine uptake (RAIU) of 2% (7–24). She was started on T_4 and the dose was adjusted over the next several months to normalize her TSH. She was maintained on 0.112 mg of T_4 daily until the present time. Family history was positive for thyroid disease in the patient's mother. Physical examination currently revealed an enlarged thyroid gland and was otherwise negative.

What Is Your Diagnosis?

Recurrent PPT with probable hyperthyroidism

Treatment

T_4 was discontinued. The patient was given a β-blocker as symptomatic therapy for her hyperthyroidism and asked to return with repeat studies off T_4 in 1 month.

Case Summary

This young woman developed PPT with her previous pregnancy and again after delivering twins. Because she had been maintained on T_4 after her first pregnancy, the thyroid tests were more difficult to evaluate. However, she was clinically hyperthyroid. The history of hyperthyroidism progressing to hypothyroidism with her previous pregnancy and a very low RAIU was compatible with PPT. It seemed likely that she had recurrent PPT with her second pregnancy, although an RAIU would be needed to rule out Graves' disease. The appropriate course was to discontinue her T_4, treat her hyperthyroidism symptomatically, and see her again in 1–2 months.

What Can We Learn From This Case?

- When PPT occurs after a pregnancy, it frequently recurs after subsequent pregnancies and the patient should be alerted to look for it.
- PPT can cause hyperthyroidism alone, hypothyroidism alone or, as in this case, progress from one to the other.
- The differential diagnosis is Graves' disease and the correct test to make the diagnosis is the RAIU. The RAIU will usually be elevated in Graves' disease and low in PPT.
- The hyperthyroidism of PPT may be treated symptomatically and followed because it tends to be self-limited, and the patient will usually either return to a euthyroid state or progress to hypothyroidism.
- PPT is an autoimmune disease and the TPO or microsomal antibody will often be positive.

CASE 5

A 27-year-old woman was referred to me because of abnormal thyroid function tests. She had delivered her third child about 8 months previously and there was no history of thyroid problems with her previous pregnancies. After her last delivery, she noted mood swings, fatigue, and heat intolerance along with a 15-lb weight gain. She was having regular menses. There was no family history of thyroid disease.

Physical examination revealed a pulse of 76 and BP of 114/72. No thyroid eye signs were noted. The thyroid gland was mildly enlarged. The remainder of the examination was normal.

The following laboratory studies were reviewed:

- The initial thyroid studies at 6 months postpartum showed a TSH of less than 0.005 and FT_4 of 1.7 (0.8–1.8).
- Repeat studies 1 mo prior to this visit revealed a TSH of 2.84, FT_4 of 0.8, and total T_3 was normal.
- RAIU was 2.4% at 24 hours (7–24).
- Thyroid ultrasound had been reported as normal.

What Is Your Diagnosis?

The diagnosis is PPT with borderline or subclinical hyperthyroidism that had resolved and might be progressing toward hypothyroidism in view of the recent borderline low-normal FT_4 with normal TSH.

Treatment

At the time of my evaluation, the patient was clinically euthyroid. She required no thyroid treatment but careful follow-up was required.

Case Summary

This 27-year-old woman had clinical and laboratory evidence of mild PPT disease. Her thyroid tests at 6 months postpartum were compatible with subclinical hyperthyroidism and the very low RAIU confirmed PPT as the etiology rather than Graves' disease. Her TSH then normalized and the FT_4 dropped to the lower edge of normal with low-normal total T_3. She will require careful follow-up to see if she progresses to hypothyroidism or becomes euthyroid. I discussed all of this at length with her and her husband and told them what to look for. They were reassured that the thyroid problem was mild and likely would resolve over time.

What Can We Learn From This Case?

- This case of PPT was much milder than those discussed previously and might have been overlooked if the patient had not developed several nonspecific complaints.

- The test results included a low TSH and upper-normal FT_4 initially, which were compatible with subclinical or borderline hyperthyroidism. The very low RAIU confirmed the diagnosis of PPT rather than Graves' disease.
- The follow-up tests showed a normal TSH and borderline low FT_4 suggesting that she might be edging toward hypothyroidism. The important point is that, when thyroid status is changing, the FT_4 will change faster than the TSH and may be a more valid reflection of current thyroid status. The TSH may take several weeks to equilibrate and reflect thyroid status. When thyroid status is relatively stable over time, the TSH is a more accurate guide to thyroid status.
- The patient will probably eventually become euthyroid, although the possibility of permanent hypothyroidism was discussed with her. She was also advised that thyroid disease may recur with future pregnancies.

SUMMARY

The cases discussed in this chapter demonstrate different clinical presentations of thyroid disease during pregnancy and in the postpartum period. Case 1 is a pregnant woman who was acutely ill. She presented with severe hyperemesis with dehydration and thyroid function tests compatible with hyperthyroidism. She required urgent treatment while the underlying cause of her hyperthyroidism was being determined. The difficulty in making the differential diagnosis between THHG and Graves' disease is discussed. The diagnosis of Graves' disease was eventually established and she was successfully treated.

The second patient presented with vague symptoms, an enlarged thyroid, and biochemical findings of subclinical hyperthyroidism. She was followed without treatment and subsequently developed clinical hypothyroidism that required treatment with T_4.

The third patient presented with overt hyperthyroidism several weeks after delivering twins. She had a history of PPT disease after her previous pregnancy. She was treated symptomatically and followed.

The last patient presented with nonspecific symptoms, an enlarged thyroid, and laboratory findings of subclinical hyperthyroidism. Her TSH normalized without treatment, but she requires follow-up. These cases demonstrate the importance of thinking about thyroid disease in pregnancy and the postpartum period, and checking thyroid tests in patients with nonspecific complaints.

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10
Thyroid Disease in Children and Adolescents

CASE 1

A 16-year-old high school student was referred because of neck enlargement, which she had discovered recently. She was evaluated by her mother's employer, a gynecologist. Thyroid studies showed a total thyroxine (T_4) of 16.1 (4.5–12) and thyroid-stimulating hormone (TSH) of less than 0.1. Her mother reported that the patient had been unusually warm and her speech had become more rapid. The rapid speech had also been noted by her teacher. She had felt shaky at times and was biting her nails. Her menses were regular. She had noted some hair loss. Her mother was being treated for Hashimoto's thyroiditis with hypothyroidism and several other family members had thyroid disease. She was on no medications.

Physical examination revealed a pulse of 84 and blood pressure (BP) of 90/60. Eye examination showed no proptosis or lid lag and the extraocular movements appeared normal. The thyroid gland was bilaterally enlarged to twice the normal size and nontender. Slight tremor of the outstretched upper extremities was present.

What Additional Tests Would You Order?

The following tests were obtained:

- Radioactive iodine uptake (RAIU): 6 hour, 1.5% (4–12); 24 hour, 0.4% (7–24).
- Thyroid microsomal antibody: 201 (<1).

What Is Your Diagnosis?

Silent (autoimmune) thyroiditis with hyperthyroidism and goiter.

Treatment

Propranolol to control the hyperthyroid symptoms.

Clinical Course

The patient was seen 1 month later with complaints of weight gain and constipation. Her mother said she was no longer hyper. Physical examination

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
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showed the thyroid to be slightly smaller, but otherwise unchanged. Her weight was up 4 lb. TSH was 14.1 (0.4–5), free thyroxine (FT_4) was 0.6 (0.8–1.8).

What Would You Conclude?

Clearly, the patient had switched from hyperthyroid to hypothyroid as evidenced by her symptoms and the elevated TSH and low FT_4. She was started on 0.088 mg of T_4 daily. One month later, she felt generally well and the thyroid had decreased further in size. Her TSH was 2.1, FT_4 was 1.1. She was maintained on T_4. She continued asymptomatic, although a small goiter persisted.

Final Diagnosis

Autoimmune thyroiditis with hypothyroidism.

Case Summary

This teenager presented with goiter and symptoms of hyperthyroidism. Laboratory studies confirmed the diagnosis of hyperthyroidism. The differential diagnosis was between Graves' disease and silent (autoimmune) thyroiditis with hyperthyroidism. The critical test was the RAIU, which was extremely low and diagnostic of silent thyroiditis. She had a markedly elevated thyroid microsomal antibody level and a strong family history of autoimmune thyroid disease. Her hyperthyroidism was treated symptomatically and she rapidly switched from hyperthyroid to hypothyroid. She was started on replacement T_4 and did well.

What Can We Learn From This Case?

- Although Graves' disease is the most common cause of hyperthyroidism, it is important to consider other possibilities, especially in the absence of eye findings of Graves' disease.
- The RAIU is the critical test in differential diagnosis. The RAIU is usually elevated or at least high normal in Graves' disease, and extremely low in silent thyroiditis.
- Hyperthyroidism secondary to silent thyroiditis may be transient and often needs only symptomatic treatment, usually a β-blocker.
- Silent thyroiditis may switch from hyperthyroidism to a euthyroid state or to hypothyroidism, as in this patient.
- The hypothyroidism should be treated if symptomatic, but the hypothyroidism may also be transient and remit spontaneously. In a young, healthy patient, T_4 may be started in an estimated full replacement dose and then adjusted based on TSH measurements.
- The TSH should not be measured more often than every 6 to 8 weeks because there may be a lag time for equilibration of TSH after starting T_4 or changing dosage.
- T_4 may be withdrawn for a trial after a few months to see if the patient has had a remission. If this is done, it is important to monitor TSH and restart T_4 if needed.

CASE 2

This 17-year-old boy was referred by a neurosurgeon. The story of how this came to pass is, I think, very instructive. I had referred a number of patients for pituitary surgery to this neurosurgeon over the years, and we were well acquainted. However, it was very unusual for me to get a referral from him. He called me one day to tell me that he thought I should see a young man who had been referred to him by a gynecologist in my town for pituitary surgery. It appears that the gynecologist had been taking care of the boy's mother. The mother mentioned to him at a routine gynecology visit that her son was not growing normally. The gynecologist ordered some tests on the boy without actually seeing him in the office. The prolactin level came back markedly elevated. A computed tomography (CT) scan of the pituitary was ordered. The CT report described marked enlargement of the entire pituitary gland. The radiologist diagnosed macroadenoma. The boy was then referred to the neurosurgeon for pituitary surgery. It should be noted at this point that the gynecologist had never seen or examined this patient.

The neurosurgeon told me over the phone that this patient appeared severely hypothyroid, and he felt that was the cause of his large pituitary gland on the CT scan. He said this patient needed an endocrinologist rather than a neurosurgeon. The boy came into my office a few days later accompanied by his mother. She described how her son had not been growing for several years and was the shortest boy in his class at school. His schoolwork had slipped and he was sleeping a lot. He always wanted the house warmer than other family members. Very little history was obtainable from the patient, who said he felt pretty well.

Physical examination revealed a short young man who appeared lethargic and answered questions with a hoarse voice and very slow speech. His face was puffy and his skin was very dry. His mentation was slow, but he did not seem aware of it. The thyroid gland was not palpable. Deep tendon reflexes showed a very slow relaxation phase, which is typical of "hung up" reflexes.

Laboratory Results

- TSH 320.
- T_4 less than 1, prolactin 503.

Diagnosis

The diagnosis was severe primary hypothyroidism or myxedema.

Treatment?

The patient was started on T_4. Because he was severely hypothyroid, I elected to start with a relatively low dose of 0.05 mg daily. The dose was slowly titrated upward over the next several months with monitoring of T_4 and TSH levels, as well as prolactin.

Clinical Course

The symptoms and signs of myxedema cleared slowly and the boy began to grow. His growth curve, which had been flat for several years, accelerated rapidly, compatible with "catch-up" growth. Laboratory studies showed early increase in T_4 with slower decline in TSH. The prolactin also decreased slowly. All of these studies eventually normalized. His height gradually increased to the normal height one would have predicted from parental height. About 1 yr after treatment was initiated, he was in an auto accident and a CT head scan was done. The pituitary gland was now normal on scan. The patient then moved to another state and I lost track of him. One day several years later he called me long distance in the office to tell me he was doing well and to thank me for helping him.

Case Summary

This young man presented to me in an unusual fashion but with typical findings of childhood hypothyroidism. His mother complained to her doctor that her son was not growing. The hypothyroidism had probably been present for at least several years and he had developed other findings of severe hypothyroidism or myxedema. The elevated prolactin and pituitary enlargement on scan were caused by pituitary hyperplasia secondary to severe primary hypothyroidism. The patient responded well to thyroid replacement therapy.

What Can We Learn From This Case?

- Always examine the patient! This patient's hypothyroidism could have been diagnosed from across the room, but the gynecologist never saw him. Fortunately, the hypothyroidism was diagnosed by an astute neurosurgeon and a tragedy (pituitary surgery) avoided.
- Elevated prolactin caused by pituitary hyperplasia may be seen in hypothyroidism. It usually returns to normal after treatment of the hypothyroidism.
- Pituitary enlargement in severe or longstanding hypothyroidism was described in the older literature based on skull films. It is due to pituitary hyperplasia related to marked increase in TSH production seen in myxedema. As we saw in this case, it usually returns to normal after treatment of the hypothyroidism.
- Think of hypothyroidism in a child who is not growing and order a TSH. Your patient and his family will be very grateful. Earlier diagnosis would have avoided a lot of problems for this family.

CASE 3

A 13-year-old junior high school student was referred for thyroid evaluation. Both the mother and patient had noted that the patient was more irritable over the preceding 8 or 9 months. The patient had also noted intermittent vertigo. On questioning, she admitted to mild heat intolerance over the past year and mini-

mal muscle weakness. Her appetite and food intake were markedly increased but her weight remained about the same. She denied tremor, palpitations, or increased sweating. Her menses had not yet started. Past history was generally negative, but family history was positive for thyroid disease in a maternal aunt who underwent thyroidectomy. She had several relatives with diabetes.

Physical examination revealed a mildly hyperactive child with rapid speech. Pulse was 126 and BP was 130/80. There were no thyroid eye signs. The thyroid was diffusely enlarged to about twice its normal size. Examination was otherwise normal.

Laboratory Results

The following laboratory tests were obtained:

- Total T_4, 18.5 (4–12), TSH less than 1 (prior to availability of sensitive TSH).
- RAIU: 6 hour, 27% (4–12); 24 hour, 36% (7–24).

What Is Your Diagnosis?

The diagnosis is Graves' disease.

How Would You Treat This Patient?

After discussion of the treatment options, including antithyroid drugs (ATDs), radioactive iodine (RAI), and surgery, we agreed on ATD therapy. She was started on 150 mg of propylthiouracil (PTU) every 8 hours.

Clinical Course

Over the next 2 months, the pulse gradually slowed and the patient noted decreased irritability and heat intolerance. The T_4 dropped to normal at 6.1. She gained 12 lb. The PTU dosage was gradually tapered. Her thyroid gland decreased in size. Several months later, the thyroid was noted to be larger and the TSH was elevated. She had iatrogenic hypothyroidism secondary to the PTU. Her PTU dosage was tapered further to 50 mg every 12 hours. Two years after diagnosis, she was clinically euthyroid on 50 mg of PTU daily, and the drug was discontinued as a trial.

Two months later, she was referred back because of recurrent symptoms of hyperthyroidism, including irritability and heat intolerance. Her pulse was 160 and the thyroid gland was larger. Her total T_4 was 27 (4.5–12). I again discussed options for treatment with the patient and her mother and we decided to restart PTU at 150 mg every 8 hours. A β-blocker was also prescribed for the tachycardia. Two months later, she was feeling better, although her pulse was still rapid at 120. T_4 was normal at 8.1. Her white blood count was 3000 with a normal differential. Two months later, her total T_4 was up to 17.5, although she was feeling well. The patient said she was taking her medication regularly. Her PTU dose was increased to 200 mg every 8 hours. Two months later she had gained 3 lb,

and her thyroid was smaller, pulse was 72, and T_4 was 13. PTU dose was tapered to 150 mg every 8 h, and this was maintained over the next several months.

Three years after the initiation of PTU therapy, the patient developed joint aches and her white blood count was down to 2200. She was thought to be having side effects from the PTU. She was switched to 10 mg of methimazole every 8 hours. Her joint aches cleared rapidly and her white blood count rose to 4800 with a normal differential. Several months later, she noted fatigue and her TSH had elevated to 25.3. The thyroid gland was larger. The methimazole dose was decreased gradually to 10 mg daily.

Four years after initiation of therapy, the patient was euthyroid and methimazole was further decreased to 5 mg daily. Several months later, her T_4 was again elevated to 15, although she felt well. Methimazole dose was increased to 5 mg twice daily and a triiodothyronine (T_3) was ordered. T_3 and T_4 were markedly elevated and methimazole dosage was increased to 10 mg twice a day. Three weeks later, her T_4 was 21 and her total T_3 was 371 (80–220). Methimazole was increased to 10 mg every 8 hours. Her T_4 remained elevated and the methimazole was increase to a total of 45 mg/day.

Five years after initial diagnosis, the patient had reached the age of 18 and was still mildly hyperthyroid on high-dose methimazole. RAI therapy was discussed with her and her mother, and they agreed to the treatment. At 1 mo post-RAI treatment, the patient said she felt better than she had in a long time. All her hyperthyroid symptoms were gone. Four months posttreatment, the patient developed cold intolerance and muscle cramps. Her thyroid was no longer enlarged. Her TSH was 146, T_4 3.9. She was started on T_4 and the dose titrated to normalize TSH. Two months later, she felt well and TSH was normal. She was continued on T_4 and placed on yearly recheck. I emphasized to her that she should never stop her thyroid medicine. She continued to do well over the next several years with yearly reevaluation and slight adjustment of T_4 dose based on TSH testing.

Case Summary

This patient presented with Graves' disease in 1979 at age 13 years. She had clinical findings of hyperthyroidism and goiter. After discussion of treatment options with the patient and her mother, the plan was to treat her with an ATD until age 18 years. We would then consider RAI therapy if she were still hyperthyroid when medication was withdrawn. The case demonstrates many of the problems of long-term drug therapy, including recurrent hyperthyroidism, hypothyroidism secondary to treatment, and side effects of the medication. Compliance is also an issue. At age 18 years she was still hyperthyroid when the methimazole was withdrawn. Her hyperthyroidism had been controlled for the most part over the preceding 5 years but was clearly not cured. She was

given one dose of RAI to cure her hyperthyroidism. She developed the expected hypothyroidism after treatment and was easily controlled on T_4. She continued to do well and only required yearly follow-up.

What Can We Learn From This Case?

- Graves' disease in children and adolescents is often resistant to treatment and may require a large dose of an ATD.
- Long-term remission or cure on ATDs is uncommon in this age group.
- Side effects of medication, such as leukopenia and arthritic complaints, are not unusual and more severe side effects, such as agranulocytosis and liver disease, occur occasionally. Fortunately, the more severe side effects did not occur in this case.
- ATD treatment in children and adolescents requires frequent office visits and laboratory tests to control the hyperthyroidism and to avoid hypothyroidism from treatment.
- Compliance with the ATD regimen may be especially difficult in this age group.
- RAI treatment resulted in cure and the expected hypothyroidism was easily controlled. The frequency of office visits and testing was markedly decreased.
- The advent of sensitive TSH and FT_4 testing has helped in caring for Graves' disease patients. These tests and free triiodothyronine (FT_3) would have been helpful in this patient, but were not easily available at the time.

Comment

I elected to include this rather long case summary to demonstrate the difficulties in treating Graves' disease in children and adolescents with ATDs. Twenty-five years ago, most thyroidologists recommended avoiding RAI treatment in patients under age 18 years. Since that time, RAI has been used more commonly in children with good results. In contrast to this case, I treated a 9-year-old with RAI as primary therapy. He was cured with one treatment and then maintained on thyroid replacement with only yearly follow-up. He did well over a number of years, although his TSH would occasionally rise when he missed some T_4 pills. However, he was able to go on with his life with minimal medical care and markedly decreased medical costs. Although treatment must be a joint decision with the family, I think RAI is the best treatment for many children with Graves' disease. The current recommendation is to avoid RAI treatment in very young children.

SUMMARY

The cases included in this chapter demonstrate some of the special considerations in diagnosis and treatment of thyroid disease in childhood and adolescence. Case 1 was a teenager who presented with symptoms of hyperthyroidism and a goiter. Her teacher noted that her speech was rapid and she

had trouble concentrating. Workup confirmed hyperthyroidism secondary to autoimmune thyroiditis. She progressed to hypothyroidism and required treatment with T_4.

Case 2 was a teenage boy who was not growing. This case emphasizes the importance of history and physical in making a correct diagnosis. The wrong diagnosis was initially made on the basis of laboratory and imaging findings because the patient was never seen in the office and examined. Hypothyroidism should always be considered when a child or teenager presents with growth retardation. The result of treatment with thyroid hormone was very rewarding.

Case 3 was a 13-year-old who developed severe hyperthyroidism secondary to Graves' disease. The challenges of treating a teenager with Graves' disease are well-demonstrated. Problems with medication side effects, patient compliance and frequent office visits and laboratory tests over a number of years are outlined.

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11
Thyroid Nodules and Cancer

INTRODUCTION

This chapter discusses several cases that illustrate common presentations of thyroid nodules in the office and the current approach to diagnosis and treatment. Thyroid nodules are common and usually asymptomatic. They are often discovered when patients present to the primary care physician with unrelated complaints, such as sore throat, or for a routine checkup. Because most thyroid nodules occur in women, they are frequently found by the gynecologist on a routine annual examination.

Discovery of a thyroid nodule by the patient or physician usually results in a lot of anxiety for the patient. The first question that comes to mind is: "Doctor, is it cancer?" Often, this thought is not expressed but there is no doubt it is on the patient's mind. The physician's job is to start a workup to answer this question as quickly as possible. Also, the physician must reassure the patient that the odds are strongly against cancer because only about 5% of thyroid nodules are cancerous, and most thyroid cancers are curable. The cases discussed here should prove helpful. Table 1 describes some risk factors for cancer.

CASE 1

A 31-year-old woman was referred by her internist because of a lump in the left thyroid area. The lump had been noted a year earlier and was enlarging. She was quite anxious, but otherwise feeling well. She denied any history of radiation to the neck. On questioning, she had no symptoms of hyperthyroidism or hypothyroidism.

Positive findings on physical examination were limited to the neck. A 3-cm hard, nontender nodule was palpable in the left lobe. There were no palpable cervical lymph nodes. No signs of hyperthyroidism or hypothyroidism were noted.

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
By: E. O. Brams © Humana Press Inc., Totowa, NJ

Table 1
Thyroid-Nodule Risk Factors Associated With Malignancy

History
Age <20 or >60 years
History of irradiation to the neck or face
Male sex
Family history of medullary thyroid cancer
Growth of nodule during observation
Hoarseness
Physical examination findings
Firm-to-hard, nontender nodule
Regional lymphadenopathy
Fixation to adjacent tissue
Vocal cord paralysis

From Singer PA. Evaluation and management of the euthyroid nodular and diffuse goiter. In: Braverman LE, ed. Diseases of the Thyroid, 2nd ed. Humana Press, Totowa, NJ, 2003, p. 217.

Laboratory Results

The following test results were obtained from the referring physician:

- Thyroid-stimulating hormone (TSH): 3.4 (0.4–5).
- Nuclear thyroid scan revealed a nonfunctioning or "cold" nodule in the left lobe.

What Is Your Differential Diagnosis?

Thyroid cancer was the patient's concern and my major concern as well. However, benign problems, such as thyroiditis and benign thyroid nodule, were far more likely. The major question to be answered was whether this nodule was cancerous (surgical) or benign (probably nonsurgical).

What Would You Do to Help Make the Diagnosis?

A fine-needle aspiration biopsy (FNAB) was performed in the office. The cytopathologist reported that this was a benign thyroid nodule (BTN). The FNAB report was discussed with the patient in the office and she was reassured that the nodule was benign and could be treated without surgery. All of her questions were answered and treatment was discussed. The importance of follow-up was also emphasized because there is a small possibility, approx 2–5%, that the biopsy might miss a cancer.

Clinical Course

The patient was started on thyroxine (T_4) to suppress TSH and she was rechecked in 3 months. The nodule had decreased in size and the TSH was low.

She was seen at 6 months and then annually and continued on T_4. The nodule decreased 50% in size and remained stable over the next 10 years. Her TSH was maintained below the lower edge of normal but not completely suppressed.

Case Summary

This young woman presented with a solitary thyroid nodule that was discovered on a routine examination by her internist. She was clinically euthyroid as confirmed by a normal TSH. FNAB established a benign diagnosis. She was maintained on T_4 and the nodule remained stable over a period of 10 years.

What Can We Learn From This Case?

- Thyroid nodules are common. In most studies they occur in at least 5% of the US population.
- Thyroid nodules are about seven times more common in women than in men.
- At least 90% of nodules are benign.
- FNAB is the first-line test in evaluating thyroid nodules. It is the most accurate and cost-effective approach to answering the main clinical question: is the nodule cancerous or is it benign? If it is cancerous, the patient clearly needs surgery. If it is benign, the patient can usually be treated without surgery. Figure 1 shows FNA findings in several types of thyroid lesions.
- Nuclear scans and ultrasound are expensive tests that are not needed in most cases. A nuclear scan had already been done when I saw this patient. My initial test would have been an FNAB.
- Suppressive therapy with T_4 has recently become controversial. Some studies show lack of effectiveness in shrinking nodules. There is also concern that long-term T_4 therapy to suppress TSH may contribute to osteoporosis and cardiac problems. However, many thyroid physicians feel it is effective in selected cases and continue to use it. The consensus at this point is that if you use T_4, the TSH should be maintained in the low but measurable range, and not completely suppressed.
- Always follow the patient. FNAB can miss cancer in a small percentage of patients. If the nodule enlarges, it should be re-evaluated.

Comment

Case 1 illustrates some of the things to look for when a patient presents with a thyroid nodule. It is important to know when the nodule was first discovered and whether it has changed in size. Although most nodules are painless, some are painful or tender, suggesting thyroiditis. Any history of radiation to the neck is important. Radiation was used to treat enlarged tonsils, thymus, and other benign problems until approx 25 years ago. Patients treated with radiation have a higher risk of thyroid cancer in a nodule and also a higher incidence of BTNs. These problems may appear decades after the radiation treatment. Look for symptoms of hyperthyroidism, such as heat intolerance, palpitations, and eye complaints, and symptoms of hypothyroidism, such as cold intolerance, fatigue,

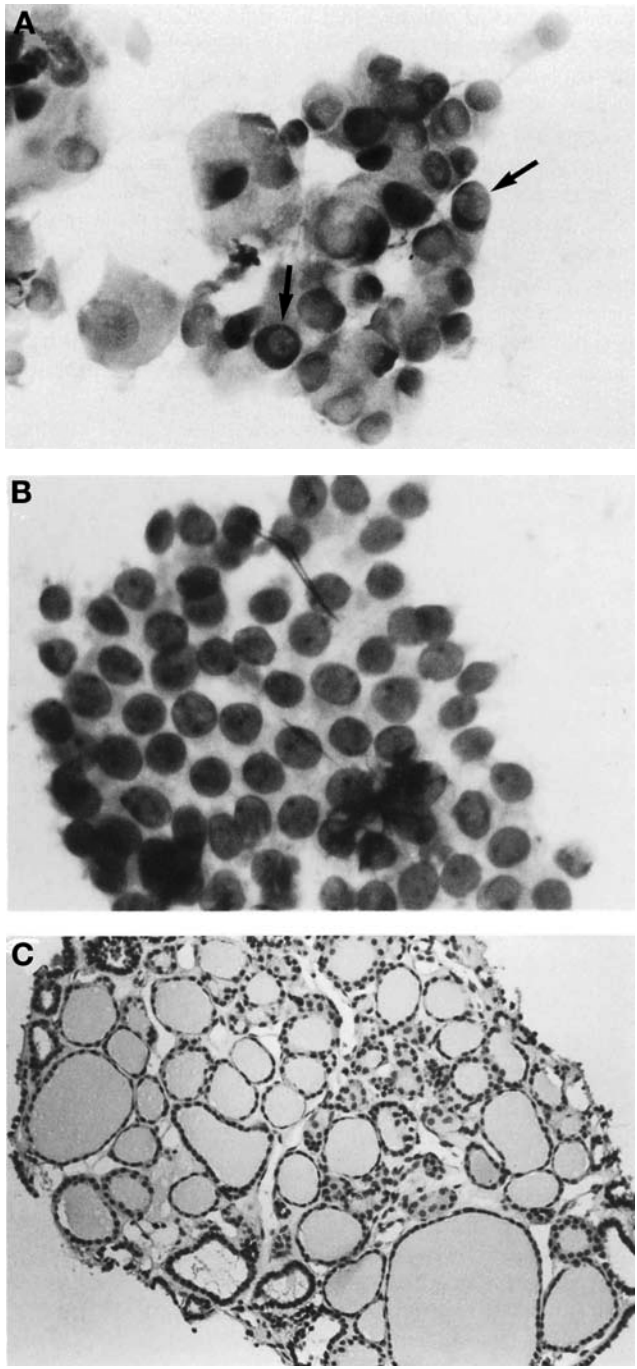

Fig. 1. Cytological findings in various thyroid lesions. **(A)** Papillary cancer. Characteristics are intranuclear inclusions (arrows). **(B)** Follicular lesions. Note the group of follicular cells that are cytologically bland and relatively uniform. **(C)** Colloid nodule. Shown are colloid-filled follicles of varying sizes. *(Figure continues)*

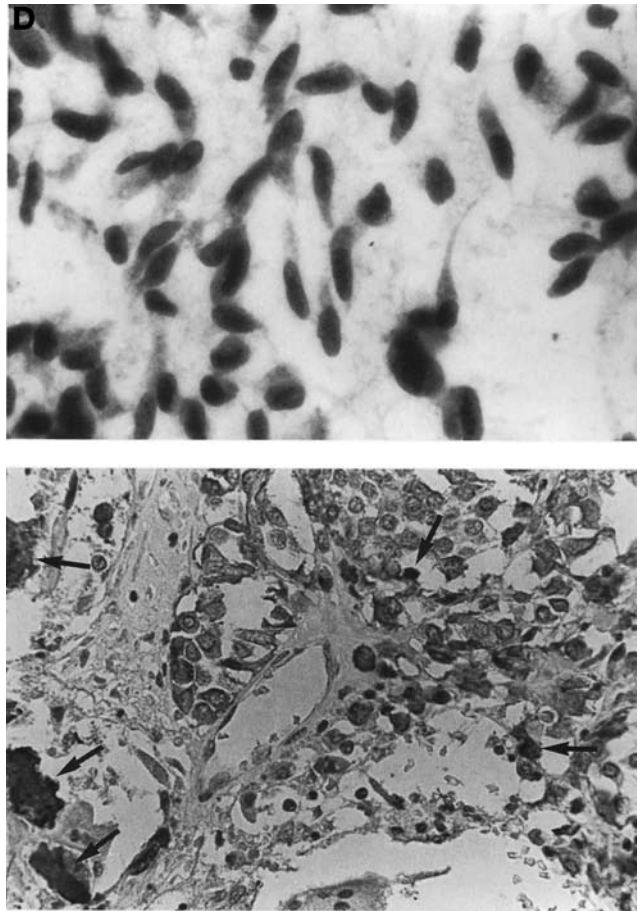

Fig. 1. (*continued)* **(D)** Medullary thyroid cancer. Spindle-type cells with eccentric nuclei are typical, but not diagnostic (top panel). The calcitonin stains (representative areas are marked with arrows) on the bottom panel of the aspirate confirm the diagnosis. All slides shown are Papanicolaou preparations, except for the calcitonin stain in D. (From Singer PA. Evaluation and management of the euthyroid nodular and diffuse goiter. In: Braverman LE, ed. Diseases of the Thyroid, 2nd ed. Humana Press, Totowa, NJ, 2003, pp. 224–225.)

and dry skin. Also, check a TSH. Most of these patients will be euthyroid, but some will have Hashimoto's thyroiditis with hypothyroidism or a "hot nodule" with hyperthyroidism.

On physical examination, a careful neck examination is most important. Most nodules larger than 1 cm in size can be felt on careful palpation of the thyroid area. I usually have the patient swallow water so I can feel the thyroid

move. The thyroid is attached to the larynx and the nodule will usually move with swallowing. The nodule can usually be characterized as to texture, tenderness, mobility, and size. Always look for cervical lymph nodes. On the general physical examination, look for findings of hyperthyroidism, such as bulging eyes in Graves' disease, tachycardia, tremor, and muscle weakness. Look for findings of hypothyroidism, such as dry skin, puffiness of the face, and slow ("hung up") reflexes. The next step will be FNAB in most cases.

CASE 2

A 31-yr-old man was referred by his family doctor for evaluation of a thyroid nodule found on routine examination for a respiratory infection. He had no symptoms of hyperthyroidism or hypothyroidism. He denied any history of radiation to the neck in childhood. He was feeling fine except for some anxiety about the nodule. The studies that he brought in included a normal TSH and a nuclear thyroid scan showing a "cold nodule" in the right lower pole. There was a family history of benign thyroid disease in his mother.

Physical examination revealed a 3-cm nodule in the right thyroid lobe that was firm and nontender. There were no palpable cervical lymph nodes. The remainder of the examination was negative.

What Is Your Differential Diagnosis?

Differential diagnosis includes benign thyroid disease, such as thyroiditis, BTN or cyst, and thyroid cancer. The next step should be FNAB.

FNAB was performed in the office. The patient was anxious about the procedure but commented afterward that it had been painless. The cytopathologist reported papillary thyroid carcinoma.

What Would You Do Next?

Bring the patient into the office for a complete discussion of the diagnosis and approach to treatment. Reassure the anxious patient that the outlook is good, with cure in more than 90% of patients.

Clinical Course

The patient was referred to a thyroid surgeon for a total thyroidectomy. This is the procedure of choice when the FNAB reveals cancer. The pathology report confirmed the FNAB diagnosis of papillary thyroid cancer. The cancer was found only in the nodule. There was no evidence of cancer in lymph nodes, muscle, blood vessels, or other surrounding tissue. The patient was in the hospital for 3 days and recovered rapidly at home. He was placed on thyroid medication with triiodothyronine (T_3; Cytomel), a short-acting thyroid hormone, and he returned to work.

He was seen in the office 1 mo after surgery. At that point, the Cytomel was discontinued in preparation for a whole-body nuclear scan with radioactive iodine (RAI; iodine 131 [I-131]). Two weeks later, he was given I-131 by mouth and a scan was done 72 hours after administration of the tracer. The scan was negative except for minimal accumulation of the RAI in the thyroid bed, a common finding after thyroidectomy. The patient was reassured and placed on T_4 for long-term hormone replacement. A relatively high dose was used to not only replace the missing hormone (post-thyroidectomy), but also to suppress TSH to a very low level. TSH suppression appears to be helpful in preventing stimulation of growth of any remaining cancer cells.

The patient did not return for his 3-month appointment as advised. He was called by our office and rescheduled several times but did not keep his appointments. Because follow-up is critical both to adjust T_4 dosage and to perform appropriate testing, his family doctor was notified and the patient finally returned. His TSH was not suppressed, although the patient assured me that he was taking the medication. The dose of T_4 was increased. On his return to the office 3 months later, he was feeling well and his TSH was suppressed to less than 0.05. He had no hyperthyroid symptoms on high-dose T_4.

A repeat I-131 scan was performed at 18 months post-throidectomy, and several areas of uptake of tracer were noted in the neck. A serum thyroglobulin (TG), a marker for thyroid cancer, was drawn and was appropriately low or negative. In view of the new neck uptake suggesting residual thyroid tissue or cancer, he was given I-131 treatment. His thyroid medication had to be discontinued for the scan and treatment and the patient became symptomatically hypothyroid. He complained bitterly about his fatigue, cold intolerance, and muscle cramping. After the treatment, he was restarted on T_4 and his hypothyroid symptoms gradually cleared. A repeat I-131 scan 1 year posttreatment was negative and the serum TG remained very low. He continued to feel well.

The patient was seen annually for neck examination and measurement of TSH and thyroglobulin. The neck examination showed no evidence of thyroid nodules or lymph nodes and the TG remained low. The TSH remained suppressed for the most part but would occasionally increase when he started missing some T_4 pills. A repeat scan 4 years later was negative. He is now 10 years post-thyroidectomy and doing well.

Case Summary

This young man was discovered to have a thyroid nodule on routine examination by his doctor for a sore throat. The diagnosis of thyroid cancer was made on FNAB. Treatment included thyroidectomy, RAI therapy, and TSH suppression with T_4. He has done well for 10 years. He will continue on T_4 with yearly follow-up to include neck examination, TSH, and serum TG. TG, a

thyroid protein, should remain very low after thyroidectomy and RAI ablation of residual thyroid. An increase in this tumor marker would suggest recurrent neoplasm. Recurrence can occur many years after initial treatment.

What Can We Learn From This Case?

- Thyroid nodules are much less common in men than in women. When one sees a nodule in a man there is a higher risk of cancer.
- FNAB is well established as the most accurate and cost-effective approach to diagnosis of thyroid nodules.
- When the diagnosis of cancer is made, it is important to reassure the patient that thyroid cancer has a far better prognosis than colon or breast cancer, with a cure rate well over 90%.
- The approach to treatment will vary with the patient and may include surgery, RAI, and TSH suppression with T_4.
- Long-term follow-up is essential because recurrences may occur years after treatment.

CASE 3

A 73-year-old woman was referred for evaluation of a thyroid nodule. Her family doctor had noted a small left lobe nodule 6 years previously. Several months prior to this visit, she was referred to another endocrinologist because the nodule was larger. FNAB failed to yield enough tissue for diagnosis on two occasions. The nodule continued to enlarge, and she was referred to me for another attempt at FNAB diagnosis. The patient was generally well and denied any history of radiation to the neck area. She had no neck complaints and wondered why she was in my office. She had been on T_4 intermittently over the previous several years as treatment for the nodule. Her TSH on 0.05 mg, of T_4 daily was 2.8. Thyroid peroxidase and TG antibodies were negative.

On physical examination, the thyroid gland was bilaterally enlarged, hard, and irregular. The nodular left lobe measured 3×4 cm and the right lobe measured 2×3.5 cm. There were no palpable cervical nodes. The patient appeared clinically euthyroid.

What Next?

I proceeded with FNA. A good specimen was obtained. The cytopathologist, an expert at FNAB, diagnosed anaplastic thyroid carcinoma. Tumor was also seen in muscle.

Clinical Course

The diagnosis and prognosis were discussed with the patient. She was referred to an oncologist. She requested referral to a university hospital and was seen by an endocrine surgeon.

Magnetic resonance imaging scan revealed tracheal deviation without invasion or compression of the trachea. There was compression of the esophagus and displacement of the carotid artery. The patient was treated with radiation and chemotherapy followed by surgery. She developed pulmonary metastases. Despite further radiation and chemotherapy, she had a progressive downhill course and died 5 months after the diagnosis was made.

Case Summary

This patient was referred because of an enlarging thyroid nodule. FNA on two occasions had failed to yield enough tissue for a diagnosis. The patient's doctor was concerned about the nodule and the third biopsy was diagnostic. Unfortunately for the patient, she had an uncommon but very malignant form of thyroid cancer and died in a few months, despite therapy.

This patient's course is typical. Anaplastic thyroid carcinoma is a rapidly progressive cancer that is usually resistant to all types of therapy and fatal in less than 1 year in most cases.

What Can We Learn From This Case?

- Follow-up of thyroid nodules is very important.
- An enlarging nodule is always cause for concern and should be evaluated, usually by FNAB.
- Repeat FNAB may yield a diagnosis when the first attempt fails.
- If a diagnosis by FNAB cannot be obtained, surgical biopsy may be needed.
- Anaplastic thyroid cancer accounts for less than 5% of thyroid cancers, but it is a very lethal disease.

CASE 4

A 47-year-old woman was referred by her dermatologist because of hypercalcemia. She was undergoing treatment for severe psoriasis. Treatment with methotrexate required monitoring of her chemistry panel. Her serum calcium varied between high normal and a high of 11.2. The patient denied history of kidney stones, fractures, or other symptoms of hyperparathyroidism except for low energy. She had a history of thyroidectomy at age 12 years for a nodule and had been maintained on T_4. She admitted to intermittent palpitations and heat intolerance that had decreased since her T_4 dosage was lowered. She also had a history of radiation treatment to the neck at age 12 years for keloids after her thyroidectomy. Family history revealed a daughter who underwent thyroidectomy for Graves' disease.

Physical examination revealed a pulse of 72 and blood pressure (BP) of 160/88. There were no thyroid eye signs. Thyroid examination revealed an irregular nodular area in the left lobe measuring approx 2×3 cm in size. There were no palpable lymph nodes. A well-healed thyroidectomy scar was present. The remainder of the examination was negative except for severe psoriasis.

What Is Your Diagnosis? How Would You Proceed With This Complicated Patient?

This patient probably has two separate endocrine problems. She was referred for hypercalcemia and may have primary hyperparathyroidism. She also has a nodular thyroid with a history of neck radiation at age 12 years.

Workup

A parathyroid hormone (PTH) level with serum calcium and phosphorus, and a 24-hour urine test for calcium and creatinine clearance were ordered to evaluate the hypercalcemia.

FNAB of the nodular thyroid was performed in the office. A thyroid ultrasound was ordered to look for additional nodules in view of the radiation history. Recent thyroid function tests on T_4 had been normal.

Results

- Intact PTH, 62 (10–65); serum calcium, 10.6 (8.8–10.1); phosphorus, 2 (2.5–4.6).
- 24-hour urine calcium: 215 mg.
- Creatinine clearance: 167 mL/min; serum creatinine, 0.7.
- FNAB: BTN (good specimen).
- Thyroid ultrasound: right lobe absent. Left lobe showed irregular echo pattern without focal nodules. It was felt to be suspicious for neoplasm in a patient with radiation history.

What Are Your Diagnoses?

- Primary hyperparathyroidism.
- BTN.
- History of radiation to the neck.

What Next? Would You Send This Woman to the Surgeon?

The results of workup and options for treatment were discussed at length with the patient. She had two separate problems, which were both related to her radiation treatment at age 12 years. She had primary hyperparathyroidism, that was probably secondary to a radiation-induced parathyroid adenoma. Although the PTH level was only high-normal, it was inappropriately high for the elevated calcium level. She also had a nodular thyroid that was benign on biopsy with a history of neck radiation at a young age.

The options for treatment of both problems were surgery or careful medical follow-up. Because the hypercalcemia was mild and she was asymptomatic, a case could be made for the medical approach to treatment of her hyperparathyroidism, especially if her bone density was normal. Because of the radiation history, she was at a higher risk for thyroid cancer. Although the biopsy was benign, the ultrasound showed diffuse abnormality rather than a discrete nodule. Because surgery would probably cure her hyperparathyroidism and allow fur-

ther evaluation and treatment of the nodular thyroid, the patient and I agreed that it was a reasonable approach. The patient underwent surgery with removal of a parathyroid adenoma and resection of the nodular left thyroid. Pathology report described a parathyroid adenoma and benign adenomatous multinodular goiter.

Follow-Up

The patient was maintained on T_4 and asked to return for annual check up. The annual evaluation should include TSH and neck examination. An ultrasound should be performed every few years.

What Can We Learn From This Case?

- External neck radiation at a young age increases the risk of benign and malignant thyroid nodules. The younger the age and the higher the radiation dose, the greater the risk.
- There is no evidence that RAI for diagnosis or treatment increases the risk of thyroid cancer.
- Parathyroid adenomas are also associated with neck radiation as in this case. Therefore, serum calcium should be measured in these patients.
- Asymptomatic patients with a history of neck irradiation should be followed at least annually with neck examination. If they are at high risk, ultrasound should be considered intermittently.
- Patients with thyroid nodules that are benign on FNAB and not treated surgically should be evaluated at least annually with neck examination and ultrasound intermittently as indicated.

SUMMARY

In this chapter, I discussed four patients who presented with thyroid nodules. The first patient is typical of the young women who present to their family doctors or gynecologists for a check-up or a sore throat and are found to have a nodule in the thyroid. Most of these nodules are benign, as was the case in this patient, and FNAB is the appropriate test to make the diagnosis. This patient's nodule remained stable over many years of follow-up.

The second case was a young man who presented to his family physician with a sore throat and was found to have a thyroid nodule. FNAB was again the test that made the diagnosis, but this nodule was cancerous. An approach to management and follow-up of thyroid cancer is reviewed. This patient required thyroidectomy, RAI treatment, and TSH suppression with T_4. He also did well on long-term follow-up.

The third patient was an older woman who was also found to have a thyroid nodule by her family doctor. FNAB on repeat also made the correct diagnosis, but this woman had an uncommon and much more aggressive form of thyroid cancer, anaplastic thyroid carcinoma. Her progressive downhill course, despite surgery, radiation, and chemotherapy, is typical of this type of thyroid cancer.

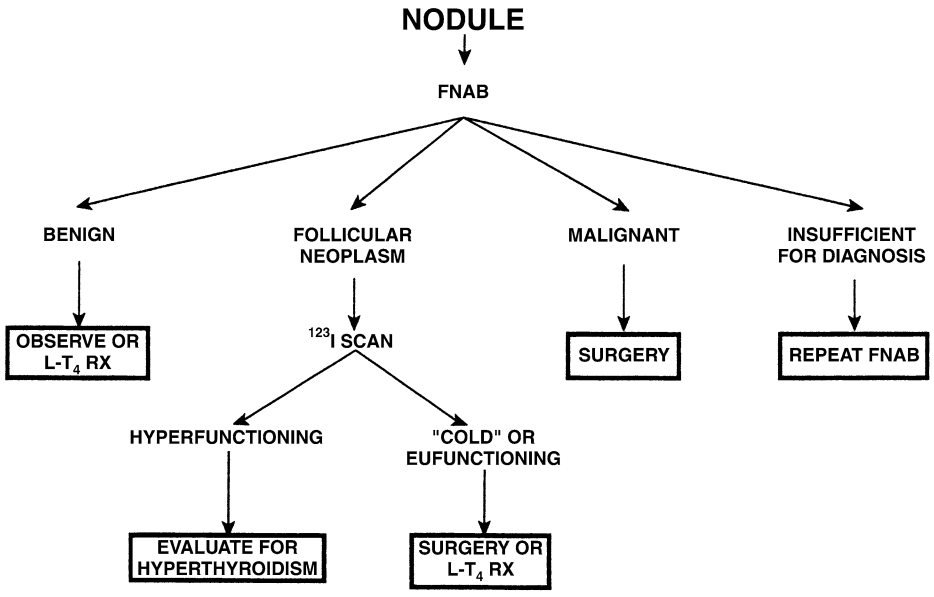

Fig. 2. Suggested algorithm for management of the solitary thyroid nodule. FNAB, fine-needle aspiration biopsy. (Reproduced with permission from Singer PA. Evaluation and management of the solitary thyroid. In: Braverman LE, ed. Diseases of the Thyroid, 2nd ed. Humana Press, Totowa, NJ, 2003, pp. 577–591.)

The fourth patient demonstrates some of the effects of neck irradiation that can occur decades after the radiation treatment. Most of these patients were treated with radiation in the 1950s and 1960s for benign diseases, such as enlarged thymus or adenoids, keloid, and facial acne. After the long-term effects of childhood radiation on the thyroid, parathyroids, salivary glands, and nervous system were discovered, radiation treatment for benign disease in this area was discontinued. This patient presented with a nodular thyroid that was, fortunately, benign, and a parathyroid adenoma with hyperparathyroidism. Surgical treatment was successful in curing the problems, but long-term follow-up is essential.

In summary, thyroid nodules are usually asymptomatic and most often found by a physician on examination for another complaint. FNA is the first step in diagnosis and will usually answer the question on the mind of both physician and patient: is this nodule benign or malignant? If the nodule is cancerous, surgery is clearly indicated. However, the majority of thyroid nodules are benign and can often be followed medically.

Figure 2 offers a general approach to evaluation of a thyroid nodule starting with FNAB.

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12
Management of Thyroid Cancer Patients

INTRODUCTION

Chapter 11 covered the evaluation and treatment of thyroid nodules and included thyroid cancer cases. This chapter presents and discusses more difficult cases of thyroid cancer that require additional testing, imaging, and treatment. Although the majority of patients with papillary and follicular thyroid cancer do well after treatment and are considered long-term "cures," some patients continue to show evidence of residual cancer and present a challenge to the physician in terms of further evaluation and treatment. Medullary thyroid cancer also usually presents as a thyroid nodule and may be diagnosed on fine-needle aspiration biopsy (FNAB), but presents a different set of diagnostic and therapeutic challenges.

CASE 1

A 44-year-old executive was referred by his family doctor because of a thyroid nodule. The nodule had been discovered by his wife approx 3 weeks previously and was painless. The patient had no dysphagia or other local compression complaints. The patient felt generally well and had no symptoms of hyperthyroidism or hypothyroidism. There was no history of radiation treatment to the neck. There was a family history of thyroid disease in his mother.

Physical examination revealed a pleasant middle-aged man in no distress with a pulse of 64 and blood pressure (BP) of 130/62. Examination of the neck revealed a hard nodule in the right lobe of the thyroid gland that measured approx 2 cm in diameter. The left lobe was felt to be borderline enlarged, and a few small submandibular nodes were present. The remainder of the physical examination was negative.

What Is Your Differential Diagnosis?

The differential diagnosis includes thyroid cancer, benign thyroid nodule (BTN), and thyroiditis.

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
By: E. O. Brams © Humana Press Inc., Totowa, NJ

What Tests Would You Order?

I ordered a thyroid-stimulating hormone (TSH), free thyroxine T_4 (FT_4), and thyroid peroxidase (TPO) antibody. FNAB was performed in the office.

Results of Testing

The FNAB revealed papillary thyroid carcinoma. TSH, FT_4, and TPO antibody were normal.

What Next?

The biopsy results were discussed with the patient. He was reassured that this type of cancer had a cure rate of well over 90%. He was referred to an experienced thyroid surgeon for total thyroidectomy. A 2-cm papillary cancer in the right lobe was confirmed. Some satellite nodules were also noted on microscopic examination of the right lobe and a small focus of cancer was noted in the left lobe. Some tumor was noted outside the capsule in the region of the isthmus.

Clinical Course

The whole-body radioactive iodine (RAI) scan showed uptake only in the thyroid bed. The patient was treated with an outpatient dose of RAI (30 mCi) to ablate the remaining neck uptake and placed on T_4 in a dose adequate to suppress TSH. Serum thyroglobulin (TG) with the patient off thyroid for the scan was elevated to 273. A desirable range for TG in a patient post-thyroidectomy is less than 2. A scan done 1 week after administration of the therapy dose of iodine 131 (I-131) showed uptake only in the thyroid bed. TG level 3 months later and with the patient on T_4 was 5.6 with a TSH of 0.04.

A follow-up I-131 scan was done 6 mo posttreatment with the patient off T_4. The scan showed a tiny area of minimal uptake in the thyroid bed with a measured neck uptake of 0.6%. TG drawn off T_4 for the scan was 198 with a TSH elevated to 114. Chest x-ray, sestamibi scan, and magnetic resonance imaging (MRI) of the neck and upper chest were all negative. The patient was referred to the university for consultation in view of the discrepancy between the negative imaging findings and the elevated TG. Repeat TG with the patient back on T_4 was 2 with a TSH of 0.047 and a slightly elevated FT_4 of 2.2. The thyroid dosage was decrease slightly because the patient had mild hyperthyroid symptoms.

Three months later, the patient was feeling well and TG was 14. Several TG levels performed over the next 2 years and, with the patient on a suppressive dose of T_4, were in the range of less than 1.5 to 5.

Three years after initial treatment, a repeat I-131 scan was done after withdrawal of T_4. The scan was negative, but the TG off T_4 was 120 and TSH was

64. A positron emission tomography (PET) scan was performed and reported as negative. However, on review of the scan, there was a tiny area of possible abnormality in the same area as the tiny area of I-131 uptake in the neck on the previous iodine scan. A repeat I-131 scan was done several months later and was completely negative. The patient has remained on 0.175 mg of thyroxine daily with a TSH in the range of 0.04 and feels well.

Case Summary

This patient was noted by his wife to have a lump in his neck. His family doctor found a thyroid nodule and referred him to me. FNAB revealed papillary carcinoma, and the patient underwent total thyroidectomy and postoperative RAI therapy. The surgical pathology did show some spread of the cancer outside the capsule and a small focus in the other lobe. He has done well on T_4 for more than 10 years despite an elevated TG level suggesting residual tumor. Imaging studies have been negative.

What Can We Learn From This Case?

- Although most thyroid nodules are benign, about 5% are cancerous and FNAB is the best way to make this differential diagnosis.
- Thyroid nodules in men are much less common than in women and carry a higher risk of cancer.
- Most differentiated thyroid cancers are cured by surgery and RAI and require only simple annual follow-up. However, some cases are more complex and require additional evaluation and treatment.
- Serum TG is useful in follow-up of thyroid cancer. The level should be very low or unmeasureable after thyroidectomy and RAI therapy. Elevated levels of TG suggest residual or recurrent cancer.
- Imaging studies are often helpful in locating the cancer. However, this case demonstrates how difficult it may be to find the source of an elevated TG.
- Close follow-up and repeat imaging studies may eventually reveal recurrent or residual cancer.
- It is important to continue a suppressive dose of T_4 and monitor TSH regularly to be sure TSH is very low. This case demonstrates the value of suppressing TSH in keeping TG down and the marked increase in TG when the patient was off thyroid for scanning.

CASE 2

A 69-year-old woman was referred regarding a thyroid nodule. She had noted a swelling in the right thyroid area for several months with slight discomfort but no real pain. She also had a history of thyroid problems dating back approx 50 years. She was initially treated with some brown pills that may have contained iodine. About 40 years earlier she had been started on thyroid medication and told that she was close to myxedema coma. She had continued on

thyroid medication since that time and most recently on 0.1 and 0.05 mg of thyroxine on alternate days. She had no symptoms of hyperthyroidism or hypothyroidism and there was no history of neck radiation. She denied any family history of thyroid disease.

Physical examination revealed a pulse of 76 and BP of 142/80. There were no thyroid eye signs. The thyroid gland was bilaterally enlarged with a 1.5-cm nodule in the right lobe, which was moderately tender. There were no palpable cervical nodes. The examination was otherwise negative.

Differential Diagnosis

Hashimoto's thyroiditis, neoplasm, and benign nodular goiter were all diagnostic possibilities.

Workup

FNAB was performed in the office. Thyroid panel and thyroid antibody were ordered.

Results

- FNAB of the right thyroid nodule revealed medullary thyroid carcinoma.
- Thyroid microsomal antibody was negative.
- TSH and FT_4 were normal.

What Next?

Calcitonin, chemistry panel, urine vanillylmandelic acid (VMA) and metanephrines, and chest x-ray were ordered. The patient was advised to have her first-degree relatives screened for medullary carcinoma. (This patient was seen prior to the advent of more specific genetic testing for multiple endocrine neoplasia and familial medullary carcinoma.)

Results

- Calcitonin: 10,455 (2–17); calcium, 9; phosphorus, 3.5.
- VMA and metanephrines were normal.
- Chest x-ray was normal.

How Would You Treat This Patient?

The patient was referred to an experienced thyroid surgeon for a total thyroidectomy. The pathology report confirmed the FNAB diagnosis of medullary thyroid carcinoma replacing the entire right lobe. There was no evidence of extension beyond the thyroid and there were no positive nodes in the specimen.

Clinical Course

Calcitonin level 2 months after surgery was 974. Although this was clearly a decrease from the preoperative level of more than 10,000, it was

still elevated and suggested residual tumor. A month later, the calcitonin was 1200. The patient was treated with a replacement dose of T_4. MRI scanning of the neck showed only postsurgical changes, no tumor mass. The patient was referred to the university medical center for consultation. Calcitonin 6 mo after surgery was 809. Several months later, an octreotide scan was performed. This study failed to show evidence of medullary cancer. PET scan was also negative.

Calcitonin levels over the next 2 years ranged between 1200 and 1500. At approx 3 years postoperatively, the patient complained of problems with her voice and inability to sing. MRI revealed a 1.5-cm mass in the right thyroid bed region and MRI-guided biopsy was positive for medullary thyroid carcinoma. The patient underwent surgical exploration of that area and removal of the mass. Her postoperative calcitonin level was 9.

Case Summary

This woman with a long history of hypothyroidism presented at age 69 with a right thyroid nodule. FNAB revealed medullary thyroid carcinoma. Her serum calcitonin level was over 10,000. She had no family history of thyroid disease or multiple endocrine neoplasia (MEN). Screening tests for pheochromocytoma and hyperparathyroidism were negative. The patient underwent total thyroidectomy, which confirmed medullary thyroid carcinoma replacing the entire right lobe. Postoperatively, her calcitonin fell to the range of 1000 but remained elevated. Initial imaging studies were negative for residual tumor. About 3 years postoperatively, she developed vocal problems, and MRI with biopsy revealed residual tumor in the neck. The mass was removed surgically. Postoperatively, calcitonin fell to 9.

What Can We Learn From This Case?

- This patient presented with a thyroid nodule.
- FNAB revealed medullary thyroid carcinoma. Medullary thyroid cancer is a cancer of the parafollicular or C cells rather than the thyroid follicular cells. The C cells produce calcitonin.
- The massive elevation of calcitonin confirmed the FNAB diagnosis of medullary thyroid cancer.
- Screening for pheochromocytoma and hyperparathyroidism should be done when medullary thyroid cancer is diagnosed. Some cases of medullary thyroid cancer are part of the MEN syndrome.
- Initial treatment is total thyroidectomy because many patients have multifocal disease.
- Calcitonin may fall slowly after surgery. Persistent elevation of calcitonin 6 mo postoperatively is compatible with residual tumor.
- Imaging studies, such as MRI, ultrasound, octreotide scanning, and PET scanning, may be helpful in localizing residual disease.

- Residual disease should be removed surgically, if possible. In this case, residual disease was not localized until 3 years postoperatively. Removal of the tumor resulted in marked decrease in the calcitonin level suggesting possible cure.
- T_4 dosage after thyroidectomy should be adjusted to maintain TSH in the normal range. It is not necessary to suppress TSH in these patients.

CASE 3

A 29-year-old woman was referred regarding a mass in the neck. She had seen an endocrinologist colleague of mine in another city after noting neck swelling. Initial evaluation by him revealed an enlarged lymph node in the right neck. The patient had a history of surgery for papillary thyroid carcinoma 10 years previously. Serum TG was more than 600. Because she was returning to my area, she was referred for further evaluation and treatment. Handwritten records from her initial surgery were reviewed. Some of them were difficult to read, but she apparently had a 5×5 cm nodule in the left lobe of her thyroid. A subtotal thyroidectomy was performed. The pathology report describes a low-grade, well-differentiated, multifocal papillary thyroid carcinoma with extensive local infiltration. She had been maintained on thyroid hormone and was currently taking 0.1 mg of T_4 daily. There was no history of radiation to the neck as a child. There was a history of thyroid disease, type unknown, in a great aunt.

Physical examination revealed a pulse of 76 and a BP 90/64. Positive physical findings were confined to the neck. A 1.5×2.5-cm lymph node was palpable in the upper right neck and very close to the carotid artery. A possible, very small, left posterior cervical node was also noted.

Laboratory data: TSH 0.26, total T_4 11.7, TG higher than 600, calcium 9.4.

What Would You Do Next?

Computed tomography (CT) scan of the neck and chest was performed. Multiple lymph nodes and abnormal appearing thyroid tissue with calcifications were noted in the neck. CT of the chest was negative.

FNAB of the large lymph node on the right was performed. The biopsy showed rare clusters of epithelial cells and no specific diagnosis could be made.

How Would You Treat This Patient?

The patient was referred for surgery. Operative report described densely adherent strap muscles with no tissue planes. On the left, a 2-cm thyroid mass was found to be growing into the trachea. Frozen section was reported as papillary carcinoma of the thyroid. As much as possible of this mass was removed, but tumor remained attached to the trachea. On the right, rock-hard lymph nodes were palpable. Two masses were present, one growing into the jugular

vein and the other growing into the carotid artery. The jugular vein was sacrificed and that mass removed. The other mass was left in place attached to the carotid artery. Pathology report on the tumor removed was consistent with follicular variant of papillary carcinoma.

About 2 months postoperatively, the patient underwent I-131 whole-body scanning. A large amount of uptake was present in the neck. She was treated with high-dose (150 mCi) RAI therapy. Serum TG off thyroid for treatment was markedly elevated at 2433. A scan done 10 days after treatment again revealed a large amount of uptake in the thyroid bed region without other abnormal uptake. The patient was placed on T_4 in a dose to suppress TSH to a very low or undetectable level.

Clinical Course

Two months after RAI therapy, the TG was down to 46.7 with a TSH of 0.02 on suppressive thyroid therapy. Six months after RAI therapy a whole-body I-131 scan was done with the patient off thyroid medication. There was only minimal tracer uptake in the thyroid bed with a calculated uptake of less than 1%.

The patient left the area to visit her family. On her return, she was seen for follow-up. Her treatment had been approx 18 months previously and her last scan was 1 yr ago. She was withdrawn from thyroid medication, and follow-up I-131 scan and TG were performed. The scan showed no abnormal uptake. However, TG drawn off thyroid for the scan was 1200. Neck examination showed no masses. Sestamibi scan was negative. She was referred to the university thyroidologist for consultation. Repeat TG at the university was more than 414. The consultant recommended a repeat I-131 scan and consideration for repeat I-131 therapy. The scan showed uptake in the thyroid bed and also high in the neck on the left. She was given 150 mCi of I-131 after withdrawal of thyroid. The TG off thyroid for the scan and therapy was 586. The posttreatment scan showed uptake of the treatment dose in the same areas noted on the diagnostic scan. She was placed back on T_4 with the goal of suppressing TSH to a very low level. She will require close follow-up.

Summary

This young woman was initially treated for papillary thyroid carcinoma with subtotal thyroidectomy. She presented 10 years later with recurrent papillary cancer in the neck. She underwent surgery in an attempt to remove the residual tumor, but the tumor was not completely resectable. She was treated with high-dose RAI postoperatively and was followed with regular TG levels and imaging as required. She required repeat RAI therapy 3 years later for increasing tumor in the neck. She was counseled that her tumor was not cured but was controlled with RAI and would require close monitoring.

What Can We Learn From This Case?

- Papillary thyroid cancer can recur years after initial treatment.
- This patient presented initially with a large tumor, and total thyroidectomy followed by RAI therapy would have given her a better chance of cure.
- The elevated TG and imaging studies confirmed significant recurrence of tumor in the neck.
- Surgery to remove the tumor was the best initial approach. Unfortunately, all of the tumor could not be removed.
- High-dose RAI postoperatively helped to control the tumor as evidenced by the fall in TG and improvement in the I-131 scan.
- T_4 was given to replace the absent hormone post-thyroidectomy. A relatively high dosage was used to suppress TSH to a very low or unmeasureable level because TSH may stimulate tumor growth.
- This case demonstrates that differentiated thyroid cancer can be quite aggressive in some patients.
- Lifelong follow-up with neck examination, TG, and imaging will be needed in this patient.

SUMMARY

This chapter discussed several patients with thyroid cancer. Like most patients with thyroid cancer, these patients presented with a thyroid nodule or neck mass. FNAB was the initial approach to diagnosis. Case 1 was a man who was found to have a papillary thyroid carcinoma on FNA and was treated with total thyroidectomy and postoperative RAI. He had elevated levels of TG over several years suggesting residual or recurrent tumor, but the source of the TG could not be found. Case 2 was a woman with medullary thyroid carcinoma. This type of cancer accounts for less than 5% of thyroid cancers. It is a tumor of the parafollicular cells (C cells) of the thyroid. These cells are of embryonic neural crest origin and medullary cancer is not related to the thyroid hormone-producing follicular cells of the thyroid. The thyroid C cells produce calcitonin, and calcitonin is often markedly elevated in patients with medullary cancer at the time of presentation. Metastases are already present in the majority of cases, mostly to cervical nodes, at the time of presentation. Imaging studies are often helpful in staging the tumor. Total thyroidectomy and removal of any metastatic tumor is the primary treatment. Patients with residual disease as evidenced by persistent calcitonin elevation have a high mortality rate. About 20% of patients have MEN (familial) and the rest are sporadic. Genetic testing is now available to detect patients with familial disease.

Case 3 was a young woman who presented with recurrent papillary thyroid cancer 10 years after initial diagnosis and treatment. The disease was widespread in her neck and could not be cured despite surgery and RAI treatment. Although more than 90% of patients with papillary thyroid carcinoma are cured

by surgery and RAI, some are not. Perhaps more aggressive initial therapy would have prevented recurrence, but we cannot know that for certain. In any case, this patient demonstrates that not all papillary cancers are relatively benign and easily curable.

Thyrogen (Synthetic TSH)

I would like to touch briefly on the use of bioengineered synthetic TSH (Thyrogen) in preparing thyroid cancer patients for RAI scanning. The standard method for preparing patients for whole-body RAI scanning is withdrawal of thyroxine for 4 to 6 weeks in order to raise the TSH and increase uptake of the isotope into any residual thyroid tissue or thyroid cancer. Patients become symptomatically hypothyroid during this time and some complain bitterly and even refuse to have the scan done again. Some patients are unable to work or function well during this time. Thyrogen has recently become available. This synthetic human TSH can be injected prior to the scan to increase tissue uptake of tracer without withdrawal from thyroxine. Although thyroid hormone withdrawal is still usually done if RAI therapy is likely, a Thyrogen scan is adequate in many patients and saves the patient the misery of temporary hypothyroidism.

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II Challenging Thyroid Disorders and Current Controversies

13
Challenging Cases of Hyperthyroidism

INTRODUCTION

This chapter outlines and discusses two patients with thyroid disease who presented unusually complex problems in management. They demonstrate the role of the thyroid specialist in the long-term care of the challenging patient. The thyroid specialist becomes, in some respects, the primary physician in conjunction with the patient's primary care physician (PCP). It has always been particularly satisfying to me as an endocrinologist to play a major role in the long-term care of a patient. These patients often require the consultation and ongoing care of several specialists and the PCP in a team approach. When the primary medical problem involves the thyroid, the endocrinologist takes on a central role in patient care. Thyroid disease may affect many organ systems and may require the help of a cardiologist, ophthalmologist, dermatologist, surgeon, occasionally a psychiatrist, and even an allergist. The patients discussed here were especially challenging to me and to the other physicians who participated in their care.

CASE 1

Graves' Disease With Complications

A 65-year-old woman was referred by her PCP for thyroid evaluation. She went to see her doctor because of tiredness and shortness of breath during the preceding 2 months. She also admitted that she felt a little depressed, with general malaise recently. On questioning, she admitted that she had lost 10 lb despite a good appetite and increased food intake. Her bowel movements had increased from one to two per day. She denied heat intolerance, although she had been sweating a bit more than usual. She also denied palpitations, shakiness, or hair loss.

Past history revealed surgery for heart valve replacement 1 year ago and asthma for many years. Family history was positive for Graves' disease in her daughter who had been treated with radioactive iodine (RAI).

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
By: E. O. Brams © Humana Press Inc., Totowa, NJ

On physical examination, the patient was a thin Asian female who appeared hyperactive. The pulse was 80 to 90 and irregular and her blood pressure (BP) was 140/62. There were no thyroid eye signs. The thyroid gland was diffusely enlarged to about twice its normal size. Cardiac examination revealed an apical rate of about 80 beats per minute (bpm) with irregular rhythm. Heart sounds were accentuated, but there was no murmur or rub. There was 1+ tremor of the outstretched upper extremities and mildly decreased proximal muscle power. The skin was smooth and warm.

Laboratory Results

- Thyroid stimulating hormone (TSH) less than 0.05.
- Radioactive iodine uptake (RAIU): 6 hour, 28.2% (4–12), 24 hour, 50.8% (7–24).
- Thyroid nuclear scan: no focal abnormalities.

What Is Your Diagnosis?

The diagnosis is hyperthyroidism secondary to Graves' disease with atrial fibrillation.

Treatment Options

Treatment options were discussed with the patient, including RAI, antithyroid drugs (ATDs), and thyroid surgery. We agreed that RAI would be the best approach to cure the problem. However, in view of her age and history of heart disease, I decided to "cool her down" with an ATD before RAI therapy. All of the possible side effects of RAI and ATDs were discussed with her. She was started on 100 mg of propylthiouracil (PTU) every 8 hours. She was specifically advised to stop the ATD and call if she developed sore throat or fever.

Clinical Course

Several days after starting PTU, the patient called to report that she had developed sore throat, fever, and a pruritic rash over her legs and trunk. She was advised to discontinue the ATD and come in for a visit. Her complete blood count was normal. Examination was unchanged except for pharyngeal injection and a fading rash.

The findings were felt to be compatible with a reaction to PTU. The options at this point were to try methimazole or proceed to RAI therapy. RAI therapy was the chosen procedure. It was explained that she would end up with a low thyroid and have to take a thyroid pill once a day for life. Also discussed were thyroid eye problems, such as bulging and double vision and she was advised that eye problems could occur even after the RAI treatment. The patient was treated with RAI.

One month after treatment, the patient said she felt better. She was no longer short of breath and her muscle weakness had improved to the point that she was

walking better. She was also sleeping better and her bowel movements had decreased to one per day. On examination, her thyroid gland had decreased slightly in size and she had no thyroid eye signs. Her pulse was irregular at 88 bpm. At 2 months posttreatment, she had gained 3 lb, her nervousness and depression had improved, and she was feeling generally well. Her free thyroxine (FT_4) was 1.2 (0.7–2), and her TSH was still suppressed at less than 0.1. On physical examination, she still had no thyroid eye signs, pulse was down to 72 bpm but still irregular, and the thyroid had decreased further in size.

The patient took a brief trip to China. Upon her return 1 mo later, she complained that she was cold and had leg cramps. She also noted that her eyes were swelling and her vision was blurry. On examination, she had mild periorbital edema, but her eyes appeared otherwise normal. Her thyroid gland was barely palpable. Laboratory tests showed a FT_4 of 0.4, and TSH of 47.9. A 0.075-mg dose of thyroxine (T_4) daily was started for her clinical hypothyroidism.

Two months later, approx 6 months after her RAI treatment, the patient returned complaining of burning and tightness in the pretibial region of both legs. Physical examination showed moderate edema of the eyelids without proptosis or diplopia. The thyroid was barely palpable. The anterior aspect of the lower legs showed large, slightly erythematous and indurated areas that were warm to the touch. She was seen by a dermatologist who confirmed a diagnosis of pretibial myxedema. She was treated with potent topical steroid ointment with occlusive dressings and 400 mg of Trental three times a day. Her T_4 dosage had been increased by her PCP to 0.1 mg daily. She was taking two of the 0.05-mg (white) tablets that she still had at home.

The patient called me a few weeks later, after she had switched to her new prescription for 0.1-mg thyroxine tablets, to tell me she had a generalized itchy red rash. She had previously been taking two of the 0.05-mg tablets. I told her that the rash was probably from allergy to the color dye in the 0.1-mg (yellow) tablet. She was switched back to two of the 0.05-mg (white) tablets. She was concerned that she was allergic to thyroid hormone. I told her that, to my knowledge, allergy to T_4 had never been reported and encouraged her to continue taking the white tablets. Two months later, her eyes were improved and she had gained 12 lb. Her TSH was 16.7. On examination, her eye exam showed no diplopia and only mild periorbital edema. Her thyroid gland was slightly larger. The pretibial myxedema was still present but improved. I increased her T_4 to 0.112 (red dye) mg daily. She was advised to call if rash developed.

I saw her 2 months later. She was now about 1 yr post-RAI therapy. She complained of watery eyes and photophobia. She had lost the weight she had gained when I saw her previously. Examination showed a small increase in exophthalmometer measurements. The pretibial myxedema continued to

improve. Her atrial fibrillation persisted. Her TSH was 1.8. She was continued on 0.112 mg of T_4 daily. Her ophthalmologist confirmed that her eyes were stable. Six months later, she appeared stable except for a TSH of 6.57 and further increase in exophthalmometry measurements. Her T_4 dosage was increased to 0.125 mg daily.

Her TSH 1 month later was elevated to 9.4 on the increased T_4 dosage. The dose was increased to 0.15 mg daily. She called a few days later to tell me she had broken out in a rash from head to foot since I had increased her T_4 to the 0.15-mg (blue) tablet. I changed her medication to three of the 0.05-mg (white) tablets daily and the rash cleared. Her ophthalmologist now reported that she had eye muscle involvement with mild diplopia on extreme gazes and corneal exposure keratopathy. He prescribed a lubricant at night.

I saw her again approx 6 months later, now more than 2 years post-RAI therapy. She was on 0.15 mg of T_4 (3 of the 0.05-mg white tablets) daily and felt well. Her eyes appeared stable and only mild skin thickening of the lower anterior legs was noted as a residual of her pretibial myxedema. Her TSH was now suppressed at 0.16. She was advised to decrease her T_4 dosage to two tablets (0.05 mg) and three tablets on alternate days. She remained stable when last seen at more than 3 years post-RAI therapy, and only required fine-tuning of her T_4 dosage. She returned to the care of her PCP.

Case Summary

This case is unusual in my experience, but demonstrates many of the complications of Graves' disease and the problems that occasionally occur with treatment. This older woman presented with symptoms of hyperthyroidism and a goiter but no evidence of thyroid ophthalmopathy. She had a history of heart disease with atrial fibrillation and asthma. She had an allergic reaction to PTU. RAI therapy cured her hyperthyroidism and resulted in the expected post-RAI hypothyroidism. Treatment of the hypothyroidism resulted in the very unusual occurrence of allergy to the color dye in the yellow and blue T_4 tablets. Fortunately, she tolerated the white (0.05-mg) tablets well and dosage could be adjusted by using the appropriate number of white tablets. After RAI treatment, she also developed thyroid ophthalmopathy, which had not previously been noted. She also developed pretibial myxedema. She required frequent adjustments of T_4 dosage. Her Graves' disease stabilized. She only required symptomatic treatment for her eye disease and T_4 replacement therapy.

What Can We Learn From This Case?

- This case allows us to observe many of the common and less common findings seen in Graves' disease. It has been said that one can learn all of medicine from a single case. I think one can learn almost everything of Graves' disease from this case.

- This woman had a history of asthma. She developed another autoimmune disease, Graves' disease. After RAI treatment, she developed further autoimmune manifestations of Graves' disease, ophthalmopathy, and dermopathy. She then proceeded to develop allergic reactions to color dyes in T_4 tablets.
- The fact that the patient developed eye and skin manifestations of Graves' disease after treatment of the hyperthyroidism raises the question of whether the RAI treatment might have contributed to these problems. This is still a controversial area with some studies suggesting an increased incidence of ophthalmopathy after RAI and others not. We cannot really know whether she would have developed the opthalmopathy and dermopathy in the course of the Graves' disease regardless of treatment.

CASE 2

Evolution of Thyroid Disease

A 30-year-old woman was referred for evaluation of a thyroid nodule. She had recently moved to the area and had been evaluated 3 years previously in another city for a left-lobe thyroid nodule. Fine-needle aspiration biopsy (FNAB) at that time showed a thyroid cyst according to the patient and a lot of fluid was drained. Those records could not be obtained. The patient was treated with T_4 until 2 months prior to this visit and the nodule had remained small. She had recently noted enlargement of the nodule after discontinuing the thyroid hormone. She had no symptoms of hyperthyroidism or hypothyroidism and felt generally well. Family history was negative for thyroid disease.

Physical examination revealed an apparently healthy young woman whose pulse was 72, and BP was 130/102. There were no thyroid eye signs. A 4×4-cm thyroid nodule was palpable on the right. It was rubbery in consistency and nontender. There were no palpable cervical nodes. Cardiac rhythm was regular with a soft systolic murmur at the base. The examination was otherwise negative.

Differential Diagnosis and Workup

The differential diagnosis included benign thyroid nodule (BTN) or cyst, Hashimoto's thyroiditis, and neoplasm. T_4, TSH, and thyroid microsomal antibodies were ordered and FNAB of the nodule was done in the office.

Test Results

- Total T_4, 5.9 (4.5–11.5); TSH, 1.8 (0.4–4.5).
- Thyroid microsomal antibody: 405 (<25).
- FNAB revealed a BTN. No evidence of Hashimoto's thyroiditis was seen on careful review of the FNA.

Treatment

The patient was reassured that there was no evidence of tumor. She was restarted on T_4 and asked to return for follow-up in 3 months.

Clinical Course

The patient did not return for follow-up as requested. She was referred back by her PCP 6 years later. She had not been taking T_4. Her doctor had obtained thyroid studies a year earlier that were normal. She had a third child about 5 years previously. Over the past year, she noted swelling again in the left thyroid area, followed by some swelling on the right. She had no pain or dysphagia. She had no symptoms of hyperthyroidism or hypothyroidism except for mild cold intolerance. She had been otherwise healthy.

Physical examination showed no evidence of thyroid eye signs. Bilateral thyroid nodules were noted with the larger one on the right. There were no palpable nodes. Examination was otherwise normal.

Diagnosis and Workup?

The most likely diagnosis again was benign disease, although neoplasm had to be ruled out. She appeared clinically euthyroid. Bilateral FNABs were performed. The pathology was now compatible with Hashimoto's thyroiditis.

Clinical Course

The patient was started on suppressive therapy with T_4. On follow-up several months later, the nodules were unchanged. The patient felt well but had lost 6 lb. On 3-month recheck, the nodule on the right was larger. Repeat FNAB on the right again revealed Hashimoto's thyroiditis. Her TSH on T_4 was less than 0.03 with an elevated FT_4. Her T_4 dosage was decreased and then discontinued.

Studies with the patient off T_4 for 1 month showed a TSH of less than 0.03, FT_4 of 3.35 (0.75–2), and total triiodothyronine (T_3) of 342 (70–180). The patient complained of further weight loss, heat intolerance, palpitations, and nervousness. Her thyroid gland had increased in size. She had no thyroid eye signs. The RAIU was 44.9% (4–12) at 6 hours and 48.8% (7–24) at 24 hours.

What Is Your Diagnosis Now?

The patient was now clinically and biochemically hyperthyroid. The diagnosis was Hashitoxicosis, a variant of Graves' disease.

Treatment

The options for treatment including RAI, ATD, and surgery were discussed with the patient. We agreed that RAI would be the best approach. She was also given a β-blocker as symptomatic therapy.

Three months later, she was asymptomatic and her thyroid had decreased in size. Her TSH was lower than 0.03 and her FT_4 was now normal at 0.98.

At 6 months post-RAI, the patient felt well but the nodule on the left remained large. The TSH was less than 0.03 and the FT_4 was elevated at 2.20.

I elected to treat her again with RAI because she was clearly still hyperthyroid. At 3 months posttreatment, the patient complained of cold intolerance, dry skin, and fatigue. Her TSH was 51.88 and her FT_4 was 0.29. She was clinically hypothyroid. The thyroid nodule on the left was smaller and the right thyroid nodule was no longer palpable. She was started on thyroid replacement.

Case Summary

This patient initially presented with a thyroid nodule that was benign on biopsy. However, she had markedly positive thyroid microsomal antibodies indicating autoimmune thyroid disease. Several years later, she developed bilateral thyroid nodules and the diagnosis of Hashimoto's thyroiditis was confirmed on biopsy. T_4 suppression was not successful in shrinking the nodules over time. While on T_4, the patient proceeded to develop hyperthyroidism with an enlarging thyroid. The suppressed TSH was initially attributed to her T_4 therapy. My focus at that point was on the enlarging thyroid and concern about neoplasm. She then developed symptomatic hyperthyroidism, T_4 was discontinued, and the diagnosis of hyperthyroidism confirmed. She was resistant to treatment and required a second RAI treatment to cure her hyperthyroidism. The resulting hypothyroidism was controlled with T_4.

What Can We Learn From This Case?

- Although Hashimoto's thyroiditis commonly results in hypothyroidism, it can occasionally lead to hyperthyroidism, so called Hashitoxicosis.
- Hashitoxicosis is a variant of Graves' disease.
- It is easy to miss the onset of hyperthyroidism in a patient on suppressive T_4 therapy. Hyperthyroid symptoms and a suppressed TSH may be attributed to the medication.
- Hashimoto's thyroiditis can present with a thyroid nodule rather than diffuse or bilateral disease.

Thoughts and Personal Comments

Case 2 was a learning experience for me. Although I had seen patients with hyperthyroidism occurring in Hashimoto's thyroiditis, this patient had been euthyroid with nodular disease for a number of years. The patient's focus and mine was really on the enlarging nodules and concern about possible neoplasm. Thyroid lymphoma was a consideration, but FNABs did not show evidence of it. In retrospect, the continued enlargement of the thyroid nodules despite suppressive therapy might have suggested autonomous thyroid function as a diagnostic possibility. However, although many nodules secondary to Hashimoto's do shrink on thyroid suppression, some do not.

Perhaps the lesson of this case is that when things are not proceeding as one might expect, one should step back, take a broader view, and consider even

unlikely diagnostic possibilities. Sometimes, when a challenging patient is seen fresh by a second physician after being followed for a long time by the first physician, the entire case is reviewed and a correct diagnosis made by the new physician. A second opinion may be helpful in a difficult case, even when the first physician is an expert in the area. I have always encouraged a second opinion if requested by my patients and have suggested it to some. Also, although a suppressed TSH in a patient on T_4 is usually the result of the medication, it may occasionally indicate developing endogenous hyperthyroidism. It may be necessary to discontinue the medication for several months to find out. This patient is another example of the fact that you can learn a lot about thyroid disease from one case.

CASE 3

Hyperthyroidism Presenting as Acute Illness

I saw this 26-year-old man in consultation while on a locum tenens assignment. He had presented to the hospital emergency room 2 weeks earlier. He was hospitalized because of tachycardia, shakiness, abdominal pain, and abnormal thyroid studies. The total T_4 was 22.7 (4–12), FT_4 was 5.3 (0.8–1.8), and TSH was 0.002 (0.4–5). He was felt to be in thyroid storm secondary to Graves' disease and was treated with high-dose PTU, propranolol, and Decadron, as well Nexium for the abdominal complaints. When I saw him, he was on 200 mg of PTU three times a day, 40 mg of propranolol four times a day, and Nexium.

The patient had been ill for almost 2 years. During that time, he had lost 90 lb and had noted fatigue, shortness of breath, palpitations, and muscle weakness. He had been unable to work at his job as a cook for several months because of weakness. He had noted no eye complaints or change in appearance of his eyes. Over the previous week, he had noted a pruritic rash. Past history was completely negative and family history was negative for thyroid disease.

Physical examination revealed a pulse of 72 and a BP of 120/70. The eyes showed bilateral stare but no proptosis or diplopia. The thyroid gland was diffusely enlarged to about twice its normal size. Cardiac rhythm was regular at 72 bpm. Moderate fine tremor of the outstretched upper extremities was noted. Muscle strength was markedly decreased, and the patient was unable to get up from a squatting position without help. The skin showed a diffuse erythematous rash. Repeat studies on treatment showed a decrease in FT_4 from 5.3 to 3.7 and TSH suppressed at less than 0.005.

What Is Your Diagnosis?

Hyperthyroidism, probably secondary to Graves' disease.

Additional Workup

RAIU and thyroid scan were ordered. PTU was stopped for several days to get an accurate uptake. The RAIU was elevated and compatible with Graves' disease.

Treatment

Treatment options were discussed with the patient and his wife including continuing PTU, RAI, and surgery. We agreed that RAI would be the best treatment. However, in view of the severity of the hyperthyroidism, we decided to continue the PTU for a few weeks before RAI therapy in order to further "cool down" the hyperthyroidism. I was concerned that the skin rash might be the result of PTU and had a dermatologist look at him. The rash was not a drug reaction but was the result of the sweating brought on by his hyperthyroidism. I reassured the patient and his wife that the end result would be good, but it would take him months to regain his strength. Because I was on a short locum, I was not able to follow him further.

Case Summary

This patient presented to the hospital emergency room in acute distress and was felt to be in thyroid storm. He had obviously been hyperthyroid for a long time. He was treated as a thyroid storm with high-dose PTU and steroids. When I saw him 2 weeks later, he was no longer acutely ill but was still markedly hyperthyroid. He had palpitations, fatigue, and shortness of breath. The most striking finding was the severe muscle atrophy and weakness that were the result of his long-term hyperthyroidism. He should respond to treatment, but it will take months for him to recover fully.

What Can We Learn From This Case?

- Hyperthyroidism can present as an acute emergency and require aggressive treatment.
- Thyroid storm is an uncommon result of long-term, untreated hyperthyroidism and can result in death. This patient may have had only severe hyperthyroidism rather than true thyroid storm.
- Earlier diagnosis and treatment would have prevented the acute symptoms, as well as the severe muscle weakness.
- RAI therapy will be the best treatment for this patient and should result in a cure.

CASE 4

Drug-Induced Thyroid Dysfunction

Whereas most thyroid problems result from endogenous thyroid dysfunction, some problems are secondary to treatment of other medical conditions. The case

discussed here demonstrates how challenging the treatment of drug-induced thyroid dysfunction may be in the face of other serious illness.

This 52-year-old man was referred because of an abnormal TSH of less than 0.03. He had a long history of ischemic heart disease with serious arrhythmias. Over the previous several months, he had noted heat intolerance, shakiness, and a 30-lb weight loss despite increased food intake. He denied recent palpitations. His first coronary artery bypass graft surgery was at age 33 years and the second at age 45 years. More recently, he had noted recurrent chest pain requiring angioplasty. He had several episodes of ventricular fibrillation and was started on amiodarone 2 years previously. An implantable defibrillator was in place, but it had not fired for about 9 months. The amiodarone was effective in controlling the arrhythmia, and his cardiologist felt it could not be safely discontinued. Family history was negative for thyroid disease. Other medications included Lasix, potassium, Isordil, Lanoxin, and Pravachol.

Physical examination revealed a pulse of 68 and BP of 110/50. There were no thyroid eye signs. The thyroid was enlarged bilaterally to about 1.5 times its normal size, firm, nontender, and without nodules.

What Additional Tests Would You Order?

The following test results were obtained:

- TSH (repeat), less than 0.03; FT_4 greater than 8 (0.75–2); total T_3, 216 (70–180).
- RAIU: less than 1% at 24 hours.

What Is Your Diagnosis?

Amiodarone-induced thyrotoxicosis. Amiodarone contains a large amount of iodine and can cause several types of thyroid abnormalities (*see* Case Discussion).

Treatment Options

Hyperthyroidism secondary to amiodarone is very difficult to treat and can be life threatening, especially in the patients with severe heart disease who are usually taking this drug. As in this patient, discontinuing the drug is not usually an option because of the severe cardiac arrhythmias that require its use. Other options include ATDs and potassium perchlorate to block the thyroid uptake of iodine and synthesis of thyroid hormones, emergency thyroidectomy (under local anesthesia if possible), and steroids.

Because this patient was not as severely clinically hyperthyroid as his high FT_4 would suggest, I elected to start him on a high dose of an ATD and follow him closely. He was treated briefly with 200 mg of PTU every 8 hours. He developed a sore throat and itching on PTU, and his family doctor stopped the

drug. Studies at that point included a total T_3 of 300 (70–180), FT_3 was 876 (230–420), and TSH was less than 0.03.

He was switched to 20 mg of methimazole twice a day. He tolerated this drug without side effects. One month later, he had lost another 10 lb but appeared stable. FT_4 was 7.23 (0.75–2). After another month of therapy, his FT_4 was down to 5.71 and the total T_3 was normal at 158. At this point, he was hospitalized for a subendocardial myocardial infarction, angina, and congestive heart failure. Cardiac catheterization showed severe triple-vessel disease with an ejection fraction of only 10% and pulmonary hypertension. After 4 months of 20 mg of methimazole therapy twice a day, he had gained 15 lb, and his heat intolerance and shakiness were gone. His TSH was normal at 0.80 and total T_4 was 8.6 (4.5–12). His methimazole dosage was decreased to 30 mg/day. He was placed on the list for a cardiac transplant. He subsequently received a cardiac transplant and amiodarone was discontinued. He is currently euthyroid without treatment and doing well.

Case Discussion

This patient developed thyrotoxicosis secondary to treatment of his serious cardiac arrhythmia with amiodarone, a potent anti-arrhythmic drug. An oral 200-mg tablet of amiodarone contains 6 mg of iodine, at least 20 times the usual daily intake. The thyroid concentrates iodine for use in synthesis and secretion of thyroid hormones. Although normal iodine intake is needed to maintain a euthyroid state, massive doses of iodine can cause either hyperthyroidism or hypothyroidism.

This patient had symptoms of hyperthyroidism along with a markedly elevated FT_4 and very low TSH. His T_3 level, however, was only moderately elevated. Amiodarone has been shown to decrease peripheral conversion of T_4 to T_3 (the active thyroid hormone at the receptor level). This may explain the relatively modest T_3 elevation and lack of more severe symptoms. The RAIU was very low, as one might expect in the face of massive iodine intake, and RAI therapy was not an option.

Thyrotoxicosis in patients with severe heart disease requiring amiodarone is a serious and often life-threatening event. They tend to be resistant to conventional treatment because of the large iodine load. Treatment is usually initiated with an ATD (methimazole or PTU) in high dosage. Potassium perchlorate (a blocker of iodine concentration in the thyroid) is often added in more severe cases and corticosteriods are sometimes added. If these drugs are not effective in controlling the hyperthyroidism, subtotal thyroidectomy (preferably under local anesthesia) may be necessary. Fortunately, this patient's hyperthyroidism was not clinically severe, and high-dose methimazole was adequate to control the problem over time. The cardiac transplant allowed his cardiologist to discontinue the amiodarone and the thyroid problem resolved.

What Can We Learn From This Case?

- Drugs that contain a lot of iodine, such as amiodarone, can cause either hyperthyroidism or hypothyroidism.
- Hyperthythroidism can be life threatening in patients with severe heart disease.
- It is important to monitor thyroid function in all patients on amiodarone.
- Treatment of hyperthyroidism may be difficult in patients on amiodarone. Emergency thyroidectomy has occasionally been required.

Comment on Thyroid Disease and Drugs

This case demonstrates the profound effect amiodarone may have on the thyroid. The drug may cause hypothyroidism and goiter in susceptible individuals, such as those with Hashimoto's thyroiditis, by blocking thyroid hormone synthesis. It may also cause hyperthyroidism in about 3% of treated patients in the United States and a larger percentage of patients in iodine-deficient areas of the world. Amiodarone-associated hyperthyroidism (AAH) can either be caused by increased synthesis of T_3 and T_4 related to increased iodine intake (type 1) or by release of large amounts of hormone from the gland secondary to a toxic effect of the drug, resulting in destructive thyroiditis (type 2).

Type 1 AAH usually occurs in patients with underlying thyroid disease, such as multinodular goiter with thyroid autonomy or Graves' disease. Type 2 AAH patients may have no underlying thyroid disease. However, in both types, the patient may present with clinical hyperthyroidism. The differential diagnosis may be difficult because the high iodine load from the drug results in a low RAIU in both types. As discussed in Chapter 4, the RAIU is usually low in hyperthyroidism secondary to thyroiditis and elevated in hyperthyroidism caused by increased hormone synthesis, such as Graves' disease. In AAH, the large iodine intake from the drug affects the RAIU test. The RAI administered for the test is diluted by the large iodine pool resulting in a low uptake in most patients with either type 1 or type 2 AAH. The patient discussed here was probably type 1 because the hyperthyroidism persisted over many months. The options for treatment of type 1 AAH are included in the previous case discussion. Type 2 is usually treated with corticosteroids. Discontinuation of the amiodarone is usually not an option in these patients.

A number of other drugs, such as inorganic iodine in drugs for pulmonary problems, organic iodine in radiocontrast materials and lithium may affect thyroid function. Also, several drugs such as oral iron preparations, cholesterol-binding resins, and some antacids, can interfere with absorption of T_4 in treatment of hypothyroidism.

SUMMARY

The cases discussed in this chapter are uncommon and present a challenge even to the thyroidologist. Case 1 was a patient with underlying allergic diathe-

sis who demonstrated the spectrum of autoimmune problems one may see in caring for a patient with Graves' disease. Case 2 is a thyroid patient who demonstrated the evolution of thyroid disease over time and presented a diagnostic challenge. Case 3 demonstrated the occasional acute emergency presentation of hyperthyroidism. Case 4 is a patient with severe underlying heart disease who developed hyperthyroidism as a complication of drug therapy with amiodarone for cardiac arrhythmia. Although these are not routine thyroid patients, I hope they are as interesting and educational to the reader as they were to me.

14

Treatment of Graves' Disease

A Personal Perspective

INTRODUCTION

During the past few years, I have had the opportunity to observe and participate in the care of patients with Graves' disease in several practice settings and locations. I retired from solo practice of endocrinology and nuclear medicine about 6 years ago. About 1 year later, I started doing locum tenens endocrinology in various parts of the country. I have worked in a small group in the midwest, a teaching Veterans Affairs hospital in the south, a large health maintenance organization in the northwest, a large multispecialty group in the northern plains, and a multispecialty group in California. In my own practice, I treated at least 90% of my Graves' disease patients with radioactive iodine (RAI). In some of my locum assignments, I have found that the majority of patients with Graves' disease are treated by endocrinologists with antithyroid drugs (ATDs). I have seen many of these patients for follow-up and compared their outcomes with my previous practice experience. Although this is admittedly an anecdotal study rather than a scientific one, I think there are some useful lessons to be derived from this experience.

CASE 1

A 35-yr-old female gynecologist developed Graves' disease about 2 years ago. She was treated with propylthiouracil (PTU) for approx 6 months and then became pregnant. She was able to remain off PTU during pregnancy, but symptomatic Graves' disease recurred postpartum with suppressed thyroid-stimulating hormone (TSH) and elevated free thyroxine (FT_4). She was restarted on PTU approx 8 months ago and is currently on 100 mg twice a day. She has heat intolerance and her TSH is suppressed at 0.02 and her FT_4 is 2 (0.8–1.8). Physical examination is normal except for a mildly enlarged thyroid gland. She wishes to become pregnant again.

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
By: E. O. Brams © Humana Press Inc., Totowa, NJ

Comment

This patient is currently hyperthyroid on PTU and will require a higher dose if we decide to continue this treatment. She has had Graves' disease for 2 years and now wants to become pregnant again. She may well need PTU during her next pregnancy.

I think RAI therapy initially or after her pregnancy would have been a better plan for her. Her hyperthyroidism would have been cured by now and she would be stable on T_4. She would probably not have to worry much about her thyroid during her next pregnancy except to monitor levels and adjust T_4. Now she is faced with the problem of possible ATD therapy during pregnancy.

CASE 2

This patient is a 27-year-old woman who was diagnosed with Graves' disease about 3 months ago. She had about a 3-month history of heat intolerance, palpitations, tremor, nervousness, and more frequent bowel movements. On physical examination, she had no thyroid eye signs. The thyroid was markedly enlarged to at least three times its normal size. Heart rate was 100 beats per min (bpm) and her blood pressure (BP) was 102/56. She had a hyperactive precordium and a fine tremor. Skin was was warm and moist. Thyroid tests showed a TSH of less than 0.02 and an FT_4 of 3.5 (0.8–1.8). RAI uptake was 96% at 6 hours. She was started on 10 mg of methimazole every 8 hours and 50 mg of atenolol daily.

Over the next month or so, the FT_4 came down to 0.9 and the patient improved. Methimazole was reduced to 10 mg twice daily. One month later, the FT_4 was 0.3 (0.8–1.8), total triiodothyronine was 0.59 (0.6–1.81), and TSH was 0.82. Her methimazole was further decreased to 10 mg daily. The thyroid gland remained markedly enlarged.

Comment

This patient has severe hyperthyroidism with a very large thyroid. It is extremely unlikely that she will get a cure even after 2 years on methimazole. Also, she could get pregnant during that time. I think the case for RAI therapy in this patient is very strong.

CASE 3

A 35-year-old female was seen for follow-up regarding Graves' disease. Review of the records revealed a 3-year history of severe hyperthyroidism with a very large goiter. She had a severe skin reaction to methimazole early on and was then treated with PTU. RAI therapy was recommended on several occasions, but she refused and elected to continue the PTU. She now complains of aching of the joints in her hands, but has no complaints of hyperthyroidism on

100 mg of PTU every 8 hours. Her current tests show a TSH of 0.02 and an FT_4 of 2.4. Physical examination shows a pulse of 100 bpm and BP of 110/78. The thyroid gland is markedly enlarged to about four times its normal size. She has no thyroid eye signs except a mild stare.

I discussed options for treatment at this point, either increasing her PTU in the face of joint aches that could be a side effect of the drug or RAI. Surgery is the least desirable option and would require better control of her hyperthyroidism first. She told me she is ready for RAI therapy.

Comment

This patient remains hyperthyroid after 3 years of PTU therapy. She has probably been controlled at times but is certainly not in remission. Initial treatment with RAI would have probably led to a far better result even if it required more than one treatment because of the large gland. She had refused RAI in the past, despite the best efforts of the thyroidologists who were caring for her.

CASE 4

While writing this chapter, I saw a patient who has had Graves' disease for 5 years. RAI was recommended initially and she opted for an ATD. She took PTU for 18 months and was not well controlled. She admits that she is not a good pill-taker. She was then switched to methimazole after she was again offered RAI. She was better controlled on methimazole, probably because she didn't have to take it several times a day. After 18 months, methimazole was discontinued and she remained euthyroid for possibly 2 years. The 1 month of the remission is not clear because she did have a suppressed TSH several months ago but was asymptomatic and did not follow-up.

She now presented with all the symptoms of recurrent hyperthyroidism, as well as suppressed TSH and elevated FT_4. I advised RAI therapy and reviewed the advantages of this approach and the poor odds of another remission on ATDs. She asked me what the advantage was of switching one pill, methimazole, for another, thyroid hormone, after RAI. I reviewed the advantages of taking T_4 over methimazole as described above. She had apparently not understood this in the past, and it may not have been carefully reviewed with her. She is now ready to go ahead with RAI after her thyroid uptake is done.

CASE 5

On the same day that I saw case 4, I saw another patient with Graves' disease. She had been treated with methimazole for several years. Each time the dose was tapered she had recurrence of symptoms of hyperthyroidism. She had a very large goiter. The chart notes stated that RAI therapy had been advised on several occasions and she had refused and opted for methimazole. She was now

on 10 mg twice a day and her FT_4 was down to normal again with a still suppressed TSH. Review of TSH levels going back several years revealed that she had not been well controlled. I discussed RAI with her at length and tried to answer all her concerns. I explained the advantages of RAI in her case along the lines discussed above. We spent at least 30 minutes discussing treatment. She had concerns about radiation and why there were such precautions after treatment, whether it was harmful, and so on. At the end of the discussion, she decided to go ahead with the RAI treatment. I told her I didn't want to talk her into it and I wanted her to be comfortable with the decision. She said she was. She signed the permit and will have her RAIU and then treatment.

RAI THERAPY FOR GRAVES' DISEASE

Advantages

1. Will result in a cure in almost all patients (90%) with a single treatment.
2. Simple outpatient treatment.
3. Simplifies follow-up long term.
4. Decreases need for office visits and testing. Most patients only require a yearly check-up.
5. Avoids future problems if patient becomes pregnant. ATD treatment is more complicated during pregnancy.
6. No major side effects except hypothyroidism

Disadvantages

1. Permanent hypothyroidism in almost all patients (the goal of therapy).
2. Controversy about effect on thyroid ophthalmopathy. This is discussed further in Chapter 5.
3. Requires annual long-term follow-up.
4. Some radiation precautions for a few days posttherapy.
5. Cannot, of course, be used during pregnancy.

ATD THERAPY FOR GRAVES' DISEASE

Advantages

1. Does not permanently damage thyroid.
2. May result in remission in up to 20% of cases.

Disadvantages

1. Does not result in remission or cure in 80% of patients.
2. Long-term pill therapy-compliance issues.
3. Occasional serious side effects, such as bone marrow depression and liver disease. More frequent minor side effects, including rash, joint aches.
4. Some patients are never really controlled.
5. Will eventually have to use RAI or continue ATD forever in majority of patients.

6. Requires frequent office visits and testing to monitor for side effects and adjust dosage.

DISCUSSION

About 70% of patients in the United States who are treated by a thyroid specialist receive RAI. I think the reason is clear. RAI results in a cure of the hyperthyroidism in almost all patients, whereas long-term ATD therapy may result in remission in about 20%. However, I find a note in the charts of people treated by endocrinologists with ATDs stating that the options for treatment have been discussed and the patient chose pills. In my practice, I also discussed the options with patients, and more than 90% chose RAI. Why is this? I think most patients' choices depend on how the options are presented to them. If the physician feels RAI is best for the patient and makes the case in a way the patient can understand, the patient will usually agree. The physician should spend the time needed to answer all the patient's questions. In my experience, most patients are very satisfied with the results of RAI treatment.

How can the physician convey to the patient his or her advice that RAI is the best treatment for that person (if the physician believes that this is the case) in a way that will make the patient more accepting of this advice? Perhaps we need to try to look at treatment from the patient or layman's perspective. Why might the patient reject RAI? I think fear of radiation is a major issue. Also, the patient may have the feeling that RAI is permanent in terms of destruction of the thyroid gland and may worry about the requirement to take thyroid medicine forever.

On the first point, the patient needs to be reassured that this radiation is safe and will not cause cancer, infertility, or genetic problems. The long-term experience with this treatment, more than 50 years, provides good data that can be shared with the patient in layman's terms.

The issue of permanent hypothyroidism and long-term medication requirement can be compared with the problems of long-term ATDs. The patient may ask, "Why take the radiation and substitute one medication for another?" The doctor can point out that these medicines are very different. Thyroid hormone is similar to what the patient's own thyroid would produce and does not usually cause side effects. Also, the dosage is pretty stable and most patients only require a yearly check-up. Taking thyroid hormone is much like taking an aspirin in the morning, perhaps safer. ATDs do have side effects and need much closer follow-up with frequent visits and tests. Most importantly, ATDs do not cure the problem in 80% of patients, even after 1 or 2 years of treatment. Thus, the patient may take medicine for 1 to 2 years with some potential risks and then face the need for RAI therapy. It can be explained to the patient that, although RAI is not a perfect treatment, it is the best option for most patients when compared with ATDs and surgery.

If the physician takes the time to present this information in a caring way, many patients will accept it or at least think about it and eventually accept it. Of course, the physician has to be convinced that this is the best option in order to convey it convincingly to the patient. After treating a large number of patients with Graves' disease and following them over many years, I am convinced that RAI is the best treatment option for most patients with this disease. The major exception, of course, is pregnant women. However, I think pregnant women should be encouraged to pursue RAI if they have persistent hyperthyroidism after delivery and before they consider another pregnancy. This offers the major advantage of avoiding the treatment of hyperthyroidism with an ATD again during pregnancy. Recent studies suggest an increased risk of worsening of thyroid ophthalmopathy after RAI treatment in comparison with ATD or surgery. However, the risk of serious progression is small (*see* Chapter 5). The occasional Graves' disease patient who presents with severe eye disease must be evaluated individually and the best overall treatment plan developed.

SUMMARY

The advantages of RAI therapy of Graves' disease for most patients are clear to the majority of thyroid physicians in the United States. The long-term remission rate with ATDs has decreased from about 50% in the 1960s to about 20% in recent studies. If the physician's experience in this regard were better conveyed to the patient and all patient concerns addressed, I think most patients would choose RAI initially. A recent study of Graves' disease treatment by members of the US American Thyroid Association found that 70% of their Graves' disease patients were treated with RAI. The majority of Graves' disease patients will probably come to RAI therapy eventually. Earlier RAI treatment would save a lot of time and trouble and be more cost-effective in the long run.

15
Iatrogenic Hyperthyroidism

CASE 1

A 45-year-old salesman was referred for consultation regarding treatment of hypothyroidism. He had been diagnosed with hypothyroidism by his internist about 20 years earlier, in 1972. Old records were not available, but he recalled that some tests were done and he was started on Thyrolar 2. Several years later, the thyroid dosage was increased to Thyrolar 3, roughly equivalent to 0.3 mg of thyroxine (T_4). Tests were done by his doctor approx 1 year prior to this visit and he was told he was taking too much thyroid. He was switched to T_4 and the dosage was slowly decreased to his current level of 0.15 mg daily. He would note generalized aching every time the dose was decreased. On the higher doses, the aching would improve after 2 or 3 months. However, after the last dose reduction, the aching persisted, and he also noted fatigue. A recent thyroid-stimulating hormone (TSH) on 0.15 mg of T_4 was low-normal at 1.03. Physical examination was completely normal.

What Is Your Working Diagnosis?

The most likely diagnosis is long-term iatrogenic hyperthyroidism with withdrawal symptoms on reduction of TSH to a more appropriate dosage. The patient has underlying hypothyroidism and is clinically euthyroid on his current dosage of T_4.

What Would You Do Next?

Antinuclear antibody (ANA) was ordered and was negative. Thyroid microsomal and thyroglobulin antibodies were markedly elevated. I had a long counseling session with the patient, during which we discussed the problem of long-term overtreatment of hypothyroidism. I told him I thought he would eventually re-adjust and feel better on the lower dosage. I did agree to increase his thyroxine dosage for a few months to 0.175 mg daily and he agreed to this approach.

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
By: E. O. Brams © Humana Press Inc., Totowa, NJ

Clinical Course

The patient returned 6 months later. He had been taking 0.175 mg of T_4 daily and still complained bitterly of muscle aching and fatigue. He said he felt "rotten" and had trouble getting through his work day. TSH was now low at 0.17 and free thyroxine (FT_4) was mildly elevated at 2.02. He was referred for rheumatology consultation and continued on his current T_4 dosage. The consultant found no evidence of underlying rheumatic disease and recommended physical therapy. He returned 3 months later with the same complaints and wanted his thyroid increased. His TSH was 1.47 and FT_4 was 1.22, both clearly normal. I increased his T_4 to 0.2 mg daily as a trial. He was referred to a thyroidologist for consultation. The consultant agreed with my recommendations. The patient advised the consultant that he would go to Mexico to get a higher dosage of thyroid. He did not return for follow-up.

Case Summary

This patient had a history of hypothyroidism with long-term overtreatment resulting in iatrogenic hyperthyroidism. When dosage reduction was attempted, he complained bitterly of fatigue and muscle aching, probable withdrawal symptoms from taking excessive thyroid over many years. Despite the best efforts of several physicians, the patient wanted to return to the high-dose thyroid treatment and planned to go to Mexico to get the medication over the counter.

What Can We Learn From This Case?

- Overtreatment with thyroid medication was common in the days before modern thyroid testing was available.
- Many of these patients either enjoy being hyperthyroid or have withdrawal symptoms on dosage reduction based on current testing.
- We are now aware that iatrogenic hyperthyroidism may lead to osteoporosis and cardiac problems such as atrial fibrillation. Therefore, it is important to lower the dose of thyroid.
- These patients will complain bitterly of fatigue and aching. However, with slow reduction of dosage over many months, it is often possible to get the patient to accept and tolerate the lower dosage. Unfortunately, that was not the case with this patient.
- These patients are among the most difficult seen by the thyroid specialist.

CASE 2

A 56-year-old woman was referred for thyroid evaluation in 1993. She had been on thyroid medication for more than 30 years. The thyroid medication was originally started in 1959 because of weight gain and fluid accumulation. She took 5 grains (roughly equivalent to 0.5 mg of T_4) of Armour thyroid daily until 1

year prior to this visit. At that time, her doctor tried to switch her to T_4 in a lower equivalent dosage. She has noted weight gain and swelling since changing medication. She decided to stop thyroid completely 3 weeks before this visit. Her thyroid tests off thyroid for 3 weeks were normal including an FT_4 of 0.85 and a TSH of 0.95. She said she felt better off the T_4. Past history revealed congestive heart failure and pericarditis. She had been in a Nazi concentration camp during World War II. Current medications included Lanoxin, Mevacor, and Premarin. System review was positive for orthopnea and paroxysmal nocturnal dyspnea, as well as chronic anxiety. Physical examination was completely negative.

What Is Your Diagnosis?

Probable long-term iatrogenic hyperthyroidism in a patient with no underlying thyroid disease.

What Are Your Options for Treatment?

I had a long counseling session with this patient and explained to her that she had been on too much thyroid for years and had withdrawal symptoms when it was decreased. We discussed the fact that thyroid testing was not very good in 1959, and thyroid was often used to treat weight gain. I gave her two options. Because her thyroid tests were normal after 3 weeks off thyroid, we could keep her off thyroid for another 3 or 4 weeks and retest. If her tests remained normal, we could follow her off thyroid and she might slowly adjust. The other option would be to put her back on T_4 and slowly reduce the dosage over many months in the hope of minimizing withdrawal symptoms. We discussed the fact that it was especially important for her not to be hyperthyroid in view of her heart disease.

The patient chose the first option. She returned 3 weeks later complaining of severe fatigue, as well as orthopnea and palpitations. Her TSH was still normal at 2 and FT_4 was 1.1. The same options for treatment were discussed with her and she chose to remain off thyroid. She was returned to her family doctor for follow-up.

Case Summary

This patient was started on thyroid in 1959, probably based on her complaint of weight gain and a low basal metabolic rate (BMR) test. She took what we now know to be an excessive dose of thyroid for many years and may have enjoyed being hyperthyroid. She had withdrawal symptoms including severe fatigue when she was switched to T_4 in a much lower equivalent dosage. Thyroid tests with the patient off thyroid suggested that she had no underlying thyroid disease. She chose to remain off thyroid in the hope that she would adjust to a euthyroid state.

What Can We Learn From This Case?

- This patient was started on thyroid when modern thyroid tests were not available. The tests used at that time, such as the BMR, were difficult to perform and often extremely inaccurate.
- Thyroid medication was used at that time to treat obesity and fatigue by some physicians.
- The thyroid preparation available, Armour (desiccated) thyroid, was extracted from the thyroid glands of cattle and contained a combination of triiodothyronine (T_3) and T_4. Dosage standardization was based on iodine content and was not reliable in terms of biological potency.
- The dosages used were much too high as assessed by modern testing. Five grains a day was unusually high, even by the old standards.
- It is especially important to lower thyroid dosage in a patient with underlying heart disease.
- Bone density testing would be useful because we now have good treatment for osteoporosis.
- Follow-up is important, and this patient may require treatment with thyroid and more gradual withdrawal if her complaints persist. She may also need treatment for underlying anxiety and depression.

CASE 3

A 77-year-old woman was referred to me for management of diabetes. While taking a history, I discovered that she was taking 3 grains of Armour thyroid daily. She had been started on this medication during pregnancy many years ago and had continued it. On physical examination, she had findings compatible with atrial fibrillation. Her TSH was less than 0.05 and FT_4 was 2.5 (0.8–1.8).

What Is Your Diagnosis?

This woman had iatrogenic hyperthyroidism, which may have been the cause of her atrial fibrillation.

What Would You Do?

The problem was discussed with the patient as with the patients in cases 1 and 2. She agreed to switch to T_4 in a low dosage. It was especially important to bring her to a euthyroid state rapidly in view of the atrial fibrillation and her age. Fortunately, she adjusted well to a euthyroid state without severe withdrawal symptoms. She was maintained on low-dose T_4 to keep her TSH in the mid-normal range.

Case Summary

This elderly lady had been maintained on excessive thyroid medication for probably 50 years. Her atrial fibrillation may have been caused by hyperthyroidism. Her thyroid dosage was reduced without significant problems.

What Can We Learn From This Case?

- This patient was similar to the other cases presented here with the additional problems of atrial fibrillation, diabetes, and advanced age. She was at high risk for additional cardiac problems from her iatrogenic hyperthyroidism.
- Her thyroid dosage was lowered rapidly in view of her cardiac status. Fortunately, she tolerated it well.
- It was common 50 years ago to treat infertility, irregular menses, and similar problems with thyroid medication. Many of these patients are now elderly and may have significant morbidity from iatrogenic hyperthyroidism.

CASE 4

A 61-year-old woman was referred by her primary care physicians (PCP) for thyroid evaluation in 1993. She was diagnosed as hypothyroid by another physician in 1963. She was told her thyroid testing was extremely low and she was started on 2 grains of Armour thyroid (120 mg) daily. She felt much better on this treatment and continued it. In 1992, the dosage was increased to 3 grains daily because she "wasn't feeling so well." Shortly before I saw her, she presented to the hospital emergency room with palpitations and shakiness. Her PCP switched her to 0.1 mg of T_4 daily. She complained bitterly that she was so tired on this new medication that she couldn't go to work. The dose was increased to 0.15 mg of T_4 1 mo before I saw her. Thyroid studies ordered by her PCP 2 wk later showed a TSH of 2.3 and a total T_4 of 7.6, both normal. She complained to me of severe fatigue and muscle aching. She had been having crying episodes.

Physical examination revealed an obese lady complaining of fatigue. Pulse was 60 and blood pressure was 142/78. There were no thyroid eye signs and the thyroid was not palpable. The reflexes were slightly slow. The patient was continued on 0.15 mg of T_4 daily after a long counseling session regarding the problem as discussed in the other cases in this chapter. She returned 1 month later. Her fatigue had decreased in intensity and she was generally better. TSH was 1.1 and FT_4 was low-normal at 0.8.

What Is Your Diagnosis?

This is another patient with iatrogenic hyperthyroidism who experienced withdrawal symptoms on decreasing her thyroid dosage. She presented to the emergency room with probable hyperthyroid symptoms.

What Next?

I encouraged her to continue on her current thyroid dosage. She was referred back to her PCP for follow-up.

Case Summary

This is another patient with iatrogenic hyperthyroidism from long-term excessive treatment with Armour thyroid. She presented to the emergency room with hyperthyroid symptoms. She was switched to T_4 in a reduced equivalent dosage. She had withdrawal symptoms of fatigue and aching, which gradually improved.

What Can We Learn From This Case?

- A patient with iatrogenic hyperthyroidism may present with acute symptoms to an emergency room.
- It may be necessary to reduce thyroid dosage slowly because of withdrawal complaints.
- It is best to switch the patient from Armour thyroid to T_4. Armour thyroid is not well standardized in terms of biological potency and may contain variable amounts of T_3. This can be especially dangerous in the older patient.
- These patients may call the physician often and complain bitterly. Try to encourage them to "hang in there" and eventually things usually get better.

SUMMARY

The cases discussed in this chapter are variations on the same theme, iatrogenic hyperthyroidism. All the patients were started on thyroid many years ago when modern thyroid testing and treatment was not available. Some of these patients probably had no thyroid disease and were treated because of other problems, such as obesity and infertility. They became accustomed to being hyperthyroid both mentally and physically and many of them enjoyed feeling this way. We now know that iatrogenic hyperthyroidism may contribute to heart disease and osteoporosis. Most of these patients are now older and are at increased risk for these complications. They are very difficult to manage because they often complain bitterly about withdrawal symptoms, such as fatigue and muscle aches, and may call the physician often. Case 1 threatened to go to Mexico to get the thyroid medication that he desired. However, most of these patients will work with the physician if the physician is sympathetic and willing to lower thyroid dosage gradually. It may take 1 year or more for some of these people to get down to a euthyroid dose of T_4. However, some patients with cardiac complications must be made euthyroid more quickly.

Final Thoughts

I have enjoyed and continue to enjoy caring for patients with thyroid problems. It is always interesting, sometimes challenging, and frequently rewarding. Writing this book has given me the opportunity to relive many of my experiences with thyroid patients in the office. As I reviewed these cases, I could picture many of these people. In this book, I have tried to convey some of the enthusiasm that I have for sorting out and treating thyroid diseases. I hope the cases and discussions in this book will help you, the primary care physician, to better detect, diagnose, and treat thyroid patients. Of course, clinical judgement is required in the individual patient, but this book should give you some tools to help in the office practice of thyroid disease.

From: *Current Clinical Practice: Thyroid Disease: A Case-Based and Practical Guide for Primary Care*
By: E. O. Brams © Humana Press Inc., Totowa, NJ

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