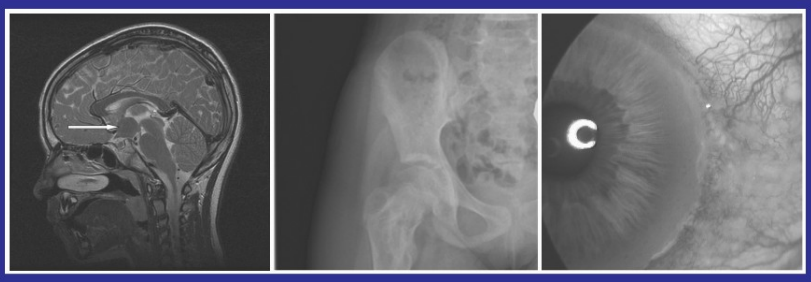
CONTEMPORARY ENDOCRINOLOGY™

A Case-Based Guide to Clinical Endocrinology

Edited by

Terry F. Davies, MD, FRCP, FACE



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A Case-Based Guide to Clinical Endocrinology

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Preface

In December 2005 I changed my mind [1]. Up until that time I had put my name on one case history in 400 publications [2]. I changed my mind and realized that reading case histories could be a good learning exercise.

I had previously considered useful case histories to be essentially live case demonstrations. Indeed, I had persuaded years of endocrine clinical fellows that writing case histories was not something to be encouraged. But the cheese moved. Live case history presentations became too complex for easy digestibility. The many investigations and vast literature review required more contemplation than a live presentation had required in the past. And writing these exercises as a formal case history allowed the complex literature to be better understood. Furthermore, as our evidence base has grown, the idiosyncratic approach so common in live case demonstrations of the past has become totally unacceptable.

The written or prepared case has become the ideal forum for demonstrating how to manage a medical case to the greatest benefit of the patient. Indeed, written case histories are clearly the very best means of showing medical care guidelines in real practice and of revealing their advantages and disadvantages [3]. That does not mean we should no longer give live case demonstrations. Demonstrating a supportive and knowledgeable patient can be a magnificent teaching tool. For many years I have presented endocrinology cases to our first-year medical students, and for many years these physicians later told me how much they enjoyed them and that they remember them well. So clearly, both formats of delivery remain effective. The use of live cases demonstrates how to talk with a patient, demonstrates clinical signs, and often arouses enthusiasm for the subject. Written cases provide a more thoughtful review of modern management and contemplation of the literature much more so than even a case presentation without the patient—something I still dislike.

But written cases also serve as an important early learning tool, and this book is designed to serve this latter purpose. The authors have done a marvelous job of stimulating our interest in a wide variety of endocrine subjects while teaching us the modern management of the conditions described and providing us entry into the literature. We have tried as much as possible to cover most of the current curriculum for clinical endocrine training as recommended by the Association of Program Directors in Clinical Endocrinology, Diabetes and Metabolism (APDEM, http://www.apdem.org/). To help readers determine if they have been concentrating,

each author provides multiple-choice questions that will test what readers have retained. Indeed, readers experienced in endocrinology may want to try the questions first! But students, residents, and fellows will find the examples to be an efficient way of reviewing their knowledge and increasing their experience in case management.

The cases as a whole have made a gem of a collection, and I thank all the contributors for their hard work and their willingness to keep to the outline constraints imposed by such a book in order to retain some cohesiveness. Thanks also to our publishers, especially Richard Lansing of Humana Press, for his patience and support, and to P. Michael Conn, for pushing me into the project. Oh, and by the way, changing one's mind is OK.

Terry F. Davies, MD, FRCP, FACE

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Part XVI Instructive Rarities

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Part I
The Pituitary Gland

Introduction

Pamela U. Freda

Physiology

Normal function of the hypothalamus and pituitary gland are essential to the function of many other glands and hormone systems. The hypothalamus and pituitary gland coordinate hormone secretion by the thyroid gland, the adrenal glands, and the gonads, and the pituitary gland directly secretes prolactin, growth hormone, vasopressin, and oxytocin. The hypothalamic-pituitary-peripheral target gland axes function by means of traditional feedback loops whereby small peptide hormones secreted by the hypothalamus act as trophic and in some cases as inhibitory factors that control the release of pituitary hormones, which in turn control target gland hormone secretion. Negative feedback of target hormone on pituitary and hypothalamic hormone secretion then occurs.

The pituitary gland lies at the base of the brain below the optic chiasm in a bony structure, the sella turcica, and is bordered by the cavernous sinuses on either side. It is connected to the hypothalamus by the hypothalamic-pituitary stalk. The pituitary gland receives its blood supply from a portal venous capillary plexus through which hypothalamic hormones reach the pituitary gland. Its venous drainage occurs through the petrosal sinuses, which drain to the cavernous sinuses bilaterally. Hormones of the anterior pituitary gland include adrenocorticotropin (ACTH), which stimulates production of cortisol by the adrenal glands, and the glycoprotein hormones: thyroid-stimulating hormone (TSH), which stimulates the thyroid gland to produce thyroid hormones, luteinizing hormone (LH), which regulates testicular testosterone production in men and ovarian estrogen production in women, and follicle-stimulating hormone (FSH), which promotes sperm production in men and stimulates the ovaries to enable ovulation in women.

Hypothalamic-pituitary gland coordination of LH and FSH are needed for normal reproductive function. The anterior pituitary secretes prolactin, which is necessary for lactation. Prolactin secretion normally is under tonic inhibitory effects of

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dopamine via the hypothalamic-pituitary stalk, and lesions of the stalk that disrupt this can raise prolactin. Growth hormone (GH), via its production of insulin-like growth factor I (IGF-I), stimulates growth in childhood, and has important metabolic and body composition effects in adulthood. Hormones secreted by the posterior pituitary are antidiuretic hormone (ADH) or vasopressin, which is produced in hypothalamic neurons and stored and released from the posterior pituitary gland. Vasopressin deficiency, diabetes insipidus, is a manifestation of some hypothalamic-pituitary lesions.

Disorders of the Pituitary Gland

The hypothalamic-pituitary axis can be dysregulated by a number of disorders. The most common pituitary disorders are pituitary tumors. These can present with symptoms due to the mass effect of the tumor, such as headaches and visual field abnormalities (classically bitemporal field cuts), and signs and symptoms of hormone hypersecretion or those of pituitary insufficiency. Two general types of pituitary tumors exist: nonsecretory and secretory.

Nonsecretory Adenomas

Nonsecretory pituitary adenomas generally come to medical attention because of symptoms of mass effect of the tumor such as headaches and vision problems and in some case because of symptoms of hypopituitarism from compression of the normal pituitary. Occasionally, if the tumor presents with an apoplectic event (see Case 1), cranial neuropathies may be present. Cranial neuropathy at presentation of a pituitary tumor alone is very rare, and if present without apoplexy suggests a nonpituitary etiology of the sellar mass such as an inflammatory process or craniopharyngioma. Nonsecreting tumors may also be detected on a head imaging study done for another reason. Clinically, nonsecreting tumors do not produce symptoms of hormone hypersecretion, but may have positive immunohistochemical staining for hormones in particular gonadotropins. Nonsecreting tumors are generally treated with transsphenoidal surgical removal. Tumors causing optic chiasm compression and vision loss require timely surgical attention. Some small nonsecreting tumors can be observed with serial magnetic resonance imaging (MRI) scans and assessments of pituitary function. Residual tumor may require additional surgery and/or radiation therapy. No medical therapies have proven of consistent benefit for nonsecreting tumors.

Secretory Tumors

Secretory tumors most often present with signs and symptoms of the hormonal hypersecretion, but they may also present with signs and symptoms of tumor mass effect, as described above.

The most common type of hormone-secreting pituitary tumors are prolactin-producing tumors, called prolactinomas. These present most commonly as menstrual dysfunction, infertility, and galactorrhea in women, and change in sexual function and infertility in men. All pituitary tumors should have a prolactin measurement performed. These tumors can typically be treated very successfully with dopamine agonists.

Growth hormone–secreting tumors cause acromegaly, which is characterized biochemically by hypersecretion of GH and resultant persistent elevation of serum IGF-I levels. Patients with acromegaly typically have multisystem manifestations including coarsening of the facial features, enlargement of the hands and feet, reproductive dysfunction, skin tags, enlarged tongue, snoring and sleep apnea, hypertension, diabetes mellitus, carpal tunnel syndrome, arthritis, and others. Acromegaly is treated initially with transsphenoidal removal of the tumor. In patients not cured by surgery, medical therapy options include dopamine agonists, somatostatin analogues, and a GH receptor antagonist (pegvisomant). Some patients may also require radiotherapy.

Adrenocorticotropin-secreting pituitary tumors cause Cushing's disease. Symptoms of Cushing's disease include plethora, easy bruisability, thin skin, purple striae, muscle weakness, supraclavicular and dorsocervical fat pads, menstrual abnormalities, hypertension, diabetes mellitus, and osteoporosis. Cushing's disease is diagnosed biochemically by evidence of ACTH-dependent cortisol excess, most reliably by an elevated 24-hour urine free cortisol and elevated nighttime salivary free cortisol levels. Ectopic sources of ACTH excess need to be considered, but can be excluded by petrosal sinus sampling demonstrating a significant central–peripheral ACTH gradient. Cushing's disease is treated initially with transsphenoidal surgery. Although cure rates are high, some patients need additional therapy, which in most cases is radiotherapy along with adrenal-acting cortisol-lowering therapy such as ketoconazole. A somatostatin analogue is in clinical trials; it holds promise for efficacy in Cushing's disease.

Thyroid-stimulating hormone–secreting tumors are very rare. They can present with hyperthyroidism with an inappropriately normal or elevated TSH level. These tumors are also treated by transsphenoidal surgery. Tumors not cured by surgery may be treated by somatostatin analogue and radiotherapy. Very rarely, pituitary tumors may secrete FSH or LH.

Other Etiologies of Sellar Masses

There is a long differential diagnosis of the sellar mass, which is shown to occur in about 9% of transsphenoidal surgeries for a pituitary mass, and these etiologies are listed in Table I.1. The most commonly occurring of such non-pituitary lesions are craniopharyngiomas, and Rathke's cleft cysts most other etiologies of sellar masses are tumors or lesions that are noncancerous growths that may be mistaken for a pituitary tumor on an MRI scan and can interfere

Table I.1 Diagnoses in 1121 patients who underwent transsphenoidal surgery for sellar masses from January 1981 through May 1998 by one neurosurgeon

Diagnosis	No. of patients (%)
Pituitary tumors	
Hormone-secreting tumors	637(48)
Nonsecreting tumors	483(43)
Nonpituitary sellar/parasellar lesions	104(9)
Cell rest tumors	
Craniopharyngioma	17(16)
Rathke's cleft cyst	35(33)
Epidermoid	1(1)
Chordoma	10(10)
Other cyst	5(5)
Benign lesions	
Meningioma	8(8)
Metastatic tumors	11(10)
Breast	3
Prostate	2
Lung	1
Renal cell	1
Parotid	1
SNUC	1
Unknown primary	2
Lymphoma	1(1)
Vascular lesions	
Aneurysm	1(1)
Granulomatous, infectious and inflammatory	
Sarcoid	1(1)
Granulomatous hypophysitis	2(2)
Pituitary abscess	1(1)
Mucocele	2(2)
Lymphocytic hypophysitis	5(5)
Miscellaneous (CSF related)	
Arachnoid cyst	4(4)
Total	1120

CSF, cerebrospinal fluid; SNUC, Sinonasal undifferentiated carcinoma.
Adapted with permission from Freda PU, Post KD (1999).

with normal pituitary activities. Other sellar lesions that are important to consider are inflammatory processes such as sarcoidosis and lymphocytic hypophysitis. Other hypothalamic diseases such as tumors, and prior radiation and head trauma can result in pituitary dysfunction. Rarely, pituitary dysfunction can be due to genetic disorders such as disruption of pituitary gene transcription factors.

Hypopituitarism

All pituitary tumors, especially those that are large or have undergone surgery and radiotherapy may be associated with hypopituitarism. A wide array of symptoms

can occur in the setting of hypopituitarism and include those of thyroid, adrenal, gonadal, and GH deficiency. Case 1 discusses the management of these hormone deficiencies.

Three cases on pituitary disorders follow. This is not a comprehensive text on pituitary disorders, and the suggested readings listed below should supplement this text.

Suggested Readings

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Chapter 1
Pituitary Apoplexy

Steven Jon Russell and Karen Klahr Miller

Objectives

To understand the clinical presentation, the evaluation, the acute medical and surgical management, the long-term management, and the complications of pituitary apoplexy.

Case Presentation

A 36-year-old woman presented to her primary care physician on an urgent basis with "the worst headache of my life." The headache started suddenly. She took an over-the-counter analgesic but vomited soon after swallowing it. She also noticed blurry and double vision while searching for her doctor's phone number. In the doctor's office her heart rate was 115 beats per minute and blood pressure was 90/50 mm Hg. Left eye ptosis was noted as well as a dilated left pupil that did not react to light. The left eye was deviated downward and outward. The patient felt light-headed but had a normal gait, and strength and sensation were grossly intact for all extremities. She was transported promptly to the nearby hospital emergency room.

In the emergency room she denied any significant medical history. Her only medication was oral contraceptive pills. A brain computed tomography (CT) scan without contrast was obtained emergently. There was no evidence of subarachnoid hemorrhage or hemorrhage into the brain parenchyma, but a heterogeneous mass of about 4 × 4 cm was seen extending superiorly from the sella turcica.

Neurosurgical and endocrine consults were obtained. Dexamethasone 6 mg was administered intravenously. An urgent magnetic resonance imaging (MRI) scan of the pituitary was performed, which revealed a mass arising from the sella turcica that was 3.6 cm wide, 4.1 cm high, and 3.6 cm in the anteroposterior dimension

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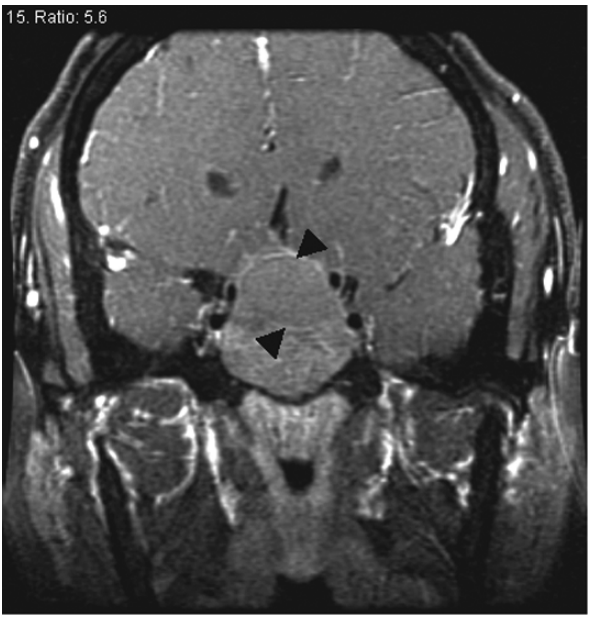

Fig. 1.1 Magnetic resonance imaging of a coronal section through a pituitary macroadenoma with hemorrhage (arrows)

(Fig. 1.1). The mass extended beyond the sella on both sides, displacing the internal carotid arteries laterally. An area in the superior portion of the mass, extending inferiorly on the left, was T1 hyperintense, T2 hypointese, and hypoenhancing compared to the remainder of the mass, consistent with hemorrhage. The optic chiasm was displaced dramatically upward. The decision was made to proceed to transsphenoidal surgery on an urgent basis to decompress the optic chiasm.

During presurgical evaluation the following additional information was obtained by the endocrine fellow: There was no history of unusually severe or frequent headaches, and the patient had not noticed any visual problems prior to the day of presentation. She started oral contraceptive pills for birth control after weaning her second child 12 years earlier, and had taken them continuously since that time. She had complained of fatigue and irritability for several years, and had gradually gained 20 pounds over the last 10 years. In the last 3 months, however, she had lost weight due to poor appetite. Her hair had become brittle, and she complained of increasing scalp hair loss. Her primary care physician had measured the thyroid-stimulating hormone (TSH) level several times at her request, and it had always been normal. There was no history of easy bruising or weakness, hirsutism, or change in ring or foot size. She had experienced some mild galactorrhea ever since weaning her last child. Comparison with a photo from 10 years earlier revealed no obvious changes in the shape of her face. There was no family history of endocrine abnormalities. She reported her height as 5’4”, and her weight was 152 pounds. On exam, vision

was limited to counting fingers bilaterally. Visual fields were difficult to define given her diffusely blurry vision and ophthalmoplegia, but she did have loss of peripheral vision bilaterally. There were no skin lesions. The thyroid was small. There was expressible galactorrhea. Reflexes were normal, and strength was 5/5 proximally in all four extremities. The endocrine fellow ordered a cortisol, free thyroxine (T_4), prolactin, and insulin-like growth factor I (IGF-I).

Late in the afternoon the patient underwent transsphenoidal surgery. Upon entering the sella, the surgeon found soft tumor, followed by dark, hemorrhagic fluid and clot as she worked upward through the mass. The mass was debulked as much as possible, but tumor adjacent to and invading the cavernous sinus bilaterally could not be safely resected. The sella was packed with fat harvested from the subcutaneous tissue of the abdomen. In the recovery room the patient noticed an improvement in vision, with acuity estimated at 20/80.

The following morning the patient's vision had subjectively recovered to that of her baseline and was measured at 20/30. The left ophthalmoplegia had resolved. Her glucocorticoid dose was reduced to 5 mg of prednisone each morning. Laboratory studies done prior to surgery were as follows: cortisol, 2.5 μg/dL; free T_4, 0.7 ng/dL (normal 0.9–1.8); prolactin, 112 ng/mL (normal <15, no dilution effect); and IGF-I, 94 ng/mL (normal 87–230). Morning cortisol on days 2 and 3 after surgery were 4 and 5 μg/dL, respectively. She developed transient diabetes insipidus postoperatively that resolved within 3 days. She was discharged from the hospital on the fourth hospital day in good condition, with instructions to stop taking the oral contraceptive pill (and use an alternative contraceptive method) and take 4 mg of prednisone daily until her follow-up appointment with the fellow in 6 weeks.

At her follow-up appointment the following information was reviewed: The tumor pathology showed mostly necrotic tissue and blood, with the few intact tumor cells staining for follicle-stimulating hormone (FSH), luteinizing hormone (LH), and α-subunit. There was no staining for adrenocorticotropin (ACTH), TSH, prolactin, or growth hormone (GH). The postoperative MRI showed residual tumor in the cavernous sinus partially encasing the internal carotid arteries, and a small amount of enhancing tissue above the fat packing. There was mild bitemporal hemianopsia by formal visual field testing. There had been no menstrual bleeding since discharge. Her only complaints were continued fatigue and irritability. She had been instructed not to take prednisone on the morning of the visit, and an ACTH stimulation test was performed.

At baseline, cortisol was 3 μg/dL, free T_4 0.7 ng/dL, TSH 1.8 μU/mL, IGF-I 90 ng/mL, estradiol <20 pg/mL, FSH 2.6 U/L, LH 3.8 U/L, and prolactin 12 ng/mL. The peak cortisol after stimulation was 10 μg/dL. The prednisone was continued and levothyroxine 112 μg daily was started. Her oral contraceptive pill was restarted.

At a return visit 6 weeks later she reported greater energy. Free T_4 was 1.3 ng/dL, TSH was <0.01 μU/mL, and IGF-I was 102 ng/mL. Peak growth hormone after growth hormone–releasing hormone (GHRH)/arginine stimulation testing was 3.2 ng/mL. Bone mineral density testing revealed hip and spine T scores of −1.7

and −2.3, respectively. Recombinant human growth hormone was started and titrated to a mid-normal IGF-I.

One year after presentation, the patient's fatigue and irritability had resolved, and she had experienced a decrease in waist circumference, although her weight was stable. An MRI revealed no change, with no growth of the residual tumor. The hip and spine T scores were −1.5 and −2.0, respectively.

How the Diagnosis Was Made

In this case, the clinical diagnosis preoperatively was pituitary apoplexy in a likely clinically nonfunctioning macroadenoma. The diagnosis of apoplexy was made based on the history of sudden headache, new visual symptoms, ophthalmoplegia, and a large sellar mass with evidence of hemorrhage. The new onset of severe headache, blurry vision, and ophthalmoplegia implied that the mass had acutely expanded. Note that hemorrhage is not always evident on imaging obtained at the time of presentation. An MRI is generally more sensitive for hemorrhage in this context. Even in the absence of radiographically documented hemorrhage, a pituitary mass in the setting of a clinical syndrome consistent with apoplexy should be treated as apoplexy until proven otherwise.

The patient had no history or clinical signs to strongly suggest an endocrine hypersecretion syndrome. Preoperative laboratory measurements revealed no evidence of elevated IGF-I or thyroid hormone. The prolactin was too low for a prolactinoma of this size, suggesting the elevation was likely due to pituitary stalk compression. The pathology showing necrosis and a population of cells staining for FSH, LH, and α-subunit confirmed the clinical diagnosis of apoplexy in a clinically nonfunctioning pituitary adenoma.

Lessons Learned

Pituitary apoplexy (apoplexy meaning "sudden attack", or "to be struck down") is a clinical syndrome in which the abrupt onset of typical signs and symptoms (see below) result from hemorrhage or infarction within the pituitary or a pituitary tumor. Although almost all cases of pituitary apoplexy occur in the setting of a preexisting tumor, in most cases the tumor has not been diagnosed previously. In retrospect, many patients have a history consistent with endocrine deficiency or hyperfunction. In this case, the preoperative history and laboratory studies were consistent with adrenal insufficiency, hypothyroidism, and growth hormone deficiency. The normal TSH measurements obtained by the patient's primary care physician could not rule out central hypothyroidism, as TSH levels are normal in the majority of patients with central hypothyroidism. The patient's continuous use of oral contraceptive pills may have masked hypogonadism.

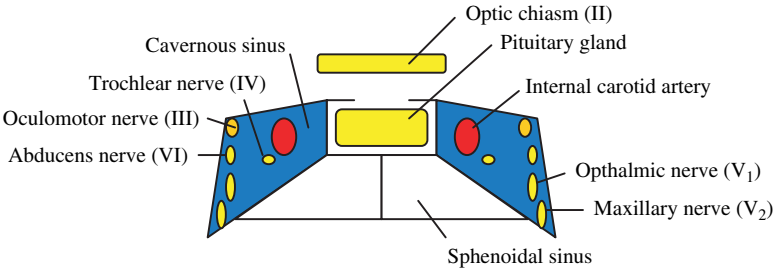

Fig. 1.2 Schematic of a coronal section through the normal pituitary gland and adjacent structures

The presenting symptoms and signs of apoplexy are headache (70–100%), ocular paresis (40–85%), visual disturbance (50–70%), vomiting (20–70%), and less commonly photophobia, meningismus, facial pain or numbness, or decreased level of consciousness. The most common visual symptoms are diplopia, blurred vision, and decreased peripheral vision (bitemporal hemianopsia), but the visual symptoms can vary from subtle ophthalmoplegia to the acute onset of binocular blindness [1, 2]. The most commonly involved cranial nerve in patients with ocular paresis is III, followed by VI, presumably due to their proximity to the sella in the cavernous sinus (Fig. 1.2) and apposition to the relatively unyielding lateral wall of the cavernous sinus. Cranial nerve (CN) III (oculomotor) paralysis may lead to ptosis, meiosis, lack of pupillary light or accommodation reflex, and deviation of the affected eye down and laterally. Cranial nerve VI (abducens) paralysis leads to inward gaze of the affected eye. Less commonly, CN IV (trochlear) paralysis results in outward and downward gaze, and CN V_1 (ophthalmic division of the trigeminal) involvement can lead to facial pain or numbness. Cranial nerves VI and IV abnormalities may not be obvious without specifically testing the extraocular movements, as the patient may move the head to align the two eyes.

It is important to note that, based on surgical series, pituitary tumor hemorrhage may also occur without symptoms or signs in up to 25% of patients, but this does not satisfy the criteria for apoplexy. A history consistent with apoplexy and evidence of pituitary hemorrhage or infarction are present in only 2% to 10% of patients at pituitary tumor surgery. The true incidence of apoplexy in all patients with pituitary tumors, including those that are undetected, is necessarily lower.

Most cases of apoplexy do not present to an endocrinologist. In the modern era, sudden severe headache associated with vomiting often leads to urgent CT imaging of the brain to rule out subarachnoid hemorrhage. If a mass arising from the sella is identified, a pituitary protocol MRI should be obtained and an endocrinologist should become involved. Hemorrhage is not reliably identified within the pituitary by CT; MRI is a more sensitive technique for detection of hemorrhage into pituitary tumors. In less severe cases, consideration of apoplexy by the clinician along with more common etiologies for headache, nausea, and visual disturbance, such as migraine, is essential. In many cases, there is a history suggestive of pituitary pathology that, if obtained by the clinician, may arouse the clinical suspicion of apoplexy.

Apoplexy associated with visual disturbance is considered a neurosurgical emergency because decompression of the optic chiasm is essential to conserve vision. There is evidence that some cases of apoplexy can be managed medically, although what fraction of patients may be managed this way, and the criteria for their selection, are controversial. One prospective study treated apoplexy patients initially with high-dose glucocorticoids, and then crossed over to surgery if glucocorticoid therapy failed to improve ophthalmoplegia, visual loss, or impaired consciousness [3]. Fewer patients in the medically managed group had residual tumor, but patients managed surgically had fewer residual pituitary hormone deficiencies, perhaps due to more complete necrosis of the sellar contents without surgical decompression ("autohypophysectomy"). More patients managed surgically had residual ophthalmoplegia or visual loss, but this may be because patients were selected for crossover to surgery as a result of more severe visual compromise. A later observational study in which 18 of 45 patients were managed medically reported similar findings and supported the idea that a subset of apoplexy patients can be managed medically [4].

Standard of care for apoplexy remains surgical decompression. Based on the available evidence, would candidates for medical management of apoplexy might be patients with mild or nonprogressive visual loss. The availability of a neurosurgeon with significant experience in pituitary surgery is also a critical factor in the management decision.

Apoplexy often is associated with adrenal insufficiency acutely. In this case, the random cortisol was too low (2.5 μg/dL) in the setting of the significant physiologic stress of an intracranial hemorrhage. Early morning values less than 3 μg/dL are strongly suggestive of adrenal insufficiency, but in the absence of significant physical stress, low cortisol values at other times of the day are not diagnostic of adrenal insufficiency. Immediate, empiric, intravenous high-dose glucocorticoid treatment is essential because the physiologic stress associated with apoplexy could prove fatal in the presence of glucocorticoid deficiency.

It is important to assess pituitary function preoperatively to the extent possible in the setting of a surgical emergency. This is especially true because surgical specimens from apoplexy cases may include mostly noninformative necrotic material and blood. Evidence of hypersecretion prior to surgery will guide postoperative monitoring. The identification of a prolactinoma might provide additional support for a trial of a dopamine agonist, as this may rapidly shrink any uninfarcted tumor. Absence of endocrine hypersecretion prior to surgery, even in the presence of tumor staining for a single hormone, might suggest clinically nonfunctioning status. In this case only prolactin was elevated, at levels most consistent with stalk compression rather than a prolactinoma.

Many patients are left with permanent endocrine deficits requiring long-term management [5]; up to 90% of patients require replacement of at least one hormone. If the tumor in which apoplexy arose is not completely removed or entirely necrotic, endocrine hypersecretion may persist. A complete evaluation of anterior pituitary hormone function should be performed approximately 6 weeks after surgical decompression of the sella. In this case, apoplexy was complicated by permanent panhypopituitarism, requiring comprehensive replacement of pituitary hormones.

It is useful to approach the management of hypopituitarism in a staged fashion. The first priority is the replacement of glucocorticoid, if necessary. Because profound adrenal insufficiency is incompatible with life, under conditions of severe physical stress patients are assumed to have adrenal insufficiency until proven otherwise. A replacement dose of glucocorticoids (e.g. 5 mg of prednisone each morning) is given postoperatively until a cortisol value of 18 μg/dL is documented, either on a morning sample or after ACTH (Cortrosyn) stimulation test. Since the ACTH stimulation test actually measures adrenal capacity for glucocorticoid release, an indirect measure of pituitary ACTH release, the test must be performed at least 6 weeks after the apoplexy event. An ACTH test performed before the adrenal zona fasciculata has atrophied, (due to lack of ACTH stimulation), may falsely indicate adequate glucocorticoid production. It is also important to know that oral estrogen (such as from an oral contraceptive pill [OCP]) increases cortisol-binding globulin and elevates cortisol levels, although not the physiologically relevant free cortisol fraction. Therefore, a value of 18 μg/dL is not adequate in the presence of oral estrogen. Because the level of cortisol that is indicative of adequate adrenal reserve is not well defined in patients taking oral estrogen, the best approach is to discontinue oral estrogen (assuming another form of contraception) for 6 weeks before determining adrenal sufficiency. If adequate cortisol production cannot be documented, glucocorticoid treatment will have to be continued indefinitely. The glucocorticoid dose should be titrated down to the lowest dose at which the patient feels well to avoid iatrogenic Cushing's syndrome, usually between 3 and 5 mg of prednisone each morning.

The second priority is to treat hypothyroidism, if present. Because the TSH (usually normal in untreated central hypothyroidism) is not useful in the setting of pituitary pathology, the diagnosis of hypothyroidism and adjustment of levothyroxine dose are based on the free T_4 and clinical signs and symptoms. Patients with a frankly low free T_4, or those with a value in the lower half of the normal range with hypothyroid signs and symptoms, may be treated with thyroid hormone initially dosed on a weight basis. The dose should be adjusted to maintain the free T_4 in the normal range and to avoid symptoms of hypo- and hyperthyroidism. The TSH usually becomes suppressed after appropriate treatment of central hypothyroidism. Misunderstanding of this principle often leads to inappropriate levothyroxine dose reductions. Treatment of hypothyroidism should only be initiated if the patient is taking adequate glucocorticoid therapy, or has been shown to be adrenally sufficient, because increased cortisol metabolism could otherwise precipitate adrenal crisis.

The third priority is replacement of sex steroids. In males, testosterone replacement (usually by patch or topical gel) is indicated when the total testosterone level in the morning (before 9 a.m.) is below the normal range unless fertility is desired, in which case gonadotropin therapy is often necessary. The testosterone dose should be titrated so that the testosterone is in the middle half of the normal range, usually 5 to 10 g of topical gel preparations. In women of premenopausal age, treatment with estrogen and progestogen (or estrogen only in women without a uterus) should be considered if amenorrhea persists for more than 3 to 6 months after apoplexy.

Low-dose oral contraceptive pills or an estradiol patch combined with 10 days a month of oral medroxyprogesterone are both appropriate options.

If the patient is a candidate for GH therapy (e.g., no history of malignancy willing and able to comply with therapy) GH deficiency can be ruled out with GHRH/arginine stimulation testing or an IGF-I that is frankly low in the presence of three additional pituitary hormone deficiencies. If GH deficiency is documented, GH may be initiated at a low dose and titrated upward to a mid-normal IGF-I value. Higher doses of GH are required in women taking estrogen.

Throughout the process of sequentially addressing hormone deficiencies, it is important to reassess dosing of each component of the replacement regimen. For example, treatment of hypothyroidism and GH deficiency may increase the prednisone requirement. Growth hormone increases deiodination of T_4 to triiodothyronine (T_3), so it is important to follow both free T_4 (to monitor for decreases) & T_3 (to monitor for increases) as well as symptoms of thyroid dysfunction it is also important to note that safety monitoring of all hormone replacement regiments over time is critical, but the specifics of such management is outside the scope of this article.

Patients with a history of apoplexy may also develop temporary syndrome of inappropriate antidiuretic hormone (SIADH) after the event (usually within the first 2 weeks) or diabetes insipidus (DI) that may become permanent; DI may be diagnosed in the setting of polyuria and polydipsia with an elevated or high normal serum sodium, or with the use of a water deprivation test when the diagnosis is in question. The DI can be simply treated with nasal deamino-8-D-arginine vasopressin (DDAVP) starting with one puff at night to avoid nocturia. If polyuria is a problem during the day, an additional dose may be added in the morning. Monitoring of the serum sodium is essential to avoid iatrogenic hyponatremia.

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Multiple-Choice Questions

1. The cranial nerve injury most commonly associated with pituitary apoplexy is:

   A. Causing headache CN V (trigeminal) nerve involvement
   B. Causing visual symptoms optic chiasm (CN II) compression

C. Causing ophthalmoplegia CN III or VI involvement
D. Causing diplopia cranial nerve IV involvement

Answer: C. Headache is the most common and nearly universal symptom in apoplexy, but in most cases it is not thought be associated with involvement of CN V. Ophthalmoplegia in general is more common than visual impairment, and cranial nerves III and VI are most commonly affected. CN VI and IV impairment may not be obvious with casual observation, so formal examination of extraocular movements is important.

2. Factors reported to be associated with apoplexy include:

A. Anticoagulants
B. Dopamine agonist treatment of prolactinomas.
C. Endocrine stimulation testing
D. All of the above

Answer: D. Many factors have been reported to be associated with the onset of apoplexy. However, it is difficult to establish that a similar number of apoplectic events would not have occurred without the specific factor at issue.

3. What is the percentage of patients with adrenal insufficiency after pituitary apoplexy?

A. ~25%
B. ~65%
C. ~90%
D. ~100%

Answer: B. Studies vary, but a review of 66 cases revealed a 66% rate of adrenal insufficiency [5]. GH deficiency and male hypogonadism were more common, and hypothyroidism was less common.

4. What is the most common tumor type in which apoplexy occurs?

A. Clinically nonfunctioning tumors
B. GH secreting adenomas
C. Prolactinomas
D. There is no clear preference for one tumor type

Answer: D. Although individual case series have reported a predominance of certain tumor types, the findings are not consistent. When taken together, the case series reports do not reveal a clear predominance for one tumor type, but the three tumor types listed are significantly more common than corticotroph adenomas and TSH secreting adenomas.

Chapter 2
When and How to Stop Cabergoline Treatment in Microprolactinomas

Annamaria Colao

Prolactinomas are the most frequent pituitary tumors with an estimated prevalence in the adult population of 100 per million population [1]. Their frequency varies with age and sex, occurring most frequently in women between 20 and 50 years of age; in the pediatric/adolescent age group, prolactinomas are rare, but represent about half of all pituitary adenomas [1].

Prolactin (PRL) excess causes gonadal and sexual dysfunction, while other symptoms related to the tumor expansion may occur in patients with large macroprolactinomas.

In the presence of clear-cut symptoms of hyperprolactinemia and after excluding pregnancy or the use of drugs known to induce increase of PRL levels [1], the diagnosis is made by serial PRL measurements and by magnetic resonance imaging (MRI) of the sella before and after contrast enhancement. Elevated (generally mildly) PRL levels in the absence of symptoms may be due to macroprolactinemia, while modestly elevated PRL levels in a patient with a large tumor may be expression of a pseudoprolactinoma (pituitary stalk section in a clinically nonfunctioning macroadenoma) [1]. However, in this latter case if PRL levels were measured by immunoradiometric assay (IRMA), the possibility of falsely low PRL levels by a hook effect should be verified by repeated PRL assay after dilution of blood samples [2].

To suppress excessive PRL secretion and its clinical consequences, such as infertility, sexual dysfunction, and osteoporosis, and to reduce the tumor mass, thereby relieving visual field defects, cranial nerve function and possibly hypopituitarism are the major objectives of treating patients with prolactinomas.

Dopaminergic agents, such as bromocriptine, lisuride, pergolide, and cabergoline, are considered the treatment of choice worldwide for either micro- or macroprolactinomas. Cabergoline has been shown more powerful and better tolerated than bromocriptine (3–7), and is tolerated very well by the large majority of patients.

In the past, treatment with dopaminergic drugs was considered to be necessarily continued lifelong due to the high recurrence rate at treatment withdrawal. More

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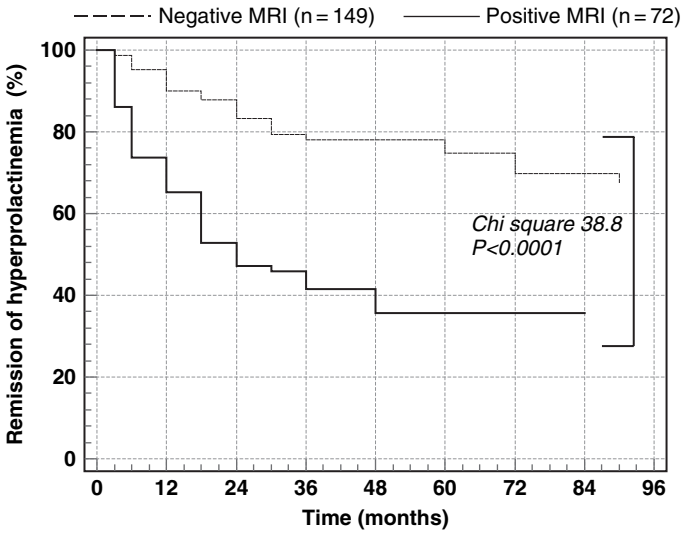

Fig. 2.1 Kaplan-Meier estimate of recurrence after 7 years of cabergoline treatment withdrawal. (Original data from ref. 1.)

recently, however, data have demonstrated a high prevalence of persistently normal PRL levels after withdrawal from cabergoline [8]. The remission rate after prolonged discontinuation of cabergoline treatment (median follow-up 72 to 90 months) was 68.4% in patients with nontumoral hyperprolactinemia, 51.8% in patients with microprolactinoma, and 52.5% in patients with macroprolactinoma [1]. The highest remission rates were found in the patients with nontumoral hyperprolactinemia or with disappeared microprolactinomas or macroprolactinomas during cabergoline therapy (Fig. 2.1). Importantly, at the last follow-up (48 to 90 months after cabergoline withdrawal) no recurrence of hyperprolactinemia was documented in the patients with no evident tumor on MRI later than 36 months.

The following case history of a 19-year-old woman with a microprolactinoma-induced amenorrhea describes the modality and outcome of cabergoline treatment withdrawal.

Case Presentation

M.M. came to our department for the first time in July 1997 at the age of 19 years because of amenorrhea lasting 5 months. She reported spontaneous menarche at the age of 13 years and oligomenorrhea since March 1996 associated with spontaneous bilateral galactorrhea. At our clinical examination, she had development of secondary sexual characteristics but axillary and pubic hair were faint while mammary glands were normally developed. At palpation, bilateral galactorrhea was found. Mean serum PRL levels at a diurnal profile were 98.5 μg/L (normal 5–25). At a

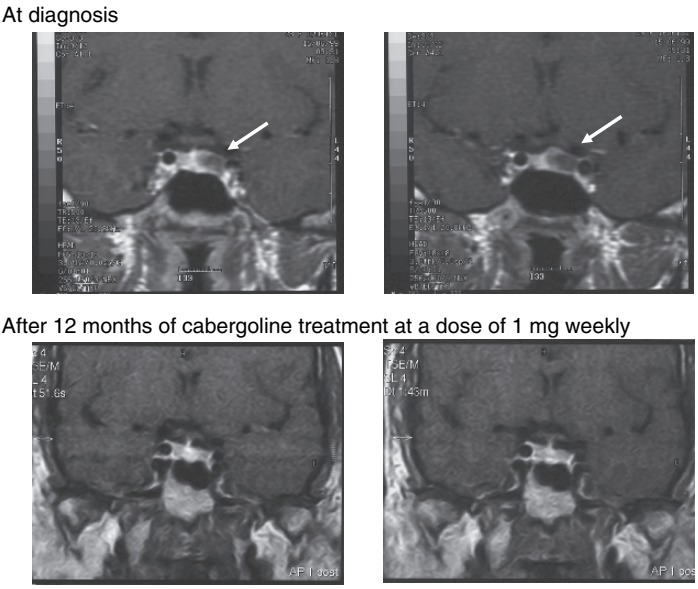

Fig. 2.2 Magnetic resonance imaging showing the 5-mm maximal diameter microprolactinoma located in the left portion of the gland (arrow) at diagnosis (top) and its disappearance after 12 months of cabergoline treatment (bottom)

sellar magnetic resonance imaging (MRI) with and without contrast enhancement, a pituitary microadenoma in the left paramedian portion was documented (Fig. 2.2). Thus, in accord with our routine clinical practice [8], in September 1997 the patient was started on cabergoline treatment at a dose of 0.5 mg twice weekly. Six months later, the mean serum PRL level was 3.6 μg/L, and we decided to continue cabergoline treatment at the same dosage.

At the 12-month follow-up after treatment, the mean serum PRL levels was 2.2 μg/L and the microadenoma was no longer visible on MRI (Fig. 2.2). In accord with our protocol [8], we decided to continue cabergoline treatment at a reduced dose to verify the possibility of subsequently withdrawing the patient from treatment. As shown in Figure 2.3, mean PRL levels remained stably in the normal range both at the dose of 0.5 mg weekly (3.8 μg/L) and 0.25 mg weekly (4.2 μg/L in a single dose). Since no microadenoma was documented on MRI performed in October 1999, treatment with cabergoline was stopped.

Cabergoline withdrawal was followed by a slight increase of PRL levels that remained in the normal range until the follow-up of January 2002. At this follow-up the mean serum PRL levels increased to 55 μg/L (Fig. 2.3). Since a PRL increase could have been caused by either recurrence of the microprolactinoma or pregnancy we performed a β–human chorionic gonadotropin (β-HCG) measurement that was 8500 mU/L (normal <50).

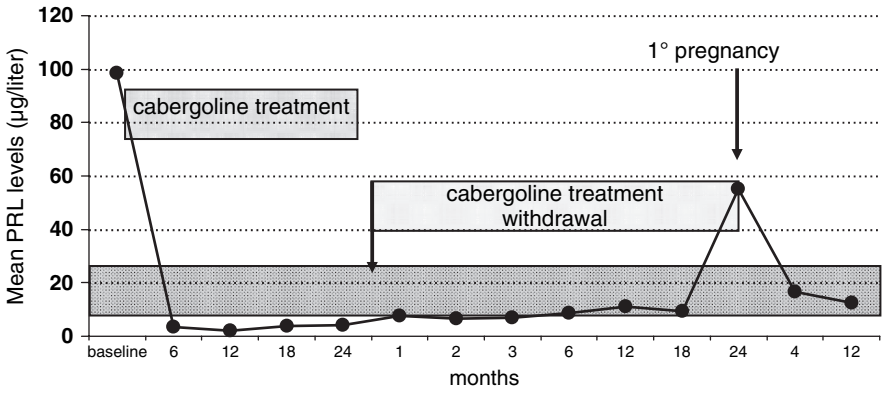

Fig. 2.3 Profile of mean prolactin (PRL) levels (diurnal profile of three to six blood samples) during the follow-up of patient M.M

On October 2, 2002, the patient delivered a healthy girl (length 51 cm, weight 3.1 kg). The patient was allowed to breast-feed her baby for 3 months. Subsequently, a reevaluation of mean PRL levels and sellar MRI were performed. Mean serum PRL levels was normal and a partial empty sella in the left paramedian portion of the gland was documented on MRI. Menses reappeared in February 2003. As shown in Figure 2.3, mean PRL levels remained normal to date. No change on MRI was found.

The patient had a second healthy pregnancy in April 2004. No recurrence of hyperprolactinemia or change on MRI were found at the follow-up performed in July 2006.

Lessons Learned

Cabergoline is considered the most effective drug for treating prolactinomas. Bromocriptine and pergolide are also very effective, but cabergoline fosters better patient compliance than bromocriptine and normalizes PRL levels even in patients resistant to bromocriptine (3–7). No comparative studies between cabergoline and pergolide are available. Note that asymptomatic patients with prolactinomas do not have an absolute requirement for treatment, since the major indications for therapy in patients with prolactinomas are to control tumor size and to reverse the effects of hyperprolactinemia [1].

The patient reported in this study had the classical amenorrhea-galactorrhea syndrome associated with a microprolactinoma, and there was no doubt that she needed to be treated. As per our routine clinical practice, the patient was informed of the benefits and risk of cabergoline and surgery, and she preferred to avoid surgery. Surgical removal of the microadenoma could also be considered a valid alternative to long-term pharmacotherapy with dopaminergic drugs, since the more modern

mini-invasive neurosurgical approach is very efficacious and results in the immediate relief of the clinical consequences of hyperprolactinemia [9, 10]. Recurrence of hyperprolactinemia is reported in approximately 20% at 10 years [1].

As already mentioned, recovery of gonadal function, control of tumor growth, and recovery from neurologic symptoms in patients with macroprolactinomas are generally obtained with primary dopamine agonist treatment [1]. In the past, cure of a prolactinoma has invariably been defined as the complete removal of tumor through surgical resection [11] due to the evidence that withdrawal from dopamine agonists (bromocriptine mainly) was followed by recurrent hyperprolactinemia in most cases [1]. In the first study reporting results of bromocriptine withdrawal, Johnston et al [12] reported recurrence of hyperprolactinemia in 94.6% of 37 patients even if PRL levels remained significantly lower than those prior to initiating therapy. Several other studies have confirmed the preliminary observation of Johnston et al (summarized in ref. 1). As a result, the principal shortcoming of dopamine agonist treatment has been its supposed lifelong requirement.

More recently, in an prospective, observational, and analytical study conducted in 200 patients with hyperprolactinemia undergoing cabergoline withdrawal, we reported a prevalence of recurrent hyperprolactinemia, independent of baseline tumor size, in less than 40% of the patients; thus, we anticipate greater long-term successful withdrawal with this drug [8]. In detail we found a Kaplan-Meier estimate of the recurrence rate of hyperprolactinemia after 5 years of cabergoline withdrawal of only 24% in patients with nontumoral hyperprolactinemia, and 32.6% in patients with micro- and 43.3% in those with macroprolactinomas without any MRI evidence of tumor regrowth. The highest remission rate was observed in patients with tumor disappearance during cabergoline treatment (Fig. 2.1).

Therefore, the case history reported in this study represents an exemplary case of patients with microprolactinoma with successful cabergoline treatment withdrawal.

Some other considerations should be addressed regarding this case. First, studies examining the natural history of untreated microprolactinomas have shown that significant growth of these tumors is uncommon [1]. Only nine (6%) of 139 women in six series of patients (with computed tomography [CT] evidence of microprolactinoma) observed without treatment for a period up to 8 years had evidence of microprolactinoma growth (13–18). Second, pregnancy [19, 20] and menopause [21] are conditions known to facilitate the remission of hyperprolactinemia, apart from previous surgery or radiotherapy and bromocriptine or cabergoline withdrawal.

In the patient reported in this study, pregnancy occurred after 2 years of successful cabergoline withdrawal. Delivery of a healthy girl was physiologic, and serum PRL levels normalized after the patient stopped breast-feeding as normally expected. In consideration of the long-term normalization of PRL levels after cabergoline withdrawal, it is unlikely that pregnancy was responsible for such a beneficial effect. In my opinion, it is more likely that pregnancy occurred because of the restoration of physiologic pituitary function than vice versa. A positive role of pregnancy in the persistence of normalization of PRL levels cannot be ruled out, however. It is, instead, uncommon that the simple observation of a microprolactinoma causing amenorrhea and galactorrhea is followed by remission of the disease, as

mentioned above. In such cases treatment (medical or surgical, according to the individual patient's preference) is indicated.

Conclusion

This case history of a young woman with a microprolactinoma-induced amenorrhea-galactorrhea syndrome demonstrates that 2 years of cabergoline treatment at a standard dose of 1 mg weekly in the first year and at a low dose of 0.25 to 0.5 mg weekly in the second year induced disappearance of the tumor together with normalization of PRL levels and restoration of normal pituitary-gonadal function. Withdrawal of cabergoline treatment was successful, but careful follow-up is required in all patients undergoing such an approach. In this case, successful withdrawal was accompanied by two successful pregnancies thereafter. Pregnancy-induced hyperprolactinemia could induce a misdiagnosis of recurrent hyperprolactinemia. Therefore, before cabergoline treatment is restarted, we suggest that β-HCG measurement be performed in all cases.

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Questions

1. Microprolactinomas are the most frequent pituitary tumors. True or false?
2. They invariably cause amenorrhea and galactorrhea in women. True or false?
3. The best treatment of microprolactinomas is

   A. Medical with dopamine agonists
   B. Surgical
   C. Both

4. Withdrawal from dopamine-agonist is invariably followed by recurrent hyperprolactinemia. True or false?

Chapter 3
Cushing's Disease

Kawaljeet Kaur and James W. Findling

Objectives

To identify the patient population that should be screened for hypercortisolism, and to understand the approach to the diagnosis, differential diagnosis, and management of Cushing's syndrome.

Case Presentation

A 58-year-old white woman presented with multiple nontraumatic metatarsal stress fractures in both feet. She denied recent falls, corticosteroid use, or prolonged immobility. She did report a progressive weight gain of about 20 pounds over the prior 4 years as well as fatigue, sleep disturbance, hypertension, and hyperlipidemia. Physical exam revealed blood pressure of 150/90 mm Hg and a body mass index (BMI) of 27.5. She was not cushingoid (Fig. 3.1). Her skin did not show significant thinning, acanthosis, or striae. There was some facial rounding but no significant supraclavicular fullness. The physical exam was otherwise unremarkable. Her bone mineral density studies done 18 months prior to the visit showed a low bone density in the hip (T score -1.5) and right femoral neck (T score -2.0), and lumbar spine was normal. Family history was negative for any pituitary, adrenal, thyroid diseases, or osteoporosis.

Because of the weight gain, hypertension, and low bone density with fractures, endogenous hypercortisolism (Cushing's syndrome) was considered. Late-night salivary cortisol levels were elevated at 5.4, 7.3, 7.3, and 8.7 nmol/L (normal range is 0.3–4.3). A 24-hour urine cortisol was 40 μg (normal is less than 45 μg/24 hours). An overnight 1-mg dexamethasone suppression test yielded a cortisol of 20.7 μg/dL (normal is <1.8). Despite the normal 24-hour urine free cortisol, the consistently abnormal late night salivary cortisol measurements as well as the abnormal low

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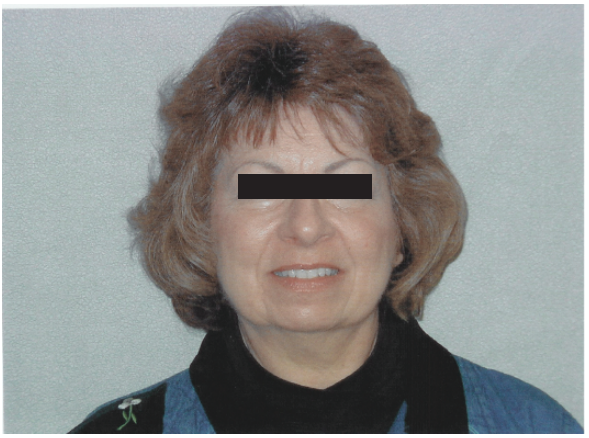

Fig. 3.1 Non-Cushingold woman with weight gain, low bone density, and hypertension

dose dexamethasone suppression test strongly supported the diagnosis of Cushing's syndrome.

To establish the cause of her Cushing's syndrome, a plasma adrenocorticotropin (ACTH) was obtained on two occasions, and the values were elevated at 134 and 117 pg/L (normal range is 9–52). Magnetic resonance imaging (MRI) of the pituitary gland demonstrated a subtle area of asymmetric decreased enhancement within the left portion of the pituitary gland, which could represent a pituitary microadenoma. Since the MRI was not definitive, bilateral simultaneous inferior petrosal sinus ACTH sampling with corticotropin-releasing hormone (CRH) stimulation was performed and demonstrated a significant pituitary to peripheral ACTH gradient as well as an exaggerated ACTH response to CRH (Table 3.1). Based on the results of the inferior petrosal sinus sampling, the diagnosis of Cushing's disease was confirmed. Transsphenoidal pituitary surgery was performed and a 5-mm ACTH-secreting pituitary microadenoma was successfully removed. Postoperatively, the patient's cortisol level decreased immediately to $<3\ \mu g/dL$ and glucocorticoid support was initiated. Seven days after surgery, the patient developed severe hyponatremia requiring rehospitalization. She recovered promptly with fluid restriction.

Table 3.1 Sample location and ACTH concentration (pg/mL)

Time	Right petrosal sinus	Left petrosal sinus	Peripheral
−2 minutes	370	654	119
0 minutes	441	579	118
	100 μg oCRH IV		
2 minutes	5240	3960	121
5 minutes	3140	3200	242
10 minutes	3000	3240	296
30 minutes	–	–	335

oCRH, ovine corticotropin-releasing hormone.

How the Diagnosis Was Made

The clinical and biochemical diagnosis of spontaneous Cushing's syndrome is challenging, particularly when the degree of hypercortisolism is mild, as in our patient. A surprisingly high prevalence of endogenous hypercortisolism has been found in certain high-risk groups. For example, studies have found unsuspected Cushing's syndrome in 2% to 5% of patients with poorly controlled diabetes. It is also well appreciated that 6% to 10% of patients with incidentally discovered adrenal nodules ($\geq$2 cm) have biochemical evidence of excessive cortisol secretion. A recent study found unsuspected Cushing's syndrome in as many as 10.8% of patients with osteoporosis and vertebral compressions fractures and in 4.8% of all patients with osteoporosis who were evaluated for a secondary cause. A recent study by Chiodini et al. found.

The clinical manifestations of Cushing's syndrome are protean, and their onset may be quite insidious over a period of many years. The classic clinical features of hypercortisolism should provoke an evaluation. These features include unexplained weight gain with a central distribution and facial rounding, increased supraclavicular and dorsocervical fat accumulation, cutaneous wasting with easy bruising, wide violaceous striae, proximal myopathy, and decreased growth velocity in children. In addition, several disorders known to be caused or aggravated by hypercortisolism should also stimulate consideration of Cushing's syndrome. For example, patients with the dysmetabolic syndrome (diabetes, hypertension, dyslipidemia, polycystic ovary syndrome), hypogonadotropic hypogonadism, and osteoporosis need to be considered for screening. Despite the fact that our patient was not cushingoid, the presence of her low bone density with fractures, weight gain, and hypertension mandated an evaluation for Cushing's syndrome.

The main screening and diagnostic tests for Cushing's syndrome include a late-night salivary cortisol measurement, an overnight 1-mg dexamethasone suppression test, and a 24-hour urine free cortisol. All three of these tests are complementary, but each has limitations. Traditionally, the 24-hour urine free cortisol was considered the gold standard; as our case illustrates, many patients with Cushing's do not have elevations of urine free cortisol and the sensitivity of this test is only 45% to 71% at a specificity of 100%. Multiple urine collections are often needed when the degree of hypercortisolism is mild, and the cumbersome nature of this test makes it less than ideal for repeat testing. Impaired renal function may also falsely decrease the urine free cortisol. Moreover, certain conditions such as alcoholism, depression, and eating disorders (pseudo-Cushing's syndrome) may result in elevations of urine free cortisol without a pathologic cause of Cushing's syndrome.

The first biochemical detectable abnormality in patients with Cushing's syndrome is the failure to decrease cortisol secretion to its normal nadir at night. This phenomenon has been utilized in the diagnosis of Cushing's syndrome by employing nocturnal salivary cortisol determinations. Salivary cortisol is a reflection of free cortisol and is unaffected by salivary flow rates. Nocturnal salivary cortisol (between 11 p.m. and midnight) yields a sensitivity and specificity approaching 95% for Cushing's syndrome and is emerging as the most reliable and simple diagnostic

test for this disorder. Although, normal ranges differ depending on assay methodology, the use of a Food and Drug Administration (FDA)-cleared enzyme-linked immunosorbent assay (ELISA) for the diagnosis of Cushing's syndrome has provided clinicians with a valuable and reliable diagnostic test. Using this ELISA assay, late-night salivary cortisol levels in normal subjects are consistently less than 3 to 4 nmol/L. Values consistently above 7 nmol/L are virtually diagnostic of Cushing's syndrome, and intermediate values require additional diagnostic evaluation. The screening test used in our patient for the consideration of Cushing's syndrome was nocturnal salivary cortisol, and her levels were between 5.4 and 7.3 nmol/L and certainly raised concern for Cushing's syndrome.

Low-dose dexamethasone suppression testing continues to be widely employed in the diagnostic evaluation of patients with suspected endogenous hypercortisolism. Normal ACTH-secreting cells decrease ACTH release following low doses of dexamethasone as a result of glucocorticoid negative feedback. In contrast, ACTH-secreting neoplasms do not fully suppress ACTH in response to low-dose dexamethasone, resulting in persistent elevations of cortisol. Two forms of the test have been used: a 2-day low-dose dexamethasone suppression test with collection of urine steroids, or an overnight 1-mg dexamethasone suppression test. The former study has been essentially abandoned due to its cumbersomeness. The overnight 1-mg dexamethasone suppression test has the same level of sensitivity and is much easier to perform. Cutoff values for suppression of cortisol following an overnight 1-mg dexamethasone measurement test have been reported between 1.8 and 5 μg/dL. Depending on which value you choose, the sensitivity and specificity obviously change. To achieve a very high sensitivity, a consensus statement suggested that a serum cortisol should be less than 1.8 μg/dL (50 nmol/L) following the overnight 1-mg test; however, this cutoff value results in a less than optimal specificity with significant number of false-positive results. False-positive results can also be caused by decreased dexamethasone absorption (in patients with chronic renal failure), drugs that accelerate hepatic dexamethasone metabolism (anticonvulsant therapy), an increase in cortisol-binding globulin (estrogen therapy), and the aforementioned pseudo-Cushing's conditions (alcoholism, depression, and eating disorders). Despite these limitations, the overnight 1-mg dexamethasone suppression test was helpful in our patient, providing further evidence for the diagnosis of Cushing's syndrome.

Once the diagnosis of Cushing's syndrome is established, the next step is determining its cause. The majority of patients with Cushing's syndrome have an ACTH-secreting neoplasm (ACTH-dependent Cushing's syndrome) usually a pituitary tumor (Cushing's disease) or occasionally a nonpituitary neoplasm (ectopic ACTH). The ectopic ACTH syndrome (particularly when due to neuroendocrine tumors such as bronchial carcinoids) may present with hypercortisolism long before a neoplasm is evident radiographically (occult ectopic ACTH syndrome). These subtypes of ACTH-dependent Cushing's syndrome are often clinically and biochemically indistinguishable and careful differential diagnostic evaluation is required.

In contrast, ACTH-independent Cushing's syndrome is due to autonomous adrenal production of cortisol (adrenal-dependent Cushing's syndrome). The

majority of such patients have a solitary, benign (or, rarely, malignant) adrenocortical neoplasm. A minority have an ACTH-independent form of bilateral nodular adrenal hyperplasia.

The initial step in the differential diagnosis is the measurement of plasma ACTH. A two-site immunometric assay has provided sensitive, specific, and reliable information. A suppressed ACTH (less than 5 pg/mL) indicates adrenal-dependent Cushing's syndrome, and imaging of the adrenal glands is needed. Plasma ACTH levels greater than 20 pg/mL suggest an ACTH-dependent cause. Values between 5 and 20 pg/mL are sometimes more difficult to characterize, and occasionally a CRH stimulation test is required for differential diagnosis. Theoretically, patients with ACTH-independent Cushing's syndrome usually have a subnormal peak ACTH response to CRH (usually less than 30 pg/mL), while patients with pituitary ACTH-secreting neoplasm usually have an exaggerated ACTH response to CRH.

Our patient had a markedly elevated plasma ACTH providing unequivocal evidence that she had an ACTH-secreting neoplasm. Since the majority of patients with ACTH-secreting tumors have pituitary microadenomas (Cushing's disease), the next step is a pituitary MRI. This procedure demonstrates a discrete microadenoma in approximately 40% to 60% of patients with Cushing's disease. When an unequivocal pituitary adenoma (greater than 6 mm) is identified with MRI, further diagnostic evaluation may not be needed and referral to a pituitary neurosurgeon can be recommended. However, it should be remembered that 10% of the normal population has incidental tumors of the pituitary gland found on MRI, although the majority are less than 6 mm. Our patient had equivocal MRI findings, and because of the marked elevation of plasma ACTH, the diagnosis of an occult ectopic ACTH secreting neoplasm was considered.

The only reliable means of distinguishing between pituitary and nonpituitary ACTH-dependent Cushing's syndrome in patients with negative imaging studies is the use of bilateral simultaneous inferior petrosal sinus sampling for ACTH. This test takes advantage of the venous drainage of the anterior pituitary through which hormones such as ACTH reach the systemic circulation. Blood leaves the anterior lobe by numerous small hypophyseal veins that empty directly into the lateral adenohypophyseal veins that converge into the confluent pituitary veins that surround the pituitary gland and then course laterally to join the cavernous sinus and eventually into the inferior petrosal sinus. Inferior petrosal sinus sampling with CRH stimulation provides excellent diagnostic sensitivity and specificity for the diagnosis of Cushing's disease; a central–peripheral ACTH gradient >3.0 is consistent with this diagnosis. The inferior petrosal sinus ACTH sampling results in our patient showed unequivocal evidence of a pituitary ACTH gradient, and the patient was referred to a pituitary neurosurgeon.

Our patient was found to have a 5-mm ACTH-secreting pituitary tumor that was successfully removed and then followed promptly by secondary adrenal insufficiency with very low serum cortisol determinations. The development of secondary adrenal insufficiency after surgery is a good prognostic sign. The majority of these patients have gratifying clinical and biochemical remissions of their Cushing's syndrome. Nonetheless, recurrences may occur, and long-term assessment of pituitary

adrenal function is essential in these patients. Exogenous glucocorticoid support was administered in our patient to help attenuate the problems with steroid withdrawal.

Our patient developed severe, symptomatic hyponatremia approximately 1 week after surgery. This phenomenon (the syndrome of inappropriate antidiuretic hormone) is a well-known complication of pituitary surgery. Theoretically, this is caused by ischemia of the neurohypophysis that occurs at surgery followed by necrosis and an abrupt release of vasopressin (antidiuretic hormone) 5 to 10 days postoperatively, often after the patient has been discharged. As in this patient, hospitalization is often required, with fluid restriction. As in our patient, this problem usually resolves spontaneously without any long-term sequelae. Rarely, patients develop permanent diabetes insipidus.

Lessons Learned

The diagnosis of mild Cushing's syndrome requires a high index of clinical suspicion, particularly in patients with clinical disorders that are caused by or aggravated by hypercortisolism. The presence of unexplained weight gain, hypertension, and low bone density with fractures resulted in a screening study in our patient, who did not have the clinical appearance of Cushing's syndrome. It is clear that the nocturnal salivary cortisol level is a reliable and sensitive screening test for this disorder and should be employed early in the diagnostic evaluation of these patients. Despite normal urinary free cortisol levels in our patient, ACTH-dependent Cushing's syndrome was confirmed with persistent elevations of late-night salivary cortisol and a grossly abnormal low-dose dexamethasone suppression test. The differential diagnosis was quite straightforward with marked elevations of plasma ACTH and an unequivocal pituitary ACTH gradient during inferior petrosal sinus sampling. Pituitary microsurgery resulted in resection of her corticotroph microadenoma followed by clinical and biochemical evidence of adrenal insufficiency portending a good long-term prognosis.

Suggested Readings

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Multiple-Choice Questions

1. Appropriate screening tests for Cushing's syndrome include which of the following?

   A. Pituitary MRI
   B. 24-hour urine free cortisol
   C. Plasma ACTH
   D. Inferior petrosal ACTH sampling
   E. Late-night salivary cortisol

2. After the diagnosis of Cushing's syndrome has been established, the initial diagnostic study should be which of the following?

   A. Pituitary MRI
   B. Dexamethasone suppression testing
   C. Plasma ACTH
   D. CT scan of the adrenal glands
   E. Inferior petrosal sinus ACTH sampling

3. A 35-year-old woman with the insidious onset of the signs and symptoms of hypercortisolism has late-night salivary cortisol values of 19 and 21 nmol/L (normal: 0.3–4.3). Plasma ACTH is 44 pg/mL (normal: 9–52). The most likely cause of her hypercortisolism is which of the following?

   A. Adrenocortical adenoma
   B. ACTH-secreting bronchial carcinoid
   C. ACTH-secreting pituitary tumor
   D. Surreptitious use of prednisone
   E. Anorexia nervosa

Part II
Thyroid Overactivity

Introduction

David S. Cooper

Hyperthyroidism is a syndrome caused by tissue exposure to excessive circulating amounts of thyroid hormone. Purists restrict the term *hyperthyroidism* to those disease entities in which the thyroid gland actively produces and secretes excessive hormones. They reserve the term *thyrotoxicosis* to refer to any condition in which an excessive amount of thyroid hormone is present, whether it is derived from excessive secretion by the gland (e.g., Graves' disease), from leakage from a damaged gland (e.g., various forms of thyroiditis), or is exogenous (e.g., iatrogenic or factitious thyrotoxicosis). However, most clinicians use the terms *hyperthyroidism* and *thyrotoxicosis* interchangeably. In population-based cross-sectional studies, hyperthyroidism is present in approximately 0.5% to 1% of individuals. It is frequently "subclinical," meaning that thyroid hormone levels are within the range of normal, but circulating serum thyrotropin (TSH) is subnormal or undetectable.

As hyperthyroidism is a syndrome, it has many potential etiologies (Table II.1). Graves' disease is the most common cause of hyperthyroidism in young and middle-aged people. It is caused by circulating anti-TSH receptor antibodies (so-called thyroid-stimulating antibody or thyroid-stimulating immunoglobulin). Hyperthyroidism can also arise from autonomous function within the gland, due to activating mutations in the TSH receptor or the G-protein signal transduction pathway. This produces solitary or multiple autonomously functioning thyroid nodules. The resulting toxic multinodular goiter is the most common etiology of hyperthyroidism in older persons. Thyrotoxicosis may develop due to destruction of thyroid follicles, leading to leakage of thyroid hormone into the bloodstream as part of the various forms of thyroiditis. These include subacute thyroiditis, a viral infection of the thyroid, as well as "silent" thyroiditis, an autoimmune disease that has a predilection for the postpartum period. Uncommon or rare causes of hyperthyroidism include ectopic thyroid tissue (struma ovarii), functioning metastases from follicular thyroid cancer, TSH-secreting pituitary tumors, and human chorionic gonadotropin (HCG)-mediated hyperthyroidism in patients with hyperemesis gravidarum or choriocarcinoma.

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Table II.1 Causes of thyrotoxicosis

- Thyroid stimulators
  - Graves' disease (thyroid-stimulating antibodies)
  - TSH - secreting tumor
  - Hyperemesis gravidarum, choriocarcinoma (HCG)
- Thyroidal autonomy
  - Toxic multinodular goiter
  - Toxic adenoma
  - Congenital hyperthyroidism due to TSH receptor activating mutation
  - Iodine-induced hyperthyroidism
- Thyroiditis
  - Subacute (also called granulomatous, viral, or de Quervain's) thyroiditis
  - "Silent" or "painless" thyroiditis (typically postpartum)
  - Amiodarone-induced thyroiditis
  - ? Interferon-induced
  - Acute (infectious) thyroiditis (bacterial, fungal, etc.)
- Exogenous thyroid hormone
- Ectopic thyroid tissue
  - Struma ovarii
  - Metastatic follicular thyroid cancer
- Pituitary resistance to thyroid hormone

Symptoms of thyrotoxicosis are well known to all clinicians, and include palpitations, tremor, weight loss despite a normal intake, anxiety, insomnia, heat sensitivity, muscle weakness, and irregular or absent menses in women. For reasons that are not well understood, older patients may have few or no symptoms or signs of hyperthyroidism, but may present solely with atrial fibrillation or unexplained weight loss.

Drugs are increasingly common causes of hyperthyroidism. Inorganic iodine can produce hyperthyroidism, especially in patients with an underlying nodular goiter (the Jod-Basedow phenomenon). Amiodarone is perhaps the most notorious cause of drug-induced hyperthyroidism, occurring in 3% to 10% of individuals exposed to the drug, depending on background iodine intake. Hyperthyroidism due to interferon-alfa and other immune mediators is being recognized with greater frequency. Interestingly, all of these drugs (iodine, amiodarone, interferon-alfa) can also produce hypothyroidism depending on the patient and the presence of underlying thyroid disease.

The diagnosis of hyperthyroidism rests with finding elevated levels of thyroxine (T_4) or triiodothyronine (T_3) in conjunction with a suppressed serum TSH level. In the very rare patients with TSH-secreting tumors or resistance to thyroid hormone, the serum TSH will be inappropriately normal or elevated. Measurement of the 24-hour radioiodine uptake may be helpful, as it would be elevated in most conventional causes of hyperthyroidism and low in thyroiditis of any cause.

The treatment of hyperthyroidism depends on the underlying etiology, but patient age, reproductive status, personal preferences, and a host of other factors go into making the final decision. In general, antithyroid drug therapy, radioiodine, and surgery are the cornerstones of treatment. β-adrenergic blocking agents,

glucocorticoids, lithium, potassium iodide, and other drugs may be used in special circumstances.

In this section, two cases of drug-induced hyperthyroidism illustrate some of the diagnostic and therapeutic difficulties that are often encountered. Following that, a case of hyperthyroidism due to subacute thyroiditis is presented that demonstrates that even classic presentations can sometimes be problematic. Finally, a patient with mild (subclinical) hyperthyroidism is presented. This case illustrates the many controversies that surround the management of this very common clinical entity.

Chapter 4
Amiodarone-Induced Hyperthyroidism

Paul Aoun and David S. Cooper

Objectives

Amiodarone is a potent antiarrhythmic drug that is associated with a wide array of adverse effects, including both hypothyroidism and hyperthyroidism. Here, we report the case of a 65-year-old man who was started on amiodarone for recurrent atrial fibrillation and 2 years later developed hyperthyroidism. We briefly review the normal changes in thyroid function tests that are seen with amiodarone. We then discuss the proposed etiologies, evaluation, and treatments of patients with amiodarone-induced thyrotoxicosis (AIT) type 1 and type 2.

Case Presentation

A.B. is a 65-year-old man with a past medical history of hypertension, atrial fibrillation, and hyperlipidemia, but no history of thyroid disease. He was referred to the endocrine clinic for evaluation of probable amiodarone-induced hyperthyroidism. Five years ago, the patient developed recurrent atrial fibrillation. After several failures of cardioversion, he was placed on amiodarone. Two years later, he noted weakness in his legs while walking or climbing stairs, and difficulty sleeping, hyperdefecation, and mild nervousness. He had no significant weight loss, palpitations, tremor, dysphagia, or neck pain.

Prior to the initiation of amiodarone therapy and for almost the first 2 years of it, the patient was euthyroid. Thyroid function tests drawn at the onset of the above symptoms revealed a thyroid-stimulating hormone (TSH) $< 0.02\ \mu U/mL$ (normal, 0.5–5.0), free thyroxine (T_4) 5.23 ng/dL (normal, 0.8–1.8), and triiodothyronine (T_3) 330 ng/dL (normal, 72–170).

On physical examination, the blood pressure was 110/68, and the pulse was 82 and irregularly irregular. Mild proptosis was present with full extraocular

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movements. The thyroid was enlarged approximately twofold, and it was firm and nontender. There were no discrete nodules appreciated and no bruits auscultated. Lungs, heart, and abdomen were unremarkable. The skin was warm and moist, there was no tremor, and deep tendon reflexes were normal.

Antithyroperoxidase (anti-TPO) and antithyroglobulin antibody titers were low, and thyroid-stimulating immunoglobulins (TSIs) activity was normal at 92% (normal, <125%). A thyroid sonogram revealed an enlarged right lobe and multiple small nodules, the largest being 1 cm in diameter. There was normal thyroidal blood flow on Doppler. A 24-hour radioiodine uptake was <0.1% (normal, 20–25%).

Background

Amiodarone is a class III antiarrhythmic agent that has been associated with a wide array of serious cardiac, pulmonary, hepatic, ocular, and thyroid side effects. Because about 37.5% of the mass of amiodarone is made up of iodine, a patient taking a daily dose of 200 mg of amiodarone consumes about 75 mg of organic iodine daily [1]. Metabolism of this amount of iodine releases an amount of free iodine into the circulation that is about 20 to 40 times higher than the daily iodine intake in the United States [1].

Although amiodarone therapy is associated with an increased risk of thyroid dysfunction, the majority of patients receiving amiodarone remain euthyroid, due to adjustments made in the body to handle the excess iodine load while maintaining normal thyroid function [1]. Also, amiodarone has direct inhibitory effects on peripheral T_4 to T_3 conversion, leading to a decrease in T_4 metabolism and concomitant elevation in serum total T_4 and free T_4. Even though total and free serum T_4 levels are high-normal or high, TSH levels are generally normal after the first few months of drug exposure. Amiodarone-treated patients remain euthyroid because the serum concentration of T_3, the thyroid hormone that interacts with target cells and mediates end-organ effects, is in the low-normal range [2]. The alterations in thyroid function tests are usually divided into acute (≤3 months) and chronic (>3 months) phases following the initiation of amiodarone therapy [1]. These adjustments are summarized in Table 4.1.

Table 4.1 Effects of amiodarone on thyroid function tests in euthyroid subjects [1]

Thyroid hormone	Acute effects (≤3 months)	Chronic effects (>3 months)
Total and free T_4	↑ 50%	Remains ↑ 20–40% of baseline
T_3	↓ 15–20%, remains in low-normal range	Remains ↓ 20%, remains in low-normal range
Reverse T_3	↑ >200%	Remains ↑ >150%
TSH	↑ 20–50%, transient, generally remains <20 mU/L	Normal

Thyroid dysfunction occurs in about 14% to 18% of patients receiving long-term amiodarone therapy, and either hypothyroidism or thyrotoxicosis can occur [3]. In iodine-sufficient parts of the world, such as the United States, hypothyroidism is more common compared to iodine-deficient areas where thyrotoxicosis prevails [4].

Amiodarone-Induced Thyrotoxicosis

Amiodarone-induced thyrotoxicosis (AIT) is usually divided into type 1 (iodine-induced) and type 2 (drug-induced thyroiditis). Table 4.2 summarizes the major differences between the two types.

Type 1

Type 1 typically appears after 1 to 2 years of therapy. It occurs in patients with underlying thyroid disease and is believed to be iodine-induced [1]. The high

Table 4.2 Comparison of amiodarone-induced hyperthyroidism types 1 and 2 [1]

Factor	AIT type 1	AIT type 2
Preexisting thyroid disease	Yes (either multinodular goiter or latent Graves' disease)	No
Physical examination	Goiter, 1 or more nodules	Normal to slightly firm; occasionally tender
Duration of amiodarone therapy	Shorter (1–2 years)	Longer (>2 years)
Thyroid function tests	High free T_4, T_3 normal or high	High free T_4, T_3 normal or high
Thyroid autoantibodies	Absent (unless Graves' disease is present)	Absent
Radioiodine uptake	Low	Very low
Thyroid ultrasound	Underlying thyroid disease (multinodular goiter, Graves' disease)	Normal or minimally enlarged; heterogeneous pattern
Color flow Doppler of thyroid	Increased parenchymal blood flow	Normal or decreased parenchymal blood flow
Serum interleukin-6	Normal or low	Elevated, (?only in iodine-deficient parts of the world)
Therapy	• Stop amiodarone if possible • High-dose antithyroid drugs; perchlorate; lithium	• Discontinuation of amiodarone may not be essential • Prednisone taper over >2 months • Lithium
Subsequent hypothyroidism	No	Often

iodine load from the drug triggers excess thyroid hormone synthesis and release (Jod-Basedow phenomenon) or, less commonly, the development of Graves' disease [1]. The mechanisms that mediate these effects are poorly understood.

Type 2

Type 2 typically appears after 2 years of therapy or longer in those without apparent preexisting thyroid disease [5]. It results from the direct cytotoxic effect of amiodarone and its metabolites on thyroid follicular epithelial cells, leading to a destructive inflammatory thyroiditis and the release of preformed thyroid hormone into the circulation [1].

Diagnosis

Distinguishing between type 1 and type 2 AIT may be difficult. Table 4.2 lists certain elements in the history as well as laboratory and diagnostic tests that may be helpful in the differentiation between the two types. For example, the presence of a preexisting multinodular goiter favors type 1 AIT. Although measurement of serum levels of interleukin-6 (IL-6) has been reported to be helpful as a marker of inflammation (and thus it would be elevated in type 2 AIT) [6], this has not been the experience of others [7, 8]. Color flow Doppler ultrasound assessment has emerged as an important diagnostic tool, as thyroidal blood flow is high in type 1 AIT and normal or low in type 2 AIT [9].

Treatment

If the diagnosis of AIT type 1 is confirmed by history and increased color Doppler flow, cessation of amiodarone therapy is usually recommended, unless life-threatening ventricular arrhythmias are present [1]. Large doses of antithyroid drugs including methimazole (40 to 80 mg/day) or propylthiouracil (PTU) (400 to 800 mg/day) have been used. Unfortunately, these drugs are less effective when the thyroidal iodine content is high, as is the case in AIT. Furthermore, because of an increased risk of side effects with high drug doses, including agranulocytosis [10], caution is advised. In patients who do not respond adequately to antithyroid drugs, potassium perchlorate, which blocks thyroidal iodine uptake, has been recommended as potential therapy [11]. Potassium or sodium perchlorate, however, is no longer available in the United States.

While some patients with mild type 2 AIT often have spontaneous resolution of their thyroid dysfunction and may not require treatment, prednisone is considered the treatment of choice for type 2 AIT, although there are no prospective randomized placebo-controlled trials [1]. Unlike the case with type 1 AIT, amiodarone discontinuation may not be necessary in type 2 AIT, and patients have been shown to improve with glucocorticoids while amiodarone therapy is continued [8]. Improvement in

thyroid function is often seen within 1 week of starting high doses of prednisone (40 to 60 mg/day). However, because exacerbations of hyperthyroidism can occur if steroids are tapered too quickly, glucocorticoid therapy should be slowly tapered over 2 to 3 months (e.g., by 10 mg every 2 weeks) [12].

If thyroid function tests do not improve after several months of treatment with either antithyroid drugs or glucocorticoids, it is very likely that the patient has a "mixed" form of AIT that may respond to both agents together [1]. When mixed AIT is suspected at the outset, or if the underlying diagnosis is uncertain, some have suggested starting patients on both antithyroid drugs and prednisone (0.50 to 1.25 mg/kg/day) [13]. If improvement in thyroid function is seen within 1 to 2 weeks, then the patient is likely to have type 2 AIT. Antithyroid drugs may then be withdrawn, and prednisone should be continued and tapered gradually; if the patient does not respond to both drugs within 2 weeks, then both antithyroid medications and prednisone could be continued until an improvement in thyroid function is noted over the next 1 to 2 months [1]. There are resistant cases that do not respond to either mono- or dual therapy with antithyroid drugs and/or glucocorticoids. Other therapeutic recommendations in such cases include lithium [14], plasmapheresis [15], and ultimately thyroidectomy [16].

How the Diagnosis Was Made

In the case described above, the suppressed serum TSH and elevated serum free T_4 and T_3 confirmed the diagnosis of hyperthyroidism, likely due to amiodarone therapy. Although the patient had what appeared to be proptosis, as well as a small goiter, the lack of clinical and laboratory data to support the diagnosis of Graves' disease (TSI <125%), and the long time lag between the initiation of amiodarone therapy and the onset of symptoms of hyperthyroidism (2 years later) suggested the diagnosis of amiodarone-induced hyperthyroidism type 2. The lack of previous history of thyroid disease, and the normal (rather than elevated) parenchymal blood flow on Doppler also favored a diagnosis of Type 2 AIT thyroiditis.

Amiodarone was continued, and the patient was started on prednisone 40 mg daily and responded promptly within 2 weeks with a decrease in fee T_4 from 5.13 to 2.3 ng/dL and total T_3 from 336 to 100 ng/dL. However, as prednisone was being tapered during the first month of therapy, the patient had a recurrence of hyperthyroidism necessitating a more protracted tapering period over 5 months, while amiodarone therapy was continued. He subsequently developed mild hypothyroidism, which persisted for several months, and he was ultimately started on thyroxine therapy with normalization of thyroid function.

Lessons Learned

1. A 200-mg dose of amiodarone contains 75 mg of organic iodine. Metabolism of this amount of iodine releases a concentration of free iodine into the circulation

that is about 20 to 40 times higher than the daily iodine intake in the United States [1].
2. The majority of patients receiving amiodarone remain euthyroid [1].
3. Thyroid dysfunction occurs in about 14% to 18% of patients receiving long-term amiodarone therapy, and results in either hypothyroidism or thyrotoxicosis [3].
4. In iodine-sufficient parts of the world, such as the United States, hypothyroidism is more common compared to iodine-deficient areas where thyrotoxicosis seems to prevail [4].
5. A miodarone-induced thyrotoxicosis (AIT) is divided into type 1 and type 2. The major differences between the two types are summarized in Table 4.1.
6. Type 1 AIT typically appears after 1 to 2 years of therapy and is believed to be iodine-induced; type 2 AIT typically appears after 2 years of therapy or longer and it results from the direct cytotoxic effect of amiodarone and its metabolites on the thyroid gland [1].
7. Distinguishing between type 1 and 2 AIT may be difficult (see Table 4.2).
8. Treatment for type 1 AIT usually involves discontinuation of amiodarone, unless a life-threatening ventricular arrhythmia is present. Also, large doses of antithyroid drugs are used to treat this type of AIT.
9. For patients with type 2 AIT, prednisone therapy with a slow taper over a period of $\geq$2 months is considered to be the treatment of choice.
10. When "mixed" AIT is suspected, some have suggested starting patients on both antithyroid drugs and prednisone [13].
11. There are severe cases that do not respond to either mono- or dual therapy with antithyroid drugs and/or glucocorticoids. Recommendations in such cases include lithium [14], plasmapheresis [15], and ultimately thyroidectomy [16].

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Multiple-Choice Questions

1. Which of the following is considered to be the most helpful test in differentiating type 1 from type 2 amiodarone-induced hyperthyroidism?

   A. Antithyroid antibody titers
   B. Serum interleukin-6 (IL-6) levels
   C. 24–hour radioiodine uptake
   D. Color-flow Doppler of the thyroid
   E. All of the above

   Answer: D. Refer to the text (diagnosis section) for an explanation.

2. A 67-year-old man is seen in consultation for amiodarone-induced hyperthyroidism (AIT). His history and laboratory data are suggestive of type 2 AIT. You decide to begin therapy. Which of the following is the preferred treatment strategy?

   A. Discontinue amiodarone, start prednisone 40 mg daily, and taper over 1 month.
   B. Discontinue amiodarone, start prednisone 40 mg daily, and taper over 2 to 3 months.
   C. Discontinue amiodarone, start methimazole 40 mg daily, start prednisone 40 mg daily, and taper over 2 to 3 months.
   D. Continue amiodarone, start prednisone 40 mg daily, and taper over 1 month.
   E. Continue amiodarone, start prednisone 40 mg daily, and taper over 2 to 3 months.

   Answer: E. Refer to the text (treatment section) for an explanation.

3. Mr. A. is a 61-year-old computer engineer who is currently on amiodarone for atrial fibrillation. TSH, free T_4, T_3, and anti-TPO antibodies checked prior to starting amiodarone were within normal limits. Thyroid function tests drawn 3 months later showed a TSH of 8.7 μU/mL (normal, 0.5–5.0), free T_4 of 2.1 ng/dL (normal, 0.9–2.0), and T_3 of 65 ng/dL (normal, 72–170). The patient denies any symptoms of hypo- or hyperthyroidism. He is concerned about these results because he has read articles on the Internet lately regarding the potential side effects of amiodarone on the thyroid gland. His father died of a "brain cancer" and his family history is significant for thyroid disease and arthritis. Your best initial approach in managing this patient is:

   A. Reassure him, observe and repeat thyroid function tests in 3 months.
   B. Discontinue amiodarone, start methimazole or PTU since an elevated free T_4 level is suggestive of hyperthyroidism.
   C. Discontinue amiodarone and start levothyroxine since an elevated TSH level is consistent with hypothyroidism.
   D. Continue amiodarone, start prednisone 40 mg daily, and taper over 2 to 3 months.
   E. Refer patient for a magnetic resonance imaging scan of the brain since the elevation of both TSH and feee T_4 is suggestive of a diagnosis central (pituitary) hyperthyroidism that is independent of amiodarone therapy.

   Answer: A. Refer to the text for an explanation.

Chapter 5
Interferon-Induced Hyperthyroidism

Paul Aoun and David S. Cooper

Objectives

Interferon-alpha (IFN-α) treatment for hepatitis C virus (HCV) and other disorders has been associated with an increased risk for thyroid dysfunction and autoimmunity. Here, we report the case of a 50-year-old woman who developed Graves' disease in the setting of IFN-α therapy for HCV. We discuss potential mechanisms of thyroid disease induction, recommendations for screening, and clinical strategies for the management of patients who develop IFN-related thyroid disease.

Case Presentation

Ms. M.B. is a 50-year old woman with hepatitis C and no history of thyroid disease. She was referred to the endocrine clinic for evaluation of abnormal serum thyroid function tests (TFTs) in the setting of interferon alfa-2b (IFN-α-2b) therapy for HCV. Three months after starting her treatment, she began experiencing insomnia, weight loss, weakness, palpitations, and shortness of breath. She denied heat intolerance, nervousness or tremor, bowel changes, dysphagia, neck discomfort, or visual disturbances.

On physical examination, the blood pressure was 120/80 and the pulse was 78 and regular. There was no exophthalmos. The thyroid was not palpable, nontender, and there was no bruit audible her skin was warm and moist. There was no tremor of the outstretched hands.

Prior to starting IFN-α, her TSH had been 1.5 mU/L (normal 0.5–5.0). TFTs drawn after the onset of her symptoms showed a thyroid-stimulating hormone (TSH) of 0.02 mU/L (normal 0.5–5.0), a total thyroxine (TT_4) of 15.6 g/dL (normal 4.6–12), a triiodothyronine resin uptake (T_3RU) of 28%, and a free thyroxine index (FTI) of 4.4 (normal 1.6–3.7). She also had markedly positive antithyroid peroxidase antibodies, and a 24–hour radioiodine uptake of 58% (normal 10–30%).

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Background

Interferons (IFNs) are naturally occurring proteins secreted by cells in response to viral infections that play a major role in modulating immune function. Thyroid dysfunction is a known complication of interferon therapy in the treatment of hepatitis B or C or during therapy for certain malignancies [1]. Thyroid dysfunction occurs in up to 15% to 20% of patients treated with IFN-α for chronic HCV [2], but others have reported numbers as high as 34%, with induction of antithyroid antibodies occurring in up to 40% of patients with negative antibodies at baseline [3]. A recent literature review found that of those who developed thyroid dysfunction with IFN-α, 60% became hypothyroid and about 40% developed hyperthyroidism [4]. Risk factors for the development of thyroid disease with interferon therapy include female sex, combination immunotherapy (especially IL-2), and preexisting thyroid autoantibodies [5].

The mechanisms by which IFN-α leads to thyroid dysfunction be divided into immune and nonimmune (i.e., direct effects of IFN on the thyroid) mediated effects.

Immune-Mediated Effects

Immune system effects of IFN-α that could potentially mediate the development of autoimmune thyroid disease include the enhancement of major histocompatibility complex (MHC) class I antigen expression, a generalized shift toward cell-mediated immunity, as well as increases in circulating interleukin-6 (IL-6) levels [2]. IL-6 may be important for the development of thyroid autoimmunity, and may also directly inhibit thyroidal iodide uptake and thyroid hormone release[6].

Nonimmune Effects

Direct effects of IFN-α on the thyroid include inhibition of thyroid hormone synthesis, release, and metabolism, and disruption of thyroidal iodine organification [2, 7]. In primary human thyrocyte cultures, IFN-α has been shown to inhibit TSH-induced gene expression of thyroglobulin, thyroperoxidase (TPO), and sodium iodide symporter (NIS) [8].

Based on the dual mechanisms by which IFN-α may induce thyroid dysfunction, Mandac et al [1] proposed a new classification of interferon-induced thyroid disease (IITD), in which thyroid abnormalities are considered to be either autoimmune- or nonautoimmune in nature,. While this classification may have some validity, it does not account for all of the features of IITD that are observed clinically (see below). Specifically, this classification categorizes destructive thyroiditis as nonautoimmune, whereas this may not be the case in some or even most patients. Our classification of IITD will be as follows:

Autoimmune IITD:

1. Increase in the titer of preexisting autoantibodies or de novo induction of autoantibodies, without clinical evidence of thyroid disease
2. Destructive thyroiditis
3. Hashimoto's thyroiditis (autoimmune hypothyroidism)
4. Graves' disease

Nonautoimmune IITD:

1. Destructive thyroiditis without thyroid autoantibodies
2. Nonautoimmune hypothyroidism

Autoimmune IITD

The most common immune manifestation occurring with IFN-α therapy is the presence of thyroid autoantibodies in the absence of clinical thyroid dysfunction [9]. In this situation, there may either be an increase in the titer of preexisting thyroid autoantibodies or the *de novo* induction of thyroid autoantibodies [10].

Preexisting Thyroid Autoantibodies

About 18% of the thyroid disease–free population have detectable serum antithyroperoxidase (TPO-Ab) and antithyroglobulin (Tg-Ab) antibodies [11]. In one prospective study, Carella et al [12] monitored changes in thyroid autoantibodies titers in patients with HCV treated with IFN-α. Tg-Ab levels increased from a median of 29 U/mL to 35.0 and 73.0 U/mL before, at 6 months after, and at 12 months after starting IFN treatment, respectively; and titers of TPO-Abs also increased from a median baseline of 1.0 U/mL before IFN therapy to 3.0 and 6.0 U/mL at 6 and 12 months into treatment, respectively.

De Novo Thyroid Autoantibodies

The prevalence of de novo induction of thyroid autoantibodies by IFN-α has varied among different studies ranging from 1.9% [13] to 40% [3]. In the study by Carella et al [12], the number of patients positive for one or both thyroid autoantibodies increased from eight of 75 (10.7%) before starting IFN-α treatment to 34 of 75 (45.3%) at 12 months into therapy, with only five of the antibody-positive patients developing thyroid dysfunction. Similar findings of de novo thyroid autoantibodies production without clinical evidence of thyroid disease were also reported by Imagawa et al [14] and Preziati et al [3].

Destructive Thyroiditis

In those patients who develop hyperthyroidism, destructive thyrotoxicosis is often the cause (5,15). Destructive thyroiditis is an inflammatory condition of the thyroid gland that usually occurs in the first weeks of IFN treatment [15]. Since some cases may occur in the absence of detectable thyroid autoantibodies, suggesting a nonautoimmune etiology [1], this issue remains unsettled. Mazziotti et al [16] prospectively monitored patients with hepatitis C for the development of thyroid dysfunction or thyroid autoimmunity during IFN-α therapy. The authors noted that the appearance of thyroid autoantibodies always preceded the development of destructive thyrotoxicosis, suggesting that the thyroid dysfunction was in fact immune-mediated. On the other hand, it could still be argued that the appearance of antithyroid antibodies was an early marker of thyroid follicular disruption, and was not truly etiologic in the development of thyroid dysfunction.

The diagnosis of destructive thyrotoxicosis is supported by a low radioiodine uptake (RAIU), negative anti-TSH receptor antibodies, diffuse hypoechogenicity on ultrasound, and, if performed, reduced thyroid vascularity on color flow Doppler [15]. Destructive thyrotoxicosis is frequently mild (subclinical) but in some cases it is more extensive and leads to overt thyrotoxicosis [15]. As is true for most types of destructive thyroiditis, hypothyroidism subsequently develops in most patients after several months [15].

Hashimoto's Thyroiditis

The prevalence of hypothyroidism among HCV patients treated with IFN-α ranges from 2.4% to 19% [15], with over two thirds exhibiting thyroid autoantibody positivity [4]. Hypothyroidism is often mild or subclinical, and is more likely to be overt in patients with preexisting thyroid autoantibody positivity [15].

Graves' Disease

The overall frequency of Graves' disease among patients who develop IFN-α–related thyrotoxicosis is uncertain. Carella et al [15] and Koh et al [5] suggest that it is less common than destructive thyrotoxicosis, whereas Prummel and Laurberg [4] believe that it is the most common etiology [16]. In addition to developing de novo, Graves' hyperthyroidism may occur after a transient phase of destructive thyrotoxicosis, following a period of hypothyroidism [15], and persist after cessation of IFN-α therapy [17]. Wong et al [17] reviewed the medical records of 321 patients receiving IFN-α for chronic hepatitis B or C between 1996 and March 2001; six out of 10 who were found to have biochemical thyrotoxicosis had other findings consistent with Graves' disease, such as diffuse uptake on thyroid scintigraphy or positive TSAb. In all six patients, the thyrotoxicosis failed to resolve with cessation of IFN-α, and required prolonged treatment with antithyroid medications [17].

Nonautoimmune Interferon-Induced Thyroid Disease (IITD)

The development of thyroid dysfunction in association with IFN-α therapy in the absence of evident thyroid autoimmunity is an important but poorly understood feature of IITD. The two forms of nonautoimmune IITD are destructive thyroiditis and hypothyroidism.

Destructive Thyroiditis

As noted above, one recent review has suggested that destructive thyroiditis is caused mainly by nonimmune mechanisms [1]. However, this interpretation is based on relatively scant clinical data. In one such report, three patients developed hyperthyroidism with biochemical and RAIU values consistent with destructive thyroiditis (low TSH, high free T_4) with negative thyroid autoantibodies (TPO and TSH receptor Abs), and without low RAIU [18].

Hypothyroidism

Non–immune IFN-α hypothyroidism have also been rarely reported [14]. Potential direct mechanisms of IFN-α to impair thyroid function were discussed earlier [2, 7, 8].

Considerations for Baseline Screening

It has been suggested that prior to the initiation of IFN therapy, serum TSH, TgAb, and TPO-Ab concentrations and perhaps thyroid sonography should be carried out to identify preexisting thyroid dysfunction or thyroid autoimmunity [15]. If all studies are normal, we recommend that TSH levels be followed every 3 months until interferon therapy is completed [1]. If TSH levels are normal but thyroid antibodies are positive, the patient is at increased risk for developing clinical thyroid dysfunction with IFN therapy [5], and therefore TSH levels be tested every 2 months [1]. If the patient develops hypo- or hyperthyroidism, a full workup is required [1].

Therapeutic Considerations

Figure 5.1 shows an algorithm highlighting therapeutic approaches for the management of patients with interferon-induced thyroid disease.

Destructive Thyrotoxicosis

In symptomatic patients, treatment with beta-blocking agents is usually sufficient to control the signs and symptoms of thyrotoxicosis [15]. If an asymptomatic patient has biochemical evidence of thyrotoxicosis and concomitant cardiac risk factors, treatment with beta-blocking agents is also reasonable. When the thyrotoxicosis is

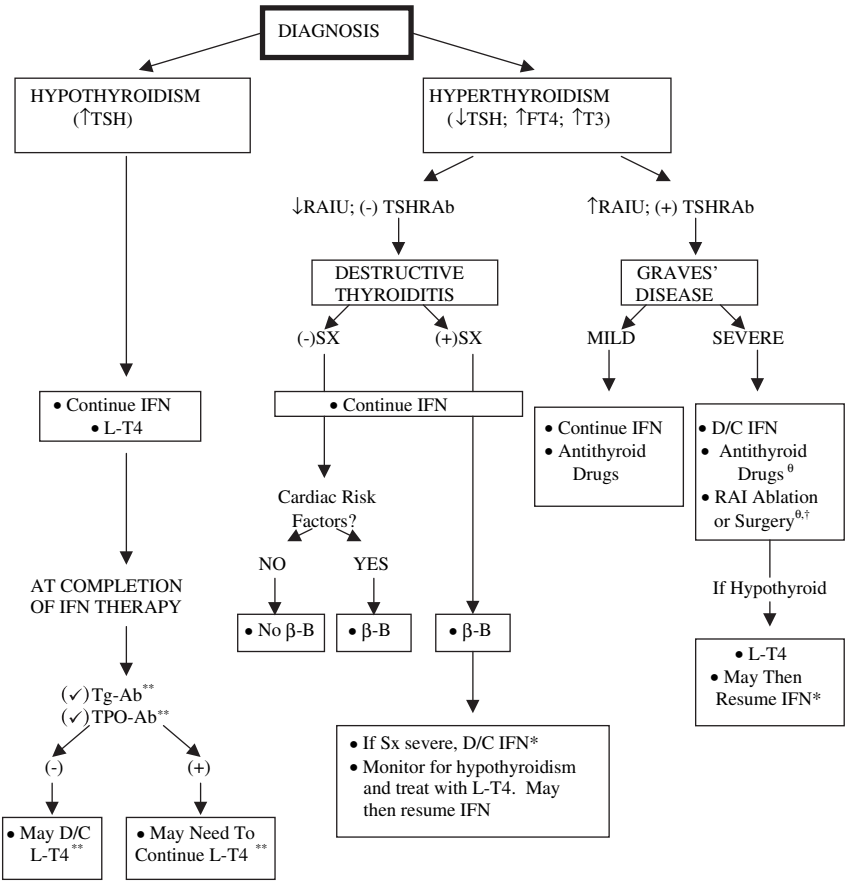

Fig. 5.1 Algorithm for the treatment of interferon-induced thyroiditis. β-B, beta blockers; D/C, discontinue; FT4, Free thyroxine; T3, Triiodothyronine; IFN, interferon; L-T4, levothyroxine; RAI, radioactive iodine; RAIU, RAI uptake; bf Sx, symptomatic; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroperoxidase Ab; TSH, thyroid stimulating hormone; TSHRAb, TSH receptor Ab
θ Remission of hyperthyroidism with antithyroid drugs is unlikely (*Carella *et al.*, 2004; **Carella *et al.*, 2001).
†Mandac *et al.*, 2006.

more severe and the symptoms are not well controlled by beta-blocking agents, Carella et al [15] suggest that IFN be discontinued. However, it is uncertain that discontinuation of IFN will lead to resolution of the hyperthyroidism any more rapidly.

While corticosteroids are helpful in other forms of destructive thyroiditis such as type 2 amiodarone-induced thyrotoxicosis, they are generally contraindicated in patients with HCV [15]. Furthermore, Minelli et al [19] showed no additional benefit of steroid therapy on the rate of normalization of TFTs 6 months after the discontinuation of IFN therapy in IFN-α–treated hepatitis C patients.

Close monitoring of patients for the development of hypothyroidism following the hyperthyroid phase of destructive thyroiditis is necessary [1]. If hypothyroidism develops, it is usually mild, asymptomatic, and self-limited. If it is more severe [15], levothyroxine therapy, which can be started and continued until the course of IFN treatment is complete. At that point, it can be discontinued and an assessment made about whether the hypothyroidism is permanent or not.

Hypothyroidism

In patients who develop hypothyroidism during IFN-α treatment, supplementation with levothyroxine is usually indicated, without the need to withdraw IFN-α [15]. Levothyroxine is usually discontinued at the completion of IFN-α therapy; however, in patients with positive Tg-Abs and TPO-Abs, hypothyroidism is more likely to be persistent, and levothyroxine therapy may need to be continued or restarted if it had been withdrawn [20]. Antithyroid antibodies may persist for years in euthyroid individuals after a course of IFN therapy, suggesting continual risk for the development of thyroid dysfunction.

Graves' Disease

In patients with mild Graves' hyperthyroidism, IFN-α treatment may be continued, with the addition of an antithyroid drug at low doses to control the excessive thyroid hormone production [14]. If Graves' disease is severe, withdrawal of IFN seems appropriate and large doses of antithyroid drugs may be necessary to control the disease [15]. Although antithyroid drugs have rare idiosyncratic hepatotoxic reactions, underlying liver disease is not a contraindication to antithyroid drug use. However, higher doses of antithyroid drugs may increase the risk for hepatic dysfunction, and some recommend against their use in patients with HCV [1]. Furthermore, since remission of Graves' disease with antithyroid drugs is unlikely in severe hyperthyroidism [21], definitive treatment with radioiodine or, rarely, thyroidectomy followed by supplementation with levothyroxine may be required.

How the Diagnosis Was Made

In the case described above, the TFTs [suppressed TSH of 0.02 mU/L (normal 0.5–5.0), TT_4 of 15.6 g/dL (normal 4.6–12), T_3RU of 28%, and FTI of 4.4 (normal 1.6–3.7)] were consistent with hyperthyroidism. The differential diagnosis included destructive thyroiditis versus Graves' disease. The subsequent laboratory data, which showed an increased 24-hour RAIU (58%) and markedly positive TPO-Ab, were consistent with Graves' disease.

Interferon-α was initially continued and the patient was started on methimazole. However, she remained biochemically hyperthyroid. IFN-α was then discontinued,

but hyperthyroidism did not remit after an additional 6 months of antithyroid drug treatment, and she ultimately received radioiodine therapy. Three months later, she developed postablative hypothyroidism and was started on levothyroxine replacement. Six weeks after starting levothyroxine, her TSH was 1.05 mU/L.

Lessons Learned

1. Up to 20% of patients treated with IFN for HCV develop thyroid dysfunction [2].
2. IFN-α–induced thyroid dysfunction can be immune and nonimmune related.
3. Autoimmune IITD: (1) increase in the titer of preexisting antithyroid antibodies or de novo induction of autoantibodies without clinical evidence of thyroid disease; (2) destructive thyroiditis; (3) Hashimoto's thyroiditis (autoimmune hypothyroidism); (4) Graves' disease.
4. Nonautoimmune IITD: (1) destructive thyroiditis; (2) hypothyroidism.

Destructive Thyroiditis

- ↓ TSH, ↑ free T_4, ↑ free T_3, (–)TSAb, ↓ RAIU, and ↓ vascularity on color flow Doppler.
- Treatment: (1) mild or asymptomatic: no treatment, continue IFN; (2) asymptomatic and cardiac risk factors: beta-blocking agents, continue IFN; (3) symptomatic: beta-blocking agents, continue IFN; if symptoms uncontrolled, discontinue IFN until patient euthyroid; (4) if hypothyroidism develops, it is reasonable to treat with levothyroxine and continue IFN.

Hypothyroidism

- Occurs in about 2.4% to 19% of the patients with HCV receiving IFN-α;
- Can be immune (Hashimoto's) or nonimmune (direct effect of IFN) mediated.

Graves' Disease

- ↓ TSH, ↑ free T_4, ↑ free T_3, (+)TSAb, and high RAIU.
- Treatment: (1) mild: continue IFN-α with low dose antithyroid drugs [15]; (2) severe: discontinue IFN, use larger doses of antithyroid drugs (controversial because of side effects); definitive treatment with radioiodine or thyroidectomy followed by supplementation with levothyroxine, may be required.

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Multiple-Choice Questions

1. 45-year-old woman, was recently started on IFN-α therapy for the treatment of hepatitis C. A few weeks later she developed symptoms of hyperthyroidism. You are suspicious of destructive thyrotoxicosis. To confirm your diagnosis, you order thyroid function tests. Which of the following laboratory sets of data is likely to be seen with destructive thyroiditis? (TSH, thyroid-stimulating hormone; FT_4, serum free thyroxine; TSHR-Abs, TSH receptor antibodies; RAIU, radioactive iodine uptake; color Doppler, color-flow ultrasound Doppler of the thyroid.)

	TSH	FT_4	TSHR-Abs	RAIU	Color Doppler
A	↓	↑	+	↑	↑
B	↓	↑	−	↓	↓
C	↓	↑	+	↓	↓
D	↑	↓	+	↑	↑
E	↑	↓	−	↓	↓

Answer: B. Refer to the text for an explanation.

2. Which of the following is NOT true regarding destructive thyrotoxicosis in the setting of IFN-α therapy?

A. Destructive thyrotoxicosis usually occurs in the first weeks after the initiation of IFN-α therapy.
B. In contrast to patients with subacute thyroiditis, neck pain is rarely present.
C. Thyrotoxicosis is frequently mild and transient.
D. Treatment with beta-blocking agents and antithyroid medications is usually the first-line therapy to control symptoms of thyrotoxicosis.
E. All of the above are true.

Answer: D. Refer to the text for an explanation.

3. 50-year-old man with a history of hepatitis C, is treated with IFN-α. A few weeks after the initiation of IFN-α, the patient returned to his primary care physician complaining of a mild tremor and heat intolerance. He has no weight changes, palpitations, or gastrointestinal symptoms, and he denied any dysphagia or visual disturbances. His thyroid function tests revealed a TSH of 0.04 mU/L (normal 0.5–5), a free T_4 of 2.0 ng/dL (normal 0.8–2.0), and a total T_3 of 220 ng/dL (normal 70–190). He was then referred to the endocrine clinic for the evaluation. You ordered a TSH receptor antibody (TSHR-Ab) assay, which was positive, and a 24–hour radioactive iodine uptake (RAIU) was 46%. The next best step in the management of this patient is:

(A) Continue IFN-α, start low-dose antithyroid medication.
(B) Continue IFN-α, start high-dose antithyroid medication.
(C) Continue IFN-α, start a beta-blocking agent.
(D) Discontinue IFN-α, start low-dose antithyroid medication.
(E) Discontinue IFN-α, start high-dose antithyroid medication.

Answer: A. Thyroid function tests are consistent with mild Graves' hyperthyroidism. Unlike in destructive thyroiditis, which is usually self-limited and treatment with beta-blocking agents is useful in controlling the signs and symptoms of thyrotoxicosis, patients who develop mild Graves' disease require the addition of low doses of antithyroid drugs to control excessive thyroid hormone production .

Chapter 6
Subclinical Hyperthyroidism Due to a Multinodular Thyroid

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Objectives

Subclinical hyperthyroidism is defined as a state of mild thyroid overactivity, in which serum free thyroxine (T_4) and free triiodothyronine (T_3) levels are within the normal range but serum thyroid-stimulating hormone (TSH) levels are subnormal. Whether the serum TSH level needs to be extremely low (e.g., undetectable), very low (e.g., <0.1 mU/L), or simply just below the lower limit of normal of the typical TSH assay (e.g., <0.4 mU/L) remains somewhat controversial. We report the case of a 50-year-old woman with mild hyperthyroidism due to a multinodular thyroid. We review the issues surrounding establishing the diagnosis, and discuss risks and benefits of treatment in this individual.

Case Presentation

Ms. D.W. is a 48-year-old premenopausal woman who was found by her primary care physician to have abnormal thyroid function tests during routine screening as part of her annual physical examination. At that time, she was noted to have a serum TSH of 0.17 mU/L. She was referred to the endocrine clinic for further evaluation. She had no prior history of thyroid disease and no family history of thyroid disease. She had no symptoms suggestive of hyperthyroidism, and has felt completely well. She had no compressive symptoms in the neck including dysphagia, hoarseness, or neck pain. Her past history was significant for mild hypertension treated with hydrochlorothiazide. The review of systems was normal, and the patient's menses were regular. The physical examination was entirely normal except for mild obesity, with a body mass index (BMI) of 30. Her pulse was 84 beats per minute. The thyroid gland was difficult to palpate, but no nodules were identified. Repeat thyroid function tests were as follows: free T_4 1.4 ng/dL, T_3 135 ng/dL, and

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TSH 0.11 mU/L. Antithyroid antibodies were negative. A thyroid scan using iodine 123 showed a mildly heterogeneous gland with several foci of increased uptake bilaterally. Thyroid ultrasound showed multiple isoechoic and hyperechoic nodules bilaterally, with overall normal thyroid size. The largest nodules measured 1.5 cm in the left lobe and 2.0 cm in the right lobe, and both corresponded to areas of increased uptake on the radionuclide scan.

Background

Subclinical hyperthyroidism is a common finding in the general population. In several large epidemiologic studies, the frequency has been approximately 1%, without a clear relationship to age [1]. This is in contrast to what is seen in subclinical hypothyroidism, which has a much higher prevalence of 8% to 10%, and an even higher prevalence in older individuals, approaching 15% to 20% [1,2]. The most common cause of subclinical hyperthyroidism undoubtedly is iatrogenic or inappropriate thyroid hormone use (exogenous subclinical hyperthyroidism). On the other hand, *endogenous* subclinical hyperthyroidism is typically caused by mild Graves' disease, solitary toxic nodules, or multinodular goiter. Some patients who are in remission after antithyroid drug therapy or following radioactive iodine therapy for overt hyperthyroidism commonly have subclinical hyperthyroidism.

It should also be noted that a low serum TSH is not the *sine qua non* of thyroidal autonomy, and may be present in patients with central hypothyroidism and severe nonthyroidal illnesses (especially if dopamine or high doses of glucocorticoids are used). In addition, low serum TSH values are seen physiologically at the end of the first trimester pregnancy due to high circulating human chorionic gonadotropin (HCG) levels, and may also be observed in the elderly with normal thyroid function due to a possible altered "set point" of the hypothalamic-pituitary-thyroid axis [3, 4].

In patients with true endogenous subclinical hyperthyroidism, progression to overt hyperthyroidism may occur, with rates of progression varying from 1% to 5% per year [5, 6]. Not surprisingly, subclinical hyperthyroidism in patients with Graves' disease who are in remission presages eventual relapse [7]. Finally, subclinical hyperthyroidism can be transient, so that treatment should only be considered when thyroid function abnormalities are clearly stable after repeated measurements over 6 to 12 months. For example, in one study, 38 of 50 untreated patients with baseline serum TSH values between 0.05 and 0.5 mU/L had normal serum TSH values 1 year later, whereas the majority of patients with TSH levels <0.05 mU/L persisted in having subnormal values [8].

The principal issues surrounding the clinical management of subclinical hyperthyroidism are [1] possible symptoms of mild hyperthyroidism; [2] bone loss, especially in postmenopausal women; and [3] possible cardiovascular disease, especially atrial fibrillation. Whether patients with endogenous subclinical hyperthyroidism have symptoms of hyperthyroidism is controversial. Studies have suggested that mild symptoms may be present in some patients [9, 10], which may

be reversible with antithyroid drug treatment [10]. Unfortunately, this latter study was not placebo-controlled, so that the possibility remains that the improvement in subjective symptoms was a placebo effect.

Women with subclinical hyperthyroidism may have diminished bone mineral density compared to age-matched controls, with improvement following therapy to correct the hyperthyroidism [11, 12]. Evidence of an increase in fractures in patients with subclinical hyperthyroidism has also been presented, but in this study it is uncertain that the patients truly had subclinical hyperthyroidism rather than overt hyperthyroidism, since only TSH measurements were available [13]. Whether premenopausal women with subclinical hyperthyroidism are at risk for bone loss is uncertain. One study showed increased levels of circulating bone turnover markers in premenopausal women with subclinical hyperthyroidism [14], but bone mineral density appears to be normal [15] or slightly lower than in controls [16].

Finally, an increased risk of cardiac abnormalities including increased heart rate, increased left ventricular mass, diastolic dysfunction, and a higher frequency of atrial fibrillation in the elderly has been well documented (reviewed in ref. 17). Furthermore, an increase in all-cause mortality and cardiovascular mortality has also been observed in older individuals with subclinical hyperthyroidism [18]. In another more recent prospective study of individuals older than 60 years of age, an increased risk of atrial fibrillation was noted even when the serum TSH was 0.1 to 0.5 mU/L, but there was no increase in cardiovascular mortality [19]. Data such as these have led to the recommendation that elderly individuals with subclinical hyperthyroidism and TSH levels <0.1 mU/L should receive therapy [20], whereas appropriate management in younger individuals or those whose TSH levels are between 0.1 and 0.4 mU/L remains uncertain [20].

How the Diagnosis Was Made

The diagnosis of subclinical hyperthyroidism was made on the basis of the patient's normal free T_4 and T_3 with a subnormal but still detectable serum TSH. There have been rare reports of patients with overt hyperthyroidism with elevated free T_3 levels despite normal total T_3 levels [21], but normal free T_3 measurements are not considered to be necessary to make the diagnosis of subclinical hyperthyroidism. The etiology of our patient's subclinical hyperthyroidism was established with the radionuclide thyroid scan and thyroid sonography, showing findings consistent with a multinodular thyroid and areas of autonomy within the gland. The negative antithyroid antibodies are evidence against autoimmune thyroid disease as the etiology of her hyperthyroidism.

After performing a dual-energy x-ray absorptiometry (DEXA) study, which was normal, and discussing the pros and cons of treatment with the patient, it was elected not to treat her, based on the lack of clear evidence of benefit. The plan was as follows: thyroid function was to be monitored every 6 months and consideration of radioactive iodine therapy would be more seriously entertained when she becomes

postmenopausal, or if thyroid function deteriorates further. After 2 years of follow-up, thyroid function has remained stable and she still has not received therapy.

Lessons Learned

1. Subclinical hyperthyroidism is commonly detected on routine screening of the general population, but it is only one tenth as common as subclinical hypothyroidism.
2. Subclinical hyperthyroidism may have consequences in terms of hyperthyroid symptoms, bone loss, and cardiac abnormalities, especially atrial fibrillation. Bone loss and atrial fibrillation are particularly noteworthy in postmenopausal women and the elderly (over age 60) population, respectively.
3. Other conditions besides subclinical hyperthyroidism can cause serum TSH levels to be diminished, and it is important to exclude them.
4. Treatment, either with antithyroid drugs or radioiodine, is based on underlying risk factors, especially age, underlying heart disease, or the presence or risk of bone loss.

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Multiple-Choice Questions

1. A 25-year-old woman notes feelings of anxiety, and is found to have a normal physical examination. She has the following laboratory results: free T_4 1.3 ng/dL, T_3 120 ng/dL, and TSH 0.4 mU/L. What of the following is true?

   A. She is 12 weeks pregnant.
   B. She has mild Graves' disease.
   C. She is biochemically euthyroid.
   D. She requires further evaluation with a thyroid scan.

   Answer: C. The patient is biochemically euthyroid and requires no further evaluation.

2. A 75-year-old woman with a long-standing multinodular goiter has developed progressive decreases in serum TSH. She has no symptoms suggesting hyperthyroidism, but has osteoporosis on bone densitometry treated with alendronate. Recent thyroid function tests are as follows: free T_4 1.6 ng/dL, T_3 132 ng/dL, and TSH 0.04 mU/L. Which one of the following statements is correct?

A. Her risk for fracture is elevated vs. similar women without subclinical hyperthyroidism.
B. She is at increased risk for myocardial infarction.
C. Treatment will lower her risk of atrial fibrillation in the future.
D. Treatment with radioactive iodine is preferred over antithyroid drugs.

Answer: D. The patient is a higher risk of atrial fibrillation in the future, but it is unclear that treating her will lower the risk, since there have been no intervention trials with this endpoint. It is unclear that her risk of fracture is elevated compared to euthyroid women who are also on bisphosphonates. There is no evidence for higher risk of myocardial infarction. Treatment with antithyroid drugs would be less desirable than radioactive iodine in a patient with a multinodular goiter.

3. Which of the following patients might have low serum TSH levels?

A. A 30-year-old woman being treated with 10 mg of prednisone daily for asthma
B. A 40-year-old man who is otherwise healthy
C. A 25-year-old woman who is 35 weeks pregnant
D. An 82-year-old otherwise healthy woman

Answer: D. High (e.g., >40 mg prednisone/day) doses of glucocorticoids are associated with low serum TSH. Low serum TSH values can be normally seen at the end of the first trimester pregnancy, but not later in pregnancy. Elderly people sometimes have low serum TSH values in the setting of otherwise normal thyroid function and no obvious illness or underlying thyroid disease, due to an altered "set point" of the hypothalamic-pituitary-thyroid axis.

Chapter 7
Subacute (De Quervain's) Thyroiditis

Paul Aoun and David S. Cooper

Objectives

Subacute thyroiditis is a relatively unusual inflammatory condition of the thyroid that likely has a viral etiology. We report the case of a 40-year-old woman with typical signs and symptoms of subacute thyroiditis. We then discuss the important clinical aspects of the disease, examine the diagnostic strategies, and review the pharmacologic management.

Case Presentation

Ms. A.S. is a 40-year-old woman who presented to her primary care physician with a 2-week history of malaise, fever, and palpitations. She also had noted a lump in the right anterior neck. Thyroid function tests had shown mild hyperthyroidism, and the patient was referred for evaluation of a possible "hot" nodule. On close questioning, the patient had had an upper respiratory infection the previous month. She then developed nightly fevers of 104°F, associated with drenching sweats and a 10-pound weight loss. She also had noted a tender swelling in the right neck for approximately 2 weeks, with the pain radiating to her right ear. There was no previous history of thyroid disease, family history of thyroid disease, or history of head and neck irradiation. The patient's physical examination was significant for pulse 100 beats per minute, blood pressure 110/60, temperature 99°F, and weight 100 pounds, with a body mass index (BMI) of 21. The oropharynx was normal. The left lobe of the thyroid was just barely palpable. The right lobe was approximately twofold enlarged, very firm, somewhat irregular over the surface, and tender to touch. There was no cervical lymphadenopathy. The trachea was in the midline. Examination of the heart, lungs, abdomen, and extremities was normal. There was no tremor, and the skin was warm and moist.

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Thyroid function tests that had been done 2 weeks earlier were as follows: free thyroxine (T_4) 2.2 ng/dL (normal 0.7–1.9), triiodothyronine (T_3) 192 ng/dL (normal 80–180), and thyroid-stimulating hormone (TSH) <0.05 mU/L (normal 0.5–5.0). On repeat on the day of the visit to the endocrinology clinic, the results were as follows: free T_4 2.5 ng/dL, T_3 206 ng/dL, and TSH <0.004 mU/L (normal 0.5–4.1). The erythrocyte sedimentation rate (ESR) was 110 mm per hour. A 24-hour radioiodine uptake was low at 1%, and the scan showed no visible thyroid activity.

Background

Subacute thyroiditis, also called de Quervain's thyroiditis and granulomatous thyroiditis, is a painful inflammatory condition of the thyroid associated with thyrotoxicosis. The cause is unknown, but is thought to be viral in etiology, although no specific virus has been definitively linked to the disease. There are a number of interesting epidemiologic observations associated with subacute thyroiditis, including its greater frequency in the summer months (in some, e.g., ref. 1, but not all reports), its predilection for women, especially those with the human leukocyte antigen (HLA) B35 genotype, and its relative lack of occurrence in tropical and subtropical areas. In an epidemiologic report from the Mayo Clinic, the incidence of subacute thyroiditis in the 1990s in Olmsted County Minnesota was 3.6 cases per 100,000 population per year, which appeared to be declining over the previous two decades [2]. For comparison, the incidence of hyperthyroidism due to Graves' disease and toxic multinodular goiter in a similar population in the United Kingdom of was 46 per 100,000 persons per year during the same time period [3].

The clinical manifestations of subacute thyroiditis are usually "classic," with pain over the thyroid gland in association with systemic symptoms such as fever, malaise, and night sweats. The anterior neck pain can radiate to the ears or down over the sternal area, and it can be exquisitely painful, such that patients cannot move their neck or tolerate anyone touching or examining the thyroid. In some patients, the pain is unilateral, and subsequently spreads to the contralateral side ("creeping thyroiditis"). In rare patients, thyroidal pain may be absent, making the diagnosis extremely difficult [4]. Symptoms of hyperthyroidism such as palpitations, tremulousness, and nervousness are seen in approximately half of all patients [5]. The physical examination is remarkable for a very tender thyroid gland that can be stony hard, quite irregular over the surface, and often asymmetrical. When unilateral it can be confused with a tender thyroid nodule or hemorrhage into a thyroid cyst. Cervical lymphadenopathy and tracheal deviation are unusual.

In the usual case, serum thyroid hormone levels are elevated, but only modestly so. For example, in the Mayo Clinic series cited above, the mean serum free T_4 was 2.8 ng/dL and the median free T_4 was 2.0 ng/mL. The mean serum T_3 was 180 ng/dL, with a mean of 134 ng/dL [2]. The ESR is inevitably elevated and may be as high as 100 mm per hour or more. The ratio of T_3/T_4 is <20, reflecting the relative normal proportions of T_4 and T_3 within the thyroid gland, rather than a ratio >20 which is typical of Graves' disease [6]. The mean and median ESR in

the Mayo Clinic series were 51 and 44 mm per hour, respectively [2]. Antithyroid antibodies may be weakly positive, and anti-TSH receptor antibodies are usually negative. The 24-hour radioiodine uptake is low, but this is not usually necessary to make the diagnosis. Thyroid ultrasound generally shows diffuse inhomogeneity and scattered hypoechoic areas typical of inflammation. Fine-needle aspiration (FNA) of the involved thyroid is not generally needed, but occasionally can be helpful when thyroidal pain is minimal and there is what appears to be a nodule on physical examination. When done, FNA shows typical findings of inflammatory cells and multinucleated giant cells [7]. Multinucleated giant cells are also seen in other inflammatory conditions of the thyroid such as sarcoidosis, tuberculosis, and fungal infections.

In the typical patient, therapy consists of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs). The usual dose of aspirin is approximately 2.4 g per day (two tablets every 6 hours). For patients with more severe or NSAID-resistant pain, glucocorticoid therapy produces more rapid relief. The usual starting dose of prednisone is 40 mg per day with a taper of 10 mg weekly over the next 4 to 6 weeks. Prednisone typically produces dramatic results with almost complete resolution of discomfort and other symptoms of inflammation within 1 to 4 days [2]. There has been some concern that glucocorticoid therapy might prolong the illness, with recurrences during or after the tapering process, but clinical evidence for this is scant. In the Mayo Clinic series, 10% of patients receiving glucocorticoids had recurrences 2 to 10 months after the drugs were withdrawn. β-adrenergic blocking drugs are also useful in those patients with symptomatic thyrotoxicosis.

Following the hyperthyroid phase, which generally lasts 1 to 2 months, there is a phase of hypothyroidism that occurs in some, but not all, patients. This is generally mild, and does not usually require thyroxine therapy. Although it has been stated that there are rarely any permanent thyroidal sequelae in subacute thyroiditis, permanent hypothyroidism has been described in 5% to 15% of patients [2,8,9]. It may be more likely in patients with more severe thyroidal inflammation [2], or in those who develop positive antithyroid antibodies during the initial phase of the disease [10]. It is not prevented by the use of glucocorticoid therapy, and may be more common in those patients who received these drugs [2].

Although subacute thyroiditis is typically self-limited, recurrences may occur years later. In one report from Japan, the recurrence rate was approximately 1.4% [11], and it was 4% in the Mayo Clinic cohort [2]. Very rarely, thyroidal pain does not remit and thyroidectomy becomes necessary. There have also been cases of Graves' disease reported following recovery from subacute thyroiditis, presumably due to exposure of thyroidal antigens to the immune system [12].

How the Diagnosis Was Made

The patient presented with typical signs and symptoms of subacute thyroiditis, and had mild biochemical hyperthyroidism and an elevated ESR. Given these findings, the 24-hour radioiodine uptake and scan were probably not necessary. However, the

patient had been thought to have a right thyroid nodule, and it was felt that further testing was needed to be sure that this was not a "hot" nodule. Once the diagnosis was established, the patient was treated with aspirin 650 mg every 6 hours with reasonable control of her symptoms of pain, fever, and malaise. Atenolol, 50 mg daily, was added because of mild hyperthyroid symptoms, but ultimately was discontinued by the patient because of light-headedness. After several weeks, the right-sided thyroid enlargement resolved, and the left lobe became enlarged and quite tender. After approximately 6 more weeks, she developed mild hypothyroidism with the following laboratory data: free T_4 1.1 ng/dL, TSH 8.6 mU/L. This resolved without treatment 12 weeks later, and she is now euthyroid biochemically with a normal thyroid exam. The entire episode lasted approximately 4 months.

Lessons Learned

1. Subacute thyroiditis can present as a thyroid nodule with unilateral thyroid enlargement, and then progress to the contralateral side ("creeping thyroiditis").
2. Subacute thyroiditis is classically associated with transient hyperthyroidism followed by transient hypothyroidism, but some patients are never overtly hyperthyroid, and hypothyroidism may be permanent.
3. Most patients can be treated with salicylates or NSAIDs for symptomatic relief, but glucocorticoid therapy may be needed in severe cases and usually affords dramatic resolution of symptoms when used.
4. Glucocorticoid therapy does not prevent the development of permanent hypothyroidism in the rare patient who develops this problem.

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Multiple-Choice Questions

1. A 35-year-old woman with a history of AIDS develops a fever, malaise, and an exquisitely tender, diffusely enlarged thyroid gland. She also has mild hyperthyroidism with free T_4 of 2.0 ng/dL and TSH of <0.05 mU/L. Which of the following would lead to consideration of a diagnosis other than subacute thyroiditis?

   A. A low radioiodine uptake
   B. An elevated ESR
   C. Multinucleated giant cells on FNA
   D. A total white blood cell count of $2500/mm^3$
   E. None of the above

   Answer: E. There is nothing specific about the low radioiodine uptake, high ESR, FNA results, or leukopenia. This patient could have infectious thyroiditis from a bacterial, fungal, or other source because of her immunocompromised state.

2. A 40-year-old woman develops severe anterior neck pain, a diffusely tender goiter, and mild hyperthyroid symptoms. Laboratory data are consistent with subacute thyroiditis, and aspirin is prescribed. However, pain continues unabated, and prednisone therapy is instituted. Which of the following statements is true about prednisone therapy?

   A. Prednisone therapy is likely to result in dramatic improvement in her symptoms within 7 to 10 days.
   B. Prednisone therapy will result in dramatic improvement in her symptoms within 1 to 3 days.
   C. Prednisone therapy will prevent the development of permanent hypothyroidism in patients with positive antithyroperoxidase antibodies.
   D. Prednisone should be started at a dose of 80 mg daily with a slow taper over 2 to 3 months.

   Answer: B. Prednisone therapy will result in dramatic improvement in most patients within a few days. The dose is 40 mg daily with a rapid taper. It does not prevent permanent hypothyroidism.

3. Which of the following is true about subacute thyroiditis?

   A. It is caused by adenovirus.
   B. It affects people who are HLA-B27 positive more often.

C. It typically occurs in tropical and subtropical areas.
D. It may trigger the development of Graves' disease.

Answer: D. Subacute thyroiditis is likely a viral disease, but no specific virus has been isolated. It affects people that are HLA-B35 positive and is more common in temperate parts of the world. It may occasionally trigger the development of Graves' disease.

Part III
Thyroid Underactivity

Introduction

Anthony P. Weetman

Physiology

Thyroid underactivity is commonly classified as either primary, the result of thyroid gland failure, or secondary to pituitary or hypothalamic disease. These two forms can readily be distinguished by measuring the thyroid-stimulating hormone (TSH) levels, which are elevated in primary hypothyroidism and low or inappropriately normal in secondary hypothyroidism; in both cases free thyroxine (FT_4) levels are low. Free triiodothyronine (FT_3) levels, on the other hand, can be normal in a quarter of patients with hypothyroidism. Primary thyroid failure can be further classified into subclinical and clinical or overt hypothyroidism. In the former, the TSH is elevated but FT_4 levels are normal, whereas in the latter TSH is elevated (typically greater than 15 to 20 mU/L) and FT_4 levels are low. There is considerable debate over the clinical importance of subclinical hypothyroidism and whether thyroid hormone replacement has any benefit, although there is a consensus that treatment is warranted if the TSH is above 10 mU/L or if the patient is pregnant [1, 2].

Pathophysiology

The main causes of hypothyroidism are shown in Table III.1. By far the commonest causes in iodine-sufficient areas are autoimmune hypothyroidism and iatrogenic hypothyroidism following radioiodine, external neck irradiation, or surgical treatment of thyrotoxicosis or thyroid cancer [3]. Thyroid autoimmunity is readily diagnosed by measuring thyroperoxidase (TPO) antibodies; in occasional patients thyroglobulin antibodies may be positive in the absence of TPO antibodies. Although thyroid cell destruction in autoimmune hypothyroidism is mainly due to the T-cell infiltrate, some patients also have antibodies that can block the TSH receptor.

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Table III.1 Causes of hypothyroidism

Primary
Autoimmune thyroiditis
Iatrogenic
Silent and subacute (viral) thyroiditis
Iodine deficiency
Congenital hypothyroidism and dyshormonogenesis
Drugs; iodine excess, amiodarone, lithium, antithyroid drugs, α-interferon
Infiltrative conditions; amyloidosis, hemochromatosis, Riedel's thyroiditis
Secondary
Hypopituitarism
Isolated TSH deficiency
Hypothalamic disease

Transient episodes of hypothyroidism arise secondary to thyroid destruction caused by viruses, drugs such as amiodarone, or the temporary exacerbation of thyroid autoimmunity that occurs in 5% of women after pregnancy (postpartum thyroiditis). There is often a phase of thyrotoxicosis prior to the appearance of hypothyroidism. Amiodarone may also cause permanent hypothyroidism through the toxic action of the drug on thyroid cells.

Treatment

The goal of treatment in primary hypothyroidism is to restore TSH levels to normal. Thyroxine (levothyroxine sodium) at a dose of 1.6 μg/kg/day in complete thyroid failure is the best replacement therapy. There is no clear benefit from the addition of triiodothyronine to thyroxine [4]. Caution is needed in the elderly and those with cardiac disease, in whom thyroxine treatment should be initiated cautiously, with very gradual building up of the full replacement dose. Once TSH levels are normal, annual checks of replacement adequacy are all that is required, although thyroxine treatment in pregnancy requires careful management, as the dosage may need to be increased by 50%.

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Chapter 8
Amiodarone-Induced Hypothyroidism

Ramzi Ajjan

Objectives

To discuss the difficulties encountered in the management of patients with amiodarone-induced hypothyroidism.

Case Presentation

A 34-year-old man with a diagnosis of dilated cardiomyopathy following myocarditis was commenced on amiodarone in February 1994 by the cardiologist as a treatment for narrow and broad complex tachycardia secondary to His-bundle arrhythmia. He was started on 600 mg amiodarone/day for 1 week, 400 mg/day for another week, followed by 200 mg/day as a maintenance dose. The rest of his treatment included bisoprolol 10 mg once/day and enalapril 10 mg twice/day. His thyroid function tests (TFTs) were not requested prior to initiating amiodarone but 4 weeks after starting treatment these showed: total T_4 (TT_4), 74 nmol/L (normal range, 60–140), and thyroid-stimulating hormone (TSH), 6.51 mU/L (normal range, 0.2–4.0).

The patient was reviewed in July 1994, when he was complaining of tiredness and his TFTs showed TT_4 of 92 nmol/L and TSH of 2.18 mU/L.

Tiredness was attributed to his heart failure, and the patient was followed up for the next 18 months with regular TFTs, which were all normal.

In September 1995 the TSH rose to 9.8 mU/L with a normal TT_4 of 93 nmol/L. In view of the abnormal TFTs, the cardiologist decided to reduce the dose of amiodarone to 100 mg/day. TFTs 8 weeks later showed TT_4 of 81 nmol/L and TSH of 10.8 mU/L. However, the arrhythmia recurred and the dose of amiodarone was increased to 200 mg in December 1995. The TFTs in April 1996 showed TT_4 of 53 nmol/L and TSH of 19.7 mU/L.

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The patient was feeling increasingly tired but had no other clear symptoms of hypothyroidism. No formal examination of his thyroid status was undertaken. In view of his tiredness and recent TFTs he was started on levothyroxine (LT_4) at 25 μg/day, which was increased to 50 μg/day 2 weeks later. Repeat TFTs in July 1996 were normal on the same dose of LT_4 and the patient reported an improvement in his tiredness. The TFTs were checked regularly every 3 to 6 months and were stable on 50 μg/day of LT_4. In November 2001 the patient was reviewed by the cardiologist, who noted clear symptoms of thyrotoxicosis including heat intolerance, increased sweating, hand tremor and weight loss occurring over a period of 2 months. The TFTs showed TT_4 of 260 nmol/L and TSH of <0.05 mU/L.

The LT_4 treatment was stopped and TFTs were rechecked 4 weeks later (December 1996). Free T_4 (FT_4) was requested together with C-reactive protein (CRP). The FT_4 was 46 pmol/L (normal range, 10–25 pmol/L), the TSH was <0.05 mU/L, and the CRP was 51 mg/L.

At this stage he was referred to the endocrinology department, where he was reviewed in February 2002. The patient's symptoms had generally subsided by that time and the endocrinologist noted mild signs of thyrotoxicosis, including fine hand tremor and brisk reflexes. He had no signs of Graves' ophthalmopathy and his thyroid gland was just palpable. He was started on carbimazole 20 mg three times/day, pending the results of the investigations, which revealed FT_4 of 18.9 pmol/L, TT_3 of 1.5 nmol/L (normal range, 1–2.5 nmol/L), TSH of <0.05, thyroperoxidase antibodies were negative, and CRP was 11 mg/L. His carbimazole was subsequently stopped after 3 weeks of treatment and his repeat TFTs in March 2002 (5 weeks after the first endocrine consultation) showed FT_4 of 9.1 pmol/L, TT_3 of 1.1 nmol/L, and TSH of 35 mU/L. Treatment was withheld at this stage and TFTs repeated 4 weeks later, with the following results: FT_4 of 6.1 pmol/L, TT_3 of 0.9 nmol/L, and TSH of 62 mU/L. LT_4 was started and the dose was increased gradually to a maintenance dose of 125 μg/day.

The TFTs remain stable after treatment for more than 4 years with the same dose of LT_4. The patient is asymptomatic and his latest results are consistent with adequate replacement: FT_4 of 22.5 pmol/L, and TSH of 1.9 mU/L.

How the Diagnosis Was Made

This 34-year-old man with cardiomyopathy was started on amiodarone as a treatment for cardiac arrhythmias. A few weeks into treatment, the TSH was found to be marginally elevated, which may be seen in the first 3 months of amiodarone treatment, particularly in patients receiving high doses of the drug. The TFTs subsequently normalized, but 18 months later the TSH was raised, with normal TT_4 consistent with subclinical hypothyroidism. As this can be a transient phenomenon in patients treated with amiodarone, it can be observed without immediate instigation of treatment. The cardiologist decreased the dose of amiodarone but the arrhythmia recurred, necessitating increasing the dose again and ruling out the option of

stopping the drug. Subsequent TFTs showed a greater elevation of TSH with a drop in TT_4 below the normal range, and the patient became more symptomatic, consistent with a diagnosis of clinical hypothyroidism. The patient was started on LT_4 therapy, which normalized his thyroid function and this was associated with symptomatic improvement.

Over the next 5 years, he required only a small dose of LT_4, indicating a partially functioning thyroid gland. In November 2001, he presented with classical symptoms of thyrotoxicosis, and his TFTs showed high TT_4 with suppressed TSH. His LT_4 was stopped, but he remained biochemically thyrotoxic, prompting a referral to the endocrinologist. Amiodarone-induced thyrotoxicosis (AIT) may be due to stimulation of thyroid hormone production by thyroid follicular cells (type 1), or may occur secondary to thyroiditis and thyroid destruction (type 2). The late presentation of thyrotoxicosis together with the negative antibody test and raised CRP is suggestive of AIT type 2. This diagnosis is further supported by the symptomatic improvement and normalization of thyroid hormone levels in February 2002. The patient subsequently became hypothyroid, both clinically and biochemically, which is known to occur following AIT type 2. He was started on LT_4 and the dose was gradually titrated up to 125 μg/day. As the patient has been stable for more than 4 years on a full replacement dose of LT_4, it is unlikely that his thyroid will recover or that he will become thyrotoxic.

Lessons Learned

The incidence of amiodarone-induced hypothyroidism (AIH) varies between different studies from 1% to 32% [1, 2]. In contrast to AIT, AIH is fourfold more common in iodine-replete areas, compared with iodine-deficient areas, emphasizing the role of iodine in the pathogenesis of the disease. Previous thyroid autoimmunity, manifested by raised TPO-antibody levels, is associated with an increased risk (relative risk [RR] 7.9) of AIH [3]. AIH is slightly more frequent in females (RR 7.3) and the elderly, which is probably due to the higher rate of thyroid autoimmunity in these subjects. The combination of female sex and detectable TPO antibodies increases the RR of AIH to 13.5 [3]. A previous history of AIT (usually type 2) and the presence of a goiter or elevated TSH prior to starting amiodarone therapy are risk factors for AIH.

A key mechanism for the induction of hypothyroidism by amiodarone is related to the high iodine content of the drug. On a maintenance dose of 200 mg a day, the free iodide released can be up to 50-fold the daily dietary iodine requirement [1]. The high plasma levels of iodine inhibits thyroid hormone metabolism through the Wolff-Chaikoff effect, and the inability to escape from this effect results in hypothyroidism. Other mechanisms include amiodarone-induced inhibition of iodine organification and a direct toxic effect of amiodarone on thyroid follicular cells resulting in decreased thyroid hormone synthesis [4]. A rather controversial issue is related to the effect of amiodarone on thyroid autoimmunity. Iodine has been

implicated in inducing thyroid autoimmunity in humans, and the excess iodine associated with amiodarone treatment may trigger thyroid autoimmunity de novo [1].

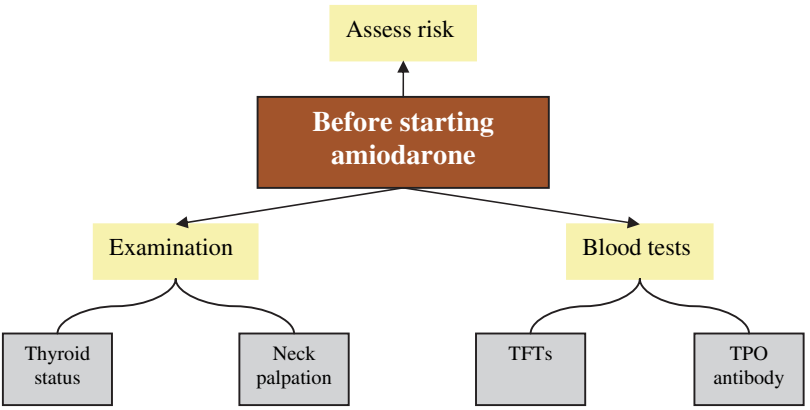
Amiodarone-induced hypothyroidism usually, but not exclusively, occurs 6 to 12 months after starting therapy, and clinical manifestations are often vague and similar to those occurring in hypothyroidism secondary to any other cause. Goiter is uncommon, occurring in less than one fifth of patients, and myxedema coma is very rare [1, 2]. The TFTs should be regularly checked in patients receiving amiodarone treatment, at least every 6 months. Amiodarone inhibits type 1 deiodinase activity, resulting in reduction of T_4 to T_3 conversion, and therefore T_4 is commonly at the upper end of the normal range and can even be above the normal range without clinical thyrotoxicosis. In the early months of treatment and particularly with higher doses of amiodarone, TSH levels can be above the normal range, which is possibly related to inhibition of type 2 deiodinase or may be due to a direct effect on TSH production and release from the pituitary. During long-term treatment, patients may experience intermittent mild elevation or decrease in TSH levels, reflecting episodes of subclinical hypothyroidism or thyrotoxicosis respectively [1, 2, 5].

If stopping amiodarone treatment is an option, thyroid function recovers in the majority of cases, but this is less likely to occur in TPO-antibody–positive patients. Potassium perchlorate has been used to restore euthyroidism after discontinuation of amiodarone treatment, by a mechanism that probably involves a reduction of intrathyroidal iodine concentration, facilitating quicker recovery of the thyroid gland. However, due the potentially fatal side effect of aplastic anemia, perchlorate treatment is not generally recommended [1, 2].

If amiodarone treatment is necessary, LT_4 treatment can be used in combination, which is perhaps the most practical approach to treat AIH. During LT_4 replacement, FT_4 levels should be kept at the upper end of the normal range without causing TSH suppression. It should be noted that patients with AIH may require higher doses of LT_4 to render them euthyroid compared with spontaneous autoimmune hypothyroidism patients [5].

In cases of subclinical hypothyroidism, treatment is probably warranted if the patient is symptomatic (trial of 3 months) or has detectable TPO antibodies [2, 5]. In the case described above, unfortunately, the patient's thyroid status and palpation of the thyroid gland were not performed before starting amiodarone treatment. Furthermore, neither TFTs nor TPO antibody levels were measured. At baseline, all patients should have their neck palpated and blood tests should include TFTs together with TPO antibodies. Some suggest requesting a thyroid ultrasound examination in the initial evaluation [1], but this is not always practical or necessary.

During the initial phase of hypothyroidism, LT_4 requirements were low, indicating the presence of some functional thyroid tissue, which was affected by AIT a few years later, demonstrating that patients with AIH may become thyrotoxic. Again, no formal thyroid assessment was undertaken during the initial diagnosis of thyrotoxicosis, which is simply due to the fact that the patient was assessed at this stage by a cardiologist, who would naturally have little experience in the management of thyroid disease. The patient subsequently received proper thyroid



TFTs: thyroid function test

TPO: Thyroid peroxidase

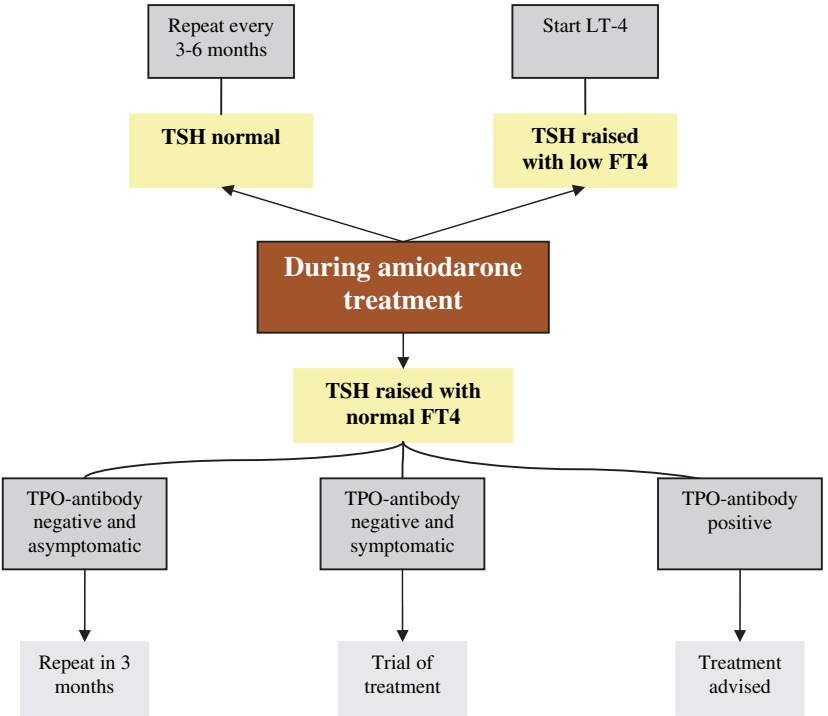


Fig. 8.1 Assessment and monitoring of patients on amiodarone treatment. TFTs, thyroid function test; TPO, thyroperoxidase

examination when he was reviewed by an endocrinologist, stressing the importance of early intervention by a specialist in the field for appropriate assessment of such patients. The patient consequently developed full-blown hypothyroidism, which is known to occur after an episode of type 2 AIT.

The case highlights some of the potential difficulties encountered in managing a patient with AIH. Appropriate assessment of all patients with amiodarone-induced thyroid dysfunction is best carried out by an endocrinologist, and therefore early referral of these patients to a specialist is recommended even in those with only mildly abnormal TFTs. Assessment and monitoring of patients before and during amiodarone treatment is summarized in Fig. 8.1.

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Questions

1. True or false: Amiodarone-induced hypothyroidism (AIH) is:

   - More common in males
   - Likely to resolve if amiodarone is stopped, particularly in patients with undetectable TPO antibodies
   - More common in iodine replete areas
   - Commonly seen with goiter
   - More likely to occur in patients with detectable TPO antibody prior to starting amiodarone treatment

2. True or false: TFTs in patients treated with amiodarone:

   - TSH often falls during the first 3 months of treatment with high-dose amiodarone.
   - FT_4 can be above the normal range without actual hyperthyroidism.
   - Persistently high TSH with symptoms of hypothyroidism does not require treatment provided FT_4 and FT_3 levels are in the normal range.
   - T_3 levels are the best indicator of adequate LT_4 replacement therapy.
   - TSH levels may fluctuate.

3. True or false: Before starting amiodarone treatment, it is essential to:

- Request a thyroid ultrasound.
- Palpate the neck.
- Request a full autoimmune screen.
- Check thyroid function.
- Measure thyroid stimulating antibody levels.

Chapter 9
Autoimmune Hypothyroidism with Persistent Elevation of TSH

Amit Allahabadia

Objectives

To understand the investigation and treatment of patients with autoimmune hypothyroidism, and to recognize causes of persistent thyroid-stimulating hormone (TSH) elevation despite adequate thyroxine treatment.

Case Presentation

A 39-year-old man presented to his primary care physician in January 2005 with a 4-month history of generalized aches and pains and tiredness. There also appeared to be increased stress in his work and personal life, and a trial of amitriptyline 25 mg/day was commenced. Although his symptoms improved, they did not resolve completely. Blood tests including thyroid function tests were performed and revealed marked hypothyroidism: TSH >150 mU/L, and free thyroxine (FT_4) 3.0 pmol/L. He was referred to an endocrinologist and was seen in April 2005. A detailed history revealed a normally fit and active person who had been unable to perform his normal activities in the preceding few months. There was no history of neck swelling or pain. His skin had become very dry but with no pigmentation, he had become constipated, and he had dizziness on standing. There was no family history of thyroid disease but he had a sister and an aunt with type 1 diabetes.

His weight was 70 kg. He had mildly hypothyroid facies but no increase in pigmentation. There was no goiter and no signs of thyroid eye disease. His pulse was 68 in sinus rhythm and his blood pressure was 100/70 with no postural drop. Systematic examination was normal.

Routine blood tests revealed a normal full blood count, thyroid function, renal and liver function, cortisol and glucose. Thyroid peroxidase antibodies were positive. The TSH was >150 mU/L (normal 0.35–4.5), FT_4 was 5.4 pmol/L (normal

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10.3–21.9), and free triiodothyronine (FT_3) was 2.6 pmol/L (normal 3.5–6.5). He was commenced on thyroxine (levothyroxine) 100 μg per day and was advised to take it 30 minutes before breakfast to aid absorption of the medication.

When next seen in early June 2005, his condition was improved although he did not feel "100 percent." The serum TSH was checked, with a planned review in 3 months. The TSH had improved but was still elevated at 10.8 mU/L. He was contacted by letter and advised to increase the thyroxine to 125 μg per day.

The patient was next reviewed 2 months later. He felt better on thyroxine 125 μg per day, but had only collected his prescription 3 weeks beforehand so it was too early to recheck the TSH. He was encouraged to have a repeat TSH test in 4 weeks, but he did not come in for this investigation until 4 months later. The TSH had improved slightly but was still elevated at 8.43 mU/L with an FT_4 of 15.3 pmol/L. His thyroxine dose was increased to 150 μg/day and he was advised of the importance of compliance and attending for blood tests at appropriate times.

He was next seen in January 2006 when he was still feeling tired, particularly over the last 2 months. The TSH remained high at 9.3 mU/L (FT_4 16.2 pmol/L), even on 150 μg of thyroxine per day. When asked about compliance, he insisted that he took the prescribed dose of thyroxine every day, and had only missed three or four doses 3 months ago when he was away on a business trip. No new medications had been introduced that could interfere with thyroxine requirements. The importance of adherence with treatment was once again emphasized, and he was advised to put a 1-week supply of thyroxine in a separate bottle and to take his medication from this bottle. If any tablets were left at the end of the week he should take them all at that time.

He was reviewed again 2 months later. His TSH was once again elevated at 10.0 mU/L on 150 μg of thyroxine. Again he insisted that he was compliant with treatment. Based on a body weight of 70 kg, 150 μg was considered to be more than adequate to normalize his TSH. In view of his previous record of not collecting prescriptions or attending for blood tests on time, and having previously missed tablets, poor compliance was suspected as the cause of his persistently raised TSH. To test this hypothesis, he was asked to come to the hospital for observed administration of thyroxine (1000 μg as single dose once weekly) and measurement of thyroid function, as follows:

Baseline week 1 (immediately before the administration of thyroxine):
TSH 9.0 mU/L, FT_4 16.6 pmol/L
Week 2:
TSH 10.2 mU/L, FT_4 13.9 pmol/L
Week 3:
TSH 9.5 mU/L, FT_4 TSH 14.2 pmol/L
Week 4:
TSH 10.5 mU/L, FT_4 11.8 pmol/L
Week 5:
TSH 9.8 mU/L, FT_4 12.0 pmol/L

Weekly observed administration of 1000 μg of thyroxine did not restore his TSH to normal, suggesting that lack of compliance was unlikely to be the cause of his persistently elevated TSH. As he already suffered from one autoimmune disease and had a strong family history of type 1 diabetes, an autoantibody screen for celiac disease was performed:

Endomysial antibody immunoglobulin A (IgA):	Positive
IgA gliadin antibody:	Equivocal
IgG gliadin antibody:	Equivocal
IgA-t-transglutaminase antibody	>300 U/mL (normal 0–15)

The autoantibody screen for celiac disease was positive, and he was referred for endoscopy and duodenal biopsy. The endoscopy showed erythematous and exudative gastritis, and duodenitis and edema in the first part of the duodenum. In the second part of the duodenum, the folds of small bowel appeared scalloped and atrophic possibly due to celiac disease. Histopathology was reported as follows: "Duodenal mucosa with villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes. The appearances are consistent with a gluten-sensitive enteropathy."

The patient was commenced on a gluten-free diet and was assessed by a gastroenterologist. Three months later his TSH was low, at 0.20 mU/L on 150 μg of thyroxine and the dose of thyroxine was reduced to 125 μg per day. His latest TSH was normal at 2.1 mU/L.

How the Diagnosis Was Made

Hypothyroidism

Epidemiology

Autoimmune hypothyroidism or Hashimoto's thyroiditis is the commonest cause of acquired hypothyroidism in iodine-replete areas [1]. Individuals who suffer from or who have a family history of autoimmune thyroid disease and other autoimmune conditions such as type 1 diabetes and celiac disease are at increased risk of developing autoimmune hypothyroidism [2].

Investigation

Thyroid-stimulating hormone is the most sensitive marker of thyroid failure and is elevated in primary hypothyroidism [3]. A raised TSH may precede a low serum FT_4 concentration by several months or years as occurs in subclinical hypothyroidism. As thyroid failure progresses, the serum FT_4 concentration falls below the normal range with the development of overt clinical hypothyroidism. Serum TSH, therefore, can be used as a primary diagnostic test provided pituitary or hypothalamic disease is not suspected, and if found to be elevated, serum FT_4 should then be measured to

confirm the presence of hypothyroidism. The FT_3 concentration may not fall below normal for some time after the development of overt hypothyroidism, and is not used for the diagnosis of primary hypothyroidism. Antithyroperoxidase antibodies are present in 95% of patients, and 60% also have thyroglobulin antibodies; their detection in a biochemically hypothyroid patient confirms the diagnosis of autoimmune hypothyroidism.

Treatment

The treatment of autoimmune hypothyroidism is lifelong. Thyroxine is the drug of choice because it is converted to triiodothyronine in the tissues, a process that is autoregulated. The main factors that influence thyroxine requirement are age and lean body mass. The mean dose of thyroxine needed to restore euthyroidism in adults with total thyroid failure is 1.6 μg per kg of body weight. In those less than 60 years of age with no history of ischemic heart disease, a full thyroxine replacement dose of 100 μg per day should be commenced. In older patients and those with heart disease, there is a risk of inducing angina or myocardial infarction, and thus smaller starting doses of 25 to 50 μg are used. The TSH should be rechecked every 6 to 8 weeks, and the thyroxine dose adjusted by increments or decrements of 25 to 50 μg until the TSH has normalized. Once euthyroidism is achieved, patients should be monitored annually with a TSH measurement to ensure that thyroxine replacement is adequate.

Case Discussion

The initial presentation of vague symptoms that could be attributable to a number of conditions highlights the difficulty that may occur in diagnosing hypothyroidism. Hence anxiety and depression were suspected before hypothyroidism was diagnosed. This reflects the need for a detailed clinical assessment and appropriate investigations before making a diagnosis.

When blood tests were first requested in the hospital visit, the serum FT_3 was measured in addition to TSH and FT_4. This was unnecessary and did not provide useful additional information. Once the diagnosis of autoimmune hypothyroidism was confirmed, treatment with the correct starting dose of thyroxine for a 70-kg man was given. The patient was reviewed with a repeat TSH 2 months later when his thyroxine was increased by an increment of 25 μg per day. The timing of this test and the increase in thyroxine dose for a modestly elevated TSH (10.8 mU/L) were both appropriate. After this consultation, the patient did not collect his prescription when requested and, therefore, when next seen in the clinic, it was too early to recheck his TSH. Furthermore, he did not come in for a repeat TSH at the correct time, delaying further titration and optimization of his thyroxine. The lack of adherence with respect to collecting a new prescription or attending for blood tests when requested and the persistent elevation of TSH created suspicion that he may also be poorly compliant with his thyroxine treatment.

In some centers, weekly observed administration of oral thyroxine is used as a means of determining whether a persistently raised TSH is the result of poor compliance and as a treatment for poorly compliant patients [4]. In this case, thyroxine 1000 μg was given weekly, which is almost equivalent to the daily dose of 150 μg that this patient was prescribed. The TSH result at the end of the test showed that poor compliance was not the cause. Although poor adherence accounts for most cases of persistent TSH elevation, a number of medical conditions, drugs, and foodstuffs containing dietary fiber may increase or decrease thyroxine requirements through altered metabolism or absorption (Table 9.1) [3, 5]. It is therefore important to record a thorough medical and drug history at the initial consultation and to update the findings when presented with a patient with a persistently elevated TSH. In this case, celiac disease was screened for and found after poor compliance had been ruled out. Treatment with a gluten-free diet improves thyroxine absorption and may even reduce the thyroxine dose needed for euthyroidism, as was seen in this case. In other conditions where there is interference with absorption due to disease, drugs, or foodstuffs, the thyroxine dose may require increase or drugs taken at a different time from thyroxine. Likewise, where metabolism is altered, an increase in the thyroxine dose may be required.

Table 9.1 Causes of altered thyroxine requirements

Poor compliance
Reduced thyroxine absorption
Coexisting diseases
Diseases causing malabsorption, e.g., celiac disease, tropical sprue
Previous small intestine surgery
Conditions associated with reduced gastric acid production
H. pylori infection
Drugs
Oral iron
Aluminium hydroxide gel
Sucralfate
Calcium carbonate
Cholestyramine
Foodstuffs
Dietary soya
Fiber
Increased thyroxine clearance
Coexisting conditions
Pregnancy
Nephrotic syndrome
Other systemic illnesses
Drugs
Carbamazepine
Phenytoin
Phenobarbitone
Rifampicin
Increased binding proteins
Hormone replacement therapy

Lessons Learned

This case illustrates some of the difficulties in diagnosing and managing patients with hypothyroidism. Thyroxine doses should be started that are appropriate for a patient's weight, age, and coexisting medical conditions. Therapy should be monitored with TSH measurements at suitable time intervals, and the dose altered as necessary. Patient compliance is important to this process. Although poor adherence is the most common cause of persistent TSH elevation and should be investigated, the influence of other conditions and drugs should not be ignored.

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Questions

1. True or false: Autoimmune hypothyroidism

   - is less common in iodine replete areas.
   - is always associated with thyroglobulin autoantibodies.
   - is often transient.
   - occurs more commonly if there is family history of celiac disease.
   - is best treated with a combination of liothyronine and thyroxine.

2. In patients with primary hypothyroidism:

   - FT_3 as well as TSH and FT_4 should be used to confirm the diagnosis.
   - TSH and T_4 should be checked when monitoring thyroid hormone replacement.
   - Three weeks is the most appropriate time interval for repeat TFTs after the initiation of thyroxine.
   - Long-term monitoring of thyroid function should be performed annually in patients taking thyroxine.
   - The optimal dose of thyroxine is reached when the FT_4 is at the upper limit of the normal range.

3. In hypothyroid patients with persistent elevation of TSH:

   - The commonest cause is malabsorption.
   - Celiac disease should be considered as a possible cause.
   - Weekly supervised administration of thyroxine can be used to investigate the possibility of poor compliance.
   - Sodium valproate is a cause.
   - Oral iron therapy may be responsible.

Chapter 10
Hashimoto's Thyroiditis and Type 1 Diabetes

Mark P.J. Vanderpump

Objectives

This case history illustrates the diagnosis of chronic autoimmune goitrous (Hashimoto's) thyroiditis and the management of subclinical hypothyroidism in a young woman with type 1 diabetes. It then addresses the evidence for an association between autoimmune thyroiditis and type 1 diabetes and the current known genetic factors, as well as the importance of screening for autoimmune thyroiditis in patients with type 1 diabetes.

Case Presentation

A 26-year-old woman with type 1 diabetes worked in the City (the financial district of London) as a trader. She had recently moved to London. She had been diagnosed 2 years earlier, after having initially presented as an emergency with diabetic ketoacidosis. She had been stabilized on a "qds" insulin regime with a short-acting insulin analogue before meals and a long-acting analogue at night. She was on the oral contraceptive pill and not considering starting a family in the next few years. She was a nonsmoker. The relevant family history included an uncle with myasthenia gravis and a grandmother on thyroxine replacement for long-standing hypothyroidism. Her most recent hemoglobin A1c(HbA1c) was 7.6%. There was no significant dyslipidemia, her blood pressure was 124/76, and there was no evidence of microvascular complications of diabetes. Thyroid function tests had been included in the most recent biochemical profile and showed total thyroxine (TT_4) of 88 nmol/L (reference range, 60–140) and thyrotropin (TSH) of 3.6 mU/L (reference range, 0.2–4.0).

Six months later at her next review, all continued to be well. On this occasion the diabetes physician had included her thyroperoxidase antibody status with

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current thyroid function tests: TT_4 94 nmol/L (reference range, 60–140); TSH 4.2 mU/L (reference range, 0.4–4.4); thyroperoxidase antibody titer 220 KU/L (reference range, <20).

On examination of the neck, an asymptomatic smooth goiter was palpable and visible. She was informed that she had evidence of autoimmune thyroiditis and that regular checks of thyroid function would be performed from then on.

At her next review, 6 months later, she complained of some tenderness in the front of her neck, which caused some mild discomfort on swallowing. The view of the physician was that the goiter was smaller but firmer, with slight tenderness on palpation. Thyroid function tests had been repeated: TT_4 78 nmol/L (reference range, 60–140); TSH: 6.4 mU/L (reference range, 0.2–4.0); thyroperoxidase antibody titer 356 KU/L (reference range, <20). As she had no other symptoms, it was decided to adopt a "wait and see" policy and not treat with thyroxine at this stage but that she would need a further check of thyroid function in 6 months.

Her next outpatient appointment was delayed, so the next assessment occurred 12 months later. She had increasingly felt more tired and her blood sugars were less well controlled, with the latest HbA1c 8.5%. The goiter was no longer tender and was less visible than previously. The thyroid function tests on this occasion showed TT_4 61 nmol/L (reference range: 60–140), and TSH 15.8 mU/L (reference range: 0.2–4.0). She was commenced on lifelong thyroxine replacement therapy and on a daily dose of thyroxine 100 μg daily.

At review 2 months later, symptomatically she was much improved. Her repeat thyroid function tests showed TT_4 124 nmol/L (reference range, 60–140), and TSH 3.5 mU/L (reference range, 0.2–4.0). She attended with her husband on that occasion, explaining that she wanted to start a family shortly. The dose of thyroxine was increased slightly to 100 and 125 μg on alternate days in order to achieve a target serum TSH of between 0.5 and 2 mU/L. She was referred to the prepregnancy clinic to ensure that her target HbA1c of 6.5% was also achieved preconception. She was informed that her dose of thyroxine would need to be increased by 25 μg daily as soon as any future pregnancy test was positive.

How the Diagnosis Was Made

Hashimoto's thyroiditis (also known as chronic lymphocytic or autoimmune thyroiditis) is named after the Japanese surgeon who first described it in 1912, but the condition was not properly understood until thyroid autoantibodies were discovered in 1956. This term is sometimes now used to describe the presence of thyroid antibodies in the blood, with or without a goiter.

Hashimoto's thyroiditis is characterized clinically by gradual thyroid failure, goiter formation, or both, due to autoimmune-mediated destruction of the thyroid gland involving apoptosis of thyroid epithelial cells. Nearly all patients have high serum concentrations of antibodies against one or more thyroid antigens; diffuse lymphocytic infiltration of the thyroid, which includes predominantly thyroid-specific B and

T cells; and follicular destruction. The cause of Hashimoto's thyroiditis is thought to be a combination of genetic susceptibility and environmental factors. The familial association with Graves' disease and the fact that Graves' disease may sometimes evolve into Hashimoto's thyroiditis (and vice versa) indicate that the two disorders are closely related pathophysiologically, albeit not functionally.

Hashimoto's disease is prevalent in about one in 10 women aged 30 years or over, and is an important cause of goiter, especially in women, but may also affect young girls and adolescents. It affects women 10 times more often than men. It is the most common cause of hypothyroidism in the developed world, although iodine deficiency is the commonest etiology worldwide.

The course of the disease is protracted over many years, and during this time it may wax and wane in its destructive effect on the thyroid gland. At any stage the progression of the disease may appear to be arrested and to lie dormant. The development of a small rubbery goiter, usually painless but sometimes associated with mild discomfort, may be the first manifestation of the disease. Alternatively and perhaps more commonly, the patient may only become symptomatic much later in the course of the condition when they become hypothyroid. Over the years a goiter caused by Hashimoto's thyroiditis may disappear and the thyroid gland is replaced by fibrous tissue (atrophic hypothyroidism).

This young woman with type 1 diabetes was diagnosed with Hashimoto's thyroiditis based on finding thyroperoxidase (TPO) antibodies in the blood and the presence of a classical smooth goiter. The serum TSH was in the upper half of the reference range at initial screening. Later, in the natural history, the antibody titre was seen to rise, the thyroid gland became atrophic, and the serum TSH also rose. The function of the thyroid gland has to be monitored at intervals throughout the long course of Hashimoto's thyroiditis even if the patient experiences few if any signs or symptoms beyond having a small goiter. Although treatment with thyroxine may prevent the goiter from becoming larger or reduce its size, this therapy becomes essential only when the TSH begins to rise and T_4 begins to fall, indicating failure of the thyroid gland. Thyroxine therapy to correct thyroid hormone deficiency may also reduce the level of autoantibodies with time. This patient was appropriately diagnosed, monitored, and then treated with thyroxine replacement once she was clinically and biochemically euthyroid.

Lessons Learned

Management of Subclinical Hypothyroidism

Hypothyroidism due to chronic autoimmune thyroiditis is an insidious condition with a significant morbidity, and the subtle and nonspecific symptoms and signs may be mistakenly attributed to other illnesses, particularly in those with other chronic diseases, such as type 1 diabetes, or in those who are postpartum. Biochemical tests of thyroid function reveal the diagnosis before it is clinically apparent. The term

subclinical hypothyroidism is used to describe the finding of a raised serum TSH but a normal free T_4 (FT_4). At the 20–year follow-up of the Whickham cohort, the risk of having developed hypothyroidism was examined with respect to risk factors identified in the first survey [1]. In the surviving women, the annual risk of spontaneous overt hypothyroidism was 4% in those who had both high serum TSH and antithyroid antibody concentrations, 3% if only their serum TSH concentrations was high, and 2% if only their serum thyroid antibody concentration was high; at the time of followup, the respective rates of hypothyroidism were 55%, 33%, and 27%. The probability of developing hypothyroidism was higher in those women who had serum TSH concentrations above 2.0 mU/L and high serum titers of antithyroid microsomal (TPO) antibodies during the first survey (Fig. 10.1).

There is debate regarding the potential benefits of treatment with thyroxine to normalize the TSH, and whether this alleviates symptoms and improves the lipid profile. There are observational data suggesting that subclinical hypothyroidism during pregnancy may be associated with suboptimal intellectual performance in children, but these data are based on relatively small numbers of cases. Some studies have even suggested that the maternal serum FT_4 level is more sensitive than the serum TSH in predicting the likelihood of adverse intellectual outcomes in the offspring. No intervention data on the effect of thyroxine therapy in pregnancy exist, although recent data suggest that treating evidence of mild thyroid failure may improve obstetric outcome [2]. The current consensus is that women with evidence of mild thyroid failure should be treated with thyroxine to normalize the serum TSH

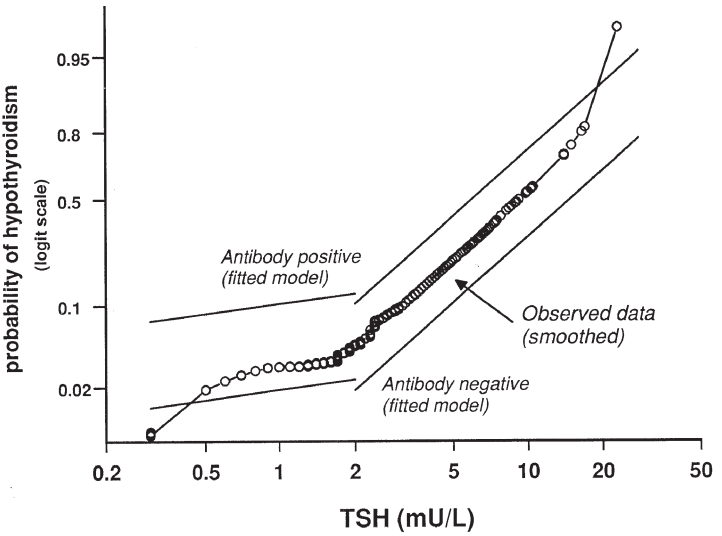

Fig. 10.1 The probability for development of hypothyroidism within 20 years with increasing values of serum TSH at first Whickham survey in 912 surviving women. (From ref. 1, with permission.)

prior to conception and that the TSH should be monitored carefully during pregnancy and targeted to within the lower end of the reference range where possible.

It was elected not to treat this patient on the basis of the initial serum TSH rise while she was asymptomatic. However, once she was symptomatic with a raised serum TSH and low T_4, she received thyroxine replacement to target a serum TSH between 0.2 and 2 mU/L in view of the possibility of pregnancy.

Evidence for an Association Between Autoimmune Thyroiditis and Type 1 Diabetes and the Current Known Genetic Factors

The occurrence of autoimmune thyroiditis in patients with type 1 diabetes and in their family members is well recognized. In large groups of families with type 1 diabetes in the United Kingdom and the United States, at least one case of autoimmune thyroid disease (AITD) was reported in relatives of 22% and 40% of patients with type 1 diabetes, respectively [3]. A higher than expected prevalence of AITD has been found in patients with other autoimmune disorders and in their families. These include other autoimmune endocrinopathies such as Addison's disease and premature ovarian failure, and nonendocrine autoimmune disorders such as pernicious anemia, celiac disease, myasthenia gravis, and rheumatoid arthritis.

Most cases of AITD along with other common autoimmune disorders are now thought to have a complex genetic basis; that is, the genetic predisposition to the disease is determined by a series of interacting susceptibility alleles of several different genes. Candidate gene studies have looked at polymorphic markers within a particular gene, which has been selected because it is thought that disruption of its function may result in the phenotype. Alternatively linkage scanning, in which widely spaced anonymous genetic markers (usually microsatellite repeat polymorphisms between genes), has been used to detect chromosomal segments with evidence for linkage in affected families. In AITD, several gene loci have been shown to determine susceptibility to the disease, with a major contribution from cytotoxic T lymphocyte antigen 4 (CTLA-4), which is an immunoregulatory molecule that is expressed on the surface of activated T lymphocytes. Other loci are involved to a lesser degree, including one or more genes in the major histocompatability complex (MHC) located on chromosome 6p2. Both CTLA-4 and MHC gene loci are associated with susceptibility to type 1 diabetes.

Screening for Autoimmune Thyroiditis in Type 1 Diabetes

There is a consensus from recent guidelines from various international organizations that screening for AITD in patients with type 1 diabetes is warranted in view of the high frequency of asymptomatic thyroid dysfunction in unselected patients, particularly women. In a randomly selected group of 1310 adult diabetic patients attending a diabetic outpatient clinic in Edinburgh, UK, who received annual screening for

thyroid disease, the overall prevalence of thyroid disease was found to be 13%, and was highest (31%) in type 1 diabetic females and lowest in type 2 diabetic males (7%) [4]. As a direct result of screening, new thyroid disease was diagnosed in 7% (89 patients) of the population screened; the commonest diagnosis was subclinical hypothyroidism (5%), followed by hypothyroidism (1%), hyperthyroidism (0.5%), and subclinical hyperthyroidism (0.5%). Women with type 1 diabetes had the highest annual risk of developing thyroid disease (12%) in a 1-year follow-up of this cohort. This study has concluded that thyroid function should be screened annually in patients with type 1 diabetes to detect asymptomatic thyroid dysfunction.

Women with type 1 diabetes are also at increased risk of postpartum thyroid dysfunction, and it has also been recommended that all such diabetic women should be tested preconception or in the first trimester for thyroid peroxidase antibodies. Forty-one women with type 1 diabetes from New York, New York, were followed prospectively during the second and third trimester of pregnancy and regularly until 1 year postpartum, with further follow-up at 31 months postpartum [5]. The incidence of postpartum thyroid dysfunction in women with type 1 diabetes was 25%, which was a threefold increase compared to a similar study by this group in a non-diabetic population.

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Questions

1. True or false: The diagnosis of Hashimoto's thyroiditis requires the following:

   A. Presence of a diffuse goiter
   B. Serum TSH greater than 2 mU/L
   C. Circulating thyroid peroxidase antibodies
   D. Lymphocytic infiltrate in the thyroid gland at biopsy
   E. Characteristic appearance on ultrasound

2. True or false: The following diseases are associated with Hashimoto's thyroiditis:

   A. Rheumatoid arthritis
   B. Chronic urticaria
   C. Down syndrome
   D. Fibromyalgia
   E. Sarcoidosis

3. Are these statements true or false with respect to autoimmune thyroiditis?

   A. A serum TSH greater than 2 mU/L is associated with an increased risk of developing hypothyroidism.
   B. The risk of developing hypothyroidism is greater in men who are thyroid antibody positive compared to women.
   C. The risk of hypothyroidism is not influenced by age.
   D. The majority of patients have symptoms once the serum TSH is greater than 4 mU/L.
   E. Thyroxine is indicated to reduce goiter size.

Part IV
Thyroid Cancer

Introduction

Kenneth D. Burman

The cases in this section demonstrate multiple aspects concerning the approach to the diagnosis and treatment of thyroid nodules and thyroid cancer. These specific topics were chosen because of their frequency or their possible clinical relevance, especially when there is a controversy. In this entire area of thyroid nodules and thyroid cancer there are few controlled studies, and as a result any recommended approach has to be considered subjective to some degree. However, to the extent possible, these chapters have taken into account the appropriate and relevant literature and consensus recommendations. Nonetheless, there may be alternative approaches that are comparable, and clinicians should form their own opinions as to the proper approach in a patient they are seeing.

In Case 11, Drs. Ehrhardt and Bernet recommend a specific, detailed approach to patients with a thyroid nodule. They emphasize that the entire clinical context (history and physical examination) must be considered in conjunction with relevant sonogram and fine-needle aspiration. Certainly, the cornerstone of the approach hinges on the fine-needle aspiration, but this technique also has a false-negative rate of about 1% to 5%. A history of head and neck radiation and family history, for example, can influence the decision to recommend surgery, as can the size of the nodule and patient gender and age. Worrisome thyroid ultrasound characteristics for thyroid cancer include irregular borders, prominent intravascular flow, microcalcifications, and size >4 cm. However, the sensitivity of these radiologic findings is relatively low [1]. These authors review the various risk factors for thyroid cancer recurrence and discuss the controversial topic of micropapillary thyroid cancer [2]. Pellegriti et al [3] studied patients with tumors <1.5 cm and found that about 14% had persistent disease over about 4 years of monitoring.

Ehrhardt and Bernet also review clinical topics regarding the efficacy of iodine 131 (^{131}I) therapy and of thyroid-stimulating hormone (TSH) suppression in decreasing tumor growth or progression. Although ^{131}I therapy is considered the standard approach in many patients with differentiated thyroid cancer, there

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are surprisingly few controlled studies evaluating its efficacy. The authors review this topic and report a recent meta-analysis by Sawka et al [4] that concludes that radioactive iodine therapy is useful for most patients with differentiated thyroid cancer, although its benefit is less well demonstrated for low-risk patients. Moreover, they note that studies on this entire topic of ^{131}I therapy are inconsistent. In summary, Drs. Ehrhardt and Bernet have been able to take the common clinical entity of thyroid nodules, an area of sometimes conflicting or inadequate studies (e.g., differentiated thyroid cancer), and have been able to make relevant and appropriate clinical recommendations for physicians confronted with these patients.

In Case 12, Dr. Burch discusses the serious issue of papillary thyroid cancer that is metastatic to bone. I will comment on his case together with the case of Dr. Wexler (Case 14), who discusses follicular cancer that is metastatic to bone and lungs. There are some areas of mutual relevance to both cases. Both emphasize that the early diagnosis and treatment of metastatic thyroid cancer is important and that constant vigilance is appropriate. This translates to trying to identify patients who have a higher risk of developing or having distant metastases, such as patients who are older with larger tumors with more aggressive histology and clinical presentations. These patients in particular should be seen frequently and should have frequent laboratory studies such as serum thyroglobulin levels as well as periodic radiologic studies, to include sonogram of the neck, chest computed tomography (CT) without contrast, and ^{131}I scans (and in specific circumstances additional tests such as positron emission tomography [PET] scan and magnetic resonance imaging [MRI]). The frequency of these procedures depends on the individual patient characteristics. Our view is that every patient who has a sufficiently serious thyroid cancer to receive radioactive iodine should also have a neck sonogram perhaps every 6 months for several years as well as an initial chest CT without contrast and periodic radioactive iodine scans. The frequency of these studies and the duration of this relatively intense monitoring depend on the individual patient context, results, and findings. However, thyroid cancer patients should be monitored for an indefinite time period since recurrences can occur many years after the initial diagnosis and treatment. However, as an aside, I would expect that our modern radiologic techniques and serum thyroglobulin monitoring are capable of detecting thyroid cancer presence many years before it would have been detected by less sensitive techniques. As a result, the likelihood that a patient who has had completely negative studies for many years would suddenly develop recurrent disease must be low.

Burch and Wexler emphasize the importance of staining a biopsy of metastatic tumor for specific thyroid cancer markers (e.g., thyroglobulin and thyroid Transcription factor [TTF-1]) and of addressing this tumor in a multidisciplinary manner with consideration of surgical extirpation and directed radiotherapy. Recombinant human TSH (rhTSH)-assisted thyroid scans help avoid hypothyroidism due to levothyroxine withdrawal, and rhTSH-assisted radioactive iodine therapy also may be beneficial in terms of delivering radioactive iodine therapeutically. However, there are only a few relevant studies utilizing rhTSH in this manner [5]. In thyroid cancer patients, the Food and Drug Administration has recently approved rhTSH-assisted

radioactive iodine ablation of remnant thyroid tissue; the European Union had previously approved this use of rhTSH.

Both Burch and Wexler emphasize the potential utility of zoledronic acid infusions for the treatment of osseous metastatic lesions [6–8]. This approach is routinely utilized for many other cancer sites that metastasize to bone, but to date there are no specific controlled studies in patients with osseous metastases from thyroid cancer. It is believed that osseous metastases proliferate in a similar manner regardless of the original tumor, and that decreasing bone turnover will decrease future osseous events and will help treat the present osseous metastases. It seems prudent at the present time to adjunctively utilize zoledronic infusions for patients with metastatic thyroid cancer to the bone. However, the dose and duration of therapy can only be speculated upon. On the one hand, there is increasing evidence of the possible adverse event of osteonecrosis with the use of bisphosphonates (especially given intravenously) [9], but, on the other hand, its use seems to be of potential benefit in decreasing the growth of present osseous metastases and decreasing new bone events [6–8]. We have reached a compromise of recommending an infusion of zoledronic acid 4 mg per month for 12 months and then decreasing the frequency to every 3 months. Bone mineral density and specific radiologic studies of the osseous metastases (e.g., bone scan, MRI, or CT) as well as bone turnover markers are periodically assessed. Obviously, specific controlled studies in this area are needed.

Monitoring for the presence or development of osteonecrosis is also important. Zoledronic acid infusions should not be used in women of child bearing potential except in very select circumstances and with the patient's understanding and consent. Zoledronic acid is considered Pregnancy Category D in all trimesters. Studies in pregnant women have demonstrated a risk to the fetus; the potential benefits of therapy in a serious or life threatening circumstance must be considered against the possible benefits.

Burch and Wexler also discuss alternative adjunctive methods of addressing metastatic bone lesions. It appears that osseous metastases are more common in follicular cancer than papillary thyroid cancer and that Hürthle cell variant thyroid cancer also has a strong predilection for distant metastases. In addition to extirpation, ^{131}I therapy, and external radiotherapy, newer techniques such as radiofrequency ablation and cryoablation may be beneficial in selected patients [10, 11].

Although it is less common than differentiated thyroid cancer, medullary thyroid cancer has a higher rate of recurrence and progression [12]. In Case 13, Dr. Jonklaas discusses multiple aspects of medullary thyroid cancer, a very complex disease. Medullary thyroid cancer represents approximately 0.5% of all thyroid nodules, and it has become controversial whether to screen routine patients with a thyroid nodule with serum calcitonin levels [13]. Serum calcitonin levels may be slightly elevated due to nonspecific effects (e.g., Hashimoto's thyroiditis), and obviously such a false-negative elevation can lead to possibly unnecessary tests. On the other hand, a fine-needle aspiration does not seem to have a high sensitivity of detecting medullary thyroid cancer, which can be a devastating disease, especially when allowed to progress without thyroidectomy [13]. This dilemma is not resolved,

although it seems that in Europe there is more enthusiasm for routinely measuring serum calcitonin levels in patients with a thyroid nodule.

Medullary thyroid cancer has multiple aspects that require attention. Perhaps about 20% to 30% of all apparently "sporadic" cases of medullary thyroid cancer are actually previously unrecognized familial medullary thyroid cancer. Every patient diagnosed with medullary thyroid cancer should be considered for a total thyroidectomy with a central neck node dissection. Further, a complete diagnostic evaluation should be performed to assess for residual or persistent medullary thyroid cancer, to include CT scans of the entire body and perhaps a PET scan. Specific attention should be directed to the neck and upper chest to try to identify residual disease deposits. Serum calcitonin (and carcinoembryonic antigen [CEA]) monitoring is important. Every patient with medullary thyroid cancer should have a germline *ret* oncogene sequencing (usually white cells), and it is important that all the relevant exons be actually sequenced [12]. Laboratories that only attempt to identify and sequence specific areas that are considered most likely to harbor mutations should be avoided. Even when all of the relevant exons are entirely sequenced there is a chance of still missing a mutation, potentially either due to a technical or laboratory error or because the mutation is outside the known frequently sequenced exons. If there is a strong suspicion that the disease is familial, a new blood sample should be sent for sequencing, and if still negative, it would be appropriate to ask the laboratory supervisor for recommendations regarding additional exon sequencing. For example, at present, exon 8 is not routinely sequenced by most commercial laboratories [14, 15], but there are now identified mutations in this area. Jonklaas wisely recommends that even if the *ret* oncogene is negative, it is reasonable to periodically measure serum calcitonin levels and perform neck sonograms in family members depending on the individual case context.

Jonklaas also reviews the literature regarding genotype-phenotype correlations, and she makes specific recommendation regarding "prophylactic" thyroidectomy in family members who have the identical *ret* oncogene mutation as the index patient. She also discusses some of the clinically relevant ethical issues surrounding familial medullary thyroid cancer. Multiple ethical issues can arise including, as she presents, a mother with medullary thyroid cancer and a known *ret* oncogene mutation who does not want her children either tested for medullary thyroid cancer or to have clinically relevant studies (e.g., thyroid sonogram and serum calcitonin level). Unfortunately, outside of a thyroidectomy with central compartment dissection, there are no known specific systemic therapeutic options for patients with residual, recurrent, progressive, or metastatic medullary thyroid cancer. Some clinicians do recommend external radiotherapy to the neck area following thyroidectomy of a potentially aggressive medullary thyroid cancer or if known neck disease remains. Targeted specific molecular therapy may show promise in patients with aggressive or metastatic thyroid cancer [16–19].

Summarizing each of these four interesting chapter topics and discussions, specific long-term prospective controlled studies are needed to direct improved clinical care. Until such studies are performed, we will continue to make the best recommendations possible for these important clinical entities.

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Chapter 11
Papillary Thyroid Cancer

Nicole Ehrhardt and Victor Bernet

Objectives

1. To understand the presentation and diagnosis of papillary thyroid cancer (PTC)
2. To review the risk factors for recurrence and mortality in PTC
3. To discuss the initial surgical recommendations for PTC
4. To examine the clinical indications for radioactive iodine for PTC
5. To review the appropriate long-term management, surveillance, and follow-up for patients with PTC

Case Presentation

A 44-year-old woman with chronic neck pain was incidentally found to have a left thyroid nodule on magnetic resonance imaging (MRI) of the neck. Her medical history was otherwise unremarkable. Thyroid ultrasound revealed a lone 1.1-cm left thyroid nodule with prominent intranodular vasculature flow, irregular borders, and microcalcifications. Endocrinology was then consulted. Free thyroxine (FT_4) and thyroid-stimulating hormone (TSH) were in the normal range. No family history of thyroid disease or cancer was noted, and the patient had no radiation exposure history.

The physical examination was unremarkable, including no palpable thyroid nodules or lymph nodes in the neck. Ultrasound-guided fine-needle aspiration of the nodule was performed, and the cytology report noted scant colloid, crowded groups of follicular cells with distinct nuclear grooving, and overall consistent with papillary thyroid cancer. Recommendation was for total thyroidectomy, and pathology confirmed a 1.1-cm well-encapsulated papillary thyroid cancer (PTC) with no evidence of local invasion or disease metastatic to lymph nodes. However, an incidental

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3-mm focus of papillary thyroid cancer was noted in the right thyroid lobe as well. The patient proceeded to receive ablation therapy with 100 mCi radioactive iodine, with posttreatment whole-body scan revealing only focal, intense uptake in the thyroid bed. Levothyroxine therapy was started and dose titrated to achieve a goal TSH of 0.1 to 0.3 μIU/mL. One year after initial surgery, the patient underwent a withdrawal whole-body scan, which revealed no evidence of local or metastatic disease. At the time, TSH was 100 μIU/mL and thyroglobulin plus antithyroglobulin antibody levels were undetectable. Neck ultrasound was also unremarkable at 1 year.

Risk Factors for Thyroid Cancer

Both the prevalence of thyroid nodules and thyroid cancer are increasing [1]. In areas that are iodine sufficient, the prevalence of palpable thyroid nodules is 5% in women and 1% in men [2]. As illustrated by this case, common use of anatomic imaging of the neck and chest is associated with an increasing incidence of incidentally found thyroid nodules, with 19% to 67% of randomly selected individuals having thyroid nodules detected on thyroid ultrasound [3]. While the majority of thyroid nodules are benign, the clinical challenge is to accurately diagnose the 5% to 10% of thyroid nodules that are malignant. Some known clinical features associated with increased cancer risk include age >60 years; male gender; radiation exposure history; family history; and a firm, fixed nodule [4]. Ultrasound characteristics that are suggestive of thyroid cancer include irregular borders, prominent intravascular flow, microcalcifications ("starry-night" pattern), and size >4 cm [5]. However, reliance on ultrasound findings alone to predict thyroid cancer is problematic, as the sensitivities range from only 32% to 87% and the specificities range between 39% and 95% [5].

In this case, a small nodule <1.5 cm was found but with multiple concerning features present, and so a fine-needle aspiration was performed. Findings suspicious for papillary thyroid cancer were noted, including scant colloid and distinctive grooved nuclei, although psammoma bodies were absent.

Well-Differentiated Thyroid Cancer

Approximately 23,500 new cases of thyroid cancer are reported each year [6]. The majority are differentiated thyroid cancers (DTCs), 90% of which are papillary or follicular thyroid cancer, with PTC predominating [7]. Recently a new tumor, node, metastases (TNM) staging of thyroid tumors has been adopted [8]. According to this new system, thyroid tumors ≤2.0 cm in size and limited to thyroid gland are classified as T1. This differs from the old staging system where T1 was defined as tumor ≤1 cm. Using extent of disease, tumor size, and age >45 years, patients can then be differentiated into three disease risk categories: very low risk, low to moderate risk, and high risk for disease recurrence and death [9]. Currently, patients with papillary thyroid cancer have a 93% ten-year survival and 100% at 5 years for those considered low risk (stage I, II) [10].

Risk Factors in Thyroid Cancer for Recurrence and Mortality

Multiple studies have attempted to determine characteristics associated with risk for recurrence and mortality. Overall, mortality from thyroid cancer is low, but reoccurrence rates range between 25% and 35% [11]. Most reoccur in the first decade after presentation, but cases of reoccurrence >10 years after initial presentation are encountered. Characteristics including age >45 years, male gender, tumor size >4 cm, follicular histology, multifocality, initial local tumor invasion, and regional lymph node metastasis have been shown to be associated with increased reoccurrence, both distant and local-regional metastases [12]. Multiple studies have looked at thyroid microcarcinomas (<1 cm), which have shown various factors including lymph node metastasis at initial presentation as a significant risk factor for disease reoccurrence [13]. However, few studies have addressed risk factors for smaller tumors falling in the 1- to 1.5-cm range just above the microcarcinoma size cutoff.

One recent study by Pellegriti [14] examined well-differentiated papillary thyroid cancers <1.5 cm, and found that approximately 20% had extrathyroidal invasion or bilateral foci. Additionally, multifocality and lymph node invasion were seen in 30%, with distant metastases in 2.7%. Even more surprising was that over 25% of the patients with tumors <1.5 cm had evidence of persistent/relapsing disease after only an average of about 4 years of follow-up, with 14.4% still having persistent disease at the conclusion of the study. By multivariate analysis, lymph node metastasis at presentation was found as the strongest predictor of development of local metastasis and recurrent disease. Pellegriti's study also revealed increasing aggressiveness of tumor, defined as the presence of multifocality, bilaterality, extrathyroidal invasion, or lymph node involvement, with increasing tumor size, in contrast with another study that found no recurrences in patients with papillary thyroid cancer <1.5 cm [15]. However, in Pellegriti's study, ultimately, tumor size >1 cm was not a significant predictor of recurrent disease with both univariate and multivariate analysis.

Although the overall prognosis is very good for patients with DTC, the ability to make evidence-based management recommendations for patients with small tumors, <1.5 cm, is hindered by a lack of prospective randomized studies.

Surgical Recommendations for Thyroid Cancer

While no uniform opinion exists regarding the initial management of thyroid cancer, present practice guidelines generally recommend near-total or total thyroidectomy for patients with DTC. The lack of consensus stems from the need to rely solely on retrospective trials for current treatment recommendations. However, results from several retrospective studies indicate a higher rate of all-cause specific mortality and recurrence in those not treated with total or near-total thyroidectomy (16–18). Another retrospective study demonstrated decreased mortality and recurrence in low-risk groups undergoing bilateral subtotal resections rather than unilateral

thyroid surgery [11]. The benefit of subtotal thyroidectomy over unilateral lobectomy for smaller DTC, especially microcarcinomas, is still not fully defined. Lobectomy may well be sufficient for management of patients with microcarcinomas, although patients with multifocality are potentially better served by a total thyroidectomy [19]. Interestingly, analysis of X-chromosome inactivation patterns in women with multifocal PTC indicates these foci many times arise as independent tumors [20]. In our case patient, irrespective of the relatively small tumor size, we suggest that the presence of multifocality calls for total thyroidectomy as the appropriate initial surgical approach.

Remnant Ablation for Thyroid Cancer

Following total thyroidectomy, common clinical practice for DTC is remnant ablation with iodine 131 (^{131}I). However, ^{131}I therapy remains controversial, especially in well-differentiated thyroid cancer <1.5 cm. Agreement exists that ablative therapy (using, for example, $\sim$1.85 GBq or 50 mCi) can destroy a functional thyroid remnant and improve the specificity of serum thyroglobulin measurements, thereby aiding in long-term follow-up. Higher ^{131}I doses (5.55 GBq or 150 mCi) are also often used in DTC patients especially, those with high-risk features [21]. For patients with high-risk disease (American Joint Committee on Cancer [AJCC] classification III and IV), a prospective, multicenter, nonrandomized study showed both an improvement in mortality (relative risk [RR], 0.03; confidence level [CI], 0.09 to 0.93) and progression (RR, 0.30; CI, 0.13 to 0.72) for PTC patients undergoing postoperative ^{131}I therapy [22]. However, the majority of patients with thyroid cancer are in low-risk groups (stage I to II). Also, the benefit of ^{131}I on recurrence rates and mortality remains unclear in these cases, with justification of ablation based only on data from retrospective studies. Data to date appear to indicate a potential improvement in recurrence rates with ^{131}I ablation but no definitive reduction in mortality rates.

A review of the existing literature by Haugen [9] concluded that radioiodine therapy does not reduce the risk of reoccurrence or mortality in patients with solitary tumor less than 1.0 to 1.5 cm and no local invasion or lymph nodes present at initial surgery. This conclusion is supported by Hay's [18] study, which found that radioactive iodine in low-risk patients (MACIS <6[*]) did not significantly improve outcome. Furthermore, Mazzaferri's [23] data, which are commonly cited as evidence in favor of ^{131}I ablation, actually revealed a reduction in cancer death ($p<.001$) limited to patients >40 years age and primary tumors ≥ 1.5 cm.

A meta-analysis of 13 studies to evaluate the role of radioiodine remnant ablation/therapy was also recently completed [24]. Overall, the data highlighted a good outcome in patients with DTC, with a mortality rate of only 1.3% to 15%. However,

[*] MACIS < 6, a system which was introduced to eliminate the need for histological grading of the tumor and uses metastasis, age, completeness of resection, invasion and size for initial staging.

the benefit of radioactive iodine was questionable, with only one of six studies examining cancer-related mortality finding a significant benefit [12], but the one study in which radioactive iodine improves the outcome was the largest study and had the longest follow-up. As far as tumor recurrence, postoperative radioactive iodine decreased the risk of recurrence in three studies. Follow-up was between 10 and 16 years, and the recurrence rate was >20%. Three smaller studies did not show improvement in recurrence rates, with recurrence in 3% to 15% and average follow-up of less than 10 years [24]. Results from pooled analysis of 18 studies (8280 patients) with 40% of total receiving ^{131}I were suggestive of a significant treatment effect of ablation for reduction in local-regional recurrence and distant metastases. Ultimately, this meta-analysis concluded that patients with DTC may benefit from radioactive iodine, given the decreased recurrence rate, but the incremental benefit of remnant ablation in low-risk patients treated with radioactive iodine and thyroid hormone suppressive therapy is unclear.

Given the inconsistent conclusions about the use of radioactive iodine in DTC among different centers, the risks of radioactive iodine must also be closely examined. Unfortunately, most of these data are from case reports and small series. One of the biggest concerns in using radioactive iodine is the risk of secondary primary malignancies. Traditional understanding has been that doses below 600 mCi are safe, but recent data seem to indicate an increased risk of chronic myelogenous leukemia even at lower doses. Another study observed a 30% increased risk of secondary primary cancer with a linear relationship between cumulative dose and solid tumors occurrence. Doses greater than 3.7 GBq or 100 mCi were calculated to cause an excess of 53 solid tumors and three leukemias per 10,000 patients over 10 years [25]. Given these concerns, Bal et al. [26] conducted a randomized prospective study looking for the minimal possible effective dose for remnant ablation in cases of DTC. They found that patients receiving 25 to 100 mCi of ^{131}I had similar rates of successful ablation. All the risks of radioactive iodine including sialadenitis, xerostomia, bone marrow suppression, diminished reproductive function, and secondary malignancies need to be discussed prior to the patient's making a definite decision before proceeding with radioactive iodine.

Common clinical practice in remnant ablation and treatment of DTC is withdrawal of thyroid hormone thereby increasing serum TSH in order to optimize the trapping and retention of radiodine. Frequently this leads to impaired quality of life and ability to work secondary to overt symptoms of hypothyroidism such as cognitive impairment, emotional dysfunction, physical fatigue. It may also increase health risk in the elderly and patients with other significant medical problems. Recombinant human TSH (rhTSH) was developed to provide TSH stimulation without thyroid hormone withdrawal. RhTSH has been approve for some time as an adjunct for diagnostic procedures in patients with DTC and just recently was approved for use in thyroid remnant ablation. Some studies have shown comparable rates of remnant ablation with both methods but one study did show that withdrawal was superior. A recent study by Pacini confirmed the non-inferiority of rhTSH preparation of patients for remnant ablation. As no long term data about recurrence or mortality is yet available, caution must be used in selecting appropriate patients for rhTSH

remnant ablation. Stage 1 or stage 2 low risk patients with no evidence of local invasion or local lymph node metastasis as in the above case's presentation should be considered for rhTSH remnant ablation in order to minimize patient discomfort and disruption of their daily activity [27].

In regard to the above case, given the questionable benefit of postiodine ablation in a DTC less than 1.5 cm, the controversy of this therapy and its risks must be clearly discussed with patients. However, the benefits including the ease of long-term surveillance after postablation therapy and the possibility that radioactive iodine may lower the risk of both local and metastatic recurrence that are seen even in microcarcinomas needs also to be considered.

Hormone Suppressive Therapy in Thyroid Cancer

Following initial treatment for thyroid carcinoma, patients are placed on thyroid hormone, usually the oral form of oral levothyroxine (LT_4). The traditional goal is not only to normalize thyroxine (T_4) levels but also to suppress serum thyrotropin (TSH) below the normal range without causing symptomatic thyrotoxicosis. By administering supraphysiologic doses of LT_4, the intent is to directly inhibit tumor growth by negative feedback on pituitary TSH secretion. Thyrotropin's main effect is on differentiated normal thyroid tissue, as the expression of TSH receptors (TSHR) is lower in malignant cells than residual thyroid, which calls into question this common clinical therapy. Other studies have also shown that ThyrCas, the tumoral TSHR alleles, are either deleted or transcriptionally silenced, and that the post-TSHR signaling pathways may be nonfunctional [28]. However, both regression of advanced thyroid cancer by TSH suppression and reduced recurrence rates have been shown on TSH suppression in multiple studies [29]. Drawbacks of these observational studies include absence of randomization, lack of appropriate controls, absence of blinding, inability to isolate the solitary effect of TSH suppression on recurrence, and no risk stratification among patients with different prognostic features [28].

A recent meta-analysis of 10 observational cohort studies of almost 3000 patients, with 69% being on TSH suppression therapy with long-term follow-up, found that patients receiving suppression therapy had a decreased risk of adverse clinical outcomes (RR, 0.73; confidence interval [CI], 0.60 to 0.88; $p<.005$) [28]. This meta-analysis seems to support the overall benefit of suppressive therapy in patients with DTC, yet it still leaves the questions of which patients benefit and to what degree of TSH suppression do patients benefit.

Conflicting data on the benefit of TSH suppression and the degree of TSH suppression has been report in the low-risk patient. It has been suggested that both nonsuppressed serum TSH and elevated serum thyroglobulin are related to an increased risk of DTC recurrence independent of tumor type and tumor stage. Conversely, Cooper [30], who stratified patients into four groups ranging from undetectable to elevated, found that while TSH score category was an independent predictor of disease progression in high-risk patients ($p = .03$), it was not a predictor for disease progression independent of initial tumor stages ($p = .7$). Wang et al [31] assessed three groups—one with recurrence, one without evidence of relapse, and

one without evidence of relapse but thyroglobulin (Tg) levels above 3 ng/mL when off of TSH suppression. From this short-term study they concluded that in patients clinically free of disease and with a Tg level <2 ng/mL, TSH can be kept in the normal range, but in those with active disease and even in those with elevated Tg level >2 ng/mL, TSH should be suppressed. Kamel et al [29] also looked at the degree of TSH suppression but in the setting of Tg levels less than 5 ng/mL, and found that maximal suppression of TSH to <0.1 mU/L did not lead to further suppression of Tg levels, concluding that maximal TSH suppression in patients who have no evidence of active disease seems unnecessary.

Initial TSH suppressive therapy has been proven to benefit patients with DTC, but the degree and duration of TSH suppression is still debated, especially given the long-term side effects of supraphysiologic LT_4 therapy, such as increased cardiac workload, high prevalence of arrhythmia, and reduced bone mass. In the patient presented here, initial suppression of TSH to 0.1 to 0.3 mU/L seems appropriate but may be normalized overtime if long-term surveillance showed an undetectable Tg and negative imaging.

Long-Term Follow-up and Surveillance for Thyroid Cancer

Long-term follow-up and surveillance guidelines for DTC continue to be debated. Optimal long-term surveillance strategies, especially for patients with DTC who appear disease free, are not well established. The National Comprehensive Cancer Network recommends that for all thyroid cancers >1 cm a physical exam should be completed every 3 to 6 months for 2 years, and then annually if the patient is felt to be disease free. Thyroglobulin levels should be measured at 6 and 12 months in those who have received total thyroidectomy with ^{131}I ablation, on or off thyroid hormone suppressive therapy, and a TSH-stimulated radioiodine whole-body scan (DxWBS) every 12 months, until one to two negative scans are documented [32]. An additional caveat is that Tg and DxWBS are less accurate in patients with large remnants, as for optimal sensitivity high TSH levels usually >25 mIU/mL are required. Further large prospective studies are needed to define the most effective follow-up paradigm. As well, given the unpleasant side effects and morbidity associated with patients purposely placed in a hypothyroid state, further studies using synthetic stimulation of TSH with recombinant human TSH (rhTSH) have been completed comparing their effectiveness to withdrawal imagining.

Traditionally, TSH-stimulated DxWBS and Tg levels have been accomplished by withdrawal of suppression therapy, while more recently rhTSH stimulation has become accepted. Multiple studies have shown that patients given rhTSH avoid the symptoms of hypothyroidism, with most demonstrating equivalence between withdrawal LT_4 therapy and rhTSH in WBS. In contrast to an early study, which reported a superior scan using withdrawal WBS in 29% of cases, Haugen [9] found that the difference between withdrawal scan results and rhTSH was not statistically different (93%vs.84%; p =?). The use of rhTSH provides an alternative to thyroid hormone withdrawal in patients undergoing evaluation for thyroid cancer persistence or recurrence (351/5 by Haugen).

The high cost surveillance with RxWBS in low-risk DTC has placed monitoring for recurrence of thyroid carcinoma with only Tg levels in the forefront of discussion. A consensus report on serum Tg levels in DTC stated that Tg measured during thyroid hormone suppression is misleading [33]. The usefulness of stimulated Tg as a clinical marker for persistent disease or disease recurrence is not debated, with recent recommendations by some authors for its use as sole monitor for thyroid carcinoma, especially in low-risk populations. However, stimulated TG alone may be better utilized in those who have had a prior negative DxWBS [34]. The patient presented here underwent testing with both stimulated Tg levels and DxWBS at 1 year. We feel DxWBS continues to be complementary to Tg levels especially in the setting of a positive Tg level, with WBS allowing for tumor localization.

However, the best imaging modality for localization of tumor recurrence/ persistence in low-risk patients is also debated. Many call Tg the gold standard for detecting recurrences and consider WBS useless in the majority of these patients [35]. Since Tg does not allow localization and is undetectable in up to 5% of patients after thyroid hormone withdrawal, some instead recommend thyroid ultrasound (US) for follow-up. A study revealed that WBS did not add any information in metastatic disease, finding foci in only 13 patients, while US uncovered node metastasis in 38 subjects (seven that were Tg negative) [33]. The authors reported a negative predictive value of 98.8% for both negative Tg and US, and concluded that US was beneficial for first follow-up in combination with stimulated Tg levels. Until a definite recommendation can be reached, the most comprehensive initial follow-up for thyroid cancer would be stimulated Tg level and WBS complemented by thyroid US, as this patient received. In regard to long-term follow-up in a patient who is clinically free of disease and has had an undetectable serum Tg level in the past during TSH stimulation, the recommendation is for serum Tg level on FT_4 suppression along with an annual physical exam [33].

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Multiple-Choice Questions

1. A 48-year-old woman recently had a lobectomy for a solitary thyroid nodule and was found on histology to have a 1.5-cm PTC without invasion or extension. What would you further counsel this woman?

   A. Recommend no further treatment was indicated, as lobectomy was curative
   B. Recommend total thyroidectomy and radical neck dissection

C. Recommend total thyroidectomy followed by 100 mCi radioactive iodine therapy
D. Recommend total thyroidectomy and radical neck dissection followed by 30 mCi radioactive active iodine therapy

Suggested answer: C. Explanation: Although of unclear benefit for lesions less than 1.0 to 1.5 cm, total thyroidectomy has been associated with an improvement in mortality and recurrent rates in tumors >1.5 cm. Radioactive iodine treatment is also controversial, with some studies showing improvement in outcomes with ablation and others showing no benefit, but common clinical practice is to give radioactive iodine therapy following surgery, as it appears to reduce morbidity, aid in ease of long-term follow-up, and may reduce mortality.

2. The initial follow-up for patients with well-differentiated PTC should include:

A. US of neck at 12 months postinitial treatment
B. Stimulated whole-body scan (WBS) and thyroglobulin (Tg) levels 6 months to 1 year after initial treatment
C. Continued surveillance annually with Tg and antithyroglobulin levels after 1 or 2 negative stimulated Tg levels and WBS
D. All of the above

Suggested answer: D. Explanation: Although no prospective studies have established long-term follow-up for PTC, current clinical guideline recommend all of the above for continued surveillance for recurrent/residual PTC after initial treatment, especially when primary was greater than 1 to 1.5 cm in size. Less involved follow-up is warranted in cases of microcarcinoma (≤ 1.0 cm).

3. All of these characteristics may be risk factors for increased aggressiveness of PTC except:

A. Psammoma bodies seen on pathology
B. Multifocality of PTC
C. Lymph node metastasis at initial presentation
D. Tumor size >4 cm
E. Age >45 years

Suggested answer: A. Explanation: Studies have showing conflicting results about risk factors for recurrence of PTC but all of the above have been associated with increased aggressiveness of PTC except psammoma bodies, which are seen in up to 50% of patients with PTC.

Chapter 12
Metastatic Papillary Thyroid Cancer

Henry B. Burch

Objectives

1. To understand the diagnosis and staging of differentiated thyroid cancer
2. To become familiar with unusual presentations of papillary thyroid cancer
3. To recognize challenges associated with the management of thyroid cancer with distant metastases
4. To review the indications and methodology of thyrogen-stimulated radioiodine therapy
5. To review the management of iodine excess in a patient awaiting radioiodine therapy

Case Presentation

A 59-year-old man with a history of toxic multinodular goiter presents to his primary care physician with progressive low back pain. A magnetic resonance imaging (MRI) scan of the spine reveals a 4.0-cm left paraspinal mass with nearly complete obliteration of the L3 vertebral body. A computed tomography (CT)-guided biopsy shows the lesion, a metastatic papillary thyroid cancer, and serum thyroglobulin levels are greater than 2100 ng/mL. The patient's past medical history is significant for type 1 diabetes mellitus complicated by advanced retinopathy and peripheral vascular disease as well as chronic renal failure. Five years earlier he underwent combined kidney and pancreatic transplantation and has remained insulin-free and off dialysis ever since. His toxic multinodular goiter was treated 6 years earlier with radioiodine therapy, resulting in hypothyroidism. He also has a history of severe scoliosis of the lower thoracic and lumbar spine.

Neck exam reveals a nodular thyroid bilaterally and no cervical adenopathy. Thyroid ultrasound shows a large calcified right thyroid nodule and smaller nodules

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bilaterally. Additional staging studies show multiple subcentimeter pulmonary nodules as well as metastatic foci in the boney pelvis. An MRI of the head is negative for metastatic disease. The patient undergoes tumor embolization followed by complete extirpation of the L3 vertebral body and paraspinal mass, with basket insertion in the L2-L4 spinal region and spinal fusion from T12 to S1. After a prolonged hospital course with several transfers to the surgical intensive care unit for volume overload, suspected superior vena cava syndrome, wound dehiscence, and upper extremity venous thrombosis, the patient recovered and was discharged. During the course of his hospital stay he was exposed to iodinated contrast on three occasions.

The patient is subsequently readmitted for total thyroidectomy with findings of a 1.2-cm papillary thyroid cancer. Postoperatively the patient recovers and is discharged. Urinary iodine excretion measured prior to discharge is markedly elevated at 7810 μg per 24 hours. He is placed on a low-iodine diet and furosemide 40 mg daily, and after 4 months, when the urinary iodine level falls to less than 100 μg daily, he undergoes thyrogen-assisted dosimetry followed by thyrogen-stimulated therapy with 192 mCi iodine 131 (^{131}I). Posttherapy scan shows uptake in the neck and physiologic uptake in the bowel. Six months later the patient undergoes recombinant human thyroid-stimulating hormone (rhTSH)-stimulated thyroglobulin testing and is noted to have a peak thyroglobulin at 180 ng/mL; a whole-body scan shows thyroid bed uptake only. He is currently being prepared for repeat radioiodine therapy.

How the Diagnosis Was Made

The diagnosis of papillary thyroid cancer is generally straightforward. Thyroid fine-needle aspiration (FNA) is both sensitive and specific for the detection of papillary thyroid cancer within a thyroid nodule. However, occasionally the first presentation for thyroid cancer is with either locoregional or distant metastases. This patient's paraspinal mass led to the discovery of an otherwise unsuspected thyroid cancer. A CT-guided biopsy revealed a follicular lesion, which was subjected to special immunohistochemical staining to pinpoint the primary source. Specifically, thyroid transcription factor 1 (TTF-1) staining was positive, indicating either pulmonary or thyroid etiologies, and thyroglobulin staining was strongly positive, confirming metastatic thyroid cancer. Ultimately, thyroidectomy confirmed the presence of a small innocuous-appearing primary papillary thyroid cancer.

Lessons Learned

Papillary thyroid cancer may have unusual presentations. When metastatic to bone, thyroid cancer may present with a large paraspinal mass, as occurred in the present case. Failure to perform special staining might have resulted in a misdiagnosis

of adenocarcinoma of unknown primary, and the patient would not have received therapy with radioiodine. Likewise, had the patient presented with colon or lung cancer metastatic to spine, he may not have been considered for the extensive tumor extirpation and spine stabilization performed in this case, which were undertaken after consideration of the comparatively favorable prognosis and general efficacy of treatment for thyroid cancer.

Exposure to iodinated contrast results in a delay of the delivery of effective radioiodine therapy. This patient's protracted and complicated hospital course necessitated exposure to iodinated contrast during the performance of diagnostic studies deemed critical to the patient's acute management. The resultant iodine overload required a prolonged period of iodine restriction and introduction of furosemide therapy to facilitate attainment of a low iodine state in preparation for radioiodine therapy.

Bone metastases from thyroid cancer present unique therapeutic challenges [1]. Bone tissue provides a rich environment for metastatic disease, with high blood flow and elaboration of local growth factors in response to tumor damage to bone [2]. Approximately 2% of papillary thyroid cancer patients experience bone metastases compared to 7% to 20% of patients with follicular thyroid cancer. The spine and pelvis are the most frequently involved sites, followed by the rib cage. Approximately half of these patients present with bone pain, 23% are asymptomatic, and the remainder present with local edema, fracture, or cord compression. Patients with spinal metastases from thyroid cancer tend to present with radicular pain and, less commonly, paresis or paraplegia.

Paraspinal masses due to thyroid cancer metastases may be quite large and hypervascular. Patients with bone metastases from differentiated thyroid cancer tend to have higher serum thyroglobulin levels, and 40% to 80% have visible uptake on radioiodine imaging. Treatment modalities considered for bone metastases from thyroid cancer include surgery to remove the focus (extirpation), tumor embolization, radioiodine, external beam radiotherapy, and bisphosphonate therapy. Complete tumor extirpation has been shown to positively affect overall survival. In the present case, extensive spine stabilization was required to prevent acute cord compression in the course of surgical extirpation and radioiodine therapy. In general, patients with radioiodine uptake within bone metastases tend to be younger and have improved survival, although radioiodine therapy per se has not always been shown to improve survival in these patients. It has been argued that radioiodine may not be able to deliver a tumoricidal dose to bony metastases. In one example in the literature, dosimetric evaluation showed that a dose of 400 mCi ^{131}I would deliver a radiation dose of 3500 cGy to a thoracic spine metastasis, while 10,000 cGy would be needed for a tumoricidal effect. Tumor embolization provides prompt relief of pain and improvement in neurologic symptoms in many patients without affecting long-term survival. Likewise, external beam radiation therapy can deliver high doses of radiation to a metastatic deposit in bone, resulting in pain relief but no demonstrable effect on survival.

Intravenous bisphosphonate therapy has been examined in a small group of 10 patients with thyroid cancer metastatic to bone [3]. Monthly pamidronate therapy

for 12 months resulted in lesion regression in two patients, stability in five patients, and progression in an additional three patients. Pain reduction and improved quality of life scores were noted in all patients.

Recombinant human TSH (rhTSH)-stimulated radioiodine therapy for metastatic disease is currently reserved for patients unable to tolerate thyroid hormone withdrawal or unable to achieve sufficient endogenous TSH elevation. Recent studies have shown rhTSH-assisted thyroid remnant ablation to be as efficacious as therapy administered after thyroid hormone withdrawal [4]. However, long-term efficacy and effects on recurrence rates have not yet been determined. Likewise, no systematic studies have been performed to evaluate the efficacy of rhTSH-stimulated therapy for known metastatic disease. Therefore, this is generally reserved for patients unable to achieve adequate serum TSH elevation due to functional metastases or hypopituitarism; those who are medically unable to tolerate prolonged thyroid hormone withdrawal, such as patients with cardiomyopathy or psychosis aggravated by hypothyroidism; and those at high risk for tumor progression during prolonged hypothyroidism. A recent review of the medical literature describing 266 courses of rhTSH-assisted radioiodine treatment of known persistent or metastatic disease found that most patients received therapy under compassionate-use conditions, and most were older patients with more advanced disease [5]. For patients with adequate follow-up information, 75% of 138 patients with posttreatment scan results showed uptake in the metastatic deposits, and 65% of 115 patients had either improved disease (tumor shrinkage or decreased serum thyroglobulin levels) or disease stability.

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Multiple-Choice Questions (3–5)

1. A 69-year-old woman with papillary thyroid cancer experiences loss of consciousness and witnessed seizure activity while undergoing rhTSH-stimulated whole-body scanning. Which one of the following is the most likely explanation for her acute presentation?

A. rhTSH has lowered her seizure threshold.
B. She has experienced a thromboembolic event due to hypercoagulability.
C. An unsuspected brain metastasis has expanded under the influence of serum TSH.
D. She has experienced cerebral ischemia due to intrinsic vascular effects of hypothyroidism.
E. She has developed thyrotoxicosis due to rhTSH stimulation of functional metastases.

Answer: C. One of the risks associated with rhTSH scanning is stimulation of known or unsuspected central nervous system (CNS) metastases, resulting in tumor growth and edema. Patients with known CNS metastases should receive concomitant corticosteroid therapy to prevent acute tumor expansion, although this is not always successful.

2. A 48-year-old man with a history of papillary thyroid cancer with lung metastases and schizophrenia is scheduled to undergo dosimetry-guided radioiodine therapy. His schizophrenia has been well controlled on antipsychotic therapy, but he develops an acute psychiatric exacerbation while undergoing initial thyroid hormone withdrawal. The patient is placed back on liothyronine (T_3) by the admitting psychiatrist, and 3 days later his serum TSH is 4.8 mIU/L. In addition to continuing thyroid hormone therapy, which one of the following will be the best course to follow in this patient?

A. Continue low-dose T_3 until 3 days before radioiodine therapy.
B. Request more effective antipsychotic therapy and resume thyroid hormone withdrawal.
C. Use rhTSH to augment delivery of an empiric dose of 350 mCi ^{131}I.
D. Change modalities to external beam radiotherapy.
D. Use rhTSH to perform both dosimetry and subsequent radioiodine therapy.

Answer: E. This represents an example of a medical contraindication to thyroid hormone withdrawal. The patient still requires radioiodine therapy, and given his pulmonary metastases should have dosimetry to ensure against excessive lung exposure to radioactivity, which can cause pulmonary fibrosis. If the patient is to be treated with rhTSH augmentation, then the dosimetry also needs to be performed using rhTSH.

3. A 55-year-old woman undergoes cardiac catheterization for atypical chest pain and electrocardiogram abnormality while hypothyroid in preparation for thyroid remnant ablation. Two weeks earlier she underwent total thyroidectomy with findings of a 3.2-cm papillary thyroid cancer. There is no local tumor extension, and none of five lymph nodes removed contain thyroid cancer. A 24-hour urinary iodine excretion is measured at 5025 μg. What is the next step in the management of this patient?

A. Institute plasma exchange to remove excess iodine.
B. Continue thyroid hormone withdrawal and treat with radioiodine as scheduled.
C. Continue thyroid hormone withdrawal and treat with radioiodine when urinary iodine is sufficiently low.
D. Reinstate thyroid hormone therapy and delay preparation for remnant ablation until urine iodine excretion is sufficiently low.
E. Manage the patient without thyroid remnant ablation.

Answer: D. Thyroid remnant ablation will enable the patient to be followed using serum thyroglobulin to assess for persistent or recurrent disease. The inorganic iodine contained in the contrast media she received will compete with radioiodine therapy, and therefore she needs to clear this prior to remnant ablation. Since this may take 2 to 4 months, it is not appropriate to leave her off of thyroid hormone while awaiting a sufficiently low urine iodine excretion rate. Thyroid hormone should be reinstated and then withdrawn again when her urine iodine excretion approaches 100 to 200 μg daily, some of which represents iodine derived from the thyroxine (T_4) or T_3 she is taking.

Chapter 13
Medullary Thyroid Cancer

Jacqueline Jonklaas

Objectives

1. To understand the presentation and diagnosis of medullary thyroid cancer (MTC)
2. To understand the differences in the presentation and diagnosis of sporadic versus familial MTC
3. To understand the relationship between the presence of a *ret* proto-oncogene mutation and the development of MTC
4. To understand the relationship between *ret* proto-oncogene mutations and their associated phenotype
5. To understand the pivotal role of screening and prophylactic thyroidectomy in the management of familial MTC
6. To understand the treatment options for MTC

Case Presentation

A 45-year-old woman was found by her primary care physician to have a 1.5-cm thyroid nodule. A serum calcitonin level was ordered and found to be elevated at 15 pg/mL (normal <6 pg/mL). A fine-needle aspiration revealed a very cellular specimen. The cells were pleomorphic and poorly cohesive. The cells seen included small cells with a granular cytoplasm, large atypical cells, and spindle cells. Binucleated cells and cells with eccentric nuclei were also seen. The cytology reading stated that a neoplastic process was suspected. The patient was referred for thyroidectomy. The cytology specimen was not stained for calcitonin or amyloid before the patient's surgery. A preoperative neck ultrasound was not performed. There was no known family history of any thyroid disorders.

The patient underwent thyroidectomy. Pathology showed multiple foci of MTC within a background of C-cell hyperplasia. A central compartment neck dissection

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revealed lymph node metastases. Following her thyroidectomy and subsequent referral to an endocrinologist, the patient was able to obtain additional family history. A 76-year-old maternal aunt had died from thyroid cancer a year previously; no further details were available. The patient's eldest sibling (55 years old) had also recently had thyroid surgery for thyroid cancer and had been told that his cancer had spread. Again, no further details could be obtained. There was no known family history of hyperparathyroidism or pheochromocytoma.

The patient's postoperative calcitonin level was undetectable (less than 1 pg/mL). A postoperative sonogram of the neck did not reveal any evidence of additional pathologic lymph nodes. She was screened for the *ret* proto-oncogene mutation and was found to have a L790F mutation (where a normal leucine is changed to phenylalanine). The patient had two children, ages 12 and 16. She initially refused genetic screening for her children, citing a concern about the privacy of their health information, and a desire not to cause the family unnecessary anxiety. However, following additional discussion, she eventually agreed to their testing. The younger child was found to carry the same mutation, whereas the older child did not. The screening results for both children were confirmed by repeat testing. The 12-year-old child underwent further evaluation. A serum calcitonin was normal at 3 pg/mL. A cervical ultrasound showed several 3-mm thyroid nodules. Screening for hyperparathyroidism and pheochromocytoma was negative with normal calcium, parathyroid hormone, and fractionated plasma free metanephrine levels. Prophylactic thyroidectomy was performed with a finding of C-cell hyperplasia.

Overview of Medullary Thyroid Cancer

Medullary thyroid cancer originates from the parafollicular C cells. Approximately 75% of cases are sporadic, and the remaining 25% are familial. Sporadic cases occur as a result of clonal expansion of a single focus of tumor cells, whereas heritable MTC usually presents with multifocal disease. C-cell hyperplasia is a common finding in familial disease. It is diagnosed when there are more than six C cells per thyroid follicle. C-cell hyperplasia is thought to progress through clonal expansion and eventual transformation to malignancy. Disruption of the follicular basement membrane by C cells is thought to mark the transition to malignancy [1]. A germline mutation of the *ret* proto-oncogene, which codes for a tyrosine kinase receptor, is the cause of familial disease. It is transmitted as an autosomal dominant trait with high penetrance linked to chromosome 10 [2]. Mutations in the *ret* proto-oncogene can occur in the extracellular or intracellular domain (Fig. 13.1). Somatic mutations may be present in some sporadic cases.

Medullary thyroid cancer cells almost invariably secrete calcitonin, and frequently also secrete carcinoembryonic antigen, neuron-specific enolase, chromogranin A, and adrenocorticotrophic hormone. Calcitonin is a clinically useful marker for MTC and is employed both as a serum marker and immunohistochemical marker [1]. Although serum calcitonin may be elevated in patients with large thyroid

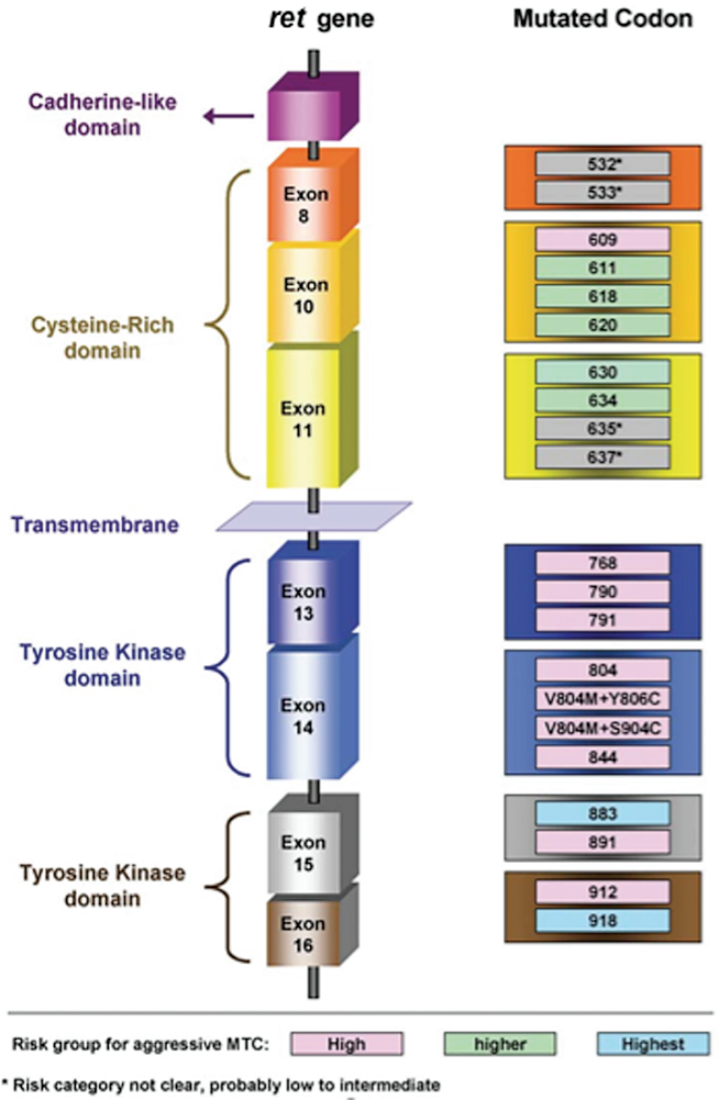

Fig. 13.1 Schematic diagram of structure of the *ret* proto-oncogene. [From Kouvaraki et al. [8], with permission.]

nodules harboring MTC, it may be normal in smaller tumors and in subjects with C-cell hyperplasia. Provocative tests using pentagastrin or calcium may confirm the diagnosis in these cases. However, the use of these biochemical tests has been replaced by *ret* proto-oncogene testing when screening for familial disease [2, 3]. Furthermore, pentagastrin is not commercially available in the United States.

When not detected by screening, MTC usually presents as a thyroid nodule. The nodule is typically painless, and may be accompanied by cervical adenopathy [1, 3]. Symptoms of ectopic hormone production such as diarrhea are uncommon. The correct diagnosis is usually reached on the basis of the cytology from a fine-needle aspiration or elevated serum calcitonin levels. However, the use of serum calcitonin as routine screening in patients with thyroid nodules remains controversial [3, 4]. Primary treatment of MTC consists of a total thyroidectomy performed by an experienced thyroid surgeon with appropriate exploration of the neck and central compartment for affected lymph nodes. Additional treatment for residual or recurrent disease with external radiotherapy, chemotherapy, or biologic response modifiers is rarely curative. Tumor stage predicts prognosis and effectiveness of treatment, and overall survival rates are approximately 75% [1]. Familial disease generally has a better prognosis than sporadic disease. This advantage is no longer seen when adjustment is made for disease stage [5], suggesting that sporadic disease is usually detected in a more advanced stage.

How the Diagnosis Was Made

Diagnosis of Sporadic Medullary Thyroid Cancer

Sporadic and familial MTC are diagnosed in different ways. Sporadic MTC is usually diagnosed by fine-needle aspiration of a palpable nodule [1], or it may be diagnosed at the time of surgery. Sporadic disease initially appeared to be the culprit in this patient. Her cytology specimen could also have been stained for calcitonin, which might have rendered a confirmatory diagnosis prior to the patient's surgery. However, fine-needle aspiration is only suggestive or diagnostic of MTC in about 50% of patients who have MTC, contributing to the controversy regarding the utility of screening calcitonin levels for all patients with thyroid nodules.

The clue to this patient's diagnosis was her elevated serum calcitonin level. Although some endocrinologists recommend routine measurement of calcitonin in patients with thyroid nodules, most do not [4]. It would appear that European endocrinologists tend to be more in favor of this approach, in contrast to North American endocrinologists. The yield from such screening would be low given the high prevalence of thyroid nodules and the rarity of MTC [3, 4]. In this case, however, such screening picked up an apparently sporadic case of MTC that was later found to be familial. Identification of the index case of a MTC kindred following serum calcitonin measurement in an apparently sporadic MTC case presenting with a thyroid nodule has been previously described [1]. It is estimated that about 20% to 30% of all apparently "sporadic" cases of MTC are, in fact, previously unrecognized familial MTC. The debate about whether to screen all patients with thyroid nodules with a serum calcitonin level remains unresolved. However, such debate should take into consideration not only the relatively low likelihood of detecting

MTC (about 0.1–0.5%), but also the serious consequences of missing a patient with familial MTC and the relevant clinical considerations and costs.

Diagnosis of Familial Medullary Thyroid Cancer

Familial MTC is usually diagnosed at the time of thyroidectomy after genetic screening has identified a *ret* proto-oncogene mutation [2]. The patient's daughter was fortunate to have been identified during the precursor stage of C-cell hyperplasia. Had her thyroidectomy been delayed, or had she carried a more aggressive mutation, MTC may have been diagnosed at the time of thyroidectomy, as unfortunately occurs in many individuals within MTC kindreds.

Lessons Learned

Use of Cytology in the Diagnosis of Medullary Thyroid Cancer

Accurate diagnosis of MTC by cytologic features alone may be difficult. MTC usually appears as a cellular specimen with clusters of pleomorphic tumors cells. Cells may be oval with eccentric nuclei, similar to plasma cells, or polygonal with granular cytoplasm, similar to Hürthle cells. They may also be spindle shaped. An aspirate from a MTC lesion, therefore, can mimic other benign and malignant entities [1], such as Hürthle cell tumors, poorly differentiated carcinoma, and metastatic renal cell carcinoma and melanoma. In one study, fine-needle aspiration detected only 75% of MTC cases that were suspected based on serum calcitonin screening. The diagnosis, however, can be confirmed by immunohistochemical staining for calcitonin. Immunostaining of the cytology specimen for calcitonin is considered the gold standard for preoperative diagnosis of MTC [3]. In this patient's case, cytologic staining for calcitonin was not performed. Recently, it has been shown that there is a relationship between the cytomorphology found in fine-needle aspirates and the *ret* proto-oncogene mutation. For example, the codon 918 mutation was found to be associated with small, spindled cells, whereas large oval or polygonal cells were seen with the codon 634 mutation.

The Role of ret *Proto-Oncogene Screening*

All patients with MTC, including apparently sporadic cases, should be screened for *ret* proto-oncogene mutations [1]. Early detection of MTC makes successful treatment possible [6]. In the case of sporadic disease, this is often not possible. In this particular case, the patient appeared to have sporadic disease, but it subsequently became apparent that she was part of a MTC kindred. If her family history had been known previously, she would have had a thyroidectomy at an earlier age, ideally

prior to development of MTC. This was obviously possible in the case of her daughter, who had a thyroidectomy before further transformation of C cells had occurred. It is not known with certainty, but it is strongly suspected that thyroidectomy will markedly decrease this carrier's development of subsequent MTC. However, since a small number of thyroid cells still remain following a total thyroidectomy, it is possible that MTC can still develop. The finding of elevated calcitonin levels during follow-up despite thyroidectomy at the stage of microinvasive carcinoma has been reported [6]. The appropriate monitoring after prophylactic thyroidectomy has not been established, but could involve periodic serum calcitonin levels and neck sonograms.

It is also critical to screen all first-degree relatives of patients with *ret* proto-oncogene mutations. Knowledge of an individual's gene status affords the opportunity to intervene before disease development or early in the course of the disease. Screening may introduce privacy issues, but there is a clear survival advantage associated with early thyroidectomy when a mutation is detected [2, 3]. This is in contrast to the case with the *MEN1* gene, where awareness of gene status does not necessarily change management significantly. Screening of family members using stimulated calcitonin levels has been superseded by genetic screening [2, 3].

Exons 10, 11, 13, 14, 15, and 16 (Fig. 13.1) are initially examined in commercially available screening tests. It is important that the entire gene be sequenced, rather than simply examining the sequence at the codons known to be "hot spots" for mutations associated with hereditary MTC. This is particularly important if the *ret* mutation in that family is unknown. However, familial MTC has also been found in association with mutations in exon 8. It has been recommended that if exons 10, 11, and 13 to 16 are negative, the other 15 exons should be sequenced [1]. However, such testing is available only in research laboratories. If screening is negative, it should be repeated on a second blood sample to exclude the possibility of errors, as was done for both daughters of the patient presented. Due to false-negative test results (2–5%), a small risk of hereditary MTC remains even if a germline mutation is not detected. It therefore may be prudent to periodically measure calcitonin levels and perform neck sonograms in family members with negative screening, as clinically indicated.

Familial Medullary Thyroid Cancer syndromes

Familial syndromes, which are associated with MTC, include familial MTC, MEN2A, and MEN2B. The different *ret* mutations (Fig. 13.1) confer different phenotypes (Fig. 13.2). The spectrum of clinical features varies widely according to the specific mutation. These varying clinical features include non-MTC manifestations such as hyperparathyroidism, pheochromocytoma, mucosal neuromas, marfanoid habitus, ganglioneuromas, cutaneous lichen amyloidosis, Hirschsprung's disease, and papillary thyroid cancer [7, 8]. For example, the 918 mutation is associated

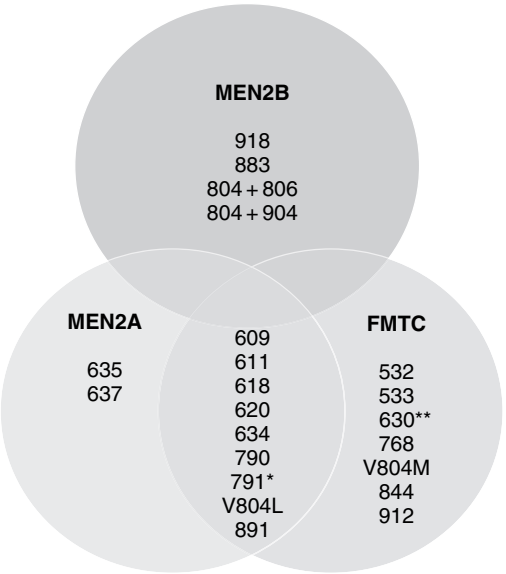

Fig. 13.2 Correlation of specific *ret* codon mutations with the phenotypic expression of hereditary MTC.* Development of Pheochromocytoma has not been reported. ** Cannot distinguish between MEN2A and familial MTC because of the small number of cases. [From Kouvaraki et al. [8], with permission.]

with pheochromocytoma, marfanoid habitus, and enlarged corneal nerves, but not hyperparathyroidism. The 768 mutation, in contrast, is typically not associated with other endocrine tumors. The 790 mutation carried by this patient is associated with papillary thyroid cancer in 9.1% of patients, and additionally is infrequently associated with hyperparathyroidism. On the other hand, the 634 mutation is commonly associated with hyperparathyroidism, pheochromocytoma, and cutaneous lichen amyloidosis.

Variability, at least partly based on the specific genetic mutation, is also manifest in the age of onset (Fig. 13.3) and aggressiveness of the MTC [7, 8]. There is an age-related and codon-specific progression of early MTC. For example, the earliest reported age of onset of MTC is approximately 1 year when codon 918 is mutated, but is around 22 years of age when the mutation is in codon 768. For this patient's mutation, the earliest age of onset appears to be 11 or 12 years of age (Fig. 13.3). The median age of onset is 3 years for codon 918, but is considerably later at 60 years for codon 768. An intermediate median age of onset of 39 years characterizes codon 790. It is these genotype-phenotype relationships that drive the screening, surveillance, and prophylaxis regimens that are critical for the management of kindreds with MTC. Various entities such as the International Workshop on MEN, the European MEN Study Group (EURO-MEN), and the University of Halle have made recommendations regarding the appropriate age for prophylactic testing and thyroidectomy based on the specific mutation [1, 2, 5]. It is usually

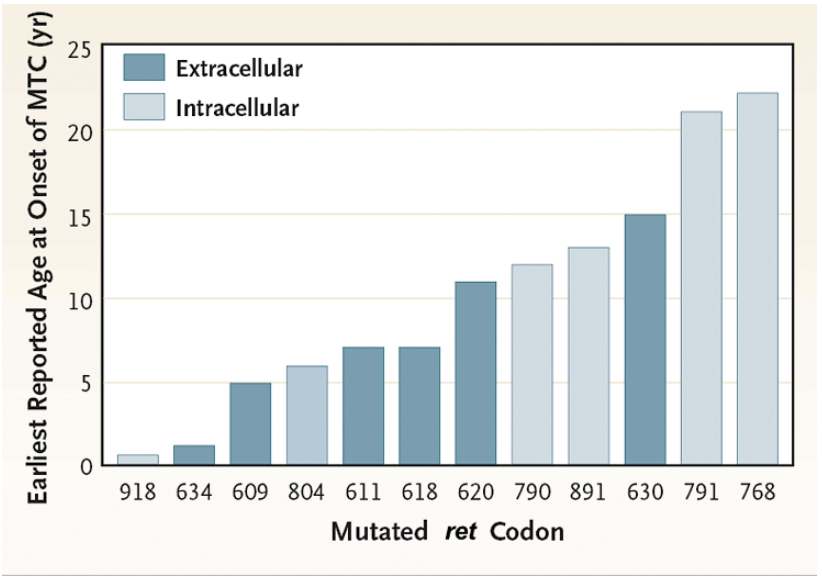

Fig. 13.3 Illustration of the earliest reported age at onset of MTC based on the *ret* mutation. (From Cote and Gagel. Lessons learned from the management of a rare genetic cancer. N Engl J Med 2003;349:1566–1568, with permission.)

recommended that carriers of the 918 mutation undergo thyroidectomy at less than 1 year of age. Operative intervention in 790 and 768 gene carriers is recommended at age 5 to 10 years. Such codon-orientated prophylactic surgery has contributed to the decline in morbidity and mortality from familial MTC [1, 3]. Despite the utility of the *ret* genotype in predicting phenotype, there remains some unpredictability about malignant transformation, thus lending additional support to the advisability of early prophylactic thyroidectomy.

Direct Correlation Between Early Diagnosis of Medullary Thyroid Cancer and Outcomes

Ten-year survival rates of patients with MTC range from 50% to 80%, depending on tumor stage and age [1]. MTC can be cured only at a stage where surgical resection is complete, thus fueling the effort to detect disease early. This is illustrated by the outcomes of sporadic disease versus familial disease. Sporadic disease is usually diagnosed at a more advanced stage than inherited disease. Ten-year survival rates average approximately 75% in several studies. In contrast, in known kindreds with familial MTC followed for 18 years, mortality rates may be as low as 5% [2], presumably due to prophylactic surgery at an early stage. In one study, patients with sporadic disease were 7.7 times more likely to die from their MTC than patients with

familial disease. However, there is no difference in survival between the sporadic and familial forms of MTC when adjustment is made for disease stage [5].

Patients who have undergone prophylactic thyroidectomy still require long-term evaluation in order to confirm that they are cured. Some patients with microinvasive MTC [6] or have been found to develop elevated calcitonin levels during later evaluation. Although this patient was found to have lymph node metastases at the time of her initial surgery, her undetectable postoperative calcitonin presumably suggests a favorable prognosis [3].

Treatment Options

There are no effective treatments for MTC beyond surgery [3]. Screening for pheochromocytoma is required before surgical intervention. Measurement of plasma free metanephrines is probably the best test to exclude a pheochromocytoma in familial syndromes where the risk of a pheochromocytoma is high. However, there has not been a consensus regarding which screening is best [2]. Therefore, it would seem wise to combine plasma and urinary catecholamines or metanephrines in order to achieve the greatest sensitivity and specificity. If a pheochromocytoma is present, adrenalectomy should be performed before thyroidectomy. New surgical technologies such as optical magnification devices and bipolar forceps coagulation have allowed systematic microdissection of entire lymph node compartments [5]. Central lymph node dissection is recommended at the time of thyroidectomy. When the tumor is palpable, larger than 1 cm, or when lymph nodes are known to be positive, bilateral lymph node dissection is usually pursued [3]. This is because of the propensity of MTC to metastasize early to regional lymph nodes. This particular patient had a palpable tumor, and in this setting bilateral neck dissection, in additional to central compartment dissection, would usually be recommended. Surgical cure is achieved in only approximately 20% to 25% of patients with tracheoesophageal invasion or cervical nodal metastases, and virtually never achieved with mediastinal or distant metastases [5].

Elevated postoperative calcitonin levels are indicative of residual disease. A second operation may be helpful to achieve normalization of calcitonin levels and presumably improve cure rates [3]. External beam radiation may be helpful for selected patients with inoperable or incompletely excised tumors [1, 3]. There is no role for radioactive iodine therapy. Radiolabeled anticarcinoembryonic antigen monoclonal antibodies, which are available on an experimental basis, have produced tumor shrinkage in some cases. Therapy with agents such as somatostatin analogues, alpha-interferon, or these agents combined can produce partial and transient symptomatic improvement in patients with metastatic disease [3]. Chemotherapy is relatively ineffective; there may be some tumor response, but there is no impact on survival. Agents that have been employed include doxorubicin, cis-platinum, bleomycin, dacarbazine, and 5-fluorouracil [3]. Inhibitors of *ret* tyrosine kinase, such as Zactima, are currently being tested as therapy for both sporadic and hereditary MTC in phase II clinical trials.

Consensus Guidelines

Consensus statements have been published regarding the management of hereditary medullary thyroid cancer [1, 2]. These guidelines address the recommended age of prophylactic thyroidectomy, screening for and management of associated endocrine tumors, carrier testing, and postoperative testing. The 790 mutation seen in the described patient is associated with either the MEN2A or familial MTC phenotype. Carrier testing is deemed mandatory for all children due to their 50% risk of carrying the 790 mutation, and the high penetrance of this mutation. Calcitonin measurements are noted to be insufficiently sensitive to guide decisions regarding thyroidectomy once carrier status is known, but are helpful to detect disease postoperatively. The 790 carriers have the least high risk for MTC and are recommended to undergo prophylactic thyroidectomy by age 5 to 10 years after testing for both hyperparathyroidism and pheochromocytoma. However, both these manifestations are not usually seen with this mutation.

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Multiple-Choice Questions

1. A 45-year-old woman carries the 804 *ret* proto-oncogene mutation. She is seeing you as her new endocrinologist. This particular mutation is characterized by a median age of diagnosis of MTC without nodal metastases of 38 years. Her serum calcitonin level is normal. She has had negative screening for pheochromocytoma. A thyroidectomy has been recommended by her previous endocrinologists. She is well informed and understands the implications of her carrier status, but has refused thyroidectomy because she has friends who have never felt

well since they have been on replacement thyroid hormone. Your wisest course of action would be:

A. Refuse to be this patient's endocrinologist
B. Ask the patient to see a psychiatrist
C. Follow the patient's serum calcitonin and cervical ultrasonography, and continue to attempt to persuade the patient to undergo thyroidectomy
D. Perform a stimulated calcitonin measurement
E. Recommend triiodothyronine as thyroid hormone replacement following thyroidectomy

Suggested answer: C. Explanation: The only course of action that will either ensure this patient is cured or limit the extent of her disease is thyroidectomy. Therefore, every attempt should be made to ensure this patient is fully informed and aware of the benefits of thyroidectomy.

2. A 12-year-old boy with the 918 mutation underwent thyroidectomy and central compartment dissection. Pathology showed multifocal MTC and central compartment lymph node metastases. Postoperatively his serum calcitonin level remains elevated at 79 pg/mL. There is no evidence of distant metastases based on appropriate computed tomography scans, bone scans, and positron emission tomography. To provide the patient with the best outcome, the next recommended step would be:

A. External beam radiation
B. Radioactive iodine therapy
C. Bilateral modified radical neck dissection
D. Treatment with an experimental tyrosine kinase inhibitor
E. Chemotherapy

Suggested answer: C. Explanation: This patient's elevated postoperative calcitonin level is likely to indicate residual cervical lymph node disease. In this setting, where there is no evidence of distant metastases, additional surgery can normalize calcitonin levels and has been proposed to improve the cure rates [3].

3. All of the following statements regarding the *ret* proto-oncogene are true except:

A. Specific *ret* proto-oncogene mutations are associated with specific phenotypes.
B. An inactivating mutation causes tumor development.
C. Screening has a 2% to 5% false-negative rate.
D. Knowledge of gene status permits intervention that may prevent cancer development.
E. Knowledge of gene status permits intervention that may allow cure of cancer.

Suggested answer: B. Explanation: The *ret* proto-oncogene mutation is an activating mutation that activates *ret* kinase activity causing oncogenic or transforming properties. In contrast, the *MEN1* gene mutation results in inactivation of a tumor suppressor gene. Determination of *ret* proto-oncogene status is one of the few examples of a genetic test that permits an effective clinical intervention.

Chapter 14
Follicular Thyroid Carcinoma with Pulmonary and Osseous Metastases

Jason A. Wexler and Kenneth D. Burman

Objectives

1. Discuss the appropriate screening modalities for osseous metastases in the setting of follicular thyroid carcinoma.
2. Discuss the role of biopsy in the evaluation of osseous metastases.
3. Discuss the role and efficacy of ^{131}I therapy in follicular thyroid carcinoma with osseous metastases.
4. Discuss the efficacy and side effects of intravenous bisphosphonates in the treatment of osseous metastases.
5. Discuss the role and efficacy of novel therapies (i.e., radiofrequency ablation, external beam radiation, and cryotherapy) in the treatment of osseous metastases.
6. Discuss the appropriate monitoring strategies for patients with follicular thyroid carcinoma and osseous metastases.

Case Presentation

A 72-year-old man underwent a total thyroidectomy in July 1989 for Hürthle cell thyroid carcinoma, which invaded lymphatic and venous channels at distant sites from the mass. A cervical lymph node also revealed metastatic involvement. He subsequently received iodine 131 (^{131}I) 168.7 mCi in August 1990, and a posttherapy whole-body scan was negative for distant metastases, although there was neck bed uptake. In November 1991, he received an additional 105 mCi 131–1 for Persistent thyroglobulin elevation. In December 1995, a left anterior cervical lymph node was palpated and a biopsy revealed Hürthle cell carcinoma. He underwent removal of this node and a third course of ablation radioiodine (208 mCi) therapy in January 1996. In 2000, on thyroid hormone suppression, his thyroglobulin was 22.3 ng/mL and thyroglobulin antibodies were negative. Following withdrawal of

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thyroid hormone, his thyroglobulin was 30.4 ng/mL and thyroid-stimulating hormone (TSH) was 63 uU/mL. A computed tomography (CT) scan of the neck and chest in June 2000 showed postsurgical changes in the left thorax related to a distant pulmonary operation for tuberculosis, but no masses or metastatic lesions were found. His past medical history is notable for tuberculosis as a teenager that required pulmonary surgery and osteoporosis. He has no allergies, and his medications include levothyroxine 150 μg daily, alendronate 70 mg once weekly, simvastatin 20 mg daily, aspirin 81 mg daily, and calcium carbonate 500 mg twice daily. He does not smoke or drink alcohol. He is retired and has no family history of thyroid disease.

On recent physical examination, blood pressure was 130/70 mm Hg, pulse 80/minute and regular, and respirations 18/minute. The thyroid scar was well healed and there were no palpable masses. The neck also had a well-healed scar in the left submandibular area without masses.

When the patient underwent a positron emission tomography (PET) scan in October 2000, two focal abnormalities highly suspicious for recurrent thyroid carcinoma were found. One focus was located in the left neck inferior to the angle of the mandible and the second was located in the superior mediastinal region involving the anterior aspect of one of the upper thoracic vertebral bodies. A magnetic resonance imaging (MRI) study of the neck and spine in November 2000 revealed an area (1.5×1.0 cm) of abnormal soft tissue to the left of the hyoid bone corresponding with the area of increased activity on the PET scan and a 1.0-cm focal lesion in the anterior and superior aspect of the T3 vertebral body most consistent with metastasis. A CT-guided biopsy of the neck mass in November 2000 detected Hürthle cell carcinoma, which was surgically resected in December 2000. The patient underwent ^{131}I dosimetry and was treated with 344 mCi of ^{131}I in March 2001. Posttherapy scanning demonstrated at least three foci of uptake in the chest compatible with metastatic disease.

In February 2002, a recombinant human TSH (rhTSH)-stimulated total body ^{131}I metastatic survey showed no evidence of abnormal ^{131}I uptake in the thyroid bed or neck. The previously noted abnormal foci of ^{131}I uptake in the lungs was no longer appreciated. The focal uptake in the midline of the lower chest/upper abdominal region was persistent, but less intense compared to prior studies.

In September 2002, his thyroglobulin rose from 50 to 98 ng/mL while on levothyroxine. The patient received 328 mCi 131-I using dosimetry, and posttherapy scanning demonstrated multiple metastases to the lung. A new left-sided cervical lymph node (1.4×1.0 cm) was seen on MRI in December 2002. The MRI continued to demonstrate a stable T3 vertebral body lesion, consistent with, but not specific for metastatic disease, without evidence of vertebral collapse. In an effort to achieve diagnostic certainty, the patient underwent a vertebral body biopsy that revealed metastatic Hürthle cell carcinoma. A whole-body bone scan was negative except for degenerative changes. The patient then received radiofrequency ablation of the T3 bony lesion. In light of the osseous metastasis, the patient was switched from alendronate 70 mg once weekly to zoledronic acid 4 mg intravenously every month.

In early 2004, the patient suffered an asymptomatic collapse of the T3 vertebral body without evidence of an enlarging mass or impingement of the spinal canal. A PET scan in February 2004 showed activity in the T3 vertebral body with a standardized uptake value (SUV) of 5.8 (SUV was 19.8 prior to radiofrequency ablation), a smaller focus in the posterior lung base, left mid-lung area of activity with an SUV of 3, and there was a focus in the abdominal area with an SUV of 2.7, but CT scans were unable to localize any specific abnormalities corresponding to the PET scan lesions. In July 2004, a repeat PET scan revealed interval worsening of the hypermetabolic focus of the T3 vertebra and a subtle new area of hypermetabolism in the T6 vertebra. These lesions were treated with cryoablation therapy. In January 2005, follow-up CT and MRI scans showed stability of his pulmonary and spine disease. Further imaging with CT and MRI in December 2005 and April 2006 showed stable disease except for the appearance of a new 1.0×2.0 cm nodule in the left lower lobe of the lung. An April 2006 ultrasound of his neck showed no evidence of disease.

How the Diagnosis Was Made

Thyroid nodules often present for clinical attention when noted by the patient, as a finding during routine physical examination, or as an incidental finding during a radiologic procedure. In recent years, the use of thyroid scintigraphy to assess thyroid nodules has become less common. Fine-needle aspiration (FNA) biopsy is now the accepted standard procedure performed in the diagnostic workup of thyroid nodules, and it is the most accurate method for selecting patients needing thyroid surgery [1]. High-resolution thyroid ultrasonography, which provides anatomic definition superior to thyroid scintigraphy, can be used to delineate the nodular makeup of the thyroid gland and can be used in conjunction with FNA to aid in performing the thyroid biopsy. Before proceeding with FNA biopsy, thyroid function should be assessed in all patients with thyroid nodules. If the serum TSH concentration is low, indicating overt or subclinical hyperthyroidism, the possibility that the nodule is "hot" or autonomous is increased and thyroid scintigraphy would be the logical next step. In those with a normal or high TSH, nodule evaluation with FNA biopsy should be the next step.

Fine-needle aspiration is a simple and safe procedure in which tissue samples are obtained for cytologic examination using small (23- to 27-gauge) needles. Often, adequate samples can be obtained in more than 90% of aspirations of solid nodules, although the success rate in degenerative nodules or cysts is lower. Ultrasound-guided FNA can be used for those nodules that are technically difficult to aspirate using palpation methods alone. The results of cytologic examination of samples obtained by FNA are usually reported as nondiagnostic, benign, suspicious or indeterminate, or malignant. It is important to realize that follicular and Hürthle-cell cancers cannot be distinguished cytologically from follicular and Hürthle-cell adenomas. As a result, approximately 15% to 20% of all biopsies are classified

as suspicious or indeterminate (or follicular neoplasm) [2]. Approximately 10% to 20% of all suspicious lesions that are surgically removed are ultimately found to be follicular carcinomas. FNA biopsy is a highly accurate procedure with false-negative rates ranging from 0% to 5% and false-positive results occurring in fewer than 5% of patients in experienced facilities.

Lessons Learned

How to Screen for Bone Metastases in Follicular Thyroid Carcinoma

Follicular thyroid cancer accounts for fewer than 15% of all differentiated thyroid cancers, but has an incidence of bone metastases of 7% to 20% [3]. The appearance of skeletal metastases is considered an ominous sign and often predicts a poor survival; mean survival has been estimated at 4 years. Detection of distant metastases may be difficult, and ^{131}I scanning has relatively poor sensitivity. X-rays and bone scintigraphy are often used in the evaluation of skeletal metastases. However, these imaging techniques detect disease only when more than 50% of bone has been destroyed, and there is no prospective study assessing their individual sensitivity and specificity in detecting osseous metastases from thyroid cancer [4]. Bone scintigraphy often detects skeletal metastases earlier than they appear on standard x-rays, but only if there is a significant osteoblastic component. Magnetic resonance imaging is superb for imaging the medullary component of bone and detailing the intraosseous and extraskeletal extent of disease. Computed tomography, on the other hand, is valuable in imaging for cortical erosion and subclinical fracture in osseous metastases. In practical terms, if a patient has pulmonary metastases or there is a clinical suspicion of osseous metastases, it seems prudent to consider obtaining a metastatic skeletal survey or a bone scan. However, once a bone lesion at a particular site is suspected, a directed MRI or CT scan is most appropriate to better define the lesion(s). An MRI or CT is particularly helpful in planning any surgical approaches to destructive skeletal metastases [4].

In a recent study [5], PET, whole-body scan with technetium-99m sestamibi (Tc-MIBI) and posttherapy ^{131}I imaging were compared under TSH stimulation for their ability to detect distant metastases. Only three of 19 patients had follicular thyroid cancer, but PET was found to be superior to Tc-MIBI body scan and posttherapy ^{131}I scan in the sensitivity of detecting distant spread. The 19 patients had 32 isolated lesions (10 lymph node, 15 lung, six bone, and one muscle) confirmed by histopathology or other imaging studies (x-ray, ultrasound, CT, MRI, and bone scan). PET detected 81.3%, MIBI 62.5%, and ^{131}I 68.8% of the total lesions. Lung metastases were detected in 73.3%, 46.7%, and 66.7% of cases, respectively. When it came to bone metastases, however, all imaging modalities were comparable, detecting about 83% of lesions.

Role of Biopsy in the Diagnosis of Bone Metastases

Even in situations where the primary carcinoma is known, it is often recommended to biopsy a metastatic lesion to bone, especially when the bone metastasis is the initial evidence of recurrence [6]. Biopsy is probably unwarranted in situations of multiple relapses when a previous biopsy has already proven there are osseous thyroid metastases. A needle biopsy is recommended for metastatic disease to the spine or pelvis. Once the biopsy specimen has been obtained, sections should be carefully examined to confirm the identity of the lesion and whether it represents a metastatic process. The osseous lesion should be examined cytologically by an experienced pathologist. Special stains for thyroid transcription factor 1 (TTF-1), thyroglobulin, as well as cytokeratin and calcitonin should be utilized. In addition, relevant supplementary stains, such as prostate-specific antigen (PSA), should be performed as clinically indicated.

Our approach is to recommend an osseous biopsy for the first such tumor even if a patient is known to have thyroid cancer, since it is still possible for another tumor to be present. However, when one bone biopsy has confirmed the origin of the tumor as thyroid, we do not necessarily recommend biopsy of each subsequent lesion except in special situations. It should also be noted that the cytologic characteristics of the osseous thyroid cancer metastases may not mimic those of the original thyroid cancer. That is, it is frequently difficult to determine the precise type of thyroid cancer (e.g., papillary, follicular, or Hürthle cell) from a bone biopsy, and the most important issue is determining the site of origin of the tumor.

Role and Efficacy of ^{131}I in Treating Pulmonary and Osseous Metastases

Prospective, randomized studies of ^{131}I in the treatment of lung and bone metastases from follicular thyroid carcinoma are lacking. Hürthle cell thyroid carcinoma is classified as a subtype of follicular thyroid cancer. Hürthle cell carcinoma is more aggressive than well-differentiated follicular cancer and it tends not to accumulate iodine as well—features that make Hürthle cell more difficult to treat with ^{131}I. The best available data regarding this topic come from retrospective studies. A recent retrospective analysis of 2200 patients with differentiated thyroid carcinoma identified 394 patients with lung or bone metastases [7]. Twenty-eight patients had well-differentiated follicular carcinoma, and 173 patients had less differentiated follicular carcinoma. Most patients underwent total thyroidectomy and received ablative therapy with ^{131}I. One third received postoperative external beam radiation therapy after surgery to the neck. Patients who had detectable lung or bone disease on posttherapy scanning received an additional 100 mCi of ^{131}I 3 months after a standard initial ablation dose of 100 mCi of ^{131}I. The same occurred for patients with a detectable thyroglobulin (Tg) during levothyroxine (LT_4) therapy or Tg >5 ng/mL off LT_4 therapy. Patients who had radiographically proven bone metastases also received

approximately 3000 rad of external beam radiation treatment to the affected region in association with ^{131}I therapy.

Patients with less differentiated follicular cancer had lower survival rates than those with well-differentiated papillary or follicular carcinoma. Positive ^{131}I uptake was associated with improved prognosis. The risk of death was greatest in those with macronodular pulmonary metastases or multiple bone metastases. Ten-year survival was 96% in those younger than 40 years old with normal chest x-rays and only 7% in those 40 years old and older with macronodular pulmonary or multiple bone metastases. Survival was 63% for all other patients. For those who had a complete response, survival was 96% at 5 years, 93% at 10 years, and 89% at 15 years. Without a complete response, survival was 37%, 14%, and 8%, respectively. Response to ^{131}I therapy was improved the earlier the disease was detected and treated. In addition to ^{131}I whole-body scans, Tg measurement is an important and sensitive marker for detecting metastatic disease. Although prolonged survival was not proven to be linked to ^{131}I treatment alone, those patients who survived more than 15 years after the detection of metastases had all been treated with ^{131}I alone or in combination with external beam radiation therapy if appropriate.

In the most recent report from the same group of investigators in the immediately preceding study mentioned above, researchers were able to distinguish survival rates among 444 patients with distant metastases from papillary and follicular thyroid carcinoma [8]. Among those who had radioiodine uptake, 20-year survival was 33% versus only 3% at 10 years for those without radioiodine uptake. Those who had lung metastases had 49% survival at 20 years, whereas those with bone metastases had 20-year survival of only 8%. For those with both lung and bone metastases, 20-year survival was 9%. Survival was not impacted if neck recurrences occurred or if metastases were discovered early or late in the course of a patient's care.

Efficacy of IV Bisphosphonates in Treatment of Bone Metastases

As just discussed, bone metastases from follicular thyroid cancer, particularly those that are less differentiated, respond poorly, if at all, to traditional treatment regimens that include ^{131}I. Since bone metastases destroy bone architecture through a local osteolytic process, some investigators have proposed using inhibitors of osteoclast activity (i.e., bisphosphonates) to slow or prevent the skeletal complications of osseous metastases. Although studies in thyroid cancer patients are quite limited, one protocol enrolled 10 patients with thyroid cancer and administered pamidronate 90 mg IV every month for 1 year [9]. Patients who received pamidronate reported significantly less bone pain by visual analogue scale, improved performance status, and a beneficial impact on quality of life. Only two of 10 patients demonstrated a partial radiographic response to therapy. Although the amount of narcotic pain medication used by patients did decline over time, the change was not statistically significant. A possible explanation for this discordant finding is that while the pain

score was lower at the end of the study, it had begun to rise again at 9 to 12 months of the study from its nadir at 3 months. Side effects, which can include fever, myalgias, and electrolyte abnormalities (mainly hypocalcemia), were mild and short-lived.

In a recent study, zoledronic acid (4 mg), a newer-generation bisphosphonate, was compared in a phase III randomized trial with pamidronate (90 mg) in breast cancer patients. Zoledronic acid significantly reduced the risk of developing a skeletal-related event (SRE), defined as a pathologic fracture, spinal cord compression, radiation therapy, or surgery to bone by an additional 20% versus 9% for pamidronate [10]. Furthermore, zoledronic acid was at least as effective as pamidronate in reducing the proportion of patients with one or more SRE and in delaying the onset of SREs. Moreover, a retrospective subset analysis of patients with one or more osteolytic lesion proved zoledronic acid more effective than pamidronate in reducing the risk and delaying the onset of SREs. Although there is no evidence to support improved survival rates, because this therapy is easy to administer and so well tolerated, it argues for the widespread adoption of these agents (with the evidence favoring zoledronic acid) in the management of those patients with bone metastases from thyroid cancer. In our center, because of the ease and rapidity of administration, as well as a growing body of literature demonstrating enhanced efficacy, we favor using zoledronic acid 4 mg intravenously on a monthly basis for 1 year followed by quarterly infusions indefinitely.

No discussion of bisphosphonates is complete without addressing the concern of osteonecrosis of the jaw (ONJ). The best review of this topic to date examined all case reports and case series of patients with bisphosphonate-associated ONJ published in Medline from 1966 to January 2006 [11]. Osteonecrosis of the jaw is a recently described side effect of bisphosphonate therapy. Patients with multiple myeloma and metastatic carcinoma to the skeleton who are receiving intravenous, nitrogen-containing bisphosphonates (e.g., pamidronate, zoledronic acid) are at greatest risk for ONJ (94% of published cases), but ONJ has been reported to occur with all of the available oral bisphosphonates as well (e.g., alendronate, risedronate, ibandronate). Eighty-five percent of affected patients have had multiple myeloma or metastatic breast cancer and 4% have had osteoporosis. The estimated prevalence of ONJ in patients with cancer is 6% to 10%, but the prevalence in those with osteoporosis is unknown. The mandible is more commonly affected than the maxilla (2:1 ratio), 60% of cases are preceded by a dental surgical procedure, and the remaining 40% related to infection or trauma. Oversuppression of bone turnover is thought to represent the predominant mechanism for the development of this condition, but there may be other contributing factors such as preexisting dental infection, radiation exposure to the jaw and a history of receiving chemotherapy. A recently issued recommendation calls for the eradication of all sites of potential jaw infection before bisphosphonate therapy is begun to lessen the need for subsequent dentoalveolar surgery. Conservative debridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses, and withdrawal of bisphosphonates are thought to be preferable to aggressive surgical measures for treating this condition.

Novel Modalities in the Treatment of Bone Metastases

Traditional therapy for differentiated thyroid cancer includes total thyroidectomy, removal of suspicious lymph nodes in the central compartment, and ^{131}I treatment. In cases of local or distant relapse, further surgery, ^{131}I, or external beam radiation therapy may be required. If none of those modalities is successful, novel treatments may be instituted to control the disease burden.

External beam radiation therapy (EBRT) is a significant component of the therapeutic options available to patients with skeletal metastases from thyroid cancer. The main objective of EBRT is to alleviate pain and neurologic complications from osseous disease. Although data on this subject as it specifically relates to thyroid cancer are lacking, it is thought that approximately 70% of patients experience pain relief with palliative EBRT [12]. Patients often report subjective improvement in their symptoms within 2 to 3 days, but some report improvement up to a month after therapy. EBRT must be tailored to the patient's life expectancy, anatomic site of the skeletal metastasis, and the size of area to be treated. EBRT is often implemented after surgical treatment of pathologic fractures or impending fractures to improve the patient's functional status. Finally, EBRT is undergoing investigation as to whether its integration with newer therapeutic modalities such as vertebroplasty and radiofrequency ablation may provide additional benefit to patients.

Radiofrequency ablation (RFA) and ethanol (EtOH) injection are relatively new, minimally invasive techniques that have been used as adjuvant therapy in other malignancies such as hepatocellular carcinoma or other malignancies that have metastasized to the liver. Radiofrequency ablation is thought to cause focal coagulative necrosis of diseased tissue in a specific region of interest. The role of these techniques in thyroid cancer is just beginning to be explored. Radiofrequency ablation has been found to reduce pain from thyroid cancer bone metastases, but data are lacking in terms of long-term resolution of disease at the treated sites.

One study recently evaluated the RFA and EtOH experience in local and focal distant metastases [13]. In this study, 16 patients underwent RFA treatment of biopsy-proven recurrent well-differentiated thyroid cancer in the neck. Under conscious sedation and local anesthesia and using ultrasound guidance, the radiofrequency (RF) electrode was connected to an RF generator and the lesions were treated with the maximum allowable current for approximately 2 to 12 minutes. The ultrasound-detected appearance of microbubbles and the achievement of a cytotoxic temperature of 50°C within the mass were accepted together as the end point of the treatment procedure.

Radiofrequency ablation works by inducing focal coagulative necrosis to eradicate small areas of tissue in a controlled fashion. Microbubbles occur from the local formation of water vapor as RF energy boils tissue within the treatment region and the temperature within the mass then achieves the cytotoxic threshold temperature of 50°C. Side effects of RFA included hoarseness (most likely thermal injury to the recurrent laryngeal nerve) and skin burns (most likely due to protrusion of the proximal portion of the electrode tip through the skin during the ablation procedure). Self-limited neck swelling and regional discomfort were reported in all 16 patients but resolved within 1 to 2 weeks.

Four patients underwent RFA for focal distant metastases. Three patients had solitary bone metastases and one patient had a solitary pulmonary metastasis. Radiofrequency ablation was performed in the same manner as described above. Six patients underwent EtOH ablation, under local anesthesia and with ultrasound guidance, of biopsy-proven recurrent thyroid cancer in the neck. EtOH is thought to induce tissue necrosis as a result of cellular dehydration and protein denaturation. Of the three patients treated with RFA for bone metastases, one presented at 1 year of follow-up with persistent disease. This individual was retreated with RFA and ^{131}I and subsequent ^{131}I whole-body scanning was negative. A second patient had persistent disease at the treated site and developed a new osseous metastasis. The third patient had biopsy-proven absence of disease at the treated site, and subsequent ^{131}I whole-body scans have been negative through 53 months of follow-up. The patient with the pulmonary metastasis had no evidence of uptake in the lung fields on follow-up ^{131}I whole-body scanning despite persistent uptake in the neck after multiple rounds of ^{131}I treatment.

This study suggests that RFA and EtOH can achieve resolution of solitary lymph node metastases from thyroid cancer in some patients. The data for bone metastases is less robust, with only one of the three treated patients showing a response at the focal distant site. RFA and EtOH have advantages and disadvantages. RFA produces a larger area of lesion destruction, and its energy delivered can be finely modulated. Therefore, RFA can be used to treat a larger region of interest than EtOH, but RFA may be more likely to cause local tissue injury from its thermal effect. Both of these techniques should be used carefully, especially when treating disease in the lateral aspect of the central compartment where the recurrent laryngeal nerve might be quite susceptible to the damaging treatment effect. This comment applies especially to ethanol injection, as extravasation can be extremely toxic to local tissues causing significant fibrosis. These techniques should only be used by experienced individuals.

The role of adjuvant EBRT in patients with locally advanced follicular thyroid cancer has been studied only retrospectively [14]. The efficacy of EBRT to the thyroid bed or to the upper cervical and superior mediastinal lymph nodes is uncertain, with some studies showing no benefit or even worse outcomes compared with those who did not receive EBRT; survival appears to be unchanged with EBRT. Of course, it is possible that only the more serious lesions were those chosen for treatment. However, some studies have shown improvements in local recurrence and disease-specific survival if EBRT was provided to those with papillary thyroid cancer but not to those with follicular thyroid cancer. Nonetheless, some centers offer EBRT to high-risk patients (age >45 years and resectable extrathyroidal disease) in conjunction with ^{131}I treatment. If EBRT is given, it is usually limited to the thyroid bed, but it can be tailored to the specific anatomic site of disease.

Newer techniques such as conformal radiotherapy intensity modulate radiation therapy (IMRT) can allow for more precise radiotherapy delivery to sites outside the thyroid bed, where more normal tissue can be spared and acute and late toxicity may be mitigated [15]. In those with solitary bone metastases for example, 50 Gy is usually given in several fractions over 4 weeks, but special caution must be taken to avoid delivering high doses (limited to 40 Gy) to the spinal cord. Side effects of EBRT include skin erythema, dry desquamation, and mucositis of the pharynx and

esophagus. Long-term sequelae include skin hyperpigmentation and esophageal and tracheal stenosis. In practical terms, patients receiving EBRT to the neck area almost invariably have some difficulty swallowing and neck pain during the last several weeks of therapy. We recommend EBRT to the neck for those patients with locally aggressive tumors, particularly those with residual disease invading the trachea.

Another adjuvant therapeutic modality for treating skeletal metastases is cryotherapy. Cryotherapy used to be performed by introducing liquid nitrogen into the tumor bed. Although this technique was somewhat successful, side effects included the formation of nitrogen emboli, bone fractures secondary to local necrosis of skeletal tissue, and damage to local neurovascular structures. More recently, cryotherapy has been performed using an argon-based system that allows for the controlled formation of ice around a metallic probe [16]. The technique is computer controlled and allows for the protection of surrounding structures. It is known that cell death occurs within 5 mm of the ice formed by the metallic probe if the temperature achieved is less than −40°C on two sequential cryotherapy cycles. In one study, 27 patients underwent argon therapy (14 patients had metastatic bone disease). No one suffered neurologic injury, and after 2 years only two of the surviving patients had a recurrence (none from the metastatic group). Additionally, there were no pathological fractures [16]. In light of these data, cryotherapy appears to be a useful addition to the therapeutic armamentarium available for the treatment of osseous metastases of thyroid carcinoma with minimal risk to local surrounding structures. Of course, definitive studies in this area are warranted.

Monitoring Strategies for Follicular Thyroid Carcinoma and Osseous Metastases

Diagnostic Tools for Follow-Up After Initial Treatment

Serum Tg Determination

Thyroglobulin is a specific and sensitive tumor marker for follow-up of patients with differentiated thyroid cancer. Serum Tg should be measured using a sensitive immunoradiometric assay (IRMA), but when using such methods, the presence of anti-Tg antibodies in the circulation may interfere with the assay, leading to false-negative serum Tg determination. Thus, the presence of anti-Tg antibodies must be ruled out by direct measurement of anti-Tg antibodies. Since Tg is produced by both normal and neoplastic thyroid cells and its production is under TSH control, serum TSH (and thyroglobulin antibodies) should always be measured at the time of Tg determination. After total thyroidectomy and radioiodine ablation, the Tg level should be undetectable (usually less than 0.2 ng/mL), and any detectable level should alert the clinician to the possibility of recurrence. In patients with a negative posttreatment ^{131}I whole-body scan (^{131}I WBS) other diagnostic imaging procedures (CT, MRI, or PET) should be performed to detect residual disease.

Management of Patients with Recurrent or Metastatic Disease

Remission can be obtained in about two thirds of patients with neck recurrence and in one third of those with distant metastases.

Lung Metastases

In the case of ^{131}I uptake, treatment consists of ^{131}I administration following prolonged withdrawal or rhTSH. A ^{131}I WBS performed about 4 to 10 days after administration of radioiodine in combination with Tg monitoring provides assessment of response to treatment. Although controversial, we also perform a pretherapy ^{123}I scan to detect areas of radioiodine uptake that were not known previously. There is no maximum limit for the cumulative ^{131}I activity that can be given to patients with persistent disease, but consideration should be given to the risks of xerostomia, increased lacrimation, neck pain, and bone marrow suppression.

Bone Metastases

Bone metastases should be treated by a combination of surgery, ^{131}I treatment if uptake is present in the metastases, and EBRT to eliminate the disease burden or in an effort to control it [3, 14, 17]. Other local treatment procedures such as the use of embolization or cement injection have been reported to be helpful in some patients.

Our Approach

Given the paucity of controlled prospective studies in thyroid cancer patients (especially with distant metastases), there is no single approach with widespread consensus. Our approach is generally as follows: total thyroidectomy, pretherapy radioiodine scan (with ^{123}I), and ^{131}I therapy for all patients with follicular thyroid cancer and for patients with papillary thyroid cancer who have lesions greater than 1 cm in size. For a select group of other patients, those with a family history of papillary thyroid cancer or tall-cell variant cancer, for example, we also recommend total thyroidectomy, 123-I scanning, and 131-I therapy. All patients who receive radioiodine therapy also have initial staging studies to include ultrasonography of the neck and CT of the chest without contrast. If there is no evidence of residual or recurrent disease, these patients will be followed with periodic lab tests and neck sonograms. Generally, the lab tests are performed every 4 to 6 months and our goal TSH is usually 0.1 μU/mL or less and serum thyroglobulin less than 0.2 ng/mL. The goal TSH depends on the status of the patient and those with potentially more aggressive disease or metastatic disease have a goal TSH of less than 0.01 μU/mL. Cardiac assessment is performed as appropriate, and bone mineral density is measured periodically.

Approximately 1 year after ^{131}I therapy, another TSH-stimulated radioiodine scan is performed in conjunction with measurement of a serum thyroglobulin level.

If there is no evidence of disease, then the patients are followed with lab tests and thyroid sonograms at 6-month intervals for about 5 years and then at yearly intervals, depending on the clinical context. A stimulated serum thyroglobulin level is obtained periodically, every 1 to 2 years for the first 5 years. At the end of 5 years, when there is no evidence of recurrent or residual disease, the frequency of these tests are decreased but are maintained for an indefinite period of time. In the course of follow-up, if a patient has known or suspected distant metastases or an inappropriately elevated serum thyroglobulin level, additional studies to include chest CT (without contrast), neck MRI, PET scans, and assessment for osseous metastases (e.g., bone scan or skeletal x-ray survey) are performed. If a specific lesion, for example in the bone, is suspected or identified, directed MRI or CT scans are performed and, as noted, a biopsy is considered.

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Multiple-Choice Questions

1. A 58-year-old man with a history of follicular thyroid cancer presents to his physician for routine follow-up. The patient underwent a total thyroidectomy 2 years ago and received an initial ablative dose of 122 mCi ^{131}I. His postoperative thyroglobulin (Tg) was 35 ng/mL (Tg antibody negative) and was undetectable on thyroid hormone withdrawal 1 year ago. The patient has been feeling well and has been taking levothyroxine 175 μg daily. His TSH is 0.089 μU/mL, and he asks you what additional tests need to be performed as part of his care. Which of the following would be the best recommendation for this patient?

   A. Positron emission tomography (PET) scan
   B. Computed tomography (CT) scan with contrast of neck and chest
   C. Plain radiograph (x-ray) of chest
   D. Thyroid hormone withdrawal with measurement of Tg and Tg antibodies
   E. Thyroid hormone withdrawal and administration of high dose ^{131}I therapy

   Answer: D. Explanation: Measurement of thyroglobulin (and thyroglobulin antibodies), either with thyroid hormone withdrawal or with recombinant human TSH administration, is the most sensitive means to detect residual well-differentiated thyroid cancer in a low-risk individual.

2. A 43-year-old woman was found to have follicular thyroid cancer 1 year ago. She underwent total thyroidectomy and received 100 mCi ^{131}I as an ablation dose at that time. She returns for follow-up now, feeling well. Her physical examination is unremarkable except for a well-healed thyroid scar without palpable masses. Her Tg level on suppressive doses of levothyroxine is 5.6 ng/mL. A thyroid ultrasound is normal. During recombinant human TSH stimulation, the patient's Tg level rises to 15.8 ng/mL, but her ^{131}I whole-body scan is negative. Which of the following is the best test to detect metastatic disease in this patient?

   A. Whole-body bone scan
   B. PET scan
   C. Thyroid hormone withdrawal followed by ^{131}I whole-body scan
   D. Sestamibi (MIBI) scan
   E. MRI of neck, chest, abdomen, and pelvis

Answer: B. Explanation: In a recent study, PET had the ability to detect more distant metastatic lesions than the other listed imaging modalities. PET, MIBI, and ^{131}I were equally sensitive in detecting bone metastases.

3. A 78-year-old man has a history of metastatic follicular thyroid carcinoma. He has been treated with total thyroidectomy and ^{131}I therapy on multiple occasions for detectable disease in the neck and chest. Despite this, the patient's Tg level has been rising steadily over the last 5 years and is now 43 ng/mL on levothyroxine suppression. He has begun to complain of lower back pain for several weeks, and on recent evaluation the patient was found to have a biopsy-proven skeletal metastasis of the L4 vertebra from thyroid cancer. He received EBRT but wants to know if there is anything else that can be done. Which of the following would you recommend?

   A. High-dose ^{131}I therapy
   B. Whole-body EBRT
   C. Intravenous zoledronic acid monthly for at least 1 year
   D. Intravenous pamidronate twice monthly for at least 1 year
   E. Intraosseous ethanol injection into lumbar spine

   Answer: C. Explanation: Intravenous zoledronic acid may reduce pain and skeletal-related events in patients with metastatic thyroid cancer to bone. Recent data suggest that zoledronic acid may be more effective than pamidronate, and it is more rapidly and easily administered in a clinical setting.

Part V
Adrenal

Chapter 15
Adrenal Insufficiency

Lynn Loriaux

Objectives

To illustrate a typical presentation of adrenal insufficiency and the dire consequences that can accrue to the failure to consider adrenal insufficiency in the differential diagnosis of unexplained abdominal pain.

Case Presentation

A 32-year-old woman was admitted to the hospital with increasing joint pain and wheezing. She had a past history of rheumatoid arthritis, chronic leukemia, fibromyalgia, and asthma. Medications included Remicade infusion every 2 months, inhaled bronchodilators, prednisone, 2 mg p.o. t.i.d., and methotrexate 2.5 mg a week.

The oral prednisone was stopped and she was given Solumedrol® intravenously, 20 mg q.i.d. for 4 days. She was discharged free of symptoms. Prednisone was not included in the discharge medication list. She was seen in the outpatient clinic 4 days later, feeling her usual self. There is no indication that prednisone was restarted at that time.

She was next seen 20 days later, complaining of steady epigastric pain with some tenderness to deep palpation in the right upper quadrant. Blood pressure was 130/98, pulse 100, temperature 37.5°C. A complete blood count (CBC) revealed a white cell count of 42,000 with 53% polymorphonuclear cells (PMNs), and 41% lymphocytes. Serum sodium was 134 and potassium 4.7, both in the normal range.

An ultrasound study of the gallbladder was consistent with "acalculus" cholecystitis, and a laparoscopic cholecystectomy was scheduled for the next day.

During the induction of anesthesia, the surgeon realized that the patient had a long history of glucocorticoid therapy, and that this had been discontinued 21 days

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earlier. He ordered Solumedrol, 40 mg, as an intravenous bolus. This was given at 1:50 p.m. The surgical procedure began at 2:00 p.m. The operation was uneventful.

Eleven hours later, at 1:15 a.m., she was found to be hypotensive and moved to the surgical intensive care unit (SICU). At 1:45 a.m., an arterial blood gas revealed a pH of 7.06. The serum bicarbonate concentration was 12 mEq/L. At 2:03 a.m., cardiopulmonary resuscitation (CPR) was initiated. It was terminated at 2:44 a.m. after massive fluid and pressor resuscitation failed.

Postmortem examination noted the cause of death to be pulmonary hypertension associated with postoperative metabolic acidosis and hemodynamic decompensation. Other contributing conditions noted were chronic cholecystitis without stones, mild cardiomegaly, and T-cell large granular lymphocytic leukemia. Other findings on gross dissection were chronic rheumatoid arthritis and marked adrenocortical atrophy.

How the Diagnosis Was Made

Unfortunately in this case, the diagnoses was a postmortem one—the clinical picture of acute adrenal insufficiency coupled with the autopsy findings of marked adrenal atrophy.

Lessons Learned

Is Prednisone at a Dose of 2 mg t.i.d. Enough to Cause Adrenal Suppression?

Adrenal suppression occurs when exogenous glucocorticoid is given in supraphysiologic doses for a long enough period. The replacement dose of hydrocortisone is 12 to 15 mg/m^2 body surface area. This patient was about 1.5 m^2 in body surface area, translating into a dose of 18 to 22 mg hydrocortisone a day. Prednisone is five times more potent than hydrocortisone, leading to a prednisone dose of 2.5 to 3 mg/day. She was taking 6 mg/day, about twice the replacement dose. This is a supraphysiologic dose. The administration schedule is important. The least suppressive regimen is a single dose given early in the morning. The most suppressive regimen is the dose distributed in three or four divided doses throughout the day. The shortest time thought to be required for clinically important adrenal suppression is 4 weeks. Thus, she was taking twice the replacement amount divided into three doses per day for years. She was a very likely candidate for developing clinically significant adrenal insufficiency.

Why Was the Prednisone Stopped?

Either the doctors did not think she needed it because of the low dose, or it was a mistake driven by the idea that it would be a good time to let the adrenal glands take

over the normal secretion of hydrocortisone. The problem with the latter approach is that the length of time it takes to recover from a suppressed hypothalamic–pituitary–adrenal axis in most cases is about 1 year. Recovery can only be made under "cover" of a low replacement dose of hydrocortisone, 12 mg/m^2, given as a single daily dose in the morning. Recovery is monitored with a Cortrosyn® stimulation test using a dose of 250 μg (B1-24 synthetic adrenocorticotropin [ACTH]) as an intravenous bolus with plasma cortisol measured 30 and 60 minutes later. This should be done every 3 months. When the plasma cortisol following ACTH stimulation exceeds 20 μg/dL, it is safe to stop the glucocorticoid supplementation. Either way, this woman was destined to have an "adrenal crisis," sooner or later, without the benefit of exogenous glucocorticoid.

What Was the Patient Really Suffering from at the Time of Her Surgical Procedure?

The signs of adrenal insufficiency include hypotension, unexplained abdominal pain, anorexia, weight loss, relative lymphocytosis, and hyponatremia with a mild metabolic acidosis. The presentation on the 21st day was characterized by abdominal pain, hyponatremia, relative lymphocytosis, and a mild metabolic acidosis. Given her history, adrenal insufficiency should have been high on the differential diagnosis.

What Test Should Have Been Done Prior to Surgery?

In this setting, the Cortrosyn stimulation test would have been both diagnostic and a qualifying criterion for the proposed surgery. It was not done.

Why Did the 40 mg of Intravenous Solumodrol Not Prevent the Appearance of Full-Blown Acute Adrenal Insufficiency?

Glucocorticoid exerts its action by coupling with its cytoplasmic receptor leading to new protein synthesis. This takes time. Using hyponatremia as an end point, the free water diuresis that corrects this abnormality, on average, begins about 12 hours after the administration of glucocorticoid. Our patient only had 10 minutes between the glucocorticoid administration and the beginning of the stressful surgical procedure—not enough time to prevent the complication of acute adrenal insufficiency.

What is the Standard Procedure Regarding Glucocorticoid Treatment in this Situation?

In short, the glucocorticoid must be given at least 24 hours before the surgical stress begins. Had this been done, the outcome in this patient might have been very different.

Chapter 16
Cushing's Syndrome

Lynn Loriaux

Objective

To illustrate the absolute necessity of defining the source of adrenocorticotropin (ACTH) secretion in cases of ACTH-dependent Cushing's syndrome.

Case Presentation

A 24-year-old woman was admitted with Cushing's disease that had failed to be cured by transsphenoidal microadenectomy at another hospital. Her doctors had recommended she consider pituitary radiation therapy or bilateral adrenalectomy. She asked for a second opinion.

The patient was in excellent health until her 21st year, when she began gaining weight in spite of a rigorous exercise and diet program. The diagnosis of Cushing's syndrome was entertained, and urinary free cortisol was measured. It was found to be between 460 and 800 μg/day on three different occasions. A diagnosis of Cushing's syndrome was made. A dexamethasone-suppression test, 0.5 mg/q.i.d. × 2 days, and 2 mg/q.i.d. for 2 days suppressed the urinary Porter Silber chromogens from a baseline of 18 mg/day to 5.4 mg/day on the last day of the test. This test was interpreted as suggestive of an ACTH secreting pituitary adenoma, and a computed tomography (CT) scan of the sella turcica was done. A 6-mm pituitary microadenoma was visualized. On the basis of these findings, a transsphenoidal microadenectomy was performed. The neurosurgeon reported that the entire tumor was removed with clear margins throughout. The pathology report described the tumor as staining positively for ACTH in a "patchy" pattern. On the morning after the surgery, the plasma cortisol was 28 μg/dL, and 22 μg/dL on the following morning. The medical and surgical team concluded that the tumor must have been multifocal, and that the risk of a second operation for hypopituitarism was too great to justify the procedure. They recommended pituitary x-irradiation or a bilateral adrenalectomy.

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When we saw the patient, the physical examination was compatible with Cushing's syndrome. She had central obesity, proximal muscle weakness, abdominal and pectoral striae, and mixed vellus and terminal hair hirsutism. Laboratory investigation showed a hemoglobin of 15 g/dL, a white count of 15,200 with relative granulocytosis, blood glucose of 174, hypokalemia, and a urine free cortisol excretion of 632 μg/day. A concurrent plasma ACTH level was 18 pg/mL.

We recommended an inferior petrosal sinus sampling for the measurement ACTH in central and peripheral blood. The study showed a central to peripheral ACTH concentration gradient of 1.5. The criterion for "central" ACTH secretion is a gradient greater than 3. Chest CT showed multiple old granulomatous lesions. Comparison of old imaging studies with current ones showed one lesion that seemed to be enlarging. A CT-guided needle biopsy, with saline infusion of the lesion, revealed an ACTH concentration in the infusate of greater than 140,000 pg/mL. This lesion was surgically removed. It was a bronchial carcinoid tumor.

Plasma cortisol on the morning following the surgery was less than 5 μg/dL. Hydrocortisone replacement therapy was initiated. The patient remains well 16 years later.

How the Diagnosis Was Made?

The point of confusion in this case was the finding of a pituitary microadenoma in a patient with well-documented ACTH-dependent Cushing's syndrome. It was assumed that this pituitary tumor was the source of ACTH secretion. Unfortunately, this approach has been given some consensual validity in recent articles on the differential diagnosis of Cushing's syndrome. It should be remembered that the prevalence of incidental pituitary adenomas approaches 15%. Thus, 15% of patients with an ectopic source of ACTH will have a pituitary microadenoma when imaged. With the current guidelines, this will lead to an unnecessary transsphenoidal microadenectomy in all of these patients. Even worse, the failure to cure the patient with the first operation might lead to a second operation or pituitary radiation, which was in fact recommended to this patient. The appropriate diagnosis was made by an inferior petrosal sinus sampling for ACTH, which in good hands has a positive predictive value of nearly 100%. There is no excuse for failing to use this test in every patient who has ACTH-dependent Cushing's syndrome.

Lessons Learned

What Are the Most Useful Tests for the Diagnosis of Cushing's Syndrome?

A florid clinical picture of Cushing's syndrome makes the diagnosis of Cushing's syndrome in the absence of biochemical tests. At the other extreme, a urinary free cortisol above 300 μg/day makes the diagnosis regardless of the clinical

presentation. The problem diagnoses are in those patients who have few or minor clinical signs of Cushing's syndrome and urinary free cortisol levels that are above the "normal" range, but less than 300 μg/dL.

The incidence of noniatrogenic Cushing's syndrome is not precisely known, but estimated to be about 200 per million per year. The average "time to diagnosis" is five years, making the prevalence about 1000 per million. The group from which these patients must be differentiated is patients with clinical depression who are overweight. If the prevalence of clinical depression is about 10%, about 40,000 per million people will fit this description. Thus, in the typical group being evaluated for Cushing's syndrome, the ratio of depressed patients to Cushing's patients will be 40 to 1. The positive predictive value of merely saying that any person in the group under study has depression and not Cushing's syndrome is about 0.98. Any test considered for this differential must be stronger than 0.98 to be useful, but none fit this requirement. Unsatisfying as it may be, the most powerful approach to this differential diagnosis is the behavior of the clinical and biochemical measures over time: Cushing's syndrome always gets worse.

What Are the Most Useful Tests for a Differential Diagnosis of Cushing's Syndrome?

The first useful test is a plasma ACTH measured at a time when the patient has active disease. If the ACTH is greater than 10 pg/mL, the disease is ACTH dependent and the source of ACTH must be identified. This can be done with almost 100% confidence using the inferior petrosal sinus sampling procedure. As noted above, imaging the pituitary gland and finding a microadenoma does not alter the need for the Inferior Petrosal Sinus Sampling (IPSS) test. This is well illustrated by this case. If the ACTH is less than 10 pg/ml, then the process is ACTH independent, and adrenal imaging will almost always reveal the source.

What Is the Best Approach to the Patient in Whom the ACTH Source Is Ectopic and a Source Cannot Be Identified?

More than 95% of the ectopic sources of ACTH are in the thorax. Repeated imaging is the key—CT scan for peripheral lesions, and MRI for central and mediastinal lesions. Blocking cortisol production with ketoconazole or other steroid synthetic inhibitors can buy time. If, at 1 year, the lesion cannot be found, or if the patient cannot be successfully "blocked down," bilateral adrenalectomy is the treatment of choice.

Chapter 17
An Incidentally Discovered Adrenal Mass

Lynn Loriaux

Objective

To define satisfactory criteria for deciding when to surgically remove an incidental adrenal mass and when not to.

Case Presentation

A 42-year-old man was involved in a motor vehicle accident and sustained what was thought to be a seat belt injury leading to chronic right flank pain. A computed tomography (CT) scan of the abdomen was negative except for a right adrenal mass, 3×4 cm in size. A magnetic resonance imaging (MRI) showed the same mass and revealed that the mass did not brighten on a T2-weighted image. The patient was referred for an endocrine evaluation.

Past medical history, family history, and review of symptoms were unrevealing. Physical examination showed normal vital signs, a body mass index (BMI) of 23, and no signs of endocrine disease. Laboratory evaluation showed a normal complete blood count (CBC), urinalysis, and biochemical profile. Endocrine tests showed normal urine metanephrine, urine free cortisol, plasma rennin activity, and aldosterone, testosterone, and estradiol. A review of the CT scan showed the tumor to have a Hounsfield index of 25. The patient was told that the lesion was likely to be benign in nature and that surgery was not recommended. The patient agreed to return in 6 months for a follow-up CT scan of the adrenal glands.

The 6-month scan showed the lesion to be larger, 4.5×3.5 cm. The patient was alarmed by this finding, and in consultation with the primary care physician decided to have the mass removed laparoscopically. It was pointed out that the mass was still most likely benign, but the patient had resolved to have the surgery. A surgeon who agreed with the plan was quickly identified by the patient, and the surgery was done. The procedure was uncomplicated. Four hours after the operation,

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however, the patient complained of increasing right flank pain. He was reassured, and anodyne treatment was increased. By the fifth post-operative hour, the patient was hypotensive and was transferred to the surgical intensive care unit (SICU). The blood pressure responded to fluid resuscitation. A CT scan showed a large right retroperitoneal hemorrhage. Two units of whole blood were administered. The pain increased, however, and the retroperitoneal hemorrhage continued to increase in size. On the second postoperative day, an open laparotomy was performed. A bleeding site was identified from the right inferior adrenal vein as it entered the inferior vena cava. The hemorrhage was evacuated to the best of the surgeon's ability. A CT scan 2 days later revealed what appeared to be a fluid reaccumulation in the site of the original hemorrhage. The imaging characteristics, however, were more suggestive of water than of blood, and the possibility of a urinoma was raised. A retrograde ureterogram showed extravasation of the contrast material into the fluid collection, and the injury was stented. The patient slowly recovered and was discharged after a long hospitalization.

The pathologic diagnosis of the tumor samples was "adrenal tissue with some atypical elements." Malignancy could not be excluded, and it was recommended that the follow-up plan should include periodic surveillance for a possible adrenal malignancy.

How the Diagnosis Was Made?

The important diagnosis in this case was the histologic appearance of tissue from the adrenal mass—adrenal tissue versus nonadrenal tissue, that is, a metastasis. In the end, this was never sorted out. Along the way, a therapeutic intervention, right adrenalectomy, was performed that almost led to the demise of the patient. When all is said and done, a surgical procedure with a consensus mortality rate of about 1%, was deployed in the absence of any conceivable benefit since the nature of the tumor was unknown at the time of surgery, and remained so after the operation was done.

Lessons Learned

What Is the Chance that the Accidentally Found Adrenal Tumor is a Malignancy?

The first tumor to consider is adrenal cancer. The death rate from adrenal cancer is well known: 1/600,000 population per year in the United States. Since adrenal cancer is uniformly fatal, this is also the incidence rate. If we assume that these tumors could all be detected by CT or MRI for 1 year prior to death, 1/600,000 would be the prevalence of this malignancy as far as current imaging modalities are concerned. A conservative estimate for the prevalence of adrenal incidentalomas

detected by CT or MRI is 5%. The incidence in postmortem examinations is about 15%, so the number of detectable lesions is likely to rise with improving technology. Using the 5% number, however, the number of these tumors would be 50,000 per million population. Compared to a prevalence of 2 per million as pointed out above, the ratio of benign to malignant adrenal lesions in incidentally discovered adrenal masses is 25,000 to 1. If it is assumed that all the incidental cancers could be surgically cured, which is not known to be the case, and the mortality of the operation is 1/10,000, 2.5 people without cancer would die from the procedure for every one saved. Thus, these lesions should never be removed surgically unless other reasons drive the decision.

These other reasons include endocrine function of the tumor, its size and growth, and the need to know the nature of the tumor to support other diagnoses for which there is definitive therapy.

What Are the Indications for Surgical Removal?

The demonstration of endocrine function by the tumor is considered an absolute indication for surgical removal. Functional lesions include pheochromocytoma, glucocorticoid excess (Cushing's syndrome), mineralocorticoid excess (Conn's syndrome), androgen excess (masculinization in women), and estrogen excess (feminization in men). These syndromes are well characterized and need not be detailed here.

Size has long been considered to be an indicator of the malignant potential of an adrenal tumor. This concept comes entirely from the surgical experience with adrenal lesions causing Cushing's syndrome. Clinical Cushing's syndrome associated with small tumors implies a well-differentiated and efficiently functioning tumor, while a large lesion implies a poorly differentiated or inefficiently functioning tumor, more likely to have a malignant course. This has no bearing on the biology of incidentally discovered lesions. However, what is known is that larger tumors are more likely to infarct, which can lead to an acute abdominal event requiring surgery under less than ideal circumstances. The risk/benefit analysis in this situation shifts toward surgery, but definitive criteria are still only a guess. The most common guess is that lesions of 6 cm or more should be considered for surgical removal.

Growth is currently considered to be an indication for surgical removal. The reasoning for this notion is vague at best. It is certain that all of these tumors have grown at some time. The ontogeny of growth in these tumors, however, is completely unknown. It may be that growing lesions have nothing to do with the potential for metastatic behavior, or even that removing them has any effect on the ultimate chances of metastasis. I, personally, do not use growth as a reason to consider surgical intervention, but others do. The data to guide this decision are unlikely to be collected at this stage of the development of standards of care for these tumors.

The adrenal gland is a common site of metastasis for many cancers and is often the first apparent metastatic site. If a cancer is known to exist in a patient with an incidental adrenal tumor, metastases can be confirmed by biopsy or excision. If a cancer is suspected, but not known, the diagnosis of malignancy can often be confirmed by an adrenal biopsy or by pathologic examination of material obtained from the surgical removal of the tumor.

What Is the Procedure of Choice for This Intervention?

The current surgical procedure of choice is the laparoscopic adrenalectomy. Mortality is 1% or less, and morbidity is low. The main complications are postoperative bleeding and injury to the urinary tract. Both happened in this case.

If the lesion is an adrenal malignancy, there is no evidence to support the idea that excision will prevent the malignant course. If the lesion is an adrenal adenoma, the operation can do nothing but prevent the complications of large adrenal tumors such as infarction and necrosis. If the tumor is a metastasis in a patient with a known cancer, nothing need be done. If there is no known cancer, then the procedure can be diagnostic and inform subsequent therapy. However, in the case of metastatic solid tumors, that therapy is not likely to be very helpful.

Part VI
Hyperparathyroidism

Introduction

Simon H.S. Pearce

In health, the serum calcium concentration is maintained within strict limits by the actions of the three major calciotropic hormones: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D_3(1, $25(OH)_2D_3$), and calcitonin. The total serum calcium concentration ranges between 2.1 and 2.6 mmol/L (8.4 to 10.4 mg/dL), about 45% of which is protein-bound (70% of which is to albumin), with a further 5% to 10% being complexed to small organic ions such as bicarbonate, phosphate, citrate, and others. The remaining 45% of the serum calcium is in the form of ionized calcium (Ca^{2+}), and the concentration of this fraction is tightly regulated within the range 1.1 to 1.4 mmol/L (4.4 to 5.6 mg/dL). A decrease in the circulating ionized calcium concentration of the order of 1% to 2% is detected by the cell-surface calcium-sensing receptor whose intracellular signal leads, within seconds, to an increase in the rate of PTH release from the parathyroid chief cells (Fig. VI.1) [1]. Circulating PTH then acts via the PTH receptors on the distal tubule of the kidney, which within minutes leads to an increase in tubular reabsorption of calcium and decrease tubular phosphate reabsorption. Parathyroid hormone secretion also enhances osteoclast and other bone cell activity, causing skeletal calcium release within 1 to 2 hours. More prolonged PTH release stimulates 1α-hydroxylase activity in the proximal tubular cells leading to $1,25(OH)_2D_3$ production, which regulates both intestinal calcium absorption and skeletal calcium turnover over days to weeks.

All of these mechanisms produce a correction of the Ca^{2+} toward the baseline value, the "feedback loop" is completed by inhibition of PTH release, and the increased $1,25(OH)_2D_3$ levels also inhibit PTH gene transcription. Thus, the two cornerstones of normal serum calcium homeostasis are first: the ability of the parathyroid glands to secrete PTH at a rate that is rapidly responsive to changes in Ca^{2+}. And second the capacity of the effector tissues, namely the renal tubule, skeleton, and intestine to respond appropriately to the resultant changes in the circulating concentrations of PTH, $1,25(OH)_2D_3$, and, to a lesser extent, calcitonin (Fig. VI.1). Additional homeostatic regulation takes place at several sites in the nephron where changes in calcium concentration are also directly detected by the

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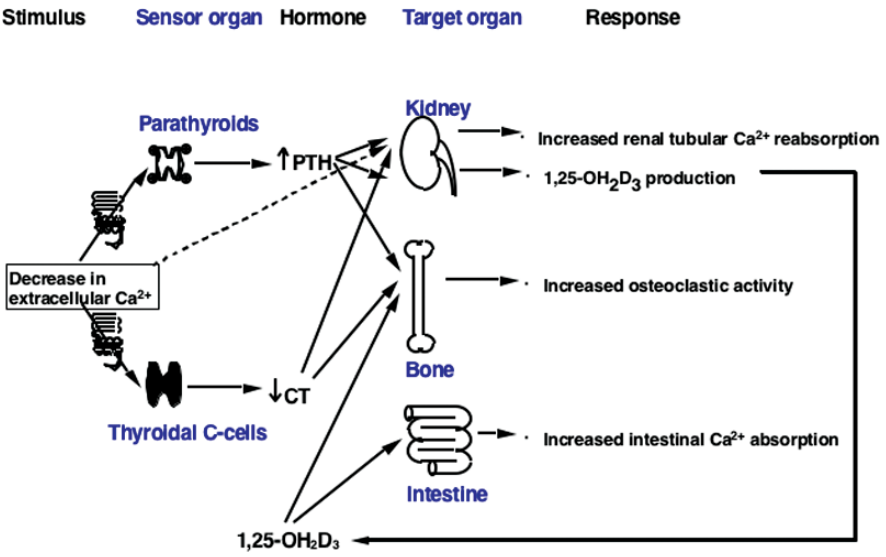

Fig. VI.1 Overview of calcium homeostasis

calcium-sensing receptor on renal tubular cells, leading to some intrinsic regulation of calcium excretion, independent of circulating PTH.

It is estimated that the skeleton contains about 98% of the elemental calcium content of the body. And in the healthy state, or in patients with stable hypercalcemia, there is an equilibrium between calcium exchanged during bone turnover (formation and resorption), absorption of calcium from the gut, and renal calcium excretion. This leads to a net balance, with 4 to 7 mmol of calcium being absorbed through the gut daily and a similar daily calcium excretion in the urine. In disease states this balance may be disrupted (sometimes termed disequilibrium hypercalcemia). This precarious condition, in which there is an impairment of renal calcium excretion, coupled with either an increased bony release of calcium or an inappropriate gastrointestinal absorption of calcium, may rapidly spiral into a medical emergency. The resulting imbalance of calcium flux leads to extreme hypercalcemia, associated with a variable combination of dehydration, nausea and vomiting, failure of renal concentrating capacity (nephrogenic diabetes insipidus), worsening renal function, and circulatory collapse.

Pathophysiology of Hyperparathyroidism

Primary Hyperparathyroidism

Primary hyperparathyroidism is a state of dysregulated PTH secretion, such that the circulating PTH concentration is inappropriate for the prevailing serum calcium level. The disease is commoner in women (F:M ratio 3:1) and has a peak incidence

between the ages of 50 and 70 years, when it may affect more than 1% of women [2], although in an unselected population the prevalence is about 1 per thousand. In 85% of patients the cause is autonomous secretion of PTH from a single benign parathyroid adenoma. A normal parathyroid gland may weigh up to 50 mg, but parathyroid adenomas are typically two- to 20-fold enlarged. In the remaining 15% of people, multiple parathyroid adenomas or four-gland parathyroid hyperplasia are found to be the cause of the primary hyperparathyroidism: parathyroid carcinoma being a rarity, accounting for about 0.5% of patients. Most cases of primary hyperparathyroidism are sporadic, but around 5% may be familial, particular in younger patients and in those found to have four-gland parathyroid hyperplasia, where there may be an underlying diagnosis of a multiple endocrine neoplasia (MEN) syndrome or the hyperparathyroidism-jaw tumor syndrome. Histologically, parathyroid adenomas consist of an expansion of parathyroid chief cells, often with a surrounding rim of compressed normal parathyroid tissue. The histologic distinction of parathyroid carcinoma may not always be clear, but vascular invasion, mitotic figures, and bands of dense fibrous tissue are the typical features. At a molecular level, parathyroid adenomas are monoclonal, with rearrangement or overexpression of the *cyclin D1* oncogene being found in about one third of tumors [3]. Mutation or inactivation of both alleles of the *MEN1* gene is also found in about 15% of sporadic parathyroid adenomas. Additional molecular defects, including deletion of the *HRPT2* (parafibromin) gene and the retinoblastoma locus are found in parathyroid carcinoma.

Secondary, Tertiary, and Uremic Hyperparathyroidism

Secondary hyperparathyroidism is a state characterized by hypocalcemia or hyperphosphatemia, and an appropriate elevation in circulating PTH concentration. Although it is found in states of chronic vitamin D or dietary calcium deficiency, in Western medical practice it is most often associated with chronic renal failure. In this situation, tubular failure leads to phosphate retention and combined with a failure of renal vitamin D_3 1α-hydroxylation, results in hypocalcemia and a strong stimulus to PTH secretion and parathyroid cell proliferation, leading to four-gland hyperplasia. Autonomous secretion of PTH may eventually develop in one or more glands following a long period of uremia, with resultant hypercalcemia and renal bone disease; this hypercalcemic state being referred to as tertiary hyperparathyroidism or refractory uremic hyperparathyroidism. Interestingly, the parathyroid glands from hypercalcemic patients with longstanding uremia also show a monoclonal cellular expansion. Management of uremic hyperparathyroidism will not be discussed further in this chapter, but the reader is referred to recent reviews [4, 5].

Clinical Features of Primary Hyperparathyroidism

When first recognized as a distinct clinical entity, primary hyperparathyroidism was a devastating disease characterized by severe malaise, renal stones, nephrocalcinosis, and progressive skeletal deformity [6]. In the 21st century, these

complications are rare and the commonest presentation of primary hyperparathyroidism is with an asymptomatic patient who has an elevation of serum calcium found on a routine biochemical profile. Nevertheless, specific symptoms of thirst, polyuria, renal stones, constipation, anorexia, nausea, dyspepsia, bone or muscle pains, and mood or memory disturbance should be assiduously sought. A history of fractures should be taken, as well as a family history of hypercalcemia, neck surgery, or renal stones. A detailed medication history should be recorded, including over-the-counter preparations. The patient's dietary habits should also be ascertained. The major differential diagnosis of hypercalcemia is disseminated malignancy, and a physical examination including for breast masses, liver enlargement, and lymphadenopathy is necessary. Specific signs of hypercalcemia are rare, but a pale white arcus due to corneal calcification (band keratopathy) is sometimes found (Fig. 19.1). A neck mass, if present, raises the possibility of parathyroid carcinoma. In the acute situation, an assessment of volume status and hydration is mandatory.

Differential Diagnosis and Investigation

Hypercalcemia is most often due to hyperparathyroidism, but malignancy is the major differential diagnosis (Table VI.1), causing hypercalcemia either through the tumoral secretion of PTH-related peptide (PTH-rP), termed humoral hypercalcemia of malignancy, or by direct bony invasion of osteolytic metastases or myeloma. Rarely, lymphoid malignancies may also induce hypercalcemia through excess $1,25(OH)_2D_3$ production within the tumor cells. More frequently a similar mechanism causes hypercalcemia in patients with granulomatous disorders, predominantly sarcoidosis. Various medications including vitamin D ingestion, vitamin A excess, lithium use, and thiazide diuretic use are also associated with hypercalcemia. Although thiazides cause a decrease in urinary calcium excretion that may worsen preexisting hypercalcemia, they are rarely found to be the sole cause of significant hypercalcemia. If a hypercalcemic patient is taking thiazides, it is prudent to stop these for at least 2 weeks before performing further investigation. Lithium causes a defect in calcium-sensing receptor signaling, which in the short-term results in a modest but reversible, PTH-dependent rise in serum calcium in many individuals. With chronic lithium use, often after 5 or more years, a state of autonomous hyperparathyroidism can develop, which appears to be identical to primary hyperparathyroidism, other than that the urine calcium excretion is low, owing to the action of lithium on the calcium-sensing receptor in the kidney. Familial benign hypocalciuric hypercalcemia (FBHH) is an autosomal dominant disorder that is a close mimic of asymptomatic primary hyperparathyroidism. Hypercalcemia is present from the first week of life, and it is caused by heterozygous mutations that cause insensitivity of the calcium-sensing receptor to circulating calcium concentrations (a state of pseudosecondary hyperparathyroidism) [7]. Clinically, it may be distinguished from primary hyperparathyroidism by family history, the presence of a low urine calcium excretion and by the relative hypermagnesemia, which is sometimes found (see Case 18).

Table VI.1 Differential diagnosis of hypercalcemia in an adult

Common	Primary hyperparathyroidism	
	Malignancy	Humoral hypercalcemia of malignancy (PTH-rP)
		Bone metastases (particularly lung and squamous cell)
		Myeloma
Less frequent	Vitamin D intoxication	
	Familial benign hypocalciuric hypercalcemia	Calcium-sensing receptor defect
	Sarcoidosis and other granulomatous disorders	1α-hydroxylation related
	Tertiary hyperparathyroidism	Uremia-associated
Rare	Lithium use	
	Thiazide use	
	Milk-alkali syndrome	
	Immobilization in a high turnover state	e.g., growing child or adolescent, athlete, Paget's disease, healing fractures
	Recovery from tubular injury	Rhabdomyolysis
	Addison's disease	
	Pheochromocytoma	
	Thyrotoxicosis	
	Vitamin A intoxication	
	Lymphoid malignancy	1α-hydroxylation related

All patients with hypercalcemia require further workup to determine its etiology, and the PTH concentration is the key investigation. The plasma PTH concentration should be measured using a reputable assay, preferably one measuring intact PTH (1–84 amino acids), with a corresponding serum calcium and albumin level taken. In the acute situation, it is important to obtain a PTH level before treatments other than initial rehydration are started. An elevated PTH, or one in the upper quarter of the reference range, is compatible with a PTH-dependent cause for hypercalcemia, namely primary or tertiary hyperparathyroidism, FBHH, or lithium use. A low or suppressed PTH concentration points to malignancy, or one of the other rarer causes of hypercalcemia (Table VI.1). Following a chest radiograph, a radionuclide bone scan and serum tumor markers are often judicious next investigations in a hypercalcemic individual with a suppressed PTH and no obvious source of malignancy. In the presence of an elevated or "high-normal" PTH, an assessment of urinary calcium excretion is mandatory, either on the second void of the morning or on a 24-hour collection, both with a contemporaneous serum sample. The urine calcium clearance to creatinine clearance ratio ($UCacl/Crcl = [UCa \times SCr] \div [SCa \times UCr]$) must be obtained in order to distinguish primary hyperparathyroidism from FBHH (see Case 18). In addition, the urine calcium excretion is helpful in deciding whether parathyroid surgery is indicated in an asymptomatic individual with primary hyperparathyroidism (Table 18.1). In an elderly or institutionalized individual, an assessment of vitamin D status (serum 25-OH vitamin D_3 level) should be made. Assuming the diagnosis of primary hyperparathyroidism is confirmed, further

assessment is directed toward staging the complications of the disease, namely renal impairment, nephrocalcinosis, nephrolithiasis, cortical bone loss, and hyperparathyroid bone disease. Investigations including a Dual Energy X-ray Absorptiometry (DEXA) bone scan of the distal radius, hip, and L-spine, and a renal tract ultrasound should be used to judge further management.

Management of Acute Hypercalcemia (see Case 19)

All patients with a serum calcium >3.5 mmol/L (14 mg/dL), and those with symptoms who have a serum calcium over 3.2 mmol/L (12.8 mg/dL) require immediate active management. Most patients with this degree of hypercalcemia will have had some additional factor, such as the onset of vomiting or sepsis that has tipped them over into a state of "disequilibrium hypercalcemia." If there is no preceding history of hypercalcemia or malignancy, a PTH level should first be obtained, along with urea, creatinine, albumin, electrolytes, and bicarbonate levels. A formal assessment about whether aggressive treatment is appropriate should be made in a patient with known advanced malignancy. Rehydration with intravenous saline (0.9%) is the mainstay of the immediate treatment, with 4 to 6 L typically being administered over the first 24 to 36 hours, depending on the initial state of hydration and underlying cardiac function. Historically, adjunctive use of furosemide has been common, but this is only justified if pulmonary edema is precipitated. If the renal function has remained stable and urine output is adequate after 8 to 12 hours of rehydration, an intravenous bisphosphonate (pamidronate 60 mg, or ibandronate 2 mg) may be safely infused [8]. Following bisphosphonate administration, the circulating PTH levels may be unreliable (elevated) for up to 6 months, so it is worth making sure the lab has received the original sample and that it is suitable for PTH analysis. Bisphosphonate inhibits osteoclast function, thus decreasing the bony contribution to circulating calcium. This leads to a gradual reduction in serum calcium, with a nadir often on the 4th or 5th day following administration. If the calcium level starts to climb again by the 6th or 7th day, a second infusion may be appropriate. If the patient has severe circulatory compromise or arrhythmia, a more rapid reduction in serum calcium may be necessary, and addition of calcitonin 200 to 400 U every 6 to 8 hours by subcutaneous injection may lead to a more rapid control of calcemia. Furthermore, if the underlying cause of the hypercalcemia is known, then a specific treatment targeting the underlying condition may be used, for example high-dose prednisone for sarcoidosis, or chemotherapy for myeloma.

Management of Primary Hyperparathyroidism

Surgical Management

Surgical resection of one or more enlarged parathyroid glands remains the definitive means of curing primary hyperparathyroidism. At neck exploration, an experienced surgeon will be able to localize and remove the parathyroid adenoma(s) 95% of the

time, in subjects without prior neck surgery. The specific complications of surgery are few, the main one being transient postoperative hypocalcemia. In a small number of individuals, perhaps those with the most elevated PTH or alkaline phosphatase, there can be a prolonged period of hypocalcemia, requiring oral α-calcidol or calcitriol therapy for several weeks. This is termed "hungry bones" syndrome and may reflect a rapid remineralization of bone, with the high turnover state of hyperparathyroidism being gradually reversed. Following successful parathyroid surgery, subjects may increase bone mineral content by 10% or more, over several years. In addition some studies have suggested an improved survival after successful parathyroid surgery [9, 10]. Because of the high success of neck exploration in experienced hands, there is no uniform approach to preoperative neck imaging. However, many institutions routinely employ technetium 99m (Tc) sestamibi radionuclide scanning in combination with a second technique, often high-definition ultrasound or magnetic resonance imaging (MRI). The justification for this is that with a positive preoperative localization the surgeon may be able to perform a focused or unilateral neck exploration, thus shortening the length of surgery, operative morbidity, and hospital stay. Furthermore, there is little doubt that preoperative imaging improves outcome in patients who have undergone prior neck surgery. Over recent years, minimally invasive or focused surgical approaches, with the use of endoscopic instrumentation or intraoperative PTH assay have become popular in many centers. A fuller elucidation of surgical aspects of primary hyperparathyroidism is provided in several recent review articles [11–13].

With the more widespread recognition of asymptomatic primary hyperparathyroidism, particularly in an elderly and sometimes frail population, the indications for parathyroid surgery have become a key issue. The recommendations of the 1990 National Institutes ofd Health (NIH) consensus conference on the management of asymptomatic primary hyperparathyroidism were recently updated [14, 15], and these are shown in Table 18.1. Any recommendation for surgery must be taken against the results of a key study [16], showing that only 27% of patients with asymptomatic primary hyperparathyroidism who had no specific intervention developed an indication for surgery over a 10-year follow-up period. This suggests that conservative management, with regular monitoring of serum calcium and renal function, may be a satisfactory approach for many people with asymptomatic primary hyperparathyroidism.

Medical Management

Any specific medical intervention for primary hyperparathyroidism needs to be set against the background, discussed above, that with no therapy, more than 70% of subjects with asymptomatic primary hyperparathyroidism remain well over a 10-year follow-up period. Medical therapies, therefore, need to be reserved for patients with symptoms or specific complications who are a high operative risk, have not been cured following one or more operations, or who are unwilling to consider parathyroid surgery. Several studies have demonstrated that estrogen-containing

hormone replacement therapy (HRT) in postmenopausal women with primary hyperparathyroidism has a modest effect in reducing serum calcium (by about 0.2 mmol/L [0.8 mg/dL] with higher estrogen doses), lowering markers of bony turnover and improving bone mineral density (BMD) [17]. In addition, similar findings have been made for the selective estrogen receptor modulator (SERM) raloxifene, with a mean decrement in serum calcium of 0.1 mmol/L (0.4 mg/dL), but with the advantage of a more favorable safety profile than estrogen HRT [18].

Calcimimetics are a novel class of compound that decrease parathyroid PTH release by modulating calcium-sensing receptor function. Studies of primary hyperparathyroidism with one such compound, cinacalcet, appear to be promising, with moderate reductions in serum calcium (a mean 0.35 mmol/L [1.4 mg/dL] decrement) and PTH, maintained over a 6-month period [19]. Currently, more long-term data are needed as to the efficacy of calcimimetics in improving the outcomes of mild or asymptomatic primary hyperparathyroidism. Although an unlicensed indication at present, the use of cinacalcet may be considered in symptomatic individuals who are unfit or unwilling to undergo parathyroid surgery. Daily oral alendronate has been shown to be effective in improving BMD in patients with primary hyperparathyroidism; however, there is no sustained effect on calcemia or PTH levels [20].

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Chapter 18
Differentiation of Primary Hyperparathyroidism for Familial Benign Hypocalciuric Hypercalcemia

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Case Presentation

An 84-year-old Caucasian woman was discovered on routine testing to have raised serum calcium of 2.63 mmol/L (10.52 mg/dL). No symptoms of thirst, heartburn, indigestion, bone pain, or constipation were elicited. She denied mood changes or a history of kidney stones. Dietary history revealed a normal mixed diet, including daily dairy products. She smoked 10 cigarettes daily.

Her past medical history was significant for a squamous cell carcinoma of the vulva, treated 10 years previously with a radical vulvectomy and external beam radiotherapy. Medications included furosemide 20 mg daily, naproxen 250 mg twice daily, and amitriptyline 25 mg at night. Family history was negative. A physical examination was unremarkable.

Her laboratory data were as follows (with reference ranges):

Total serum calcium = 2.63 mmol/L (2.12–2.60)
Albumin = 37 g/L (34–50)
Ionized calcium = 1.38 mmol/L (1.19–1.37)
Phosphorus = 1.00 mmol/L (0.8–1.44)
Magnesium = 0.98 mmol/L (0.7–1.00)
Alkaline phosphatase = 65 U/L (35–120)
Parathyroid hormone (PTH) = 111 ng/L (10–65)
Serum creatinine= 125 μmol/L (70–145)
Thyroid-stimulating hormone (TSH) = 0.95 mIU/L (0.3–4.7)
24-hour urine Ca = 2.6 mmol/24 h (2.5–7.5)
24-hour urine Cr = 5.1 mmol/24 h (7.0–17.7)
24-hour urine vol = 1164 mL
Spot calcium clearance/creatinine clearance ratio = 0.011
25-OH Vitamin D = 42 nmol/L (15–75)

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How the Diagnosis Was Made

The differential diagnosis in an elderly cigarette smoker with asymptomatic mild hypercalcemia was wide, but an elevated PTH level narrowed the diagnosis substantially to either primary hyperparathyroidism or familial benign hypocalciuric hypercalcemia (FBHH), in the absence of lithium use. More than 95% of individuals with FBHH have a 24-hour urine calcium excretion of less than 5 mmol, with 75% having a calcium excretion of less the 2.5 mmol/day. Her low urine calcium clearance to creatinine clearance ratio of 0.011 was strongly suggestive of FBHH, particularly given her concomitant furosemide use, which may act to increase urinary calcium excretion. The threshold calcium clearance to creatinine clearance ratio for diagnosis of FBHH being 0.01 or less, with most patients with primary hyperparathyroidism having a value in excess of 0.01. In the elderly, coexisting vitamin D or dietary calcium deficiency can lead to a "falsely low" urine calcium excretion in the presence of primary hyperparathyroidism, but she was vitamin D replete. The serum magnesium, which was close to the upper limit of normal, is also very typical of FBHH in this case, whereas serum magnesium is often low-normal or slightly below the reference range in primary hyperparathyroidism. Normal bony turnover, as reflected by alkaline phosphatase also supported FBHH rather than primary hyperparathyroidism. In FBHH, the plasma PTH is most frequently within the normal range, but in about 20% of cases there is modest elevation of the circulating PTH, to less than twofold the upper limit of normal. These individuals may have a relatively low calcium intake. Genetic testing of the calcium-sensing receptor gene was not requested, as only about 70% of patients with typical FBHH have mutations. Thus, in the majority of cases a diagnosis of FBHH needs to be reached on clinical grounds. This patient had very mild hypercalcemia with no complication, so there was little question of the patient proceeding to parathyroid surgery even if the diagnosis was revised to primary hyperparathyroidism (Table 18.1 for guidelines for surgery in asymptomatic primary hyperparathyroidism).

Diagnosis

(Familial) benign hypocalciuric hypercalcemia (FBHH).

Table 18.1 Guidelines for surgical intervention in asymptomatic primary hyperparathyroidism

Indication	Recommendation for surgery if:
Serum calcium	>0.25 mmol/L [>1 mg/dL] above reference range
24-hour urine calcium	>10 mmol/day [>400 mg/day]
Creatinine clearance	Reduced by 30% from expected
Bone mineral density	T-score <–2.5 at any site
Age	<50 years
Other	Erratic, undesirable, or uncertain medical surveillance

Lessons Learned

1. Familial benign hypocalciuric hypercalcemia can present as asymptomatic hypercalcemia at any age. It is caused by dominant mutations in the calcium-sensing receptor gene, and parathyroid surgery is unnecessary.
2. Urinary calcium clearance to creatinine clearance is the key investigation in differentiating FBHH from primary hyperparathyroidism
3. It is essential to assess vitamin D status in the elderly or institutionalized with hypercalcemia. Coexisting vitamin D deficiency can mask hypercalciuria in primary hyperparathyroidism.

Suggested Readings

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Multiple-Choice Questions

1. A high plasma PTH can be associated with hypercalcemia in the following conditions:

   A. Metastatic parathyroid carcinoma
   B. Milk-alkali syndrome
   C. Sarcoidosis
   D. Lithium ingestion
   E. Familial benign hypocalciuric hypercalcemia

   Answers: A. True. B. False. C. False. D. True. E. True.

2. Primary hyperparathyroidism may occur in association with the following conditions:

   A. Chronic renal failure
   B. Vitamin D deficiency
   C. Gastrinoma
   D. Autoimmune polyendocrine syndrome
   E. Sjögren's syndrome

   Answers: A. False. B. True. C. True. D. False. E. False.

3. Important investigation in FBHH includes the following:

   A. Measurement of 25 OH vitamin D
   B. Measurement of 1, 25$(OH)_2$ D
   C. Measurement of 24-hour urine calcium and creatinine
   D. Measurement of serum and urine calcium in the first degree relatives
   E. Electrocardiogram

   Answers: A. True. B. False. C. True. D. True. E. False.

4. The following features can be seen in FBHH:

   A. Band keratopathy
   B. Hypertension
   C. Acute pancreatitis
   D. Proximal myopathy
   E. Chondrocalcinosis

   Answers: A. False. B. False. C. True. D. False. E. True.

Chapter 19
Management and Investigation of Acute Hypercalcemia

Suresh Vaikkakara, Chankramath S. Arun, and R. Andrew James

Case Presentation

A 57-year-old woman presented acutely unwell with a 3-week history of sore eyes, on a background of fatigue and polyuria for 6 months. There was a 3-day history of anorexia. She denied weight loss, hemoptysis, or hematochezia. There was a history of hypertension treated with bendroflumethiazide 5 mg daily and atenolol 50 mg daily. She smoked one pack of cigarettes daily. Examination revealed bilateral limbal white deposits of calcium in the cornea and congestion of the bulbar conjunctiva (Fig. 19.1). The blood pressure was 135/76 mm Hg, with pitting ankle edema. There was no cachexia, lymphadenopathy, hepatomegaly, or other abnormal signs.

Her laboratory data were as follows (with reference ranges):

Serum calcium = 3.8 mmol/L (2.12–2.60)
Serum albumin = 40 g/L (34–50)
Serum urea = 16.3 mmol/L (2.5–6.4)
Serum creatinine = 616 μmol/L (65–105)
Arterial pH = 7.58 (7.35–7.45)
Serum bicarbonate = 37 mmol/L (22–30)
Serum alkaline phosphatase = 222 IU/L (35–120)
Urine dipstick-negative for blood, protein, glucose
Chest x-ray was normal

Blood was drawn for a parathyroid hormone (PTH) level, and the patient was managed with intravenous saline 0.9%, 3 L over 18 hours. An ultrasound of the abdomen and pelvis, obtained to exclude renal tract obstruction, was reported as normal. The following morning the serum calcium was 3.2 mmol/L and the creatinine 410 μmol/L. Intravenous pamidronate 60 mg was administered. The admission PTH level became available: 4 ng/L (reference range 10–65). Malignancy was the

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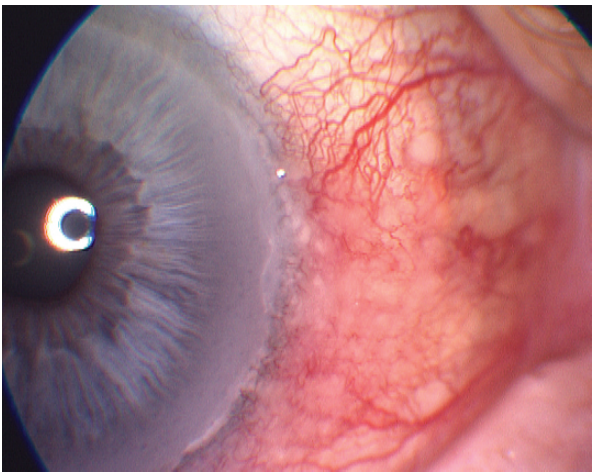

Fig. 19.1 Corneal calcification (band keratopathy) in hypercalcemia

likely diagnosis, but an isotope bone scan and serum tumor markers were normal. A computed tomography (CT) scan of chest and upper abdomen was normal. A plasma PTH-rP, the tumor product that mediates humoral hypercalcemia of malignancy, was requested and later came back within normal limits. On close questioning, the patient admitted daily use of calcium and magnesium carbonate tablets (Proprietary brand – Rennie) for dyspepsia. Following prescription of a Proton pump inhibitor (PPI), there was no return of hypercalcemia over 5 years of follow-up.

Diagnosis

Milk alkali syndrome due to use of calcium-containing antacid, exacerbated by thiazide use.

How the Diagnosis Was Made

The leading cause of severe hypercalcemia in a 57-year-old smoker with a suppressed PTH is malignancy. However, there was no physical sign of malignancy, and PTH-rP, other tumor markers, and imaging for malignancy was negative. The presence of alkalosis at presentation in the face of significant renal failure was suggestive of milk-alkali syndrome. This disorder, also known as calcium-alkali syndrome, develops in individuals with a habitual large intake of calcium carbonate, in whom a concomitant alkalosis impairs renal calcium excretion. In this instance, the alkalosis and impairment of renal calcium excretion was compounded by thiazide use. The patient was reluctant to admit to ingestion of antacids, which she had been purchasing over the counter. These are often packaged like confectionery and may

not be perceived as medication. However, after a PPI was prescribed, her calcium and PTH levels became normal and remained so over 5 years of follow up.

Lessons Learned

1. Decompensated or disequilibrium acute hypercalcemia most often has multifactorial etiology. A combination of milk-alkali syndrome and thiazide use in this instance.
2. The plasma PTH level is a key initial investigation in hypercalcemia.
3. Advanced malignancy is the most likely diagnosis in acute hypercalcemia presenting with a suppressed PTH. Early evaluation of such patients must be geared to a rapid diagnosis.
4. Circulating PTH-rP is found in humoral hypercalcemia of malignancy and may disclose an underlying covert tumor.
5. Severe hypercalcemia is managed with rehydration therapy followed, after several hours, by bisphosphonate infusion.
6. Patients with milk-alkali syndrome are often so habituated to antacid use that they may not consider use of antacid tablets as medication.

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Questions

1. True or false: Milk alkali syndrome

   A. is now most commonly caused by excess intake of calcium carbonate.
   B. is best treated with hemodialysis against a low calcium dialysate.
   C. presents with a classical triad of hypercalcemia, alkalosis, and renal failure.
   D. PTH levels could be high or normal.
   E. Renal function always returns to normal on treatment.

   Answers: A. True. B. False. C. True. D. False. E. False.

2. True or false: In patients with acute hypercalcemia

   A. if serum calcium is more than 3.5 mmol/L, the first-line treatment is parenteral bisphosphonate followed by rehydration.
   B. intravenous bisphosphonate takes up to 18 hours to have maximum effect.
   C. thiazide diuretics reduce urinary calcium excretion.
   D. calcimimetic agents inhibit PTH release by its action on the calcium-sensing receptor.
   E. the diagnosis of malignancy is most commonly associated with skeletal metastases.

   Answers: A. False. B. False. C. True. D. True. E. False.

3. True or false: Medications useful in treating acute hypercalcemia include

   A. glucocorticoids.
   B. calcitonin.
   C. plicamycin.
   D. dihydropyridine calcium channel blockers.
   E. thiazide diuretics.

   Answers: A. True. B. True. C. True. D. False. E. False.

4. True or false: In humoral hypercalcemia of malignancy

   A. squamous cell carcinoma of lung is the most common cause.
   B. hypercalcemia is most often due to tumor production of PTH-rP.
   C. both PTH and PTH-rP will be elevated in all patients.
   D. there is no response to hydration and treatment with bisphosphonates.
   E. there is an association with good long-term survival following appropriate therapy.

   Answers: A. True. B. True. C. False. D. False. E. False.

Chapter 20
Evaluation of Complex Primary Hyperparathyroidism

Ee Lin Lim and Simon H.S. Pearce

Case Presentation

A 24-year-old woman was evaluated for persistent symptoms of stomach pain and vomiting following surgical treatment for hyperparathyroidism 2 years previously. She had undergone a neck exploration with excision of an enlarged left upper parathyroid gland; histology reported parathyroid hyperplasia. She was fatigued, had a poor appetite, and complained of intermittent constipation. She denied thirst or polyuria. She had a long history of mental illness, having been on lithium carbonate treatment for more than 6 years. Her 52-year-old father was currently being evaluated for hypercalcemia at another center. She was also taking omeprazole 20 mg daily. Examination showed a thin but otherwise healthy young woman with a neck scar.

Her laboratory data were as follows (with normal ranges):

Serum calcium = 2.91 mmol/L (2.12–2.60)
Serum albumin = 38 g/L (NR 34-50)
Ionized calcium = 1.56 mmol/L (NR 1.19–1.37)
Serum magnesium = 0.76 (NR 0.7–1.0)
Serum creatinine = 78 μmol/L (NR 70–140)
Serum alkaline phosphatase = 128 U/L (NR 35–140)
Urine calcium clearance to creatinine clearance ratio = 0.006 (on lithium)
Urine calcium clearance to creatinine clearance ratio = 0.024 (7 days off lithium)
24-hour urine calcium excretion = 7.8 mmol (7 days off lithium)
Plasma PTH = 238 ng/L (NR 10–60)
Serum gastrin 220 ng/L (NR 1–100) while taking omeprazole

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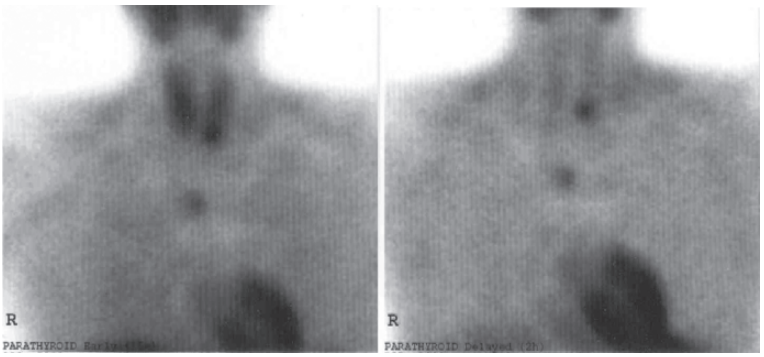

Early image 2hr image

Fig. 20.1 Sestamibi scan with early and late thyroid "wash out" images, showing left lower and mediastinal parathyroid glands

A sestamibi scan was obtained (Fig. 20.1). The thoracic focus of sestamibi uptake was found to correspond to an anterior mediastinal mass on contrast-enhanced magnetic resonance imaging (MRI). The patient underwent a repeat neck and mediastinal exploration, with excision of two enlarged parathyroid glands in the neck and an ectopic hyperplastic parathyroid gland in her mediastinum. Her serum calcium was normal after the operation and her symptoms improved. Subsequently, genetic screening confirmed a heterozygous mutation (*H*181*R*) in the *MENIN* gene, confirming a diagnosis of multiple endocrine neoplasia type I (MEN-I). Three years later, her gastrin level had increased to 880 ng/L and a 2-cm malignant gastrinoma of the neck of pancreas was localized and excised.

How the Diagnosis Was Made

Recurrent hypercalcemia following neck surgery with parathyroid hyperplasia reported as the initial histology in a 24-year-old with a family history of hypercalcemia was strongly suspicious of a MEN-I or familial benign hypocalciuric hypercalcemia (FBHH). Hyperparathyroidism-jaw tumor syndrome, MEN-II, or familial isolated hyperparathyroidism were lesser possibilities. Historically, about 10% of subjects who remain hypercalcemic following neck exploration have had FBHH as the underlying diagnosis [1]. As lithium treatment produces hypocalciuria, which would mimic FBHH, it was essential to find out what her urine calcium excretion was without lithium. This showed a near quadrupling of her urinary calcium excretion during 7 days off lithium treatment, confirming primary hyperparathyroidism as the underlying diagnosis. This was consistent with her high levels of PTH, which are almost never more than twice the upper limit of the normal range in FBHH. It should be noted that sestamibi scan cannot distinguish FBHH from primary hyperparathyroidism, as some degree of parathyroid hyperplasia may

be seen in FBHH, particularly when PTH is elevated. More than 80% of subjects with MEN-I have germline mutations in the *MENIN* gene, and this was used to confirm the diagnosis in her case.

Lessons Learned

1. Lithium treatment lowers urinary calcium excretion, as well as inducing transient hypercalcemia and permanent hyperparathyroidism in some individuals.
2. Measurement of urinary calcium excretion is essential to exclude FBHH.
3. Physicians need to be aware of the possibility of familial hyperparathyroid disorders such as MEN-I, MEN-II, and hyperparathyroidism-jaw tumor syndrome, so that genetic testing can be offered when appropriate
4. Parathyroid imaging studies, including the mediastinum, are essential in individuals undergoing second surgery for hyperparathyroidism.

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Multiple-Choice Questions

1. In the MEN-I syndrome:

   A. Hyperparathyroidism is associated with low urinary calcium excretion.
   B. The age of onset of hypercalcemia is often in the twenties to thirties.
   C. Disease is inherited in autosomal recessive fashion.
   D. Hyperparathyroidism is due to four-gland hyperplasia.
   E. Parathyroid carcinoma is common.

   Answers: A. False. B. True. C. False. D. True. E. False.

2. In primary hyperparathyroidism, the following biochemistry is typical:

   A. Hypophosphatemia
   B. Hypomagnesemia
   C. Hypochloremic acidosis
   D. Normal urinary phosphate excretion
   E. Raised alkaline phosphatase

   Answers: A. True. B. False. C. False. D. False. E. True.

3. Indications for a surgical approach in primary hyperparathyroidism are:

   A. Young age
   B. Lack of symptoms
   C. Dementia
   D. Urinary calcium excretion of <5 mmol (200 mg) per 24 hours
   E. T score of <–2.5 at any bony site on dual-energy x-ray absorptiometry (DEXA)

   Answers: A. True. B. False. C. False. D. False. E. True.

4. The following are well-described complications of primary hyperparathyroidism:

   A. Gallstones
   B. Renal impairment
   C. Osteitis fibrosa cystica
   D. Arterial hypertension
   E. Pseudogout

   Answers: A. False. B. True. C. True. D. True. E. True.

Chapter 21
Evaluation of Hypercalcemia in Infancy

Reena Thomas, Murthy Korada, and Timothy D. Cheetham

Case Presentation

A male neonate presented with drowsiness and failure to feed on day 4 of life. An infection screen was negative but a biochemical profile revealed a serum calcium of 4.9 mmol/L. He was the second child of healthy nonconsanguineous parents. He was born at term, weighing 3.2 kg following an uneventful delivery. His biochemical abnormalities were initially attributed to a laboratory error, but the following morning the tests were repeated (with reference range):

Serum calcium = 5.2 mmol/L (2.2–2.7) 20.8 mg/dL (8.8–10.8)
Ionized calcium = 2.1 mmol/L (1.19–1.37) 8.4 mg/dL (4.76–5.48)
Serum magnesium = 1.21 mmol/L (0.7–1.0) 2.94 mg/dL
Alkaline phosphatase = 330 IU/L (0–300)
Serum parathyroid hormone (PTH) = 1470 ng/L (10–60)
Urine calcium/creatinine ratio = 1.96 mmol/mmol (normal <0.74)

A skeletal survey showed widespread bony undermineralization with an irregular moth-eaten periosteal region (Figure 21.1).

The baby was treated with intravenous fluids and a low calcium feed. Ultrasound of the neck and kidney was reported to be normal. The mother was found to have modest hypercalcemia (2.66 mmol/L [2.12–2.60]) but the father was normocalcemic (2.60 mmol/L). Both parents had normal PTH levels and a low urinary calcium excretion (calcium clearance to creatinine clearance ratios <0.01). A presumptive diagnosis of neonatal severe hyperparathyroidism (NSHPT) was made. On days 7 and 10, pamidronate 1 mg/kg was infused to control hypercalcemia. A four-gland parathyroidectomy was performed on day 24 of life. There was immediate and profound hypocalcemia, which was treated with intravenous calcium infusion and alpha-calcidol (1α-hydroxyvitamin D_3). Histology showed parathyroid hyperplasia. Mutational analysis revealed compound heterozygosity for

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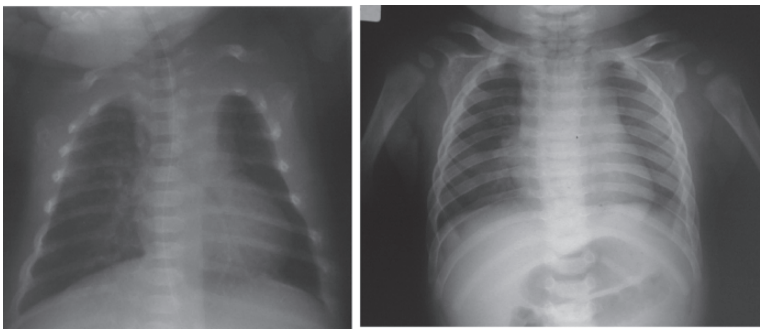

Before parathyroidectomy Age 9 months

Fig. 21.1 Effects of neonatal severe hyperparathyroidism on the skeleton, including undermineralisation, ribcage deformity and subperiosteal resorption

two inactivating mutations ($R680C$ and $C60F$) of the calcium-sensing receptor gene, confirming the diagnosis of neonatal severe hyperparathyroidism. The child remains well, now in his fourth year of life, with normal development on lifelong alpha-calcidol.

How the Diagnosis Was Made

Hypercalcemia is uncommon in the neonatal period, and profound hypercalcemia to this degree in the first days of life is very unusual. Key investigations at this stage included a serum PTH with a raised level excluding iatrogenic causes, malignancy, and conditions such as hypophosphatasia. The PTH levels would have been unrecordable in Jansen's disease where hypercalcemia is the consequence of activating mutations of the PTH/PTH-rP receptor. Primary hyperparathyroidism due to a parathyroid adenoma has not been described in the neonatal period and would not be expected to cause such high PTH levels. The focus, therefore, moved to maternal and paternal biochemistry; while only the mother had an elevated calcium level, both parents had a very low 24-hour urinary calcium clearance, suggesting that they may be heterozygous for calcium-sensing receptor mutations with the infant inheriting the two abnormal alleles.

Lessons Learned

1. The differential diagnosis of hypercalcemia in the neonatal period includes hypervitaminosis D, Williams-Beuren syndrome, FBHH, neonatal severe hyperparathyroidism, secondary hyperparathyroidism from maternal hypocalcemia, high bony turnover states, hypophosphatasia, and idiopathic hypercalcemia of infancy.

2. Neonatal severe hyperparathyroidism is characterized by complete insensitivity of the parathyroid glands to extracellular calcium due to both copies of the calcium-sensing receptor gene being mutated. PTH secretion is effectively autonomous and the hypercalcemia is extreme.
3. The management of NSHPT includes early diagnosis, total parathyroidectomy, followed by lifelong vitamin D/calcium supplementation. Bisphosphonate therapy can be used to control the hypercalcemia while surgery is being planned.

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Multiple-Choice Questions

1. The following may be associated with hypercalcemia in early life:

   A. Maternal type 1 diabetes
   B. Subcutaneous fat necrosis
   C. Candidiasis
   D. Skeletal dysplasia
   E. A raised alkaline phosphatase

   Answers: A. False. B. True. C. False. D. True. E. True.

2. Important investigations in the hypercalcemic baby include:

   A. Detailed cardiac assessment
   B. Measurement of maternal calcium concentrations
   C. Studies of the elastin gene
   D. Renal ultrasound
   E. Determination of alkaline phosphatase levels

   Answers: A. True. B. True. C. True. D. True. E. True.

3. A diagnosis of FBHH in an apparently well neonate is unlikely if:

   A. Magnesium concentrations are low
   B. Plasma PTH concentrations are undetectable
   C. Maternal total calcium concentrations are normal
   D. Mother recently underwent total parathyroidectomy
   E. The baby has nephrocalcinosis

   Answers: A. True. B. True. C. False. D. False. E. True.

Part VII
Metabolic Bone Diseases

Introduction

Mone Zaidi

The constant restructuring or remodeling of the skeleton in adult life requires an exactingly fine balance between the processes of bone resorption and bone formation. These two activities are closely coupled both in time and space so that precisely the same quantity of bone is deposited as has been previously removed [1]. Osteoclasts, formed from hematopoietic stem cell precursors in the bone marrow, are unique in their ability to resorb bone (Fig. VII.1). They do so by secreting acid and proteolytic enzymes that dissolve the hydroxyapatite and digest the matrix, respectively. Osteoblasts subsequently lay down type 1 collagen and which is then mineralized. Bone is lost, leading to an osteoporotic skeleton, when osteoclastic bone resorption exceeds osteoblastic bone formation in either absolute or relative terms. An absolute increase of bone resorption occurs during hypogonadal states, and in thyroid and parathyroid disease. These conditions result from increased osteoclast formation, function, or survival. In contrast, as a consequence of aging and with corticosteroid therapy, osteoblasts are rendered dysfunctional, and fall behind normal or even slightly reduced osteoclastic bone resorption. These two forms are termed high-turnover and low-turnover osteoporoses, respectively.

Osteoporosis is a public health problem that is now so common that it poses a major health hazard [2]. It affects men and women alike, but women undergo a phase of accelerated bone loss across the menopausal transition, and therefore hit the fracture threshold earlier than men. However, as the population continues to get older, we are likely to diagnose osteoporosis in both men and women alike. Osteoporotic fractures in postmenopausal women far exceed the incidence of heart disease, breast cancer and stroke combined (Fig. VII.2). Yet, only 3% to 5% of hip and wrist fracture patients are ever diagnosed with osteoporosis. Only 12% of patients with established vertebral fractures ever get a diagnosis of osteoporosis, and 2% are treated.

Currently, we use the bone densitometer to measure bone mineral density at the hip, spine and wrist. We also follow the World Health Organization (WHO) guidelines for diagnosing osteoporosis on the basis of T-scores, which represent

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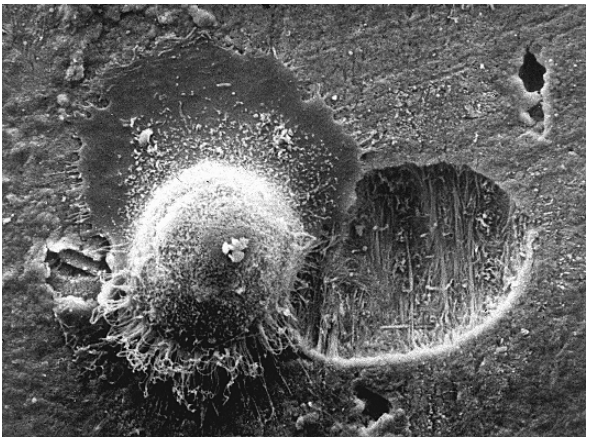

Fig. VII.1 A rat osteoclast resorbing devitalized cortical human bone

the number of standard deviations below or above the mean of a young reference population of women. This epidemiologic definition has drawbacks, and has led to increasing interest in developing clinical criteria for determining who is at a high risk of fracture (Table VII.1). Equally important has been the realization that microarchitectural deterioration of bone precedes a decline in bone mineral density (Fig. VII.3). Thus, there is a new trend toward identifying rapid bone losers at the very outset by measuring markers of bone resorption, such as the collagen degradation product N-telopeptide in the urine. A number of therapeutic agents have been developed for osteoporosis, but the armamentarium still remains small compared to similarly prevalent diseases, such as diabetes and hypertension. There are two therapeutic strategies. One is to inhibit osteoclast formation or function using an antiresorptive agent, which, by suppressing bone resorption, gives formation a better chance to fill preexisting resorption cavities. The other strategy is to use a direct stimulator of osteoblastic bone formation, an anabolic agent, which acts irrespective of the rate of resorption.

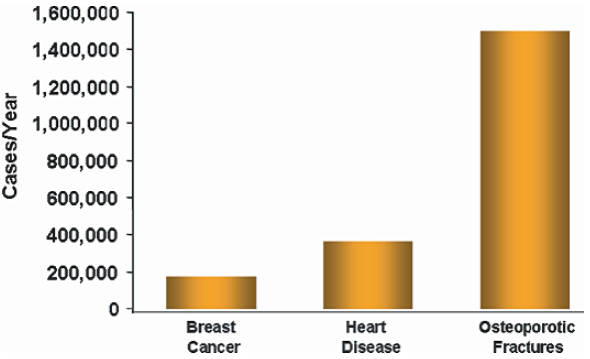

Fig. VII.2 High incidence of osteoporotic fractures. (From Women's Health Facts and Figures. Washington, DC: ACOG, 2000)

Table VII.1 Clinical risk factors for a fracture

Low bone mineral density
Prior fracture after age 50
Maternal history of prior fracture after age 50
Age > 65 years
Low body mass index (BMI) or body weight
Smoking
Corticosteroid usage
Secondary causes

From the National Osteoporosis Foundation.

Currently used bisphosphonates reduce fracture risk by inhibiting the activity of mature osteoclasts [3]. Their use, however, is fraught with compliance and tolerability issues, and this has led to the rapid development and availability of new bisphosphonates. The designer estrogen raloxifene induces hot flashes and has an unacceptably high rate of deep vein thrombosis. Estrogen is highly regarded for postmenopausal symptoms, but doses used for skeletal protection increase breast cancer risk. Parathyroid hormone is the only approved anabolic agent used as a daily subcutaneous injection, but only for end-stage bone disease. Much research is focused, therefore, on the identification of new targets both on the osteoblast and osteoclast.

Poor removal of bone or osteopetrosis occurs when the osteoclast is rendered dysfunctional. Osteopetroses are generally congenital, and result from mutations of molecules that are necessary for bone resorption. For example, a mutation in the gene for a critical osteoclastic enzyme, cathepsin K, results in pyknodysostosis. The latter is characterized by short stature and osteopetrosis, with a high fracture risk despite the accompanying high bone mass because of inefficient skeletal repair. Another way by which skeletal integrity is maintained is by constant mineralization of the resorbed skeleton. Hydroxyapatite is deposited by the osteoblast, but the supply of calcium is ensured by its vitamin D–dependent absorption from the gut. Thus, vitamin D deficiency causes poor skeletal mineralization or osteomalacia. A negative calcium balance also activates the calcium-sensing receptor to increase the secretion of parathyroid hormone (PTH) from the chief cells of the parathyroid gland. PTH in turn stimulates the renal enzyme 1α-hydroxylase to convert 25-OH-vitamin D to activate 1,25-dihydroxyvitamin D. PTH also has direct

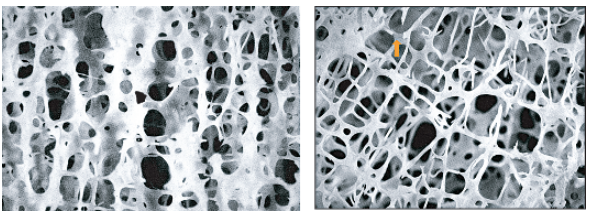

Fig. VII.3 Scanning electron micrographic images showing early microarchitectural deterioration of bone. Bone without trabeculae is 16–fold less strong than bone with trabeculae. (From David Dempster)

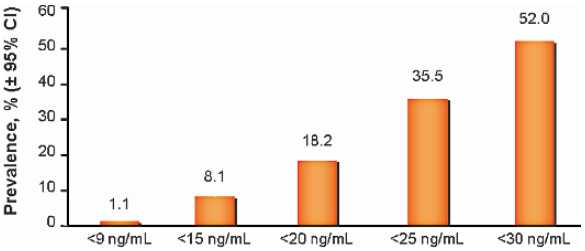

Fig. VII.4 Low vitamin D levels in North American women. [From Holick [4]]

effects on the skeleton resulting in excessive resorption and bone loss. Thus, vitamin D deficiency results not only in osteomalacia, but also in secondary hyperparathyroidism. Both diseases are reversed by high-dose vitamin D supplementation. It is important to consider, however, that vitamin D deficiency is profoundly underdiagnosed (Fig. VII.4) [4]. It confounds the diagnosis of osteoporosis, as it is impossible to differentiate mineral loss in osteoporosis from poor mineralization in vitamin D deficiency on bone densitometry. Secondary hyperparathyroidism also results from renal failure. In this instance, poor phosphate excretion and hyperphosphatemia lowers serum calcium to maintain the Ca × P product, and hence activates the parathyroid calcium sensor to release PTH. PTH has significant skeletal effects ranging from typical radiologic patterns of bone loss to life-threatening arterial calcification and calciphylaxis. Phosphate binders and calcimimetic agents (allosteric activators of the parathyroid calcium sensing receptor) are utilized together with 1,25-dihydroxyvitamin D to control the hyperphosphatemia and prevent skeletal and extraskeletal complications.

When bone formation becomes erratic in both time and space compared with resorption, the condition is termed Paget's bone disease. Here, the primary defect is in the osteoclast, but formation somehow becomes excessive and autonomous, resulting in severe focal osteosclerosis. Note that osteosclerosis and osteopetrosis, which both result in dense skeletons, are different diseases, the former resulting from excessive bone formation and the latter arising from poor resorption. Paget's disease is usually treated by a bisphosphonate that suppresses osteoclastic bone resorption and thereby osteoblastic bone formation. While the precise pathophysiology is unclear, a genetic predisposition and prior measles virus infection has been implicated as being pathophysiologic.

Finally, acute, rapid, and severe bone loss (ARSBL) [5] occurs when osteoblastic bone formation falls precipitously or bone resorption dramatically increases. In these conditions, microcracks that occur upon terrestrial impact are not repaired, resulting in a high fracture incidence despite a normal bone mineral density. For example, 65% patients fracture within 6 months of a liver transplant. Major culprits that reduce bone formation include high-dose glucocorticoid therapy, the immunosuppressants cyclosporin A and FK506, stroke and immobilization, and microgravity. Diseases that cause a sharp stimulation of bone resorption include

gonadectomy in men and women, chemical menopause, and hormone replacement therapy (HRT) withdrawal.

Thus, metabolic bone diseases, particularly osteoporosis and vitamin D deficiency are increasingly common, but poorly diagnosed. Clinical research focuses on establishing criteria for early detection and well as testing new agents for human use. The use of genetically manipulated mouse models and Affymetrix gene arrays has allowed the identification of novel targets for potential interventions in the future.

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Chapter 22
Osteoporosis Due to Hormonal Withdrawal: Common Mistakes

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Objectives

1. To understand the presentation of osteoporosis across the menopausal transition
2. To appreciate the high rates of bone loss, which occur upon hormonal withdrawal

Case Presentation

A 52-year-old woman executive presented to her primary care physician with a T-score of –1.7 by heel ultrasonography. She was otherwise healthy and was a regular tennis player, who took one multivitamin tablet per day, together with other health pills. There was a family history of breast cancer, but prior mammograms were normal. There was no history of cortico steroid intake. Menarche was at 13 years. The patient indicated that she had been amenorrheic for 2 years during her stint as a ballet dancer. However, she had given up dancing at age 18, and since had normal menses. Physical examination was unremarkable. Her blood work revealed normal electrolytes, in particular a serum calcium 9.8 mg/dL, (normal range 8.5–10.5), and a 25-OH-vitamin D of 33 ng/dL (normal sufficient: >32 ng/dL). Her primary care physician referred her for a central dual-energy x-ray absorptiometry (DXA). Her T-scores were as follows: lumbar spine L1-L4 of −1.9 and total left hip −1.6 (non dominant). The physician prescribed 1200 mg calcium citrate and 800 IU vitamin D qd, and asked her to return for a central DXA 2 years later. But she returned to the physician's office 6 months later complaining of irregular menses; her last menstrual period was 6 months ago. The primary care physician reassured her that she was entering normal menopause, and no further workup was required.

About 18 months later the repeat DXA showed considerably lower T scores: −2.2 at L1-L4 and −1.7 at total left hip. The patient was concerned, and asked for therapy. She was also having significant hot flashes and other postmenopausal

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symptoms. Without further testing, she was offered hormone replacement therapy (HRT) (Premarin plus Provera) and was told to return for further workup in 1 year. She also consulted a gynecologist, who ratified the decision.

One year later, her DXA scan showed a T-score of −2.3 at L1-L4 and −1.9 at total left hip. The patient was reassured. At that visit, the physician noted that her serum calcium was borderline high at 10.5 mg/dL, and decided to see her again in 6 months. The serum calcium remained stable and the patient was seen 2 years later. At this point, her DXA had shown a marked decline at the hip (T score of −2.2) while the spine had remained at −2.3. Further workup for secondary causes revealed a serum PTH of 180 pg/mL (normal range 15–65), and calcium of 11.0 mg/dL. A parathyroid scan showed a right upper parathyroid adenoma, which was excised by radio-guided surgery. The patient remained well and a DXA scan repeated 2 years later showed T scores of −2.1 at L1-L4 and −2.0 at total left hip. Thereafter, the patient remained on HRT, and had DXA scans every 2 years, which showed stable bone mineral densities (BMDs) in the osteopenic range, until about 2002.

Upon publication of the results of the Women's Health Initiative, and considering that the she had a family history of breast cancer, the patient asked if she could discontinue the estrogen-progesterone combination. Her physician agreed, but as her BMD was stable at both sites (−1.9 at L1-L4 and −1.8 at the total left hip), her physician decided to place her on only calcium and vitamin D. This decision was based on the fact that current guidelines did not merit therapy at these T scores, without a significant risk factor for osteoporosis.

Four years later, traveling in an airplane, the patient was attempting to place heavy luggage in an overhead compartment when she experienced acute back pain. A lateral x-ray showed a wedge fracture at T12. The physician repeated the DXA, which showed that the BMD had dropped precipitously to T scores of −2.3 at L1-L4 and −2.0 at the total left hip. He therefore prescribed a weekly bisphosphonate and advised precautions in lifting heavy objects and exercises. The patient did not have further fractures, despite a fall, and sequential height measurements on a yearly basis revealed no decrement.

Two years later, a mass was discovered in her left breast on routine mammography, which turned out to be an adenocarcinoma on core biopsy. Mastectomy and sentinel lymph node dissection were followed by radiotherapy and the aromatase inhibitor Anastrozole. The patient did well in general, but lost height by >1.5 inches over the next year. Lateral spinal x-ray revealed a new fracture at T10, and DXA revealed BMDs of −2.6 at L1-L4 and −2.1 at the total left hip. Six months later she suffered a Colles' fracture and two further vertebral compression fractures, despite being on an oral bisphosphonate. She has recently been switched to an intravenous bisphosphonate, every 3 months, and has had no further fractures. Before starting an intravenous bisphosphonate, the oral cavity was examined and the patient was referred to a facial-maxillary surgeon who cleared her for intravenous therapy. This workup was necessary useful, as a potential known side effect of intravenous bisphosphonates in cancer patients is osteonecrosis of the jaw.

How the Diagnosis Was Made

Many perimenopausal or premenopausal women, such as the patient presented here, present with heal ultrasound measurements and undergo a central DXA on the advice of their physician. Once a central DXA establishes a reduced BMD, the key clinical decision is to attempt differentiate between active bone loss and the lack of achievement of peak bone mass. The latter is due to a variety of causes, such as a period of amenorrhea secondary to ballet training, as is the case in our patient, or sports. A low peak bone mass, but above the osteoporotic range, does not always warrant bisphosphonate therapy. Instead, if there is no fracture and a high risk of fracture is excluded, it is adequate to perform a repeat DXA in 2 years, optimize calcium and vitamin D intake, and counsel patients on the disadvantage of a low T (or Z) score upon entering menopause. Measurement of the patient's urinary N-telopeptide level could have given essential information on the rate of bone loss, and guided more effective therapy. Had the level been high (generally considered to be >38 nmol/mmol Cr), a bisphosphonate or estrogen should have been prescribed. Instead, only calcium and vitamin D were prescribed, and upon entering late perimenopause (interval between periods $\sim$6 months), the patient lost bone rapidly. The Study of Women's health Across the Nations (SWAN) has shown recently that maximum bone loss occurs during late perimenopause [1].

The second critical decline in the patient's BMD occurred during the 2-year lapse after the physician had noted borderline high serum calcium. Her normal borderline 25-OH-vitamin D at the outset was inconsistent with the high-normal calcium. Although no change in serum calcium was noted 6 months later, a serum PTH level was indicated at that time. It would have also been more helpful if the DXA was repeated at 1- rather than 2-year intervals. The primary hyperparathyroidism is associated with a sharp decline in hip BMD, which is characteristic, whereas spinal BMD remained relatively constant [2].

The third relatively precipitous decline in the patient's BMD, which was noted after a fracture had occurred, resulted from her withdrawal from HRT, due to the fear of breast cancer because of her family history. The physician, however, instructed the patient to take only calcium and vitamin D as her T-scores were > -2.0 without risk factors. This approach should have been avoided, as withdrawal from HRT is known to cause enhanced bone resorption and bone loss. The latter should have been assessed 6 to 8 weeks after withdrawal by measuring a urinary N-telopeptide level. Even if the N-telopeptide level was not high, bisphosphonate therapy should have been seriously considered. Notable also is that a fracture occurred even at a T-score of -2.3 at L1-L4. Thus, weight lifting should have been avoided as a precaution, although this advice was given only after the first fracture, which, it is known, will beget a second fracture within 1 year (Table 22.1).

Finally, in this patient acute, rapid, and severe bone loss (ARSBL) followed therapy with Anastrozole, and several fractures occurred despite an oral bisphosphonate. ARSBL is also seen upon gonadectomy in both sexes and gonadotropin-releasing hormone (GnRH) analogues for prostate cancer in men and is due to intense bone

Table 22.1 Effect of an existing fracture on future fractures (fold-increase)

	Wrist	Vertebral	Hip
Wrist	3.3	1.7	1.9
Vertebral	1.4	4.4	2.3
Hip	–	2.5	2.3

Modified from Klotzbuecher et al. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J. Bone Miner Res 2000;15: 721–739.

resorption. Recombinant parathyroid hormone may be considered, as it reduces recurrent vertebral fractures by ∼85%. This drug was not indicated in our patient because of prior radiation therapy. Alternatively, there is anecdotal evidence for the use of an intravenous bisphosphonate for ARSBL, although this is not proven.

Lessons Learned

1. Heel ultrasonography is a useful tool for screening populations and educating women on bone health. It also predicts fracture in elderly men and women. The World Health Organization (WHO) criteria for T-scores do not apply for diagnostic purposes, nor should the results be used to follow patients on therapy.
2. Urinary N-telopeptide levels are valuable markers for bone resorption. High N-telopeptide levels positively predict bone loss at the time of measurement; low or normal levels are generally noncontributory. The specificity of an elevated N-telopeptide level for increased resorption is high. One should measure N-telopeptide on a 24-hour urine sample to avoid the confounding influence of diurnal variation. Alternatively, one can use a second-void morning sample and take the average of two estimations.
3. A urinary N-telopeptide level >38 nmol/mmol Cr has been shown to increase the risk of future bone loss in postmenopausal women.
4. Urinary N-telopeptide levels are useful for:

    a. Assessing elevated bone resorption in early menopause, allowing for therapeutic decisions (illustrated by this case)
    b. Assessing elevated bone resorption in premenopausal women with metabolic bone diseases
    c. Examining the effects of treatment (urinary N-telopeptide levels generally fall in about 6 weeks after initiating a bisphosphonate)
    d. Investigating nonpersistence or noncompliance
    e. Examining increased bone resorption in patients off therapy—either HRT (as in the above patient) or following a drug holiday with a bisphosphonate
    f. Examining elevated bone resorption within 6 to 8 weeks of cessation of parathyroid hormone therapy; if high, a bisphosphonate is mandated to lower resorption and maintain bone mass

Table 22.2 Causes of acute, rapid, and severe bone loss (ARSBL)

Increased resorption
Oophorectomy
Orchiectomy
GnRH analogues
Aromatase inhibitors
Chemotherapy-induced menopause
Decreased formation
High dose glucocorticoid
Calcineurin inhibitors
Stroke
Immobilization
Microgravity

Modified from Epstein et al [3].

5. High serum calcium is inconsistent with a low or normal 25-OH-vitamin D level. A workup for primary hyperparathyroidism is mandated.
6. A fracture begets a future fracture within 1 year. Table 22.1 shows that this is applicable to any site. This effect is irrespective of BMD. The more the number of baseline vertebral fractures, the higher is the incidence of a future fracture.
7. The rate of hormone withdrawal, as illustrated in this case, is reflected generally in the rate of bone loss: oophorectomy > Anastrozole > HRT withdrawal > natural menopause.
8. ARSBL requires empiric bisphosphonate therapy [3], as patients fracture despite having normal or osteopenic BMDs. If there are recurrent fractures, as was the case in this patient, recombinant human parathyroid hormone should be considered. Causes of ARSBL are listed in Table 22.2.

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Questions

1. True or false: A borderline high serum calcium level is consistent with:

   A. Borderline low 25-OH-vitamin D level
   B. Primary hyperparathyroidism
   C. Elevated 1,25–OH-vitamin D in lymphoma
   D. Paget's disease

   Answers: A. False. B. True. C. True. D. True.

2. A 34-year-old woman, with normal periods, and not on any medications, has T-scores of −1.0 at L1-L4 and −3.0 at the left hip. Which of the following tests are useful for therapeutic decision making:

   A. Urinary N-telopeptide to measure the rate of bone formation
   B. Serum PTH
   C. Lateral x-ray of thoracolumbar spine
   D. Serum 1,25-OH-vitamin D
   E. Urinary 24 hour calcium

   Answer: B, C, and E.

3. Which of the following can create artifacts with spinal posteroanterior DXAs:

   A. Calcified aorta
   B. Paraaortic lymph nodes
   C. Degenerative disc disease
   D. Fracture
   E. Multiple myeloma

   Answer: A, C, D, and E.

4. In which of the following should bisphosphonate therapy be considered:

   A. A 65-year-old postmenopausal woman just off HRT
   B. A 27-year-old woman with normal menses and a urinary N-telopeptide of 20 nmol/mmol Cr
   C. A 55-year-old woman with a compressed vertebra and normal BMD
   D. A 68-year-old man with a DXA T-score of −1.4 at L1-L4 and no secondary causes of osteoporosis
   E. A 70-year-old man who is on Lupron therapy for prostate cancer

   Answer: A, C, and E.

Chapter 23
Osteomalacia: A Cause of Bisphosphonate Failure

Michael Pazianas and Mone Zaidi

Objectives

1. To understand presentations of vitamin D deficiency
2. To understand how vitamin D deficiency can confound interpretation of dual-energy x-ray absorptiometry (DXA; bone densitometry) results, particularly following bisphosphonate therapy.

Case Presentation

A 52-year-old woman from India who moved to Minnesota 6 years ago was referred to us because of a clinically significant decline in her bone mineral density (BMD) despite treatment with bisphosphonates. She also complained of back pain and muscular weakness.

Upon entering perimenopause, she visited her family physician for a comprehensive osteoporosis risk assessment. Her menses were delayed at age 16, but were regular since then. She had never been pregnant. There was no other significant medical history, and she was not on medications that would increase the risk of osteoporosis. Risk factors, including her family history, were negative for osteoporosis. Her weight at 140 lb (63.5 kg) and height at 5'5" (1. 68 m) had been stable. Clinical examination was unremarkable.

Her family doctor requested a DXA, which showed a low T-score for both lumbar spine (L1–L4) and total hip at –2.2 and –2.3, respectively. Routine blood work showed normal serum creatinine and total calcium at 8.9 mg/dL (normal range 8.5–10.5 mg/dL). Serum 25-OH-vitamin D was 10 ng/mL (normal sufficient: >32 ng/mL).

The patient was started on an aminobisphosphonate, which she took "religiously" every week. One year later, a repeat DXA scan performed on the same densitometer

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by the same technician showed further deterioration of her BMD with T-scores for spine and total hip at –2.6 and –2.7, respectively.

How the Diagnosis Was Made

Two clinical issues arose. The first was that of her low density at the outset, the question being whether she had lost bone or failed to acquire it, as is commonplace. The second issue centered on the further decline in her BMD following a potent bisphosphonate.

The Study of Women's health Across the Nation (SWAN) has shown that women could lose bone at the highest rate around late perimenopause, even in the absence of an ovarian shut down [1]. However, it is likely that this patient's low BMD at the outset resulted from not having achieved peak bone mass due to late onset of her menses, on the second issue, measurement of a bone resorption marker, such as urinary N-telopeptide, would have provided vital information. A high, >38 nmol/mmol Cr would have indicated ongoing bone loss, and a low level would have provided the assurance that the patient had not entered into the rapid perimenopausal bone loss phase. In the latter case, it is suggested that a DXA be repeated a year later, and that the patient be informed that she will be disadvantaged compared with her peers upon entering the phase of maximum bone loss. Hence, extreme caution is warranted.

That the BMD had declined at both sites, despite the patient's being on a bisphosphonate, raises another level of concern. The question always is whether a secondary diagnosis is missed, or whether the patient is a true bisphosphonate failure. In such instances, it is critical to first exclude the possibility of artifacts, such as results from uncalibrated bone densitometers and inappropriately analyzed DXA scans. In follow-up measurements, a densitometer from a different manufacturer could produce widely discrepant results; this was not the case here, as the same technician performed the tests one year apart on the same densitometer. Precision error of the given DXA machine, generally below 3% and 5% at the vertebral column and hip, respectively, must be taken into consideration to label a change as being clinically significant. This percent change should be calculated from raw numbers (g/cm^2) rather than from T-scores, as T scores are database-derived. This patient did have a significant decline at the lumbar spine and hip.

Almost 90% of cases of bone loss despite bisphosphonate therapy, in our experience, arise for reasons that are not truly medical. These include poor adherence (taking the medication irregularly) and poor compliance (taking the medication incorrectly). In the case of our patient, we believe that she was taking the medication every week, and separating it from meals and calcium pills by several hours.

The obvious cause of this falling BMD was her severe vitamin D deficiency, obvious from a serum 25-OH-vitamin D value of 10 ng/mL. Hence, upon referral, the patient should be worked up for causes other than osteoporosis, with osteomalacia the most likely diagnosis. Total serum calcium at 8.8 mg/dL and phosphorus at

2.6 mg/dL (normal range 2.5–5) were low normal. Total alkaline phosphatase was raised at 197 IU/L (normal range 50–125), with the bone isoenzyme also increased significantly. Parathyroid hormone (PTH) at 115 pg/mL (normal range 15–65) was elevated, and 25-OH-vitamin D was low at 10 ng/mL. An isotope bone scan showed generalized increased uptake with a "hot spot" in the proximal femur. A pathologic pseudofracture (Looser's zone) was confirmed by x-ray. The clinical, biochemical, and imaging studies were thus overwhelmingly compatible with a diagnosis of osteomalacia. To establish the diagnosis in unequivocal terms, the patient was offered a bone biopsy, but due to the invasiveness of the procedure, we agreed to treat the vitamin D deficiency first and then reevaluate.

Lessons Learned

1. Vitamin D insufficiency or deficiency (25-OH-vitamin D levels <32 ng/mL) is a common clinical problem worldwide. Recently literature confirms that its prevalence is grossly underestimated [2]. Patients at high risk are not only the institutionalized elderly but also those who migrated from sunny climates to higher latitudes. Patients using sunscreens are at a particularly high risk.
2. Vitamin D insufficiency or deficiency remains mostly undetected, and can result in a failure to increase BMD when patients are treated with a bisphosphonate, the mainstay of osteoporosis therapy. DXA does not differentiate between excessive bone resorption in osteoporosis and demineralization caused by osteomalacia. The latter worsens with time, mainly as a result of poor vitamin D supplementation, despite bisphosphonate action to prevent excessive resorption.
3. Overt osteomalacia, as was seen in this patient, is characterized by accumulation of unmineralized bone matrix, or osteoid, caused by delayed or defective mineralization (Fig. 23.1). Bone biopsy after tetracycline double labeling unequivocally establishes the diagnosis [3], with the hallmark finding of delayed or defective bone mineralization per unit volume. This procedure is rarely considered necessary.

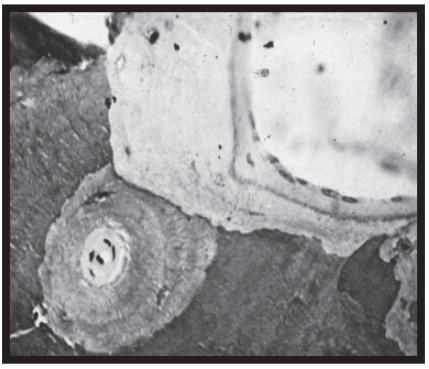

Fig. 23.1 An area of unmineralized osteoid next to an osteocytic lacuna

4. Extraskeletal symptoms of vitamin D deficiency include easy fatigability, proximal muscle weakness, generalized bone tenderness and pain, and atraumatic fractures. Our patient did complain of fatigue and difficulty in climbing stairs. While clinical examination showed no kyphosis, there was poorly localized pain and general skeletal tenderness. Getting up from a chair was difficult. All of these features were consistent with osteomalacia.
5. "Normal" levels of 25-OH D have been revisited recently [4]. There is a consensus that serum 25-OH-vitamin D >32 ng/mL is required for adequate control of PTH levels and for fracture prevention in older adults. Serum 1, 25-$(OH)_2$-vitamin D measurement is not necessary in routine practice. Its levels can be elevated in isolation in patients with lymphoma and sarcoidosis.
6. Other biochemical findings of vitamin D deficiency include a low-normal serum calcium and phosphorus caused by the reduced absorption of both elements in the gut. A compensatory increase in PTH levels follows that tends to normalize serum calcium, but further decreases serum phosphorus. Bone alkaline phosphatase is usually increased.
7. Skeletal x-rays and bone densitometry are not helpful in differentiating osteomalacia from osteoporosis. Even the finding of Looser's zones alone is not specific for osteomalacia (Fig. 23.2)
8. Vitamin D insufficiency or deficiency with or without overt osteomalacia needs to be treated vigorously [5]. This patient was treated with 50,000 IU ergocalciferol weekly and 1200 mg of calcium daily for 12 weeks. All biochemical bone parameters normalized at 6 weeks. Thereafter, the patient continued with 800 IU vitamin D and 1200 mg of calcium daily, and a DXA scan in 6 months showed a remarkable improvement in T-scores, with L1–L4 and total hip at –1.3 and –1.4, respectively. A repeat x-ray showed a complete healing of the pseudofracture.
9. The bisphosphonate was stopped for the 6-month period. However, this is not warranted except in severe disease, such as in this patient. In cases where

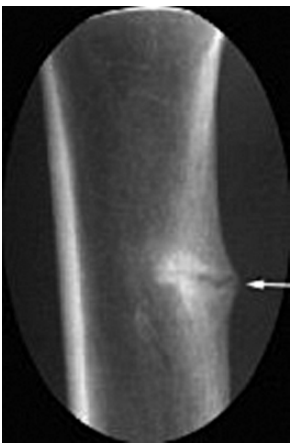

Fig. 23.2 A typical Looser's fracture

25-OH-D is above 25 ng/mL, we personally recommend continuing the bisphosphonate, but using the same regimen for vitamin D replacement.

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Questions

1. True or false: Vitamin D deficiency is

   A. highly underdiagnosed.
   B. mainly the result of poor intake.
   C. treated with 800 IU vitamin D.
   D. always associated with a high PTH.
   E. common in persons using sunscreens.

   Answers: A. True. B. False. C. False. D. False. E. True.

2. Osteoporosis treatment

   A. requires that vitamin D levels are normalized.
   B. can be confounded by high PTH levels.
   C. should only begin when T-scores >2.5.
   D. requires a bisphosphonate alone.

   Answers: A. True. B. True. C. False. D. False.

3. Osteomalacia

   A. is a disease of the elderly alone.
   B. can be associated with musculoskeletal symptoms.
   C. always causes abnormalities on isotope scans.
   D. should be treated with high doses of vitamin D.
   E. must be treated with calcitriol (Rocaltrol).

   Answers: A. False. B. True. C. False. D. True. E. False.

4. Vitamin D (ergo- or chole-calciferol)

A. cholecalciferol (D_3) is more potent than ergocalciferol (D_2).
B. should be used to increase serum phosphate in hypophosphatemic rickets.
C. up to 10 000 IU of D_2 daily for 5 months are safe.
D. should be administered with Rocaltrol in D-deficiency.
E. is the active form of vitamin D.

Answers: A. True. B. True. C. True. D. False. E. False.

Chapter 24
Unusual Manifestations of Paget's Disease of Bone

Mone Zaidi and Michael Pazianas

Objectives

1. To understand the manifestations of Paget's bone disease
2. To be aware of emergencies associated with Paget's bone disease

Case Presentation

A 72-year-old healthy Caucasian man presented to his primary care physician with deafness in his right ear. Appropriate referral leading to audiometry revealed sensorineural deafness, and he was provided with a hearing aid without much avail. He had no history of prior ear problems.

He did complain of the occasional band-like headache that was not of an acute onset, severe, site-specific, or migraine-like. There was no associated nausea, vomiting, eye disease, or vertigo. The physician attributed the headaches to "stress" and prescribed paracetamol, which did provide the patient with some relief.

Several months later, he developed a painful left hip after slipping in the shower, after which he could not bear weight due to intense pain. He was admitted to the emergency room, where on questioning, he recollected having occasional pain in his arms and legs that often "felt warm." On examination, there was some superficial bruising, and his left leg was externally rotated with painful movements. Vitals remained normal while in the emergency room. X-ray revealed a subtrochanteric fracture. There was some sclerosis around the area of fracture, but the x-ray was generally of a poor quality.

Even after 4 months, the fracture was found not to unite. He then went in for an elective hip replacement, and while in the hospital developed pneumococcal pneumonia and remained bedridden for almost 2 weeks.

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During convalescence from pneumonia, his relevant chemistry was as follows:

Alkaline phosphatase	602 IU/L (normal range 50–125)
Urinary N-telopeptide	182 nmol/mmol Cr
Calcium	13.1 mg/dL (normal range 8.5–10.5)
Albumin	4.0 g/dL (normal range 3.5–5)
Blood urea nitrogen (BUN)	10 mg/dL (normal)
Complete blood count (CBC)	Normal
Parathyroid hormone (PTH)	17 pg/mL (normal range 15–65)
25-OH-vitamin-D	26 ng/mL (normal sufficient: >32)
Parathyroid hormone related protein (PTH-rP)	Normal

He was treated for hypercalcemia by hydration, furosemide, and a single pamidronate infusion (60 mg IV). His serum calcium dropped to 11.3 mg/dL, but his alkaline phosphatase remained high at 452 IU/L.

While hospitalized, a formal diagnosis of Paget's disease of bone was made. Skeletal survey revealed mainly osteosclerotic lesions in the right pelvis, hip, lumbar spine, left humerus, and skull. A bone scan was performed that showed evidence of active uptake in the pelvis, lower vertebral column, left humerus, skull, and mid-femur. The patient was subsequently given five further intravenous pamidronate (60 mg) infusions and at 6-month his alkaline phosphatase fell to 87 IU/L (normal). His bone lesions improved radiologically and he became pain-free. He then underwent an elective hip replacement and became progressively more ambulatory.

Three years later, he started complaining of pain in the lower back that radiated along both legs followed by weakness in both lower limbs and was referred to a neurologist. A neurologic examination was consistent with a lesion at the L1/2 segment with some flaccid paresis. There was no thoracic spine involvement. X-ray revealed an expanded vertebral body, and magnetic resonance imaging (MRI) showed considerable narrowing of the spinal canal.

He was given hydrocortisone 100 mg stat, and then 50 mg q 8 hourly, and a stat infusion of pamidronate (60 mg). The neurologic symptoms were relieved within a week. He was then put on Actonel (30 mg qd). At 3 months, his alkaline phosphatase dropped to 89 IU/L, and there was full radiological remission. Neurologic examination was nonfocal.

How the Diagnosis Was Made

The telling clinical features upon initial presentation included a typical feeling of warmth in painful limbs, subtrochanteric fracture with sclerosis and nonunion, and evidence of skull involvement in the form of deafness and band-like headaches. Indeed, the clinical presentations of Paget's disease can range from asymptomatic (alkaline phosphatase elevation) to severe bone pain with warmth, as in this patient, due mainly to cortical expansion or microfractures. Skull and face involvement

can result in frontal or facial deformities, including dental problems, band-like headaches, sensorineural or conduction deafness, and uncommonly life-threatening platybasia. Unlike typical fractures in osteoporosis, fractures in Paget's disease are mainly subtrochanteric, as in this patient, or in the femoral shaft. Small fissure fractures in long bones can remain asymptomatic, but fracture healing is often delayed, again, as noted here. An alternate initial presentation is that of high-output cardiac failure, particularly in older men with coronary artery disease. This is due to high vascularity and hyperdynamic circulation.

Another interesting aspect revealed in this case was that the serum calcium rose to 13.1 mg/dL, while the patient was hospitalized for pneumonia. Although Paget's disease could occur in "common coincidence" with primary hyperparathyroidism, serum calcium in this patient with active Paget's disease was elevated because of immobilization. Osteoblastic bone formation, typically at its height, is reduced with osteoclastic resorption predominating.

With that said, secondary hyperparathyroidism can occur in patients with Paget's disease in two specific instances. First, high bone formation rates in fulminant disease require increased calcium for mineralization, resulting eventually in negative calcium balance and secondary hyperparathyroidism. Second, if the disease is treated too vigorously with an intravenous bisphosphonate, resorption can be

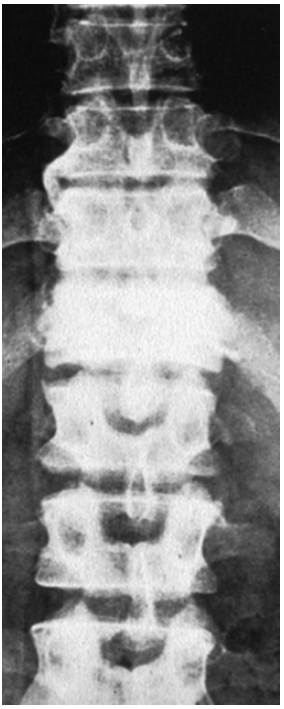

Fig. 24.1 Expanded vertebra typical of paget's disease of bone; it is differentiation from an arthritic vertebra, which is rarely expanded

suppressed to a point that a potential decline in serum calcium results in high PTH output. Both patient groups require 1 g to 1.5 g calcium per day.

Recurrences are common, as in this patient, specifically affecting the vertebral column. Such presentations may include back pain, due mainly to spinal stenosis, enlarged vertebrae, compression fractures, and specifically reduced blood supply to the thoracic spine leading to upper arm weakness (thoracic steal). This patient had evidence of both an expanded vertebra (Fig. 24.1) and spinal stenosis.

Lessons Learned

1. Paget's bone disease can occur at any age, but is rare before 45 years and common over 50 years. The commonest sites are pelvis > femur > spine > skull > tibia > hands and feet (Fig. 24.2). This 72-year-old patient had multiostotic disease.
2. We did not take a family history in the patient, but a positive family history is common in up to 30% of patients affected with Paget's. The risk is sevenfold higher in first-degree relatives. There is also evidence of geographic clustering.
3. Alkaline phosphatase elevations may be the sole presentations of symptomatic disease. Alkaline phosphatase and C- and N-telopeptides, bone resorption markers rise in parallel. The degree of rise of alkaline phosphatase is a reflection of disease severity. A greater than 10-fold increase above upper normal values suggests skull involvement, which merits vigorous therapy, and an increase less than threefold from basal indicates either monostotic or burned-out disease.
4. Alkaline phosphatase should be used to monitor patients on therapy, as was appropriately done here. About two thirds of bisphosphonate-treated patients show a 50% reduction in alkaline phosphatase in 2 to 3 weeks. Disease remission takes 2 to 3 months.
5. X-ray of affected bone is pathognomonic. Highly specific findings include coarse trabeculae, widening of bones, blade of grass lesions, and cotton wool appearance of the skull (Fig. 24.3). Look specifically for fissure fractures near joints.
6. Scintigraphy is precise and sensitive, but not specific. It should be used for screening to evaluate the extent of the disease. Repeating scans are unnecessary without new symptoms.
7. If x-ray findings are less than characteristic, particularly in old patients with bone pain, even with a positive bone scan, it is not necessary to rush into diagnosis. It is critical to compare with old x-rays.
8. Paget's disease occurs commonly in a genetically susceptible host. Indeed, an autosomal dominant pattern of inheritance has been reported. However, a causal link with a prior infection by the measles virus remains controversial. Supporting evidence is provided by reports that the osteoclast is primarily infected by the measles virus nucleocapsid protein. Viral inclusions have been noted only in Pagetic osteoclasts, but not in normal osteoclasts of the same patient. Increased

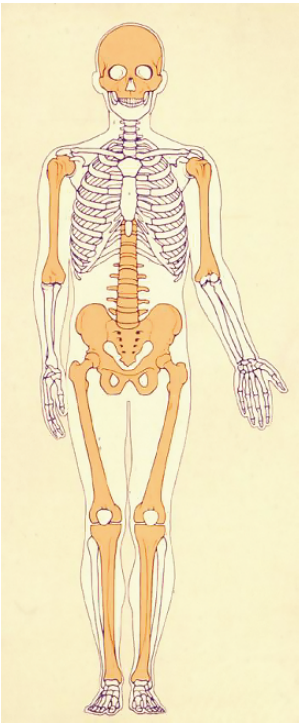

Fig. 24.2 Common sites for pagetic lesions in humans (in grey)

osteoclastic bone resorption leads, through the liberation of growth factors, to stimulated and erratic osteoblastic bone formation (Figs. 24.4 and 24.5). Thus, the clinical spectrum of Paget's bone disease can range from a purely sclerotic form to the rarely pure lytic form. Mixed varieties are most common.

9. Inhibition of osteoclastic bone resorption is the primary therapeutic goal, and bisphosphonates are the drugs of choice. Calcitonin is no longer used.

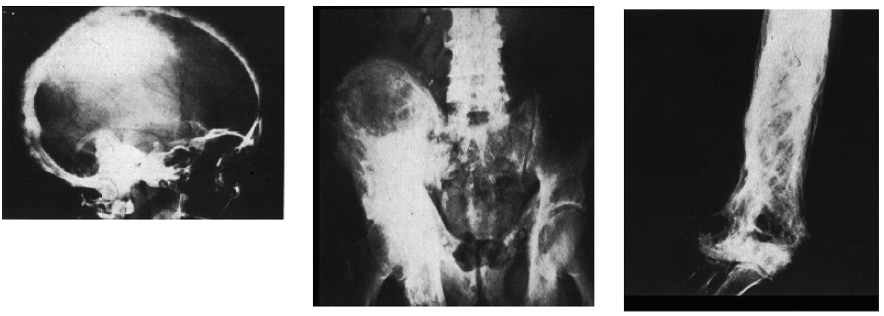

Fig. 24.3 Typical x-rays showing pagetic lesions in the skull, pelvis, and arm

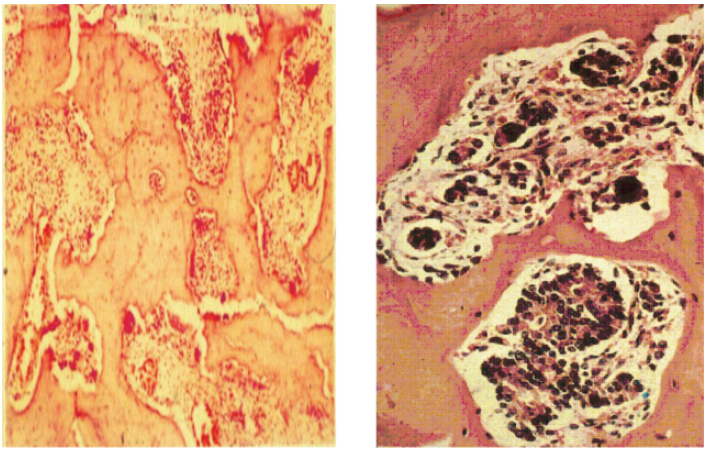

Fig. 24.4 Microscopic evidence of intense osteoclastic resorption evident in transiliac bone biopsy specimens

10. Bisphosphonates provide relief from bone pain and warmth, headaches, and neurologic complications, as was noted in this patient. They do not reverse pain due to secondary arthritis, the blade-of-grass lesions, bowed extremities, or the hearing defect.
11. We prescribe intravenous pamidronate in fulminant multiostotic disease, particularly in patients prior to hip surgery. Note that the highly vascular lesions in Paget's bone disease bleed easily; hence, hip fracture patients must be monitored for occult bleeds.

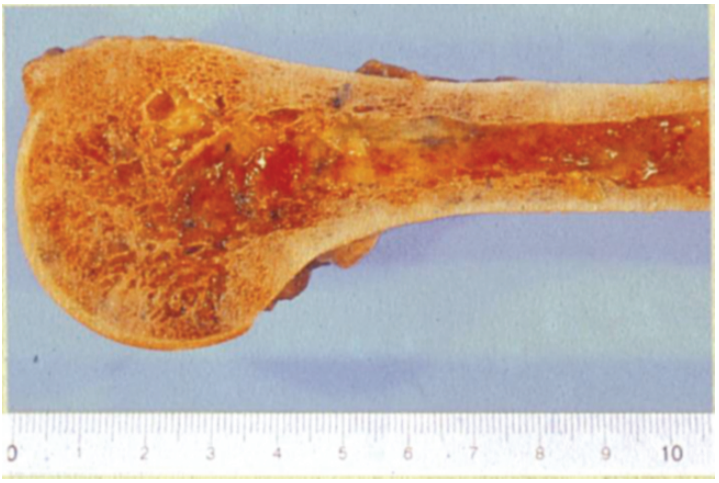

Fig. 24.5 Autopsy specimen from a patient with Paget's disease, showing intense destruction of cortical and trabecular bone

12. Pamidronate (30 to 90 mg) is infused over 3 to 4 hours; in severe cases up to a total of 500 mg of Pamidronate could be infused during a period of several weeks. If serum Cr>1.8, we tend to prolong the infusion time. This protocol is most useful for neurologic symptoms and painful lytic lesions. Zoledronic acid, as a one-time infusion has recently been approved for use in Paget's disease of bone. A convenient single 15 minute IV infusion of 5 mg has been reported as more effective than 30 mg/day risedronate taken for two months.
13. Oral bisphosphonate therapy should be continued for at least 2 to 3 months.
14. Relapses lead to new bone pain, which was once a common due to osteomalacia associated with the use of Etidronate (Didronel). This is not seen with newer bisphosphonates. Rarely, new bone pain is the harbinger of sarcomatous degeneration (1%), particularly in fulminant disease of older individuals.

Suggested Readings

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Questions

1. True or false: Paget's disease of bone

   A. is often a radiographic or laboratory incidental finding.
   B. mainly affects the skull.
   C. is treated with parathyroid hormone.
   D. has a strong genetic predisposition.
   E. is common among young persons.

   Answers: A. True. B. False. C. False. D. True. E. False.

2. True or false: The treatment of Paget's bone disease

   A. requires bisphosphonates.
   B. should last until alkaline phosphatase is reduced by 50%.
   C. should last indefinitely.
   D. relieves deafness.
   E. attenuates bone pain.

   Answers: A. True. B. False. C. False. D. False. E. True.

3. True or false: Medical emergencies arising from Paget's bone disease include

   A. hypercalcemia.
   B. persistant hypocalcemia.

C. fracture.
D. platybasia.
E. occult bleeding.

Answers: A. True. B. False. C. True. D. True. E. True.

4. True or false: Paget's bone disease can

A. present in almost all bones.
B. be confused with arthritis.
C. cause sensory neural deafness due to involvement of middle ear bones.
D. present as severe cardiac failure.
E. convert to sarcoma.

Answers: A. True. B. True. C. False. D. True. E. True.

5. True or false: Paget's bone disease

A. with slightly raised alkaline phosphatase, must always be treated.
B. recurs at new skeletal sites.
C. has been documented in pets (variant).
D. is due to viral infection of the osteoblast.
E. occurs prominently in persons of European descent.

Answers: A. False. B. False. C. True. D. False. E. True.

Chapter 25
Solid Organ Transplantation, Chronic Renal Impairment, and Skeletal Complications

Michael Pazianas and Mone Zaidi

Objectives

1. To understand complications of solid organ transplant affecting bone metabolism
2. To understand the concept of renal osteodystrophy

Case Presentation

A 58-year-old Caucasian man with a history of successful orthotopic liver transplantation 7 years ago for idiopathic cirrhosis, renal insufficiency [baseline serum creatinine of 3.4 mg/dL – estimated glomerular filtration rate (GFR) ~20mL/min/1.73m^2 – stage 4 according National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI)], secondary to interstitial nephritis, anemia, and recently diagnosed atrial fibrillation for which he is anticoagulated and rate controlled, presented for management of his metabolic bone disease(s).

There was no history of fractures and his family history was unremarkable. He had smoked for 20 years at one pack per day and quit 12 years ago. Currently, he was consuming two glasses of wine per week.

His medications included tacrolimus, a calcineurin inhibitor, as the main immunosuppressant drug, warfarin, Epogen, metoprolol succinate extended-release tablets (Toprol XL), and multivitamins. He had been on corticosteroid regimens for 4 years following his liver transplant at doses of 10 mg daily or higher.

Recent blood tests showed borderline low-normal total serum calcium at 8.5 mg/dL (normal range 8.5–10.5), high-normal phosphorus at 4.8 mg/dL (normal range 2.5–5.0), alkaline phosphatase at 115 IU/L (normal range 50–125), elevated intact parathyroid hormone (PTH) at 142 pg/mL (normal range 15–65), and low 25-OH vitamin D at 10 ng/mL (normal sufficient: >32 ng/dL) and 1,25$(OH)_2$ vitamin D at 14 pg/mL (normal range 15–75 pg/mL). There was a degree of anemia with hemoglobin at 9.9 g/dL with reduced serum iron. His thyroid-stimulating hormone

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(TSH) at 1.62 μIU/mL (normal range 0.40–4.0), fasting blood glucose, and B_{12} and folate levels were normal.

A dual-energy x-ray absorptiometry (DXA) scan showed normal bone mineral density (BMD) at the lumbar spine (L2–L4), 1.181 g/cm^2, and a T-score of 0.5, although the report cautioned that there was a moderate degree of spinal dextroscoliosis, which could have artificially elevated the lumbar BMD. The proximal right femur BMD, measured in his dominant (right) side was low, 0.658 g/cm^2, and the T-score was −3.3.

How the Diagnosis Was Made

Within the first 6 months of a liver transplant, patients are known to lose 5% to 10% bone mass and experience a fracture risk of up to 65% [1]. Corticosteroid therapy has been used as the dominant immunosuppressant in solid organ transplants. However, the two calcineurin inhibitors, cyclosporine and tacrolimus, have now become the cornerstone of immunosuppressive therapy. These drugs cause profound bone loss, and in addition, by causing tubular atrophy and interstitial fibrosis, can cause chronic renal failure and osteodystrophy. Another potential contributor to bone loss in this case is the vitamin K antagonist warfarin. Vitamin K is required for the γ-carboxylation of osteocalcin and two more bone matrix proteins for their binding to hydroxyapatite. Liver disease per se in this patient should not be considered a risk factor, as his liver function was rendered and remained normal posttransplantation. In general, however, chronic liver disease of obstructive etiology has been reported to cause osteoporosis.

The patient's biochemical profile is compatible with secondary hyperparathyroidism due to vitamin D deficiency and renal failure [2]. His vitamin D deficiency is consistent with low 25-OH vitamin D, low normal serum calcium, high normal alkaline phosphatase, and high PTH. The high-normal serum phosphorus, low estimated GFR (∼20 mL/min/1.73 m^2), and borderline-low 1,25-$(OH)_2$D are compatible with renal failure–induced secondary hyperparathyroidism.

BMD measurements are not helpful in establishing the diagnosis. Subperiosteal bone resorption on hand x-rays is pathognomonic (Fig. 25.1). Bone biopsy with double tetracycline labeling, however, is the gold standard. In the presence of high bone turnover, osteitis fibrosa, characterized by increased osteoblastic and osteoclastic activity, is the most common finding. This results in excess deposition of osteoid tissue and an increased number of resorption lacunae. Bone formed is primarily of the woven type. In advanced cases, the bone marrow may be replaced by fibrous tissue. Other characteristic imaging findings include Rugger Jersey spine, Looser's fracture, Brown's tumor, amyloidosis, chondrocalcinosis, ligament calcification, and vascular calcification [3].

Therapeutically, the major goal is to normalize the patient's 25-OH vitamin D levels, reduce phosphorus intake without jeopardizing adequate protein intake

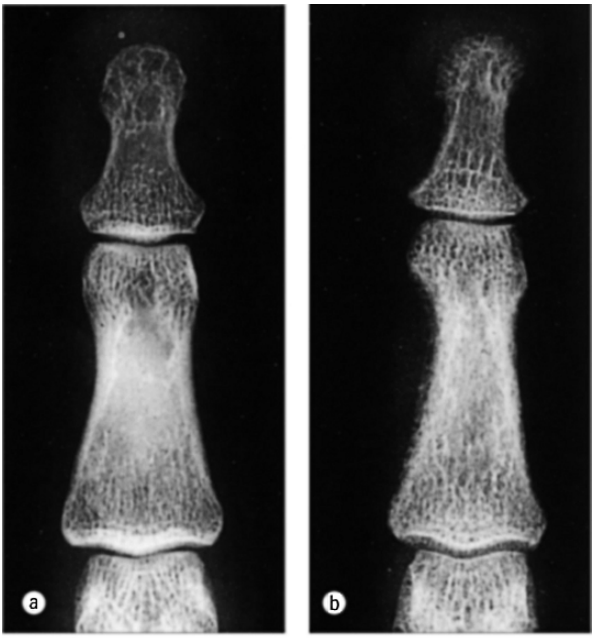

Fig. 25.1 Radiographs of fingers. Comparison of (a) a normal right middle finger with (b) the right middle finger of a patient on maintenance hemodialysis for 6 years. There is marked evidence of subperiosteal resorption of bone, especially on the lateral aspect of the middle phalanx but also involving the terminal phalanx [From Eastwood and Pazianas [3], with permission.]

and prescribe a calcium containing phosphate binder such as calcium carbonate or citrate. Normalization of the biochemical profile should aim for elevated serum PTH concentrations, preferably in the 70- to 110-pg/mL range for this stage 4 patient. This is considered an optimal response and could help avoiding the development of adynamic bone disease. The latter condition of suppressed bone turnover leads to increased susceptibility to fractures. It is important also to note that, until recently, PTH fragments such as PTH (7–84) were measured together with the intact PTH (1–84) molecule. The concentration of these fragments is increased in patients with chronic renal impairment, and although their clinical significance has not been established, there are strong evidence that they blunt the effects of PTH (1–84).

For the vast majority of stage 4–5 patients, control of hyperphosphatemia is a daunting task. Phosphate binders and one of many vitamin D analogues should be considered. Calcium containing phosphate binders include calcium carbonate or citrate. It is important to use calcium-citrate with caution, as it binds with trace aluminum and could cause aluminum bone-disease. Newer non calcium containing phosphate binders include lanthanum carbonate, and sevelamer hydrochloride

(Renagel), used commonly in dialysis patients is. The latter has been shown to reduce significantly LOL cholesterol concentrations. The FDA approved recently sevelamer carbonate (Renvela), a new buffered form. Vitamin D analogues act on the parathyroids to reduce PTH production, and thus improve the hyperparathyroidism. However, it is important to consider that vitamin D analogues facilitate the absorption not only of calcium but also of phosphorous. Hyperphosphatemia, therefore, is always a concern, and attempts should be made to drive the Ca × P product to below $55\,mg^2/dL^2$ and the serum phosphate down to 5.5 mg/dL in stage 5 patients (up to 4.6 in our stage 4 patient). Higher Ca × P products have been associated with significantly increased risk of vascular calcification. Published data suggest beneficial effects of the vitamin D sterols on cardiovascular mortality.

Recently, cinacalcet (Sensipar), a calcimimetic compound, allosterically activates the calcium-sensing receptor of the parathyroid glands and thus reduces PTH secretion and possibly parathyroid cell proliferation. It is reserved for cases where other treatments have failed, but there is no evidence for a reduction in cardiovascular mortality.

Parathyroidectomy is reserved for persistent hypercalcemia, intractable pruritus, progressive extracellular calcification, calciphylaxis, and severe pain or fractures.

The other challenging aspect in this case is the detrimental direct effects of calcineurin inhibitors on bone in transplanted patients. Of course, it is part of the overall strategy to keep the concentration of these agents at the lowest possible level, but under no circumstances should we withdraw them. Therefore, an antiresorptive medication, most preferably a bisphosphonate, is mandated to prevent the acute, rapid, and severe bone loss that is associated classically with liver transplantation [1]. The administration of this class of antiresorptives is considered safe and effective down to GFR levels of 15 mL/min if osteoporosis but not other forms of metabolic bone diseases are present i.e osteomalacia, adynamic bone disease or hyperparathyroidism. In patients with more severe renal failure, reduction of the dosage to half is recommended. Despite oral bisphosphonates, these patients continue to have fractures. Unfortunately, parathyroid hormone therapy cannot be considered in renal failure patients, but can be used effectively in patients with organ transplant who fracture despite being on a bisphosphonate.

Lessons Learned

1. Known risk factors for renal osteodystrophy

   - Female
   - Tubulointerstitial nephritis
   - Young age
   - Increased duration of renal failure

2. Aggressively reducing PTH levels down to the normal range increases the risk of adynamic bone disease in chronic kidney disease patients. The target range of intact plasma PTH by stage of chronic kidney disease (CKD), according to National Kidney Foundation (NKF), is as follows:

CKD Stage	GFR Range (mL/min/1.73 m^2)	Target "intact" PTH (pg/mL [pmol/L])
3	30–59	35–70 [3.85–7.7 pmol/L] (OPINION)
4	15–29	70–110 [7.7–12.1 pmol/L] (OPINION)
5	<15 or dialysis	150–300 [16.5–33.0 pmol/L] (EVIDENCE)

3. Calcitriol increases the absorption of phosphate from the intestine. Hence, hyperphospatemia may be worsened.
4. Bone disease improves during the first year on dialysis.
5. Hyperparathyroidism in patients with end-stage renal disease
   - involves all four glands.
   - is heavily influenced by serum phosphate concentration.
   - shows good response to calcimimetics, but there is no data on cardiovascular mortality.
   - could require surgical intervention (parathyroidectomy) in up to 10% of the dialysis population.
6. Posttransplant immunosuppression could cause acute, rapid, and severe bone loss due to reduced bone formation [1]. It is difficult to ascertain the effects of glucocorticoids and calcineurin inhibitors in humans. In rodents, however, suppression or genetic deletion of the enzyme calcineurin causes severe bone loss [4].

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Questions

1. True or false: Bone mineral density (BMD) measurement in end-stage renal disease (ESRD)

   A. can distinguish between osteomalacia and hyperparathyroidism.
   B. should be performed in all patients on dialysis every year.
   C. values are extremely low in patients with end-stage renal disease.
   D. distal radius measurements could be more revealing than those of lumbar spine or hip.

   Answers: A. False. B. False. C. False. D. True.

2. True or false: Pathologic features of renal bone disease include

   A. both osteitis fibrosa and osteomalacia in the same patient.
   B. renal cysts.
   C. adynamic renal osteodystrophy as the most common form of low-turnover bone disease.
   D. amyloidosis only with low-turnover bone disease.

   Answers: A. True. B. False. C. True. D. False.

3. True or false: The following occur after successful renal transplantation:

   A. Bone/soft tissue lesions improve.
   B. Hyperparathyroidism may persist.
   C. Fracture risk decreases.
   D. Acute rapid and severe bone loss may result due to immunosuppressants.

   Answers: A. True. B. True. C. False. D. True.

4. True or false: In the treatment of ESRD-related bone disease:

   A. Phosphate binders reduce the Ca $\times$ P product.
   B. Renagel has potential antiatherogenic properties.
   C. A calcilytic should be used in ESRD patients to reduce PTH.
   D. Calcium citrate should be used to bind phosphate in ESRD.

   Answers: A. True. B. True. C. False. D. False.

Part VIII
Endocrine Disorders of Males

Introduction

Stephen J. Winters and Sathya Krishnasamy

Testicular function is under the control of gonadotropin-releasing hormone (GnRH) produced by neurons in the anterior hypothalamus. GnRH stimulates the synthesis and secretion of the pituitary gonadotropic hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are composed of a common alpha-subunit, shared also with thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (HCG), and specific β-subunits (LH-β and FSH-β). Both LH and FSH are released into the circulation in pulses, and activate G-protein–coupled receptors on Leydig and Sertoli cells, respectively, in order to stimulate testosterone production and spermatogenesis.

Normal testicular function is also maintained by an elaborate negative feedback mechanism controlling GnRH and gonadotropin synthesis and secretion. Sex steroids inhibit GnRH production apparently by affecting neurons that produce Kisspeptin-1, which in turn, stimulate GnRH. Other interneurons and neurotransmitters may also be involved in this process. Estrogens affect GnRH production as well as the pituitary directly to inhibit responsiveness to GnRH perhaps by regulating proteins involved in hormone exocytosis Soluble N-ethylmaleimide Sensitive Factor Attachment Protein Receptor (SNARE proteins). There is selective control of FSH by the testicular peptide inhibin-B. This dimeric glycoprotein member of the transforming growth factor β (TGF-β) family competes with activin for binding to its receptor on gonadotrophs, but fails to initiate activin signaling. In this way, inhibin restrains the synthesis and secretion of FSH. When the testes are damaged, inhibin-B production falls, and unchecked activin causes FSH to increase. These control mechanisms are summarized in Figure VIII.1.

The willingness of patients to discuss the symptoms of hypogonadism, and the availability of new, safe, and effective treatment approaches have increased substantially the number of men being evaluated and treated for hypogonadism. Men with hypogonadism present with symptoms and signs of androgen deficiency or with infertility. The symptoms of androgen deficiency are nonspecific, and the signs may be subtle. Other than azoospermia, the semen parameters that distinguish

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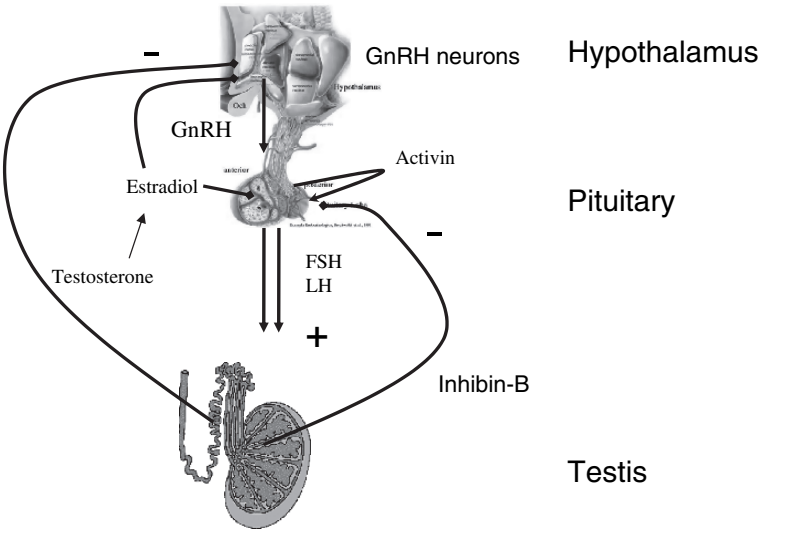

Fig. VIII.1 Diagram showing feed-forward and feedback mechanisms governing hypothalamic–pituitary–testicular function

fertile from infertile men are indistinct. A careful medical history and physical examination, including measurement of testicular size, is essential. Most often the total testosterone level is sufficient to confirm the clinical diagnosis of hypogonadism, with most reference ranges approximating 300 to 1000 ng/dL. The level of sex-hormone binding globulin (SHBG) is a determinant of total testosterone, however, and increases or decreases in SHBG produce parallel changes in total testosterone. When total testosterone levels are borderline, or the total testosterone level is not consistent with the clinical findings, free testosterone or non-SHBG (bioavailable) testosterone levels should be measured. Analogue assays for testosterone are inaccurate, and should not be used.

Disorders that affect the testis are classically divided into those in which the gonadotropin drive to the testes is impaired (hypogonadotropic hypogonadism), and disorders that damage the testes directly (primary testicular failure). Systemic illnesses may affect both the production of gonadotropins and damage the testes. Several illustrative cases follow.

Chapter 26
Congenital Isolated Hypogonadotropic Hypogonadism

Stephen J. Winters and Sathya Krishnasamy

Objectives

1. To review the variable clinical presentation of men with congenital isolated hypogonadotropic hypogonadism
2. To review new information on the causes of congenital isolated hypogonadotropic hypogonadism
3. To understand treatment options

Case Presentation

A 34-year-old man was referred because of a low testosterone level. At age 18 he had not entered puberty, and was prescribed testosterone injections, which he received for 5 years. He gained weight, body hair developed, and he became sexually active. He married and was told he was sterile. He is otherwise healthy, and has had no bone fractures. He denies anosmia or other physical abnormalities. The family history is negative for hypogonadism and midline defects. His parents are unrelated.

Physical Examination

The patient was healthy and well appearing. He was somewhat hypogonadal in appearance with reduced muscle mass and body hair. His height was 71 inches, and his arm span was 72 inches. There was no gynecomastia. The testes were each quite small, measuring about 1.5 cm in length (3 mL in volume)

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Laboratory Data

Serum testosterone 30 ng/dL, luteinizing hormone (LH) 1.2 U/L, follicle-stimulating hormone (FSH) 2.6 U/L, free thyroxine (FT_4) 1.3 ng/dL, prolactin (PRL) 5 ng/mL, and insulin-like growth factor I (IGF-I) 254 ng/mL (normal 114–492). On a dual-energy x-ray absorptiometry (DEXA) scan, the bone mineral density (BMD) of the lumbar spine T-score was −2.4 and hip −1.5 S.D.

The patient was treated for a few months with testosterone enanthate 200 mg every 2 weeks intramuscularly (IM), and then changed to human chorionic gonadotropin (HCG) 1000 U three times a week. His testes increased in size to 5 mL over 6 months, and his sperm count rose to 24 million/mL with normal motility (40%) and morphology. Two months later his wife became pregnant, and she subsequently delivered a healthy full-term girl. HCG injections were replaced with the daily application of a 1% testosterone gel, and the patient was treated with a bisphosphonate as well as calcium with vitamin D for osteopenia.

How the Diagnosis Was Made

This young man presented with clinical hypogonadism, but was otherwise healthy. Puberty did not occur until he received testosterone by injection. His height was normal, and there was no clinical or biochemical evidence for hypothyroidism or cortisol deficiency. The PRL level was not increased. The testosterone level was typical for a prepubertal boy, and the serum levels of LH and FSH were in the low-normal range. There was no clinical evidence for a tumor or other pathologic condition affecting the pituitary or suprasellar region, and mass lesions were excluded by a normal magnetic resonance imaging (MRI). Thus the presumptive diagnosis was congenital isolated hypogonadotropic hypogonadism (CIHH). The patient was not anosmic, and there were no congenital abnormalities identified. The family history was negative for hypogonadism and midline defects. Most cases of CIHH are sporadic with no family history of the condition. Patients with CIHH have been classically divided into those with anosmia or hyposmia (Kallmann syndrome) and those with normal olfaction.

Lessons Learned

Hypogonadotropic hypogonadism (HH) results from an inability to stimulate the secretion of the gonadotropic hormones from the pituitary, and isolated hypogonadotropic hypogonadism (IHH) has a variable clinical presentation [1]. The prevalence of the disorder is estimated to be 1:10,000 males and 1:50,000 females. Men may present with sexual infantilism as newborns with a microphallus, with failure to enter puberty, or with infertility or osteoporosis as partially sexual mature adults. The testes can be smaller than those of a prepubertal child (< 3 mL in volume), but are sometimes of normal adult size (20–25 mL). These latter patients were

Table 26.1 Clinical findings in patients with isolated hypogonadotropic hypogonadism

Cryptorchidism	Anosmia/hyposmia	Cleft lip
Microphallus	Deafness	Cleft palate
Bifid scrotum	Coloboma	Phocomelia
Hypospadias	Color blindness	Polydactyly
	Seizures	Short fourth metacarpal bones
	Cerebellar ataxia	Renal agenesis
	Hypotonia	Horseshoe kidney
	Synkinesias	

historically termed "fertile eunuchs" because they were clinically hypogonadal with soft smooth skin and reduced body hair, but the testes were not small. Affected females present with primary amenorrhea and minimal breast development. Clinical characteristics sometimes found in these patients are listed in Table 26.1.

The endocrine findings in CIHH are also variable. The circulating testosterone level can range from <30 to 200 to 300 ng/dL; LH may be undetectable, or LH pulse amplitude or frequency may be reduced. Because infertility is a component of the syndrome, and there is incomplete penetrance of the clinical characteristics, studies of the inheritance of CIHH are problematic. Kindreds in which the inheritance is X-linked, autosomal dominant, or autosomal recessive have been reported. This clinical, laboratory, and genetic variability implies that CIHH was a syndrome with multiple etiologies.

Congenital isolated hypogonadotropic hypogonadism is now known to result from at least four separate gene mutations. In 1944 Kallmann et al reported several kindreds in which men had IHH and anosmia, suggesting an X- linked trait. The discovery of mutations in the *KAL-1* gene and its localization to the short arm of the X chromosome establish an explanation for gonadotropin-releasing hormone (GnRH) deficiency, and has greatly expanded understanding of normal GnRH neuronal development and its link to olfaction, a critical sense for reproductive success among lower animals. *KAL-1* encodes a protein, anosmin, which shares homology with other proteins involved in axon path-finding and neuronal migration. Many mutations of *KAL-1* have been identified, with most mutations in exons 5 to 14, which encode four fibronectin III domains. These regions of the molecule have heparan sulfate (HS) binding affinity, and are present in a number of adhesion proteins that are involved in cell-cell or cell-matrix interaction. It is now known that GnRH neurons originate with olfactory epithelium outside of the brain, and migrate to arrive at their hypothalamic location during fetal development. This process fails to occur normally in Kallmann syndrome. Anosmin is thought to play a role in neuronal migration and in the development of the olfactory structures; hence the connection between anosmia and CHH. *KAL-1* transcripts are found not only in the developing olfactory bulb together with GnRH, but also in the retina, spinal column, and developing kidney. The latter location may explain the renal agenesis and horseshoe kidney that are sometimes found. In many families with only males affected, the coding region of the *KAL-1* gene is normal, however [2].

Genetic studies in individuals with contiguous gene syndromes lead to the finding of fibroblast growth factor receptor 1 (FGFR-1) mutations in males and females with sporadic or autosomal dominant familial IHH [3]. At least 22 different mutations have been reported, accounting for about 10% of patients with IHH, and the disorder is sometimes designated KAL-2. In addition to hypogonadism, some patients have anosmia, cleft lip, cleft palate, dental agenesis, and other skeletal anomalies. There are four functional FGF receptors, and more than 20 FGFs that are paracrine stimulators of these receptors. FGFR-1 is a transmembrane receptor tyrosine kinase that activates phosphatidyl inositol and other signaling pathways by forming a dimer in the presence of FGF, and requires a heparan sulfate glycosaminoglycans. FGF signaling is involved in the development and growth of a variety of tissues. Mutation of *FGFR-1* in mice causes early embryonic death. The disorder is thought to represent a loss of FGFR function with defective embryonic development.

Only about 25% of KAL patients have mutations in the coding regions of *KAL-1* or *FGFR-1*. Thus, mutations of other genes, or in the promoter regions of *KAL-1* or *FGFR-1*, are yet to be discovered

Gonadotropin-releasing hormone activates a G-protein–coupled seven transmembrane receptor that signals primarily through the inositol phosphatase–protein kinase C pathway to stimulate α-subunit, LH-β, and FSH-β gene transcription and LH and FSH release from the pituitary. The finding that LH secretion in some patients with IHH responds poorly or not at all to GnRH stimulation focused interest on the GnRH receptor in this disease. The GnRH receptor gene is found on chromosome 4q13.1. At least 16 different mutations in *GnRH-R* have been associated with partial or complete GnRH resistance and hypogonadism. The disorder demonstrates autosomal recessive inheritance, in which inactivating mutations are inherited in a double heterozygous or sometimes a homozygous mode. Heterozygote carriers appear to be normal. Mutations of the GnRH receptor are found in 5% to 15% of IHH patients. The most common mutations are Gln^{106} to Arg^{106} and Arg^{262} to Gln^{262}. These mutations result in loss of ligand binding, or defective intracellular signaling, respectively. Males and females are affected, and predictably these patients have no midline defects.

A few patients with normosmic IHH due to loss of function mutations of the G-protein–coupled receptor 54 *(GPR54)* gene located on chromosome 19p13 have been described. *GPR54* is expressed in GnRH neurons, and kisspeptin-1, the ligand that activates *GPR54*, is now known to be an important upstream regulator of GnRH secretion. The HH phenotype of the *GPR54* mouse indicates that *GPR54* is necessary for normal gonadotroph function. Kisspeptin-1 appears to function as a proximate regulator of GnRH secretion in puberty, and may mediate steroid negative feedback control, but so far no mutations of the Kisspeptin-1 gene have been reported in IHH patients. Patients with *GPR54* mutations respond to GnRH treatment with increased LH, FSH, and testosterone secretion, and spermatogenesis.

One patient with a totally inactivating mutation of the LH-β gene has been reported. He presented with no pubertal development at age 17. He was found to have a low testosterone level and a high level of LH, suggesting primary testicular failure. But unlike patients with that condition, he had a robust increase in testosterone secretion following the administration of HCG. When his serum was

examined in the dispersed Leydig cell bioassay, there was no stimulation of testosterone secretion implying a lack of LH bioactivity. Sequencing of his LH-β subunit gene revealed a homogyzous A-to-G mis-sense mutation causing the replacement of glutamine by arginine in codon 54. It is important to emphasize that he had a masculine phenotype at birth because fetal testosterone production is governed by HCG, whereas the postnatal production of testosterone is under LH control and failed to occur.

Homozygous and compound heterozygous mutations of the *FSH*-β gene have been reported in a few women with absent sexual development and low FSH but elevated serum LH levels. Affected male relatives were discovered to have small testes and azoospermia with variable but impaired Leydig cell dysfunction causing LH levels to increase. The abnormal FSH-β protein is unable to associate with the common α-subunit to form the active dimer. Impaired testosterone synthesis may occur because FSH deficiency leads to abnormal communication between seminiferous tubules and Leydig cells.

Adrenal hypoplasia congenital (AHC) is a disorder characterized by primary adrenal failure in infancy or childhood, and isolated hypogonadotropic hypogonadism. Mutations in the *DAX1* gene (dosage-sensitive sex reversal–adrenal hypoplasia congenita [AHC] critical region on the X chromosome gene) cause X-linked AHC. More than 60 mutations have been reported. Frame-shift or mis-sense mutations produce a truncated protein with limited function. *DAX1* is a repressor of steroidogenic factor 1 (SF-1) mediated gene transcription with targets including the α-subunit, LH-β and GnRH-receptor genes accounting for the IHH. Adrenal and gonadal failure result from the disruption of the StAR (steroidogenesis acute regulatory) protein CYP11a (P-450 cholesterol side-chain cleavage enzyme) and 3β-hydroxysteroid dehydrogenase (3β-HSD). There is evidence that *DAX1*-inactivating mutations result in export of the protein from the nucleus to the cytoplasm, but the mechanism for reduced transcription of the SF-1 target genes is uncertain.

Interestingly, mutation in the GnRH gene, itself, has not been reported to cause CIHH in humans, in contrast to the hypogonadal (HPG) mouse. GnRH and its receptor are found in the human placenta, and inactivating mutations of GnRH may be embryonic lethal in humans (Table 26.2).

Table 26.2 Gene mutations in congenital isolated hypogonadotropic hypogonadism

Gene	Chromosome	Phenotype	Inheritance pattern
KAL-1	Xp22.3	HH and anosmia	X-linked
FGFR-1	8p11	HH, anosmia, craniofacial abnormalities	Autosomal dominant
GnRH-R	4q21.2	HH	Autosomal recessive
GPR54	19p13	HH	Autosomal recessive
LH-β	19q13.3	Testosterone deficiency	Autosomal recessive
FSH-β	11p13	Azoospermia, Leydig cell dysfunction	Autosomal recessive
DAX1	Xp21	HH, adrenal and testicular hypoplasia	X-linked

Testosterone treatment stimulates secondary sex characteristics and increases male sexual behaviors, but does not appreciably activate spermatogenesis. The testes of men with CIHH are generally normal other than lacking in LH/FSH activation, and most men with CIHH can produce sperm. To stimulate spermatogenesis in this patient, treatment was changed to HCG, which is generally an effective stimulator of spermatogenesis in men with acquired HH due to pituitary tumors, and is often effective as a sole agent in patients with congenital IHH, especially those men with partial gonadotropin deficiency [4]. It stimulates spermatogenesis by stimulating Leydig cell production of testosterone and Leydig cell proteins. A dose of 750 to 1000 IU intramuscularly or subcutaneously three times weekly is generally thought to be sufficient, whereas larger doses may increase estradiol production and produce gynecomastia. In this case, HCG alone stimulated sperm production and resulted in pregnancy in spite of very small testes prior to treatment (3 mL). If HCG alone remains ineffective after 6 months, human recombinant FSH at a dose of 75 IU three subcutaneously times a week is added. Most men with partial IHH and nearly 50% of men with more severe IHH will produce sperm with this regimen. The presence of cryptorchidism portends a poorer prognosis. Pulsatile GnRH can also be used to stimulate spermatogenesis in men with GnRH deficiency and normal pituitary function. GnRH administered continuously, however, will downregulate testicular function because it depletes GnRH receptors and disrupts GnRH receptor signaling. The dose of GnRH that effectively increases adult testosterone levels and stimulates spermatogenesis has ranged from 5 to 20 μg/pulse. More defined diagnostic testing to exclude patients with GnRH receptor mutations might improve the overall result for GnRH therapy. GnRH is not an appropriate treatment for men with pituitary disease.

Testosterone and estradiol are important regulators of bone metabolism. There is a progressive increase in bone density throughout childhood, with a marked increase in bone mineralization during puberty. This patient was found to have osteoporosis, and osteoporosis is a well-established complication of CIHH. Testosterone replacement increases bone density in young, previously untreated men with CIHH, whereas the effect seem to be less in older men [5]. Bisphosphonates along with testosterone are recommended.

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Multiple-Choice Questions

1. A 27-year-old man presents with delayed pubertal development. He is otherwise healthy, and has a normal sense of smell. He looks hypogonadal with sparse beard and body hair, and lack of musculature. His height is 65 inches and his arm span is 68 inches. His testes are each 4.2×2 cm. There are no other positive findings. Which of the following tests is indicated at this time?

   A. Sex hormone–binding globulin (SHBG)
   B. LH/FSH
   C. TSH
   D. IGF-I
   E. Pituitary MRI

2. Your clinical diagnosis of hypogonadotropic hypogonadism is confirmed with a testosterone level of 35 ng/dL, LH 1.2, and FSH 2.5 U/L. Each of the following should be assessed at this time, except:

   A. PRL level
   B. MRI pituitary
   C. Iron and iron binding capacity
   D. Peripheral blood karyotype
   E. Free thyroxine

3. Other than hypogonadotropic hypogonadism, his endocrine function is normal, the iron saturation is 35%, and there is no mass on the MRI. Which additional tests are needed at this time?

   A. DEXA scan
   B. Peripheral blood karyotype
   C. GnRH stimulation test
   D. Estradiol
   E. HCG stimulation test

4. The patient and his wife would like to have children. After counseling the extragonadal defects that sometimes occur in the offspring of IHH cases, and obtaining a baseline semen analysis. You recommend which of the following treatments:

   A. Human FSH
   B. Testosterone gel
   C. HCG
   D. GnRH
   E. Clomiphene

Chapter 27
Klinefelter Syndrome

Stephen J. Winters and Sathya Krishnasamy

Objectives

1. To present a representative patient with primary testicular failure
2. To review the pathophysiology, mechanism, and genetics of Klinefelter syndrome
3. To discuss the clinical implications of undiagnosed primary testicular failure
4. To review management options for men with testicular failure

Case Presentation

A 64-year-old man residing in a nursing home was admitted to the geriatric psychiatry service because of major depression. The endocrinology service was consulted to evaluate clinical androgen deficiency. The patient recalled normal birth events and childhood developmental milestones, but he viewed himself as the most fragile of four siblings. He believed that he always had small testes (he used the term "pea-grape" sized), and he never had much axillary or body hair. He was a poor student, and did not graduate from high school. He joined the Air Force, but was discharged within a few weeks. He married in his early twenties, and subsequently learned that he was infertile and azoospermic. He was evaluated and treated with testosterone injections every 2 weeks, which increased his body hair, but he remained impotent. He first began to shave his beard in his thirties. His marriage ended in a divorce, as did two subsequent marriages, also with no children. He worked as a foreman for six years until he sustained a shoulder injury. Since then he has received medical assistance. He developed depression and discontinued testosterone treatment after 15 years. He was socially isolated, and his sister was his only personal contact. He has had multiple hospitalizations for suicide attempts by hanging, starvation, and self-mutilation.

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T.F. Davies (ed.), *A Case-Based Guide to Clinical Endocrinology*,

He was recently admitted to a nursing home by his family members because of a decline in mental and physical health. He was unable to live independently or make financial decisions. He had no peer interactions at the nursing home. He was diagnosed with Parkinson's disease and hypertension. He denied anosmia, head trauma, testicular injury, orchitis, radiation, cancer, AIDS, or other chronic illness. There was no history of alcohol or drug use. There was no family history of hypogonadism or midline defects.

On physical examination he was a Caucasian male with a depressed, flat affect. The blood pressure was 105/60, and the pulse was 68 beats per minute. His height was 69″, and his arm span was 66″. His weight was 235 lb. He had smooth skin, sparse pubic hair, and no axillary or chest hair. His extraocular movements and the bedside visual field examination were normal. There was no goiter. He had bilateral gynecomastia. The phallus was small (4 cm in length) but normally formed. The left testis was 2 mL and the right was 1 mL compared to a Prader orchidometer.

The following laboratory tests were obtained: testosterone 14 ng/dL (normal 250–1100), follicle-stimulating hormone (FSH) 43.3 mIU/mL (normal 1.5–12.4), and luteinizing hormone (LH) 27.7 mIU/ml (normal 1.7–8.6). A dual-energy x-ray absorptiometry (DEXA) scan revealed a bone mineral density T-score of the left hip of −2.8 standard deviation (SD) and −1.0 in the lumbosacral (LS) spine.

Peripheral blood karyotype analysis indicated 20 cells analyzed had a chromosome number of 47 with two X chromosomes and one Y chromosome indicative of the 47,XXY karyotype of Klinefelter syndrome.

How the Diagnosis Was Made

We present a very interesting but unfortunate older man who endured tremendous hardships during young adulthood and middle age, and eventually was diagnosed with Klinefelter syndrome when he was admitted to a geriatric psychiatry service.

The patient presented with many symptoms and signs of hypogonadism including smooth skin, little body hair, gynecomastia, and small testes. Symptomatic hypogonadism and infertility had been present since young adulthood. While testosterone levels decline as normal men grow older, the patient's hypogonadism was far more pronounced biochemically and clinically than is typical of normal aging.

The diagnosis of hypogonadotropic hypogonadism was considered, but there was no history of head trauma, or headaches, no evidence of dysfunction of other endocrine systems, and no congenital anomalies associated with isolated hypogonadotropic hypogonadism (IHH). Nevertheless, the diagnosis of IHH remained in the differential until the levels of LH and FSH were known.

The finding of elevated serum LH and FSH levels indicated, however, that the diagnosis was primary testicular failure. Of the causes of testicular failure listed in Table 27.1, many were readily excluded by the medical history and physical examination. Klinefelter syndrome is a relatively common disorder affecting one in 450 to

Table 27.1 Causes of primary testicular failure

Congenital	Acquired
Klinefelter syndrome	Trauma
Cryptorchidism	Orchitis
Immune polyglandular failure	Spinal cord injury
Congenital anorchia	Cancer chemotherapy
Noonan's syndrome	X-irradiation
Lawrence-Moon-Bardet-Biedl syndrome	Retroperitoneal fibrosis
Myotonic dystrophy	Amyloidosis
Sickle cell disease	AIDS
Noonan's syndrome	Medications: ketoconazole,
	Alcoholic liver disease
	Chronic kidney disease

500 men. Tall stature, delayed puberty, clinical androgen deficiency, gynecomastia, small firm testes, and infertility are cardinal manifestations of Klinefelter syndrome [1], and that diagnosis was confirmed by the finding of a 47,XXY karyotype.

Lessons Learned

In 1942 Klinefelter described a group of unrelated adult men with small firm testes, hypogonadism, gynecomastia, and elevated gonadotropin levels (bioassays for gonadotropins in urine were performed at that time). Only in 1959 was the chromosomal basis of the disorder described. Subsequently, the diagnosis of Klinefelter syndrome has required the demonstration of the 47,XXY karyotype, or one of its variants. Klinefelter syndrome is the most common form of congenital male hypogonadism and sex chromosome aneuploidy. The incidence is 0.1% to 0.2% in the general population. Klinefelter syndrome is the most frequently established genetic cause of infertility, occurring in 11% of azoospermic men. Intrauterine mortality does not appear to be a feature of Klinefelter syndrome. The diagnosis is generally made in teenage boys with gynecomastia or delayed pubertal development, or in men with small testes or infertility. Sometimes the diagnosis is made prenatally with amniocytosis for genetic screening, or in the workup for another illness such as leukemia or cancer. The diagnosis is uncommon in early puberty, however, a time when many boys experience disease-related physical and emotional problems. Like our patient, many men remain undiagnosed, especially those with mild disease due to chromosome mosaicism. Bojesen et al [2] estimated that only one fourth of adult men in Denmark with Klinefelter syndrome have been diagnosed.

Genetics/Etiology

Chromosome analysis of rapidly dividing T-lymphocytes in peripheral blood that are chemically arrested in metaphase and stained is used to establish the

diagnosis. In individuals with more than one X chromosome, all in excess of the one X chromosome condense to form Barr bodies, a darkly staining mass of chromatin at the cell's nuclear rim.

The extra X chromosome in Klinefelter syndrome results from nondysjunction during meiotic division in germ-cell development, or in less than 5% in early embryonic mitotic division. About half of the cases are paternally derived, and result from the formation of an XY sperm in meiosis-I. Maternal XX oocytes can result from errors in either meiosis-1 (more common) or meiosis I & II. Increasing maternal age has been implicated in certain studies.

Higher-grade chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY) also produce the Klinefelter phenotype, whereas about 10% of cases are 46, XY/47,XXY mosaics. In the latter group of patients, peripheral blood lymphocytes may occasionally be genetically normal, especially if only 20 cells are counted, and karyotyping of skin fibroblasts or testicular biopsy specimens may be needed to confirm the mosaic diagnosis. For this reason, the prevalence of the mosaic karyotype is underestimated. Some men with congenital primary testicular failure have a 46,XX karyotype. The condition generally results from the translocation during paternal meiosis of the distal end of the short arm of the Y chromosome, containing the testis determining gene (SRY), to the X chromosome, or sometimes to an autosome. While resembling Klinefelter syndrome, these men sometimes have cryptorchidism or hypospadias. Some patients with this karyotype are true hermaphrodites, however (both testis and ovarian tissue; ovotesticular disorder of sexual differentiation).

Phenotypic Manifestations

The major phenotypic manifestations of Klinefelter syndrome are listed in Table 27.2. In general, the greater the number of X chromosomes, the more marked are the phenotypic consequences, both gonadal and extragonadal, including mental retardation, while mosaicism is associated with less classical clinical features [3]. While the stature and body hair in men with Klinefelter syndrome are variable polygenic traits, all patients with classical 47,XXY Klinefelter syndrome have small firm testes. Gynecomastia is present in 33% to 50% of cases, and is composed mostly of periductal tissue.

Klinefelter patients are often tall. They usually do not have classic eunuchoidal skeletal proportions (arm span at least 6 cm greater than height), but instead have

Table 27.2 Clinical features of Klinefelter syndrome

Small testes	Tall stature
Infertility (Azoospermia)	Abnormal crown-pubis ratio
Delayed puberty	Microcephaly
Cryptorchidism	Subnormal intelligence
Small phallus	Decreased libido/potency
Hypospadias	Learning disabilities
Gynecomastia	Behavioral disorders

exaggerated pubis-floor growth. Even prepubertal boys with Klinefelter syndrome may too have long legs, implying that this skeletal abnormality may not be a consequence of the sex hormone disturbance. Testosterone deficiency, however, may contribute to the abnormal body proportions.

Bone mineral density is significantly reduced, and osteoporosis is more common in men with Klinefelter syndrome than in normal men, although less common than in men with isolated hypogonadotropic hypogonadism. The physiological age-related decrease in bone mass is thought to be more pronounced in Klinefelter syndrome than in normal men. Free testosterone levels are highly correlated with bone mineral density (BMD), and our patient had a very low testosterone level as well as osteoporosis. The BMD has been reported to increase after the initiation of testosterone replacement especially in younger men.

Language and Behavioral Problems

The intelligence of 47,XXY individuals is slightly below that of controls, whereas patients with higher-grade aneuploidies tend to be mentally retarded. Boys with Klinefelter syndrome demonstrate a verbal cognitive deficit with significant underachievement in reading, spelling, and writing. Some also have reduced mathematical ability. These learning disabilities lead to poor school performance and to less skilled occupations in adulthood. Nevertheless, some patients with Klinefelter syndrome are intelligent and professionally and financially successful. For others, behavioral problems and difficulty with social relationships may accompany academic underachievement. Many patients are quiet, sensitive, and insecure. They also tend to lack insight and have poor judgment. Most studies have not found an increased risk for criminal behavior.

The CAG repeat length in the androgen receptor N-terminus, coding for polyglutamine repeats, influences receptor function, in vitro and in vivo, with more repeats favoring decreased function. CAG repeat length in the androgen receptor has been proposed to influence various phenotypes in Klinefelter syndrome including height, gynecomastia, and penis size, but other reports have not confirmed these associations.

Laboratory Findings

Serum LH and FSH levels are almost always elevated in men with Klinefelter syndrome, indicative of Leydig and seminiferous tubule dysfunction. Exceptions are prepubertal boys, and men with other illnesses that suppress gonadotropin secretion including morbid obesity. Mean total testosterone levels are lower than those of normal men, but in nearly one third of cases total testosterone is in the low normal range, especially in adolescents. Sex hormone–binding globulin (SHBG) levels are increased, which increases total testosterone. On the other hand, non-SHBG

testosterone and free testosterone levels are almost always low. Serum estradiol levels tend to be elevated since testicular aromatase is upregulated by high LH levels. The level of inhibin-B, a product of Sertoli cells, overlaps the normal range in prepubertal boys with Klinefelter syndrome, but levels decrease significantly during late puberty when germ cells and Sertoli cells die and are replaced by fibrosis.

Histopathology of Testis

Microscopic examination of the testis from adults with Klinefelter syndrome reveals absent spermatogenesis with hyalinizing fibrosis of the seminiferous tubules (Fig. 27.1). In some individuals, especially those with mosaic forms of Klinefelter syndrome, focal areas of spermatogenesis are preserved, however, or tubules contain Sertoli cells but no germ cells. On the other hand, testicular tissue from XXY fetuses or prepubertal boys contains nonsclerotic tubules with reduced germ cells and normal-appearing Sertoli cells. These findings imply that downstream effects of aneuploidy trigger the degeneration of germ cells and produce hyalinization of the tubules at puberty rather than the proliferation of germ cells that occurs normally. To date, the factor(s) that accelerate germ cell and Sertoli cell destruction are not known.

How testosterone deficiency occurs in Klinefelter syndrome is also unclear. The number of Leydig cells is maintained or increased producing the histological picture of Leydig cell hyperplasia (Fig. 27.1). Increased LH drive is thought to contribute to this finding, but disruption of the extensive communication among Sertoli cells, germ cells, and Leydig cells may also affect Leydig cell structure and function.

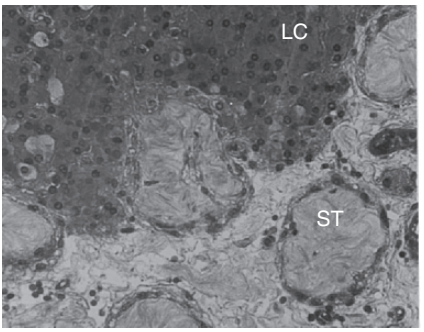

Fig. 27.1 Testicular biopsy from a man with Klinefelter syndrome. Note the hyalinized seminiferous tubules (ST) that are devoid of germ cells and Sertoli cells, and the hyperplastic Leydig cells (LC) (Courtesy of Dr. C. Alvin Paulsen.)

Table 27.3 Comorbid conditions associated with Klinefelter syndrome

Glucose intolerance	Breast carcinoma
Dyslipidemia	Thyroid dysfunction
Osteopenia	Taurodontism
Chronic leg ulcerations	
Pulmonary embolism	

Comorbid Conditions

Comorbid conditions associated with Klinefelter syndrome are listed in Table 27.3. A multicenter study from the United Kingdom Cytogenetics Group found an overall increased standardized mortality ratio related to cardiovascular diseases, respiratory illness, and nervous system diseases. Mortality was related particularly to diabetes, epilepsy, peripheral vascular disease, pulmonary embolism, and femoral fractures.

The likelihood of the metabolic syndrome or type 2 diabetes is increased in Klinefelter syndrome [4]. When compared to eugonadal height-matched controls, men with Klinefelter syndrome had increased body mass index (BMI), waist circumference, total body fat, and visceral fat. Low-density lipoprotein (LDL) and triglycerides were increased, and high-density lipoprotein (HDL) was reduced. Fasting insulin was increased and Homeostasis Model Assessment of Insulin Resistance (HOMA) was reduced, indicating insulin resistance. Moreover, values in men receiving testosterone treatment tended to be midway between those of normal controls and those of untreated patients, suggesting that long-term testosterone deficiency contributes to the metabolic findings in these men.

Pulmonary diseases such as chronic bronchitis, bronchiectasis, and emphysema are more common, and pneumonia was noted as a cause of mortality in the Danish registry study.

Varicose veins and leg ulcers are far more common in men with Klinefelter syndrome than in normal men, and may predispose to pulmonary embolism. Platelet hyperaggregability, factor V Leiden mutation, deficient fibrinolysis, and increased activity of factor VIII coagulant have been proposed to explain the chronic leg ulcerations. A variety of cardiovascular abnormalities have been reported as case reports, especially in higher-grade chromosome aneuploidies, including aortic and mitral valve disease, atrial septal defect, pulmonary stenosis, Ebstein's anomaly, and tetralogy of Fallot.

Men with Klinefelter syndrome are at increased risk for certain malignancies, including breast carcinoma (20 times greater incidence than men with XY); nonlymphocytic leukemia; non-Hodgkin's lymphoma; midline germ cell tumors, particularly extragonadal tumors involving the mediastinum; and marrow dysplastic syndrome. The risk for mediastinal germ cell tumors is more than 50–fold higher than in the general population. It is not known whether X-chromosome genes or hormone disturbance contributes to these associations. Testosterone deficiency predisposes to gonadotroph hyperplasia, and prolactin (PRL) levels may be slightly elevated, but pituitary tumors do not appear to occur more often in Klinefelter

syndrome. Whether the risk for testicular cancer is increased is controversial; however mortality from prostate cancer may be reduced.

Sex hormones and gender are important determinants in many autoimmune diseases. On the basis of case reports, the prevalence of systemic lupus erythematosus, thyroiditis, and systemic sclerosis may be elevated among men with Klinefelter syndrome. There are case reports of patients with lupus treated with testosterone whose hematologic and serologic abnormalities, including elevated levels of anti-DNA antibodies and depressed complement levels, returned to normal.

Treatment

At diagnosis we began replacement therapy using a testosterone gel, and upon receiving the bone density evaluation, risedronate and calcium with vitamin D were added.

Testosterone replacement corrects the classic features of hypogonadism including sexual infantilism, reduced muscle size and strength, fatigue, osteopenia, and anemia. Sexual interest and function improve. Priapism and acne as well as behavioral abnormalities may occur if a full dose is begun immediately in men with longstanding severe androgen deficiency. Tempered dose-escalation is suggested. While most authors propose beginning androgen replacement therapy in teenagers with Klinefelter syndrome, controlled trials are lacking. To what extent early intervention helps initiate puberty and improves social adjustment, self-esteem, and goal-directed thinking remains to be clarified. Some have suggested a low total testosterone level as a criterion for treatment; however, non-SHBG testosterone may be more accurate because SHBG rises with testosterone deficiency. High levels of circulating testosterone are needed to suppress LH into the normal range in men with testicular failure perhaps because of increased gonadotropin-releasing hormone (GnRH) receptors due to inhibin deficiency. Therefore, non-SHBG testosterone levels, rather than LH, should be used to guide the treatment dose.

Fertility

Men with mosaic 46,XY/47,XXY karyotypes occasionally produce sperm in their ejaculate and can be fertile, especially early in adulthood. On the other hand, men with 47,XXY are usually azoospermic. Nevertheless, foci of spermatogenesis are often present in the testes of these men, and pregnancy may occur in up to 33% to 50% of 47,XXY patients treated in experienced clinics using testicular sperm extraction (TESE) coupled with intracytoplasmic sperm injection (ICSI). Because there is increased risk for producing sex chromosome aneuploidy in ICSI offspring, preimplantation genetic diagnosis can be offered in which one or two blastomeres are biopsied from embryos at the eight–cell stage. Some couples do not accept this approach, whereas others will chose to terminate the pregnancy if abnormalities are

found. Finally, young men with Klinefelter syndrome who have sperm identified in the ejaculate can cryopreserve semen for future ICSI.

Some authors have suggested that lowering LH and FSH androgen replacement may reduce the likelihood that sperm will be found by TESE, and may therefore negatively impact fertility treatment. Further, they propose that if fertility is desired and the TESE/ICSI approach will be used, androgen treatment should be withheld and human chorionic gonadotropin (HCG) added. While thoughtful, this approach is unproven, and needs to be weighed against the consequences of withdrawing androgen replacement, since return of spermatogenesis after prolonged testosterone treatment may require a washout/recovery period of substantial duration.

Gynecomastia

Breast pain may occur with breast enlargement in adolescence. Malignant breast lesions are very rare in adolescents, but diagnostic ultrasound can be useful when breast enlargement is asymmetrical. Gynecomastia can be psychologically disturbing, especially to adolescents, and treatment is often needed. Conspicuous and long-standing gynecomastia does not respond to androgen replacement therapy. Claims that antiestrogens or aromatase inhibitors decrease breast tissue mass have come from open-labeled uncontrolled trials with self-reported outcomes. These drugs are unapproved for this purpose, and cannot be recommended at this time. The goals of surgical treatment are to restore the breast contour with minimal scarring, and to protect areolar anatomy and sensation. Plastic surgery is often by liposuction using small incisions in the axilla and sternum. Corrective surgery will often impact favorably on the emotional disturbance and academic difficulties that these boys endure.

Perhaps the most telling aspect of the patient presented in this case was the delay in diagnosis. Although the patient had symptoms and signs of hypogonadism beginning in his teenage years, and he was treated with androgen replacement, his condition was never diagnosed. For this man, the long-term social, economic, and physical impact of undiagnosed Klinefelter syndrome was enormous.

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Multiple-Choice Questions

1. You are consulted by the parents of a 13-year-old boy who has a scrotum but no palpable testes. He is otherwise healthy. He has soft smooth skin and little body hair. The phallus is 4 cm stretched and normally formed. Which of the following diagnostic tests should be performed at this time?

   A. Pituitary magnetic resonance imaging (MRI)
   B. Peripheral blood karyotype
   C. LH/FSH
   D. Free testosterone
   E. Inhibin-B

2. A 23-year-old with a history of testicular failure diagnosed at age 17 has become a body builder. In addition to the testosterone replacement you are prescribing, you believe that he is abusing anabolic-anabolic steroids. Which of the following statements about anabolic-androgenic steroids is incorrect?

   A. The urinary ratio of testosterone to its endogenous epimer, epitestosterone, of >4–6:1 is considered highly suspicious of exogenous testosterone abuse.
   B. Testosterone preparations that are made from plant sterols have a higher ratio of 13C:12C in urinary metabolites of testosterone.
   C. There is increased incidence of injection site abscesses in androgenic-anabolic steroid users due to needle sharing.
   D. Urine screening using liquid chromatography with dual tandem mass spectrometry identifies the designer steroid tetrahydrogestrinone (THG) effectively.

3. Which of the following statements with respect to testosterone replacement therapy is not correct?

   A. Erythrocytosis is more likely with transdermal testosterone than with long-acting injectable testosterone preparations.
   B. Peliosis hepatis, hepatoma, and cholestatic jaundice are common side effects of 17-alkylated testosterone preparations.
   C. Patients should be referred for prostate biopsy if a prostate nodule is palpated at any time or if the serum prostate-specific antigen (PSA) concentration, confirmed by a repeat value, is >4.0 ng/mL initially or increases by 1.4 ng/mL in any 1-year period.
   D. Overzealous treatment in adolescent boys with open epiphyses can cause early fusion and limit linear growth.
   E. Testosterone treatment may be associated with weight gain.

4. A 25-year-old man presents with gynecomastia and small testes. The LH is 35 IU/L and the FSH is 46 U/L. Which of the following is not in the differential diagnosis?

   A. XX male
   B. Klinefelter syndrome
   C. 5α-reductase deficiency
   D. Mumps orchitis
   E. Congenital androgen insensitivity

Chapter 28
Low Testosterone in Obesity and Type 2 Diabetes

Stephen J. Winters and Sathya Krishnasamy

Objectives

1. To understand how obesity and diabetes affect testicular function
2. To understand some pitfalls in the analysis of testosterone in obese men

Case Presentation

A 40-year-old man and his wife presented because of infertility. The couple had been married for 5 years, and failed to conceive after 3 years of unprotected intercourse. The wife has regular menstrual periods and a normal pelvic laparoscopy. The patient's libido and sexual potency were satisfactory and unchanged. He has been overweight or obese since childhood. He has had type 2 diabetes mellitus (T2DM) for 8 years, and is treated with glargine insulin at bedtime, and lispro insulin prior to meals. He had a herniated lumbar disk 10 years ago that resulted in chronic low back pain, for which he is treated with OxyContin and hot baths.

The patient is 6′1″ tall and weighs 330 pounds (body mass index [BMI] 44 Kg/m^2). He was normally virilized, and there were no signs of Cushing's syndrome. There was no goiter. There was bilateral gynecomastia. The phallus was normal. The testes were both scrotal. The right testis was just less than 25 mL in volume and measured 5.0 × 2.8 cm; the left testis was 15 + mL and measured 2.7 × 2.3 cm. There was a left varicocele in the upright posture.

The sperm density is 3 million/mL with 19% motile forms (normal >60). The percentage of ovalocytes is low at 1% (normal >14%). The total testosterone level is 195 ng/dL. The sex hormone–binding globulin (SHBG) level is low at 10 nM, and the non SHBG-testosterone (bioavailable testosterone) level is 144 ng/dL (normal >75). The direct free testosterone level is 7.5 pg/mL (normal 9–30). The luteinizing hormone (LH) is 2.31 mIU/mL, follicle-stimulating hormone (FSH) 3.6 mIU/mL,

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free thyroxine 1.2 ng/dL, and prolactin (PRL) 2.4 ng/mL. A magnetic resonance imaging (MRI) of the pituitary is normal. The couple was referred for in vitro fertilization, and conceived in the first intracytoplasmic sperm injection (ICSI) cycle.

How the Diagnosis Was Made

This man presented with low sperm count, poor sperm motility, and abnormal sperm morphology (oligoasthenospermia), and was found to have low serum testosterone and LH levels. The hormone findings were thought to be consistent with hypogonadotropic hypogonadism, perhaps due to a pituitary tumor, but no tumor was found on MRI. The low total testosterone level was instead explained by obesity, T2DM, and oxycontin therapy, whereas the small left testis and abnormal sperm count were partly due to the presence of a varicocele. The MRI was probably unnecessary since the patient had no clinical features of hypogonadism, no symptoms of testosterone deficiency, and his serum non-SHBG testosterone, free thyroxine, and PRL levels were normal.

Lessons Learned

This patient's findings highlight several common problems in andrology. Nowadays, endocrinologists are often asked to evaluate men with low testosterone levels who are obese or have T2DM, since asthenia and erectile dysfunction are consistent with hypogonadism. There is a well-established inverse relationship between testosterone and BMI in adult men, and the decrease, to a great extent, reflects a low level of SHBG in obesity. Hyperinsulinemia is believed to be a main factor lowering SHBG in obesity since SHBG messenger RNA (mRNA) levels are suppressed by insulin in vitro, circulating SHBG levels are inversely related to c-peptide concentrations, and SHBG increases when insulin levels fall because of weight loss or metformin treatment.

We recently found that total testosterone levels were below 300 ng/dL in 30% of men who were being treated for T2DM at a Veterans Administration hospital. Multiple linear regression analysis revealed that much of the decline could be attributed to coexistent obesity. Earlier studies have also found low testosterone in men with T2DM, and prospective studies established low testosterone as a risk factor for developing T2DM and the metabolic syndrome. In our study the prevalence of low testosterone was greater in diabetic than in nondiabetic men, after controlling for BMI, suggesting that there are additional factors predisposing to low testosterone in men with T2DM. Hypogonadism may be present in patients with secondary diabetes due to Cushing's syndrome, acromegaly, or hemochromatosis.

To determine whether hypogonadism is present when SHBG levels are low, the free or non-SHBG (bioavailable) testosterone levels can be calculated (go to http://www.issam.ch/freetesto.htm), or assayed directly using equilibrium dialysis

or ultracentrifugation. The non-SHBG testosterone level is determined by ammonium sulfate precipitation. Each of these approaches also requires the measurement of total testosterone. Gas or liquid chromatography followed by mass spectroscopy represents a new and accurate nonradioactive technique that is gaining wide acceptance, but the values for total testosterone with this method tend to be lower than with immunoassays. Sometimes the level of free testosterone has been measured using an analogue or direct assay. These one-step assays are simple to perform, and are precise, but they are inaccurate. Free testosterone levels measured by analogue assays in obese men are often low, much like the total testosterone, resulting in a misdiagnosis of testosterone deficiency. Other methods should be used.

Free and bioavailable testosterone levels in obese men are strongly positively correlated, and are generally within the normal range, as in the present case. If so, no further endocrine workup is probably needed. Free and bioavailable testosterone levels do decline as BMI rises, but the values tend to fall below the normal range only in extreme obesity.

Mean LH and FSH levels in men with obesity or T2DM who also have low free testosterone levels are slightly lower than values in normal controls, although high LH and FSH levels are sometimes found. Thus low testosterone in obesity and T2DM is most often associated with a disturbance in gonadotropin-releasing hormone (GnRH)-LH secretion. LH pulsatility studies have found reduced pulse amplitude with normal pulse frequency, although other studies have not confirmed the low pulse amplitude. Low LH pulse amplitude could be due to a reduction in GnRH production or a decrease in responsiveness of gonadotrophs to GnRH activation because of changes in GnRH receptors or receptor signaling. There is also some evidence that obesity impairs Leydig cell function directly.

Plasma estrone and estradiol levels are increased in obese men, and testosterone deficiency in obesity is most often proposed to be due to increased production of estrogens. Estrogens decrease LH secretion in men by slowing the GnRH pulse generator and by inhibiting the gonadotroph response to GnRH stimulation. Estrogen effects on GnRH have recently been proposed to be mediated by receptors on neurons producing kisspeptin-1. In spite of many experiments, the mechanism for inhibitory effects of estrogens on the pituitary remains uncertain. Estrogen receptor antagonists such as clomiphene or tamoxifen, or aromatase inhibitors such as anastrazole, increase LH and testosterone levels in obese men, as in normal men, because they interrupt estrogen negative feedback.

In subcutaneous adipose tissue, there is a high level of expression of the aromatase enzyme cytochrome P-450 aromatase, encoded on 15q21. This enzyme converts testosterone to estradiol, and androstenedione to estrone, with the cofactor, flavoprotein, and reduced nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome P-450 reductase. The aromatase gene contains 10 exons, and alternate splicing of exons 1 and 2 produces at least five tissue-specific promoters. The promoters in fibroblasts are activated by dexamethasone, and by the cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α. Some studies show increased cortisol production in obesity, and there may be enhanced conversion of inactive cortisone to cortisol by 11β hydroxy steroid dehydrogenase type 1

(11β HSD-1) in adipose tissue and the brain. Adipose tissue also produces inflammatory cytokines, which may suppress testosterone production.

Obesity appears to impair sperm production and predispose to infertility. A recent survey of American couples in Iowa and North Carolina revealed a twofold increased risk for infertility among men with BMI >32 after adjusting for age and female BMI. Among Danish military recruits, those men with a BMI >25 had a 21.6% reduction in sperm concentration and 23.9% lower total sperm count than men with a BMI between 20 and 25; obese men also had lower levels of inhibin-B. The finding of low inhibin-B levels in healthy but obese young adults, but not in prepubertal boys, allows for the untested hypothesis that a reduced proliferation of Sertoli cells during puberty explains the lower sperm count in obesity.

Testosterone levels are often low in men treated with opiates, including oxycodone (OxyContin). Based on experiments with opiate antagonists, the endogenous opiate β-endorphin as well as opiate drugs are thought to influence gonadal function via the regulation of GnRH release. While opiate neurons may directly contact and regulate GnRH neurons, various neurotransmitters, including catecholaminergic, dopaminergic, and serotoninergic systems, have been proposed as mediators for the opiate effect on GnRH.

Gynecomastia, enlargement of the male breast, is a common finding in obese men. Although it is often difficult to distinguish glandular breast tissue from adipose tissue clinically, a firm button or mass of subareolar tissue is sometimes palpable, and the areolae can be pigmented and enlarged. Gynecomastia is thought to result from an imbalance in the physiologic estrogenic stimulation and androgenic inhibition of breast tissue growth, and to require stimulation of the breast by PRL and growth hormone (GH)/insulin-like growth factor I (IGF-I). When breast enlargement occurs rather suddenly, or is painful, a thorough evaluation should be conducted. Some of the causes of gynecomastia are listed in Table 28.1. Notably, human chorionic gonadotropin (HCG)-producing tumors cause gynecomastia by stimulating testicular aromatase, much like LH, while hyperthyroidism increases

Table 28.1 Disorders associated with gynecomastia

Tumors
Testis: Leydig cell tumor, Sertoli cell tumor
Adrenal: adenoma or carcinoma
Choriocarcinoma, testicular, or extratesticular
Primary testicular failure
Klinefelter syndrome, trauma, mumps, cancer chemotherapy
Hypogonadotropic hypogonadism congenital or acquired
Acromegaly
Prolactinoma
Hyperthyroidism
Familial aromatase excess
Androgen insensitivity syndromes
Alcoholic liver disease
Chronic kidney disease
Drug-induced gynecomastia

Table 28.2 Drug-associated gynecomastia

Estrogen bioactivity	Increased estrogen levels	Inhibit testosterone synthesis	Block androgen receptors	Damage testes	Other mechanisms
Estrogen containing embalming lotions	HCG	Spironolactone	Spironolactone	Alkalating agents	Risperidone
Meat from estrogen-fed animals	Testosterone	Ketoconazole	Flutamide	Methotrexate	Amphetamine
Clomiphene	Androstenedione	GnRH analogues	Bicalutamide		Cyclosporine
Marijuana leaves	Estrogen receptor-α antagonists		Cimetidine		Reserpine
					Amiodarone
					Metronidazole

SHBG, LH levels rise, and testicular estrogen production increases. In many conditions, several mechanisms may be operative. Many drugs have been associated with gynecomastia (Table 28.2). In some cases effects on androgen or estrogen production or metabolism have been established, whereas for other drugs the mechanism is ill- defined.

This patient also had a small left testis and a left varicocele, a dilatation of the meshwork of veins forming the pampiniform plexus within the scrotum. Varicocele may produce discomfort, and is mostly readily appreciated when the patient is standing. It is usually left sided, and associated with a dilated and incompetent left internal spermatic vein. Venography suggests that the disorder is often bilateral, however. Clinical varicocele is a more common finding among infertile men than among fertile men, and is usually first evident during adolescence. There is generally a loss of volume of the left testis compared the right and histologic evidence of impaired spermatogenesis. Many but not all men with varicocele have low sperm count and poor sperm motility. However, the mechanism linking varicocele and male infertility is not known. Elevated FSH levels or an exaggerated FSH response to GnRH stimulation are associated with worse testicular function, but these values are often normal. Varicocele surgery is commonly performed, but its efficacy has been debated for 50 years. At present, there is no proof that treatment of varicocele in male partners from couples with otherwise unexplained subfertility improves their likelihood of conception.

The most effective treatment for the low testosterone of obesity is gradual weight loss. SHBG levels rise so that total testosterone levels increases more than free or non-SHBG testosterone. Extreme low calorie diets may lower testosterone because calorie restriction and energy deprivation may suppress GnRH. Estrogen receptor antagonists such as clomiphene or tamoxifen, or aromatase inhibitors such as

anastrazole, will increase LH and testosterone levels in obese men, as in normal men, because they interrupt estrogen negative feedback control of GnRH and LH secretion. HCG will also increase testosterone levels in obese men. There are no controlled studies to support the use of these agents in the treatment of the oligospermia of obesity, however. Therefore, the couple was referred for in vitro fertilization.

Suggested Readings

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Multiple-Choice Questions

1. A 42-year-old man presents with erectile dysfunction. He was married for 11 years and has two children, but he divorced 2 years ago. He is otherwise healthy and takes no medications. His libido is strong. His maternal and paternal grandmothers each had type 2 diabetes. On physical examination, he is healthy and appears well. His height is 6′ and his weight is 190 pounds (BMI 26). There is no goiter or gynecomastia. Both testes are 4.6 × 2.8 cm, and 20 to 25 mL in volume. His total testosterone level was 236 ng/dL. Each of the following tests is useful at this time, except:

   A. Lipid profile
   B. Fasting blood sugar
   C. Free testosterone
   D. PRL
   E. TSH

2. A 30-year-old man presents with bilateral breast enlargement. He was previously healthy, and is the father of two children. Hypertension was diagnosed 2 years ago, and he is treated with lisinopril. He lost 10 pounds in weight during the past year. On physical examination, the pulse is 100. There is a small goiter. He has prominent breasts that are tender to palpation. The testes are each 4.8 × 2.7 cm. The serum testosterone level is 988 ng/dL. Each of the following tests is useful at this time except:

A. TSH
B. HCG
C. Mammogram
D. SHBG
E. LH/FSH

3. A 40-year-old man presents with low libido. His skin is smooth, and he has bilateral gynecomastia. His serum testosterone level is 110 ng/dL, LH 1.0 IU/L, FSH 1.2 IU/L, and estradiol 145 pg/mL. Which of the following diagnostic tests is indicated next?

A. Pituitary MRI
B. Testicular ultrasonography
C. GnRH stimulation test
D. SHBG
E. Clomiphene stimulation test

Part IX
Female Reproduction

Introduction

Janet E. Hall

Physiology of the Reproductive System

Normal menstrual function requires repetitive cycles of follicle development, ovulation, preparation of the endometrium for implantation should pregnancy occur, and shedding of the endometrium if conception does not occur. Normal cycles are approximately 28 days from the onset of menstrual bleeding in one cycle to the onset of bleeding in the following cycle. This pattern of regular cyclic function begins as one of the final pubertal milestones and ends with menopause. For up to 2 years after the first menstrual period, or menarche, and for several years before the final menstrual period, it is normal for cycles to be irregular. However, throughout the remainder of reproductive life, regular cycles are the rule. Deviations from regular monthly vaginal bleeding should prompt a thorough history and physical examination and possibly laboratory testing.

This pattern of regular menstrual cycles requires precise integration of hormonal signals from the hypothalamus, the pituitary, and the ovary. The endometrial lining of the uterus is exquisitely responsive to ovarian hormones and serves as a marker of reproductive function. Hypothalamic and pituitary function are intact at the time of birth, and active in the neonate, but and then suppressed until the time of puberty when neuroendocrine signals, which appear to include the newly discovered kisspeptin/GPR54 system, result in reactivation of gonadotropin-releasing hormone (GnRH) secretion and subsequent synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

At birth, the ovary has its full complement of oocytes. The oocyte is surrounded by a layer of granulosa cells and subsequently by an outer layer of theca cells that together form a follicle. These small follicles remain in a quiescent state until puberty, when a cohort of follicles is stimulated by FSH to enter a phase of active growth. Inhibin B and mullerian inhibiting substance (MIS), also known as antimullerian hormone (AMH), increase and are markers of functioning granulosa cell

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number. The theca and granulosa cells work together to produce estradiol; under the stimulus of LH, the theca cells synthesize androgenic precursors, which are transferred across the basement membrane to the granulosa cells where they are aromatized to estradiol under the control of FSH.

In women, a single follicle generally emerges as dominant. This follicle is distinguished by its size, increasing responsiveness to FSH, and increasing concentration of estradiol and inhibin A, which is also secreted from granulosa cells (Fig. IX.1). The rising concentrations of estradiol and inhibin A restrain the secretion of FSH through actions at both the hypothalamus and pituitary so that further follicles are not stimulated to grow to maturity. With further growth of the dominant follicle, estradiol increases exponentially, resulting in marked proliferative changes in the endometrium. Growth of the dominant follicle is associated with an accumulation of fluid within the antrum of the follicle and therefore can be monitored on ultrasound, as can the increase in endometrial thickness. The exponential increase in estradiol triggers the LH surge (positive feedback), which is responsible for resumption of meiosis in the oocyte, ovulation, and luteinization of the granulosa cells.

The corpus luteum, which forms from the ruptured follicle, produces progesterone, estradiol, and inhibin A with the support of LH. Progesterone and estradiol produce the complex secretory changes in the endometrium that are required for potential implantation. The responsiveness of the corpus luteum diminishes over time, and with it the hormonal support of the endometrium. If conception does not occur, the endometrium is shed. Importantly the decline in progesterone, estradiol, and inhibin A, releases the hypothalamus and pituitary from negative feedback, FSH is allowed to increase, and a new cohort of follicles is recruited, beginning the cycle again.

If conception occurs, human chorionic gonadotropin (HCG) from the developing trophoblast takes over control of the corpus luteum, maintaining estradiol and progesterone secretion and the integrity of the secretory endometrium until the placenta takes over steroid hormone production at approximately 8 to 10 weeks of gestation.

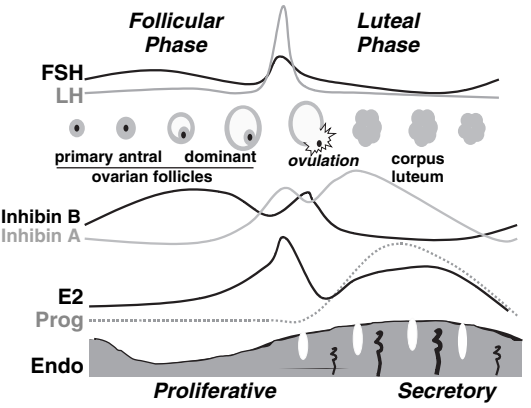

Fig. IX.1 Ovarian, hormonal, and endometrial changes during the normal menstrual cycle

Thus, within the ovary, gonadotropins play dual and differential roles. Both are necessary for normal steroidogenesis while FSH is critical for folliculogenesis and LH for ovulation. Negative feedback of ovarian hormones on pituitary secretion of FSH and LH and release from negative feedback are essential for cyclic ovarian function and are key to ovulation of a single follicle. The negative feedback of ovarian hormones on FSH and LH is also critical to the diagnosis of disorders of reproductive function.

Menstrual Dysfunction

In the United States, menarche occurs at an average age of 12.7 years, though somewhat younger in African-American that in Caucasian girls. Cycles should become regular and predictable within 2 to 4 years of menarche, with a range of 25 to 35 days considered as normal. The duration of the luteal phase is relatively constant at 12 to 14 days, and thus the major variability in cycle lengths is due to differences in the length of the follicular phase.

Primary amenorrhea is diagnosed by the absence of menses by age 16, but girls who have no evidence of breast development or are less than the third centile for height should be evaluated by age 14. Secondary amenorrhea is used to describe the cessation of menstrual periods once they have begun. The absence of menses for 3 to 6 months is generally used as the criteria for amenorrhea. Oligoamenorrhea is defined as fewer than 10 menses per year or a cycle length of greater than 35 days and is the term that is generally given to irregular and often anovulatory cycles.

Causes

The diagnosis of disorders of reproductive function in women can be approached by first considering potential abnormalities of the uterus and outflow tract. Once these have been ruled out, the clinician should systematically consider disorders that can result in anovulation, using the principles of ovarian negative feedback on gonadotropin secretion and historical clues to narrow the diagnostic possibilities (Table IX.1).

Uterine and Outflow Tract Disorders

Although they account for a relatively small percentage of patients with amenorrhea, disorders of the uterus and outflow tract are an important consideration, particularly in patients presenting with primary amenorrhea. For the diagnosis of such patients, understanding the process of normal embryologic development of the internal reproductive organs provides a critical backdrop. During embryologic development, the internal genitalia are formed from paired mullerian ducts that fuse in the midline to

Table IX.1 Causes of amenorrhea

Source of abnormality	Primary amenorrhea	Secondary amenorrhea	Specific causes
Disorders of the uterus/ outflow tract	21%	5%	Obstruction (imperforate hymen, transverse septum) Mullerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome) Androgen insensitivity syndrome Asherman syndrome
Ovulatory disorders:			
Hypothalamus	25%	35%	*Genetic: KAL1, FRFR1, GPR54, PCI, LEP, LEPR, NROBI* *Tumors:*- craniopharyngioma, germinoma, glioma, meningioma, endodermal sinus tumor, metastatic tumors, midline dermoid cyst *Infiltrative diseases*: histiocytosis X, tuberculosis, sarcoidosis, Wegener granulomatosis *Other:* head injury, cranial radiation, surgery, eating disorders, systemic disease, thyroid disease, Cushing syndrome *Functional:* exercise, weight, or metabolic balance
Pituitary gland	2%	20%	*Genetic: GnRHR, PROP1, HESX1, LHX3* *Tumors:* prolactinoma, acromegaly, gonadotropin- secreting tumors *Infiltrative diseases:*– lymphocytic hypophysitis, hemochromatosis *Other:*– infarct (Sheehan syndrome), empty sella syndrome, pituitary irradiation, surgery
Ovary: premature ovarian failure	45%	10%	*Genetic:*- Turner syndrome, fragile X premutation carriers, triple X syndrome, blepharophimosis (*FOXL2*), dystrophic myotonia,, mutations in *LHβ, FSHβ, FSHR, LHR* *Destructive:* galactosemia, radiation, chemotherapy, viral infections *Autoimmune:* polyglandular failure
Hyperandrogenic	7%	30%	*Polycystic ovarian syndrome* *Congenital adrenal hyperplasia:* virilizing and late onset *Drugs:* anabolic steroids, valproic acid *Tumors:* ovarian, adrenal

form the uterus, cervix, and proximal third of the vagina. In the male, secretion of MIS from the developing testis causes regression of the mullerian system, whereas testosterone promotes development of the male internal genitalia and virilization of the external genitalia.

Obstruction of the outflow tract can result from a transverse vaginal septum or an imperforate hymen. Mullerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome) is a congenital anomaly that is characterized by hypoplasia or aplasia of the uterus or vagina that has been associated with mutations in the *WNT4* gene. Patients with either obstruction or mullerian agenesis will have normal and cyclic gonadotropin and ovarian hormone levels in the absence of menses and can be diagnosed by pelvic examination. A pelvic ultrasound can be useful to determine the level of the defect.

Approximately 10% of patients with primary amenorrhea have complete androgen insensitivity syndrome (AIS). While these patients have a male karyotype, they are phenotypically female, presenting with normal breast development and body habitus. They have normal female external genitalia and scant body hair because of resistance to testosterone, but lack internal female genitalia because of the gonadal production of MIS. On examination, there is a blind vagina and, biochemically, testosterone levels and estradiol levels are high and LH and FSH levels are generally in the slightly elevated range.

Uterine abnormalities can be the cause of either secondary amenorrhea or decreased menstrual bleeding in patients in whom uterine instrumentation has led to the formation of scar tissue within the uterus. This usually occurs in association with curettage for pregnancy complications, but can also be associated with infection.

Ovulatory Disorders

Once abnormalities of the uterus and outflow tract have been excluded, all other causes of amenorrhea or oligoamenorrhea are due to anovulatory disorders. It is important to rule out pregnancy in almost all cases. Further evaluation depends on gonadotropin levels and the presence or absence of hyperandrogenism.

Hypogonadotropic Hypogonadism

The absence of normal hypothalamic secretion of GnRH or normal pituitary responsiveness to GnRH ultimately results in the failure of normal ovulatory cycles. Low levels of estradiol are accompanied by low levels of both FSH and LH. This clinical picture can result from anatomic or genetic abnormalities that interfere with hypothalamic or pituitary function or from functional suppression of normal hypothalamic GnRH secretion. Although neuroanatomic causes of amenorrhea are relatively uncommon, it is critical that tumors and infiltrative diseases of the hypothalamus and pituitary be excluded in all patients presenting with primary amenorrhea and normal or low levels of LH and FSH (Table IX.1). Even if a patient presents with secondary amenorrhea and normal or low levels of LH and FSH, neuroanatomic causes should be considered, particularly in the presence of other features of hypothalamic or pituitary disease including short stature, diabetes insipidus, galactorrhea, central hypothyroidism, or headache. It is important to measure prolactin levels in patients with hypogonadotropic hypogonadism,

as hyperprolactinemia is not only a marker of prolactinomas, which are relatively common in women in their reproductive years, but also because even mildly elevated levels of prolactin may be a sign of other neuroanatomic lesions. Several conditions causing hypogonadotropic hypogonadism occur in the postpartum period and include pituitary necrosis (Sheehan syndrome) and lymphocytic hypophysitis.

Although rare, hypogonadotropic hypogonadism may be due to genes that interfere with GnRH secretion or action (Table IX.1). A number of genes have now been described in patients presenting with complete or partial phenotypes that range from the total absence of breast development and primary amenorrhea to incomplete breast development and one or two episodes of vaginal bleeding. Anosmia is present in some, but not all of these patients and the diagnosis requires exclusion of neuroanatomic lesions.

A third of cases of amenorrhea are due to functional causes that are now thought to relate to a mismatch between energy intake and energy expenditure. Leptin appears to be one of the key hormones that transduces signals regarding energy balance from the periphery to the hypothalamus, and the hypothalamic-pituitary-adrenal axis may also be involved. Hypothalamic amenorrhea commonly presents as secondary amenorrhea, but may also present as delayed puberty. It is critical to exclude eating disorders and systemic disease. There should be a low index of suspicion for excluding neuroanatomic causes, but cranial imaging is not necessary in all patients who present with secondary amenorrhea.

Hypergonadotropic Hypogonadism

Premature ovarian failure (POF) is diagnosed in less than 1% of the female population and is defined as menopause in a woman less than 40 years of age. Ovarian failure is associated with loss of negative feedback regulation on the hypothalamus and pituitary and increased levels of both FSH and LH. However, increased FSH is both a more specific and a more sensitive marker of ovarian failure than is LH. There is a range of other health problems associated with conditions that cause POF, and thus a search for its cause is warranted.

Turner syndrome accounts for the largest percentage of patients with POF and may be associated with not only short stature and other somatic features, but also hearing loss, cardiac defects, and hypothyroidism. POF has recently been found to be associated with the premutation carriers of the fragile X syndrome and testing for this abnormality is now being recommended due to the potentially devastating consequences should the patient or her sisters conceive. POF may also be seen with autoimmune diseases; it is frequently associated with autoimmune thyroid disease, and from 2% to 10% of patients with POF have Addison's disease or are at risk of adrenal failure due to antibodies against adrenal or steroid cells.

Rarely hypergonadotropic hypogonadism results from abnormalities in the β-subunit of FSH (or LH) or their receptors. While gonadotropin-secreting tumors theoretically may be associated with POF, in a significant number of cases, the FSH

secreted from these tumors is biologically active, and patients present with ovarian hyperstimulation or dysfunctional bleeding.

Hyperandrogenic Menstrual Dysfunction

Polycystic ovarian syndrome (PCOS) is diagnosed in the presence of hyperandrogenism and menstrual dysfunction, which manifests as amenorrhea or, more commonly, irregular bleeding that is associated with frequent anovulation. Hyperandrogenism is generally chronic in nature and can be detected by an increased total or free testosterone level or by the presence of acne, hirsutism, and occasionally alopecia. Signs and symptoms of virilization are rarely caused by PCOS. Lean patients will have increased LH levels in the presence of relatively normal FSH levels, although the LH/FSH abnormality may be less apparent in obese patients. Insulin resistance is a common feature of PCOS and is amplified in the presence of obesity. The vast majority of patients will have the classic polycystic ovarian morphology on pelvic ultrasound, with ovarian enlargement or an increased number of small antral follicles that are generally peripherally arrayed. There is some controversy regarding the diagnostic criteria for PCOS with respect to whether menstrual dysfunction or hyperandrogenism is required if polycystic ovaries are present. Polycystic morphology can be present in women with regular cycles and without clinical evidence of hyperandrogenism, and these women do not progress to menstrual dysfunction over time. To date, there is little evidence that insulin resistance is present in women with a less severe phenotype, and thus it is important to reserve the use of insulin sensitizers for those patients for whom they are clearly indicated.

Polycystic ovarian syndrome is a diagnosis of exclusion of other causes of hyperandrogenism. Thus, the workup should include a careful history of the timing of onset and pace of hyperandrogenic symptoms and the presence of associated features. A sudden onset and rapid development of symptoms should lead to consideration of androgen secreting tumors of the adrenal or ovary, as should the development of hyperandrogenic symptoms in a postmenopausal woman, and Cushing's syndrome should be included in this differential. Patients with late-onset congenital adrenal hyperplasia may appear clinically indistinguishable from patients with PCOS. Specific testing should target ethnic populations in whom the prevalence is increased, including Ashkenazi Jews and patients of Mediterranean origin. There is also recent evidence that the use of valproic acid for treatment of seizure disorders or bipolar disease may be associated with hyperandrogenism and menstrual dysfunction.

Diagnostic Approach to Menstrual Cycle Disorders

A careful and specific history is key to the diagnosis of menstrual dysfunction. A developmental history should include questions relating to growth and timing of pubertal milestones. The menstrual history should include the age and weight at menarche, characteristics of recent cycles including symptoms such as breast

tenderness, food cravings and mood changes that might suggest ovulation, as well as the date of the last menstrual period. Health and lifestyle factors should include sexual activity and use of contraception, medications, illnesses, previous pregnancies, uterine instrumentation, stress, diet, weight changes, and exercise patterns. Finally, a number of localizing symptoms should be specifically addressed including the presence and pace of androgenic symptoms; nausea, ongoing breast tenderness, and weight gain; galactorrhea or visual symptoms; significant loss or increase in weight; hot flashes or difficulty sleeping; and anorectic behavior or perceptions.

The physical examination should specifically address height, weight, and arm span; somatic features of Turner syndrome; and Tanner staging of secondary sexual characteristics. A thorough skin examination can be extremely instructive, looking for acne, oiliness, hirsutism, acanthosis nigricans; signs of weight loss, hypercarotenemia, lanugo hair, dental carries; centripetal obesity and pigmented striae. The breast exam should include a specific search for expressible galactorrhea. Finally, in all patients with amenorrhea, a pelvic examination must be performed.

As pregnancy is the most common cause of amenorrhea, a β-HCG should be performed in all patients with some degree of pubertal development and in whom the pelvic examination has excluded a blind vagina. Prolactin and FSH levels should be performed as first-line tests, with additional testing as determined by the history and physical examination, but possibly including LH, thyroid function tests, androgen levels, pelvic ultrasound and cranial MRI.

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Chapter 29
Central Hypogonadism

Maria A. Yialamas

Objective

To illustrate the presentation and diagnosis of central hypogonadism.

Case Presentation

A 35-year-old woman presented for evaluation of amenorrhea. She described an unremarkable menstrual history with menarche at age 12 and normal menstrual cycles (30 days in length) since that time, with the exception of two successful pregnancies. However, in the previous 6 months, she has had no menses. Her only evaluation was a Provera (10 mg × 5 days) challenge with no subsequent withdrawal bleeding. Otherwise, she had been feeling well. She denied visual changes, hot flushes, or night sweats. She also denied heat or cold intolerance, changes in her skin or hair texture, weight changes, or changes in her bowel habits. Interestingly, she did describe galactorrhea during this same 6-month period. No new symptoms of acne, hirsutism, or alopecia were present. She claimed to eat three well-balanced meals per day, a sum total of approximately 1500 calories per day, and to jog 5 miles two or three times per week.

Her past medical history was remarkable for migraine headaches, which had recently increased in frequency and intensity. She had no prior surgeries or gynecologic procedures. Her only hospitalizations were associated with the births of her two children, ages 5 and 3. Her only medications were Excedrin on an as-needed basis for her migraines and a daily multivitamin. She had no known drug allergies.

Her family history was unremarkable for any reproductive disorders, thyroid disease, or infertility. She was a successful corporate lawyer and had been working with her present firm for the past 5 years. She was very happy there and had not had any increased stress in the previous few months. In addition, everything was going

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well at home. She did not smoke, drank alcohol only one or two times a year, and described no illicit drug use.

On physical examination, she was a well-developed, well-nourished woman in no acute distress. Her body mass index (BMI) was 23 kg/m^2, blood pressure 110/65, and pulse 72. Skin examination revealed no acne, hirsutism, alopecia, or vitiligo. No acanthosis nigricans was present. Head and neck exam revealed full visual fields and a normal funduscopic exam. Cranial nerves II to XII were intact and symmetric, and the oropharyngeal exam showed moist mucus membranes with no mucosal freckling. The thyroid was 20 g and without nodules. Lungs were clear to auscultation bilaterally. Back examination revealed no spinal or paraspinal tenderness. Breast examination revealed expressible galactorrhea bilaterally. No breast masses were present. Cardiovascular exam was normal with a regular rate and rhythm and no murmurs, rubs, or gallops. Abdominal exam showed normal active bowel sounds. No tenderness, abdominal mass, or hepatosplenomegaly were present. Pelvic examination revealed normal-appearing female genitalia. No clitoromegaly was present. The vaginal mucosa was normal. The cervix was unremarkable, and the uterus was normal in size. No cervical motion tenderness, adnexal tenderness, or adnexal masses were appreciated. Extremities were without clubbing, cyanosis, or edema. Neurologic examination was grossly nonfocal, with normal proximal muscle strength and reflexes 2+ throughout.

Laboratory evaluation included a negative human chorionic gonadotropin (HCG), prolactin 42 ng/mL (normal 2.6–13.1), follicle-stimulating hormone (FSH) 3 mIU/mL (normal 1–18), and thyroid-stimulating hormone (TSH) 3.0 mIU/L (normal 0.5–5). The elevated prolactin was confirmed on a subsequent blood draw. An MRI of the pituitary gland revealed a 2.7-cm suprasellar mass (Fig. 29.1). Mild compression of the optic chiasm was noted. Further evaluation included an insulin-like growth factor I (IGF-I) level and free thyroxine (T_4), which were normal. An

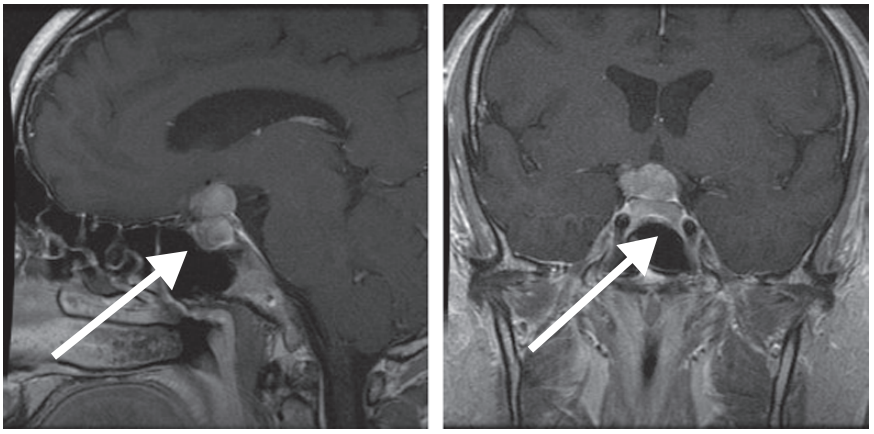

Fig. 29.1 Sagittal and coronal views of the pituitary gland. The arrow points to the tumor

overnight dexamethasone suppression test to rule out Cushing's syndrome was normal as well.

The patient had transphenoidal surgery and subsequently received hormone replacement therapy when her menses did not resume.

How the Diagnosis Was Made

This young woman presented with a 6-month history of amenorrhea. When investigating secondary amenorrhea, the initial differential diagnosis must be broad, including pregnancy, anatomic etiologies, and ovulatory disorders. Pregnancy was excluded in our patient, and she had no history of any gynecologic instrumentation or scanty menses, making Asherman's syndrome unlikely. Therefore, an ovulatory disorder seemed the most likely etiology. The fact that she did not have a withdrawal bleed in response to a Provera challenge provides an important clue to hypoestrogenism. This led to further questions about her eating patterns, exercise regimen, and stress level at home and work to determine whether her diagnosis could be functional hypothalamic amenorrhea. This is the most likely diagnosis in a young woman with amenorrhea and a negative progesterone challenge test. However, the patient's responses to these questions were unremarkable.

When evaluating ovulatory disorders, initial testing in all patients should include a TSH, prolactin, and FSH to exclude thyroid disease, hyperprolactinemia, and premature ovarian failure, respectively. The patient had no signs or symptoms of thyroid disease (weight changes, skin or hair texture changes, heat or cold intolerance, bowel habit changes) or premature ovarian failure (hot flushes, night sweats), and her TSH and FSH values were in the normal ranges. Since she had a negative progestin challenge and did not have any signs or symptoms of polycystic ovary syndrome, such as acne and hirsutism, androgen levels were not ordered. The only positive physical exam finding was galactorrhea. Galactorrhea can be present in approximately 10% of normal women in the absence of increased prolactin levels, particularly if there is a history of previous pregnancy. However, new-onset galactorrhea combined with amenorrhea is highly suspicious for hyperprolactinemia, as was the case in this patient.

The patient's history of increasing headaches in the setting of hyperprolactinemia raises the possibility of a prolactin-secreting adenoma. Alternatively, as prolactin is controlled by its inhibiting factor, dopamine, a pituitary tumor that causes compression of the pituitary stalk, will also result in hyperprolactinemia. The best imaging modality for pituitary tumors is magnetic resonance imaging (MRI). The patient's MRI revealed a large suprasellar mass. A prolactin of greater than 200 ng/mL would be expected in the presence of a mass >2 cm if this mass were a pure prolactin secreting adenoma. A prolactin of level of 42 ng/mL, as was seen in this patient, is more consistent with a nonfunctioning adenoma with hyperprolactinemia occurring on the basis of stalk compression.

The patient's amenorrhea was likely secondary to interference with normal GnRH stimulation of the pituitary on the basis of the suprasellar mass effect or

the secondary effect of prolactin inhibiting GnRH secretion. Occasionally, pituitary tumors within the pituitary gland can interfere directly with gonadotrope function by a mass effect.

Lessons Learned

1. Since the differential diagnosis of secondary amenorrhea is broad, every patient with this diagnosis should have a complete history and physical examination. This evaluation will help guide what further testing should be pursued.
2. Every patient with secondary amenorrhea should have an HCG, prolactin, TSH, and FSH to exclude pregnancy, hyperprolactinemia, hypo- or hyperthyroidism, and premature ovarian failure, respectively.
3. All patients with persistent hyperprolactinemia, no matter how slight the elevation, should have a pituitary MRI to assess for a mass.
4. Prolactin-secreting microadenomas, in addition to any macroadenoma with pituitary stalk compression, can result in hyperprolactinemia.
5. Pituitary masses can cause amenorrhea via a mass effect on the hypothalamus or pituitary stalk as in this case, via elevated prolactin levels, which result in decreased GnRH secretion, or through a mass effect on pituitary gonadotropes.

Multiple-Choice Questions

1. Which of the following lab tests should you order when a patient presents with secondary amenorrhea?

   A. HCG
   B. Prolactin
   C. TSH
   D. FSH
   E. All of the above

   Answer: E. Pregnancy should always be a consideration in the workup of secondary amenorrhea, and it is important to rule out premature ovarian failure. Thyroid dysfunction (either hypo- or hyper-) can cause menstrual cycle abnormalities, although this is a relatively infrequent cause of secondary amenorrhea. Prolactin-secreting microadenomas frequently present in this age group in association with menstrual cycle abnormalities, and increased prolactin can also be a marker of hypothalamic or pituitary disease.

2. In a patient with amenorrhea and an elevated prolactin, which of the following would be the next appropriate step?

   A. Treat with a dopamine against.
   B. Perform a pituitary MRI.

C. Treat with an oral contraceptive pill.
D. Perform a mammogram.
E. Treat with hormone replacement therapy.

Answer: B. It is essential that a patient with a persistently elevated prolactin level have a neuroimaging study to rule out a large hypothalamic or pituitary tumor. Treatment with a dopamine agonist will mask the symptoms and needs to be reserved for use after the cause of the elevated prolactin has been ascertained. Oral contraceptives and hormone replacement will likewise obscure the problem and may mask the appropriate diagnosis. A mammogram is not helpful in this setting.

3. How does hyperprolactinemia cause amenorrhea?

A. Increases GnRH pulse frequency
B. Decreases GnRH pulse frequency
C. Blocks estrogen binding to estrogen receptor
D. Accelerates estrogen metabolism

Answer: B. Hyperprolactinemia can interfere with normal LH and FSH secretion by decreasing GnRH pulse frequency.

4. Which of the following hypothalamic-pituitary disorders can cause secondary amenorrhea?

A. Hemochromatosis
B. Lymphocytic hypophysitis
C. Sheehan's syndrome
D. Sarcoidosis
E. All of the above

Answer: E. All of the options presented can cause hypothalamic or pituitary dysfunction and result in secondary amenorrhea.

Chapter 30
Premature Ovarian Failure

Corrine K. Welt

Objective

To review the diagnosis, diagnostic workup, and long-term follow-up of women with premature ovarian failure.

Case Presentation

A 31-year-old woman presented with a 2-year history of infertility. She underwent menarche at the age of 12 years and had regular cycles with intermittent development of ovarian cysts. The cysts were treated with oral contraceptive pills (OCPs) from age 24 to 26 years. She became amenorrheic after discontinuing the OCPs 5 years ago. She denied headaches, visual field loss, excessive hair growth or acne, galactorrhea, and hypo- or hyperthyroid symptoms. She did low-impact aerobics and denied eating disorders. She noted very occasional hot flashes. Her past medical history was remarkable for hypothyroidism, diagnosed at age 11 years, for which she took thyroid hormone replacement. Her family history was unremarkable. She did not smoke cigarettes and worked as a lawyer. On physical exam she was not orthostatic; height was 156 cm, weight was 47.3 kg, and body mass index (BMI) was 19 kg/m^2. She had no vitiligo, hirsutism, acne, or acanthosis, normal peripheral visual fields, a 10-g thyroid, no galactorrhea, and slightly enlarged ovaries.

Her laboratory evaluation demonstrated a thyroid-stimulating hormone (TSH) of 2.27 mU/L (normal 0.5–5), prolactin 12.8 μg/L (normal 0–15), β-human chorionic gonadotropin (HCG) negative, and follicle-stimulating hormone (FSH) 19.9 IU/L (postmenopausal >30 IU/L; 1 standard deviation [SD] above the mean for normal women, 15 IU/L) and estradiol <20 pg/mL. An inhibin B level was very high at 1000 pg/mL (normal follicular phase average 173 pg/mL). An ultrasound demonstrated multiple ovarian cysts bilaterally (1 of 10 mm, 3 of 12 mm, and one each at

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17, 20, 22, and 30 mm). Magnetic resonance imaging (MRI) demonstrated a normal pituitary gland.

The patient underwent several cycles of ovulation induction using a combination of purified luteinizing hormone (LH) and FSH. Although she grew two to three dominant follicles with each treatment, she had very low estradiol levels and did not become pregnant. After three cycles of treatment she was again amenorrheic, and a repeat FSH level reached the postmenopausal range. An ultrasound performed at the same time demonstrated inactive ovaries. Antiadrenal antibody testing was negative. Fragile X premutation testing and a karyotype were normal. The patient was treated with estradiol and cyclic progesterone for hormone replacement. She and her husband adopted two children.

The patient subsequently developed achy joints and a positive antinuclear antibody with a homogeneous, 1:160 titer. Ten years later, the patient developed darkening of the skin and extreme fatigue. A Cortrosyn stimulation test demonstrated baseline cortisol 108 nmol/L, which was unchanged 1 hour after 0.25 mg Cortrosyn. Adrenocorticotropin (ACTH) was elevated at 176 pmol/L. She was treated with prednisone and fludrocortisone.

How the Diagnosis Was Made

Premature ovarian failure is the diagnosis given to women under age 40, with amenorrhea, elevated gonadotropin levels, and low estradiol. It can present as primary amenorrhea and failure to go through puberty, as in Turner's syndrome, or as secondary amenorrhea. Symptoms include hot flashes, insomnia, worsening premenstrual syndrome, and night sweats, as seen in this patient. The FSH level is typically elevated into the postmenopausal range.

Despite its name, premature ovarian failure is characterized by intermittent follicle development and ovulation that can occur even after several months of amenorrhea. During these times of intermittent follicle development, which can be detected on ultrasound, the FSH may be in the normal range due to negative feedback from estradiol or inhibin B. In this case, the patient's FSH level did not reach the postmenopausal range initially, but was greater than 1 SD above the mean for reproductive aged women on day 3 of the menstrual cycle with a very low estradiol but a high inhibin B. There is evidence that an FSH level 1 SD above the mean for normal women on menstrual cycles days 2 to 4 indicates reduced fertility during assisted reproductive technology treatments, even when menstrual cycles are still regular. As illustrated in the patient's follow-up course, such a pattern may represent an early presentation of ovarian failure. Unfortunately, the prognosis for fertility is quite low with a relatively elevated FSH level whether there is intermittent follicular development and normalization of FSH or even regular menstrual cycles.

The FSH should be repeated for confirmation before a diagnosis of premature ovarian failure is given to a patient, keeping in mind that intermittent follicular development can transiently normalize the FSH level. It is important to remember

that the diagnosis of premature ovarian failure is devastating and should be discussed with the patient in person and with a sufficient amount of time for questions. When the diagnosis of premature ovarian failure is established, a workup for the cause is warranted. Although the etiology of premature ovarian failure can be determined in only approximately 30% of cases, it should be sought to improve medical management.

Women who carry the fragile X premutation, a triplet repeat expansion of the *FMR1* gene that can lead to fragile X mental retardation syndrome in offspring if the repeat expands, are at risk for early menopause. Fragile X premutation carriers account for approximately 16% of familial premature ovarian failure and 2% of sporadic cases. The premutation is defined as 55 to 200 CGG repeats in the 5′ untranslated region of the *FMR1* gene (Xq27.3), while >200 repeats results in the full fragile X mental retardation syndrome. Determining the presence of the premutation is particularly important in women who are still considering pregnancy because premutation carriers have a risk of bearing a child with mental retardation if the repeat expands in the progeny. Genetic counseling is warranted before testing and in cases in which the test is positive. Other family members may need testing and counseling if they are still of childbearing age. Male (and possibly female) carriers of the fragile X premutation are also recognized to be at risk for a tremor-ataxia-dementia syndrome in old age and may therefore also benefit from testing.

A karyotype should be performed in all women with premature ovarian failure (POF) under the age of 35 years, since a Turner's mosaic could present with premature ovarian failure after years of normal menstrual cycles, and these patients should be screened for the complications of Turner's syndrome. Chemotherapy or radiation can cause premature ovarian failure; therefore, a careful history of childhood illness is important. A FSH secreting tumor in reproductive aged women typically presents with ovarian hyperstimulation and increased FSH levels. In the current case of an elevated FSH level in a woman with multifollicular development, a MRI was warranted; however, in cases with small or inactive ovaries, a MRI is not necessary. A bone density is important as a baseline in women with amenorrhea.

Autoimmune premature ovarian failure often occurs in the setting of polyglandular failure type I (mucocutaneous candidiasis and hypoparathyroidism) or type II (adrenal insufficiency and other autoimmune disease). The patient in the case presentation has polyglandular failure type II with autoimmune ovarian failure as her second manifestation. Autoimmune disease is important to identify because of the life-threatening risk of adrenal insufficiency, which developed in this patient. A history of autoimmune disease should be elicited and evidence of orthostatic hypotension, vitiligo, darkening of the skin or freckling of the mucous membranes, premature graying, and thyroid abnormalities sought. A morning fasting cortisol or Cortrosyn stimulation test should be performed if there are concerning signs/symptoms of adrenal insufficiency. Adrenal and thyroid antibodies should be tested. The presence of adrenal antibodies indicates a 50% risk of developing adrenal failure in the future. Therefore, yearly adrenal and thyroid testing are needed particularly if antibodies are positive. However, negative tests do not rule out the possibility of future autoimmune disease in these target organs as demonstrated in

this patient. Ovarian antibodies are not specific or diagnostic of autoimmune ovarian disease, and are therefore not necessary.

In autoimmune ovarian failure, ovaries are cystic appearing or normal. Microscopically, a lymphocytic infiltrate is demonstrated in the theca layer of developing follicles with increasing cellular infiltrate during development. The granulosa cell layer is spared until luteinization. Primordial follicles are also spared. Up to 95% of patients with adrenal autoimmunity and concomitant premature ovarian failure have positive steroid cell antibodies. Specific targets include the 21 hydroxylase, P-450 side chain cleavage, and 17α-hydroxylase enzymes.

The destruction of theca cells and therefore androstenedione substrate explains the very low estradiol levels in this case. In contrast, sparing of the granulosa cells explains the robust inhibin B levels. The initial FSH level did not reach the postmenopausal range likely because of the high inhibin B levels, which are a specific negative feedback regulator of FSH, despite the absence of estradiol.

Pregnancy options are limited for women with premature ovarian failure. Previous work suggests that fertility treatment does not increase the pregnancy rate over the spontaneous pregnancy rate in women with this diagnosis. Patients followed with weekly ultrasounds for 12 weeks to identify spontaneous follicular activity had a 14% pregnancy rate. While conservative management and the use of ultrasound monitoring has limited success, it can help patients to accept their diagnosis. Adoption and oocyte donation are the most successful means to start a family depending on the patient's preference. There are anecdotal reports that menses resumes and that pregnancy can occur in women with autoimmune ovarian failure using high-dose immunosuppression with corticosteroids. The risks of high-dose steroid use apply, however. Randomized clinical trials should be sought to treat these patients with steroids if pregnancy is desired. If pregnancy is not desired, oral contraceptives may be necessary both for estrogen replacement and to suppress cystic follicle growth.

The treatment for this patient consists of estrogen to protect her bone mass and progesterone to protect the uterus. Postmenopausal hormone replacement doses are adequate for this purpose and should be continued until the average age at menopause, 45 to 50 years old. Although birth control pills can be used for women with premature ovarian failure, hot flashes often occur during the placebo week of the pills, necessitating a continuous regimen. Continuous birth control pills are often a good option for women with intermittent follicle and cyst development, and were appropriate for this patient earlier in the course of her diagnosis.

Lessons Learned

1. Premature ovarian failure can be associated with intermittent follicular development, ovulation, and menses.
2. Follicle-stimulating hormone levels may be in the postmenopausal range in patients with premature ovarian failure, but can also be in the normal range during the intermittent follicle development that occurs frequently during the early stages after diagnosis.

3. The causes of premature ovarian failure include X chromosome deletions or translocations, fragile X permutations, autoimmune disease, and previous history of chemotherapy or radiation, but in the majority of cases the etiology is unclear.
4. A history and diagnosis of adrenal insufficiency should be sought yearly in women with an autoimmune cause of premature ovarian failure or in women in whom the etiology is not clear.
5. Infertility is common with this diagnosis and oocyte donation is the best means to achieve pregnancy.

Multiple-Choice Questions

1. Which test results are consistent with premature ovarian failure?

   A. FSH 3.2 IU/L, LH 0.6 IU/L, estradiol <20pg/mL
   B. FSH 68 IU/L, LH 57 IU/L, estradiol <20pg/mL
   C. FSH 9 IU/L, LH 56 IU/L, estradiol 45 pg/mL
   D. FSH 25 IU/L, LH 80 IU/L, estradiol 300 pg/mL

   Answer: B. Results in A are consistent with hypothalamic amenorrhea, results in C are consistent with polycystic ovary syndrome, and results in D are typical of day of the LH surge in a normal menstrual cycle.

2. When the diagnosis of premature ovarian failure is made, which additional tests should be ordered?

   A. Karyotype
   B. Fragile X premutation screen
   C. Adrenal autoantibodies
   D. Thyroid autoantibodies
   E. All of the above

   Answer: E. All of these tests are important after an initial diagnosis has been made.

3. What can occur commonly after a diagnosis of premature ovarian failure is made?

   A. Adrenal failure
   B. Intermittent folliculogenesis and irregular withdrawal bleeding
   C. Weight loss
   D. Pregnancy

   Answer: B. Although adrenal failure can occur in women with autoimmune premature ovarian failure, it is more common to have intermittent follicle growth with or without ovulation and withdrawal bleeding as a result of follicle growth and increased estradiol. The other symptoms are not known to be associated with ovarian failure.

4. What therapy should be used in women with premature ovarian failure?

   A. Estradiol and progestin in hormone replacement doses
   B. Oral contraceptives
   C. Bisphosphonates
   D. Serotonin reuptake inhibiting antidepressants

   Answer: A. Hormone replacement therapy remains the mainstay for treatment of women with premature ovarian failure, whether given in the form of estradiol patches or pills. Estradiol prevents bone loss during the reproductive years when estradiol should be present and can be given until the average age at menopause. Progesterone reduces the risk of uterine cancer from unopposed estrogen replacement. Oral contraceptives are useful in women who tend to develop ovarian cysts because of their high FSH levels; however, many women will have hot flashes during the placebo week on therapy. Therefore, oral contraceptives need to be given in a continuous fashion (skipping the placebo week).

5. What is the best treatment for infertility in women with premature ovarian failure?

   A. In vitro fertilization
   B. Ovarian stimulation with luteinizing and follicle stimulating hormone
   C. Estradiol replacement
   D. Glucocorticoids
   E. Donor oocyte

   Answer: E. While there are case reports of patients with premature ovarian failure becoming pregnant during treatment with steroids, estradiol, or gonadotropin stimulation, these have not been demonstrated to be effective in case-control studies. Donor oocyte remains the best means for a woman with premature ovarian failure to achieve pregnancy.

Chapter 31
Oligomenorrhea and Hyperandrogenemia

Sabrina Gill

Objective

To review the diagnosis of oligomenorrhea and hyperandrogenemia and the approach to appropriate therapy.

Case Presentation

A 26-year-old Hispanic woman presented with an 8-month history of worsening of hirsutism. She had noted the development of coarse dark hairs on her face, chest, suprapubic region, and upper legs. She had previously shaved and used depilatory creams and recently started electrolysis for her face. She had also noted exacerbation of acne on her face and back. She complained of mild frontal hair thinning in the temporal regions of her scalp.

Historically she noted that acne had been a problem since her teenage years. When she started the birth control pill, her acne improved. She had no prior history of alopecia or hirsutism. With regard to her menstrual cyclicity, she had menarche at age 12 years with adrenarche at 10 years of age and thelarche at age 11. She had cycled irregularity with menses every 2 to 4 months with dysmenorrhea. She was prescribed an oral contraceptive pill (OCP) to improve dysmenorrhea, menstrual cyclicity, and acne at the age of 15 years. She remained on the OCP for 11 years and had regular menses every month.

However, she had recently gained approximately 15 lb over the last 5 years, which she attributed to lifestyle changes with less physical activity and poor diet, as she was living on campus during her university years, and she recently quitting smoking. She had struggled with various diets and had recently increased her exercise routine to lose weight. She associated OCP use with her weight gain and

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stopped taking the OCP about a year previously. Since then, she noted increased hyperandrogenic symptoms and had had only four periods in the past year. She rarely noted premenstrual symptoms such as breast tenderness and occasionally had intermenstrual spotting. She had not experienced galactorrhea or symptoms of thyroid dysfunction.

Her past medical history is remarkable only for tonsillectomy. She was not currently taking medications except for a multivitamin. She had no allergies to any medications. She smoked one pack per day for 7 years and quit 18 months ago although she had recently restarted at half a pack per day. She consumed a few drinks per week, usually on the weekend.

Her family history was significant for type 2 diabetes in her father, who also had coronary artery disease with his first myocardial infarction at the age of 54 years. Her mother had a history of hypothyroidism, hypertension, gestational diabetes mellitus (GDM), and two miscarriages in the past. Her older brother had noted some early hair loss.

She was a teacher and recently engaged. She was planning to be married in 2 months and to start a family within the next 6 months.

On examination, height was 65 inches, weight 135 lb, waist circumference 31 inches, and body mass index (BMI) 23.2 kg/m^2. Blood pressure was 128/82 (both arms) and heart rate 86 beats per minute. There was no evidence of thyromegaly, but she was noted to have mild supraclavicular fullness. Respiratory, cardiovascular, and abdominal examination was unremarkable. She had no other features of hypercortisolemia. She had mild acanthosis in the axilla and terminal hairs on the chin, chest, lower back, upper legs, and suprapubic region (Ferriman-Gallwey score of 14). She had acne on the face and upper back, and mild hair thinning in the temporal regions of her scalp.

The differential diagnosis of hyperandrogenism and menstrual dysfunction includes polycystic ovary syndrome (PCOS), androgen-secreting tumor of the adrenal or ovary, nonclassic congenital adrenal hyperplasia (NCAH), medication-related (e.g., Danazol, androgens), Cushing's syndrome, hyperthyroidism, hyperprolactinemia, and severe insulin resistance syndrome.

Investigations were performed between 8 and 10 a.m., and her last menstrual period was 7 weeks previously. Results of testing revealed the following: total testosterone 88 ng/dL (normal 14.2–74.3) [3.1 nmol/L (normal 0.5–2.6)], dehydroepiandrosterone sulfate (DHEAS) 2115 μg/L (normal 692.3–3961.5) [5.5 μmol/L (normal 1.8–10.3)], random 17-hydroxyprogesterone 2.7 μg/L (normal 0.16–3) [8.3 nmol/L (normal 0.5–9)], adrenocorticotropin (ACTH)–stimulated 17-hydroxyprogesterone 1.4 μg/L [4.2 nmol/L], thyroid-stimulating hormone (TSH) 1.23 mU/L (normal 0.3–5.5), prolactin 28.6 μg/L (normal 3.0–26), luteinizing hormone (LH) 22.2 U/L, follicle-stimulating hormone (FSH) 2.9 U/L, and a.m. cortisol following dexamethasone suppression <1.1 μ g/dL [<30 pmol/L]. Pelvic ultrasound: right ovary $26 \times 21 \times 25$ mm with 12 follicles <10 mm; left ovary $15 \times 18 \times 14$ mm with one 10-mm follicle; endometrial thickness 5 mm; no endometrial or adnexal pathology was noted.

Further investigations included a 75 g oral glucose tolerance test (OGTT) and fasting lipid profile, which found: fasting glucose 88.2 μg/dL [4.9 mmol/L], fasting insulin 15.0 mIU/L (normal <10 mIU/L) [105 pmol/L (normal <70)], 2-hour glucose 144 μg/dL [8.0 mmol/L], total cholesterol 247.9 mg/dL [6.42 mmol/L], low-density lipoprotein (LDL) cholesterol 158.3 mg/dL [4.10 mmol/L], triglycerides 350.4 mg/dL [3.96 mmol/L], high-density lipoprotein (HDL) cholesterol 62.5 mg/dL [1.62 mmol/L], total/HDL ratio 3.96.

How the Diagnosis Was Made

The clinical presentation of hyperandrogenemia includes hirsutism in androgen-sensitive locations, acne, androgenetic alopecia, and increased sebaceous secretion. It is important to distinguish hirsutism from hypertrichosis, which involves androgen-insensitive vellus hair growth often associated with medication use. The Ferriman-Gallwey score of 8 or more is an objective assessment of coarse male pattern hair growth. Characterization of menstrual irregularity, medication use, family history of hyperandrogenemia and anovulation, presence of metabolic disease, and the time course of the onset of symptoms help distinguish between the various etiologies. Rapid-onset virilization with significant temporal balding, increased muscle mass, deepening of the voice, and clitoromegaly are often associated with an androgen-secreting tumor. Conversely slow progression of mild-moderate hyperandrogenic symptoms over years is more compatible with PCOS or late-onset congenital adrenal hyperplasia (LOCAH).

Polycystic ovary syndrome is one of the most common endocrinopathies impacting premenopausal women. The diagnosis is generally made in the presence of hyperandrogenism and menstrual irregularity after excluding other etiologies of hyperandrogenemia and oligo-ovulation. It has recently been suggested that the diagnostic criteria for PCOS be revised to include two of three criteria: oligo- or anovulation, clinical or biochemical hyperandrogenemia, and polycystic ovarian morphology on ultrasound in appreciation of the wide spectrum of presentation of women with PCOS. While polycystic ovary morphology is commonly associated with PCOS, it is recognized that approximately 20% of unaffected women may have this feature on ultrasound. Further studies will determine whether these less stringent criteria are of significant advantage in managing hyperandrogenic patients. PCOS is currently recognized to be a familial disorder, and it is not uncommon to have a family history of hyperandrogenemia (such as male pattern balding) or infertility.

As in the described case, adolescent girls with PCOS may often present initially with premature adrenarche or irregular cycles without clinical features of hyperandrogenemia. Discontinuation of the OCP may unmask clinical hyperandrogenemia. Furthermore, weight gain is associated with increased insulin resistance and hyperinsulinemia, which can also increase ovarian hyperandrogenemia.

Biochemical assessment of hyperandrogenemia in women is based on measurement of circulating androgens, primarily LH-driven testosterone produced by

ovarian thecal cells. While total testosterone measured by immunoassays may not accurately reflect testosterone concentrations in women, it is standardized and adequate to establish clinically significant biochemical hyperandrogenemia. Importantly, total testosterone can be used to identify androgen-secreting tumors, which are often associated with considerably elevated testosterone levels (>200 ng/dL). Current commercial assays measuring free testosterone are not as accurate as the reference methods (e.g., equilibrium dialysis and centrifugal ultrafiltration-dialysis), which are impractical in routine commercial laboratories. Bioavailable testosterone can be measured by ammonium sulfate precipitation or calculated with measured total testosterone and sex hormone–binding globulin levels using equations described by Vermeulen, but is not generally of additional value in the diagnosis of PCOS. While the presence of an elevated LH/FSH ratio >2 supports the diagnosis of PCOS, the lack of an elevated ratio does not exclude it. Hypersecretion of LH is a pathophysiologic feature of PCOS, but recent ovulation and obesity result in lower LH levels.

Exclusion of other etiologies for hyperandrogenemia and oligo-ovulation is warranted. To screen for LOCAH due to 21-hydroxylase deficiency, basal morning follicular phase 17-hydroxyprogesterone level <200 ng/dL (6 nmol/L) can be used to exclude the diagnosis, although an ACTH-stimulated 17-hydroxyprogesterone level >1000 ng/dL (30 nmol/L) is the most sensitive test for the diagnosis of LOCAH. In patients with clinical features of hypercortisolemia, including hypertension, hyperglycemia or insulin resistance, centripetal obesity, striae, and dorsocervical or supraclavicular fullness, a 24-hour urine collection for measurement of urine free cortisol or serum cortisol after 1 mg dexamethasone suppression is warranted to exclude Cushing's syndrome. Mild hyperprolactinemia is observed in approximately 10% of hyperandrogenic women. A TSH level is ample in assessing for thyroid dysfunction except in cases of pituitary dysfunction, where a free thyroxine (FT_4) is warranted. Further imaging by pelvic ultrasound is warranted to assess ovarian morphology for polycystic ovaries or an androgen-secreting ovarian tumor. If suspicion of an adrenal tumor is high, abdominal imaging by computed tomography (CT) or magnetic resonance imaging (MRI) should be considered.

There are ample data to support the association of insulin resistance with PCOS. This association is important not only because of the association with increased ovarian hyperandrogenemia but also because of the increased risk of type 2 diabetes and possible cardiovascular disease with aging, independent of BMI. Clinical features of hyperinsulinemia such as acanthosis nigricans and a family history of metabolic disease can identify persons at risk of insulin resistance. Evidence demonstrates the unreliability of fasting plasma glucose levels in identifying women with impaired glucose tolerance or type 2 diabetes and the need for standardized 2-hour glucose levels after a 75-g oral glucose load as an appropriate screening test in this population. As insulin resistance is associated with metabolic disease, assessment of hypertension, hyperlipidemia, and cardiovascular disease is also warranted in women with PCOS.

Based on her presentation of clinical and biochemical hyperandrogenemia, oligomenorrhea, and polycystic ovary morphology, the diagnosis in this patient was consistent with PCOS with impaired glucose tolerance. Treatment options for

PCOS are based on symptomatic relief, and the therapeutic options for regulation of menses, control of hyperandrogenic symptoms, contraception and infertility, and prevention of potential long-term metabolic complications were discussed with the patient.

For regulation of menstrual cyclicity, treatment options would include OCP, cyclic progestins, or metformin. The choice depends on the patient's need for contraception (i.e., OCP) versus fertility and the presence of other symptoms. Hirsutism can be effectively treated by cosmetic options (e.g., laser hair removal, depilatory creams, shaving, electrolysis), but often medical management is also needed for optimal results. Eflornithine HCl (Vaniqa^{R}) cream, OCPs, antiandrogen agents (such as spironolactone, flutamide, cyproterone acetate, finasteride), or metformin may all be of benefit, but may need to be used in combination. Other hyperandrogenic symptoms such as alopecia or acne can be alleviated with antiandrogens, OCP, or topical therapies (e.g., minoxidil). The patient has impaired glucose tolerance and insulin resistance (not unexpected with her family history), which, in conjunction with her history of smoking, mild hypertension, and family history of premature coronary artery disease, increases her risk of cardiovascular disease in the future. Counseling on diet and lifestyle modification is imperative, particularly discontinuation of smoking, and an insulin sensitizer may need to be added.

Because of the presence of impaired glucose tolerance and given her interest in pursuing pregnancy in the near future, the patient was prescribed metformin starting at 250 mg daily increasing up to 500 mg t.i.d. She experienced some nausea, abdominal bloating, and diarrhea, but this was self-limiting and alleviated by taking the medication with food. She continued cosmetic treatment, but was advised to use laser therapy with Vaniqa cream due to the potential teratogenic effects of antiandrogen agents. She was advised to maintain barrier contraception until her symptoms stabilized, particularly while using Vaniqa. Lifestyle changes were evaluated and she was seen by a dietitian along with a trainer to guide her in developing an exercise program.

In the subsequent 6 months, she lost 10 lb with weight resistance and cardio exercise, and noted some improvement of facial hirsutism with combined laser and eflornithine HCl (Vaniqa). Her menstrual cyclicity improved with menses every 4 to 6 weeks, and an appropriately elevated luteal-phase progesterone confirmed ovulation in one cycle. She then started prenatal vitamins and discontinued the eflornithine HCl. Her husband's semen was evaluated and found to be normal, and she tried to pursue pregnancy but without success after 4 months. She underwent a hysterosalpingogram, which excluded tubal or endometrial obstructive lesions. Laparoscopic evaluation for any pelvic pathology such as endometriosis was postponed due to the likelihood that her anovulatory status was the primary cause of infertility in this case.

Ovulation induction with an antiestrogen agent, clomiphene citrate, was initiated at 50 mg on days 5 to 9 after a progestin-induced bleed, and metformin was continued. The patient conceived on her third cycle of treatment. If pregnancy did not occur, further therapies might include injectable gonadotropins, pulsatile gonadotropin-releasing hormone (GnRH), laparoscopic ovarian drilling, and assisted reproductive techniques.

Small studies have shown a decreased miscarriage rate in women with PCOS who continued metformin for part of or throughout the pregnancy, but a large randomized controlled trial has not confirmed these. In this current case, given no prior history of miscarriage, it was decided to discontinue metformin at the time of confirmation of pregnancy. Furthermore, given her mild insulin resistance, the patient was at risk of gestational diabetes and hypertension during pregnancy, warranting prompt evaluation as per current guidelines. The patient was eventually diagnosed with gestational diabetes, which was successfully managed with diet and lifestyle changes alone.

Lessons Learned

1. Evaluation of hyperandrogenemia involves characterization of menstrual irregularity and anovulation, medication use, family history of hyperandrogenemia, and the presence of metabolic disease. The time course of the onset of symptoms may help to distinguish between the various etiologies.
2. The diagnostic criteria of PCOS are controversial. After exclusion of other etiologies of hyperandrogenemia and oligo-ovulation, menstrual irregularity and hyperandrogenism have traditionally been used to diagnose PCOS. It has recently been suggested that the diagnosis be based on two of three criteria: oligo- or anovulation, clinical or biochemical hyperandrogenemia, and polycystic ovarian morphology on ultrasound.
3. Treatment options for PCOS are based on symptomatic relief with consideration of (a) regulation of menses, (b) control of hyperandrogenic symptoms, (c) contraception and infertility, and (d) prevention of potential long-term metabolic complications.
4. Fasting plasma glucose levels are unreliable in identifying women with impaired glucose tolerance or type 2 diabetes. Glucose levels drawn 2 hours after a 75–g oral glucose load is an appropriate screening test in women with PCOS.
5. Metformin in combination with clomiphene citrate is found to be an effective treatment option in improving ovulation induction in women with PCOS and may improve the risk of miscarriage.

Multiple-Choice Questions

1. A 56-year-old postmenopausal woman presents with a history of mild hypertension and a 6-month history of significant frontal alopecia, hirsutism (Ferriman-Gallwey score 22) and deepening of her voice. What are the most important initial test(s)?

   A. Total testosterone and urinary 17-ketosteroids
   B. Free testosterone
   C. Dexamethasone suppression test
   D. Total testosterone and insulin-like growth factor I (IGF-I)

Answer: A. The development of hyperandrogenic symptoms in a postmenopausal woman raises concerns for an androgen-secreting tumor of the ovary or, less commonly, the adrenal. In this woman other concerning signs for significant hyperandrogenism include deepening of the voice and the rapid progression of symptoms. The most useful initial tests in this instance are a total testosterone and urinary 17-ketosteroids. Ovarian tumors or other pathologic processes cause secretion of testosterone, while adrenal tumors often secrete androgen precursors that are detected as 17-ketosteroids. Some adrenal tumors make only testosterone. Some adrenal tumors lack sulfotransferase, and therefore DHEAS is not the best tumor marker. Free testosterone has no advantage over total testosterone in this setting. This patient does not have signs of Cushing's syndrome or acromegaly, and therefore a dexamethasone suppression test or an IGF-I level are not the most important tests to order.

2. A 36-year-old woman with a 5-year history of oligomenorrhea, 15-lb centripetal weight gain, treated hypertension, impaired glucose tolerance, and polycystic ovary morphology on ultrasound complains of hirsutism and increased edema and bruising. What is the most appropriate diagnostic test to perform?

   A. DHEAS
   B. 24-hour urine free cortisol
   C. 17-hydroxyprogesterone
   D. TSH

   Answer: B. In this patient with hirsutism, the signs and symptoms suggest the presence of Cushing's syndrome. An overnight dexamethasone test or a 24-hour urine free cortisol are the best screening tests.

3. A 22-year-old college student (BMI 24) is diagnosed with PCOS based on a history of amenorrhea and biochemical hyperandrogenemia. Clinically she has mild acne on her face, which she manages with topical cleanser. She is not currently interested in pregnancy and is sexually active. What is the most appropriate first-line treatment option?

   A. Lifestyle changes
   B. Metformin 500 mg t.i.d.
   C. Oral contraceptives
   D. Medroxyprogesterone 5 mg daily for 14 days per month
   E. Spironolactone 100 mg daily

   Answer: C. In this hyperandrogenic patient who is sexually active, management of cycle irregularity and acne can most easily be accomplished using oral contraceptives. Third-generation oral contraceptives are generally favored in this patient population as the progestins contained in the pill have less androgenicity than those in earlier generations. Oral contraceptives both suppress gonadotropin stimulation of ovarian androgen secretion and increase sex hormone–binding globulin, therefore decreasing circulating free testosterone.

4. Metformin has been associated with which effects in women with PCOS:

   A. Improved cycle regularity
   B. Decreased insulin resistance
   C. Improved hirsutism
   D. Fertility
   E. All of the above

   Answer: E. Metformin has been shown to improve insulin sensitivity and increase sex hormone–binding globulin. Free testosterone levels are decreased, and hirsutism has been shown to improve over time. Cycles generally become more regular, though not necessarily normal, and fertility is improved.

Part X
Pregnancy

Introduction

Alex Stagnaro-Green

Pregnancy is marked by rapid changes in multiple endocrine systems, including the thyroid gland, glucose homeostasis, blood pressure control, and calcium and bone metabolism. Other hormonal abnormalities, in particular polycystic ovarian disease, have a direct impact on fertility. The impact of pregnancy on multiple endocrine systems happens simultaneously, and for any given system the impact of pregnancy varies based on the trimester. New endocrine diseases are triggered during pregnancy (gestational diabetes) and postpartum (postpartum thyroiditis), while other endocrine disorders either become quiescent as pregnancy progresses (Graves' disease) or require increased therapy due to pregnancy induced metabolic changes (type 1 diabetes mellitus). Finally, although parturition is only partially understood, endocrinologic changes are believed to play a critical role in the cascade of events resulting in the initiation of labor.

The last few decades have seen a rapid expansion of our knowledge of the impact of endocrine disorders during pregnancy. The explosion of knowledge is best reflected in the interplay between thyroid hormonal abnormalities, thyroid autoimmunity, and pregnancy outcome. A number of studies have linked minor abnormalities of thyroid hormone function with a decreased IQ in the offspring. Other investigators have demonstrated a relationship between subclinical hypothyroidism and both spontaneous miscarriage and preterm delivery. Prospective studies have also documented a two- to fourfold increase in spontaneous miscarriage in euthyroid women who are thyroid antibody positive in the first trimester. Most recently, the first prospective study evaluating the impact during pregnancy of thyroid hormone treatment in euthyroid antibody positive women demonstrated a significant decrease in both spontaneous miscarriage and preterm delivery [1].

From an epidemiologic perspective, the endocrinologic disease increasing most rapidly, both in the United States and worldwide, is diabetes mellitus. Not only has there been a marked increase in type 2 diabetes, highly correlated to increases

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in obesity, but the incidence of new-onset type 1 diabetes is increasing as well. Recent studies have also evaluated the incidence of gestational diabetes. Gestational diabetes is defined as glucose intolerance first diagnosed during pregnancy. Typically diagnosed in the second half of pregnancy, gestational diabetes mellitus (GDM) is associated with a variety of adverse fetal outcomes, including macrosomia and jaundice. Furthermore, despite the fact that most women return to euglycemia at delivery, long-term studies have demonstrated a prevalence rate of maternal type 2 diabetes that exceeds 50% at 10 years postpartum. Children born to mothers who developed GDM are at increased risk of developing type 2 diabetes as adults. It is therefore of concern that the incidence of GDM is accelerating in the United States. Recent data reveal that in the last decade of the 20th century there was almost a 50% increase in incidence of GDM (5.1% to 7.4%) in a large cohort of women (267,051) followed in California [2].

Polycystic ovarian syndrome (PCOS), with its concomitant anovulation, hyperandrogenism, and insulin resistance, is a common cause of infertility. Although due to space limitations PCOS will not be one of the areas of focus here, it is important to highlight advances in the treatment of this syndrome. Historically, anovulatory women with PCOS are treated with clomiphene citrate to restore ovulation and fertility. Second-line treatment is more complex and requires a combination of gonadotropin therapy and follicle-stimulating hormone (FSH). Recent research has demonstrated that metformin therapy in women with PCOS is effective in restoring ovulation and facilitating fertility. Furthermore, preliminary data indicate that intervention with metformin may reduce the rate of spontaneous miscarriage, which is substantially increased in PCOS. As insulin resistance is one of the hallmarks of PCOS, it is not surprising that most studies have documented an increase in gestational diabetes mellitus in women with PCOS. Preliminary research indicates that treatment of PCOS with metformin may have a marked impact on decreasing the frequency of developing gestational diabetes mellitus [3].

This part focuses on three disease entities that complicate pregnancy. In Case 32, Krakoff discusses the evaluation of hypertension prior to and in early pregnancy, focusing on endocrinologic diseases associated with hypertension. Both the diagnostic workup and management during pregnancy are reviewed. As hypertension in pregnancy is present in 5% to 10% of women, and predispose to both preeclampsia and eclampsia, early diagnosis and intervention are critical for a healthy outcome for both mother and child. In Case 33, Mandel focuses on the management during pregnancy of women with preexisting hypothyroidism. The importance of frequent monitoring in the first trimester, a time when physiologic changes often result in the need for an increased dose of levothyroxine, is discussed with an emphasis on the deleterious impact of subclinical hypothyroidism during pregnancy. In Case 34, Levy and Omry present a woman with type 1 diabetes and focuses on issues of glycemic control from preconception, through gestation, and into the postpartum period. The importance of maintaining tight glycemic control and the challenges presented in each trimester and postpartum are delineated.

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Chapter 32
Hypertension in Pregnancy and Women with Child-Bearing Potential

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Objectives

1. To learn the impact of pregnancy on hypertension and how hypertension during pregnancy should be managed
2. To learn the diagnostic workup of identifiable hypertension during pregnancy

Case Presentation

A 35-year-old married woman sees her internist because she is planning to become pregnant for the first time. She has been healthy and active with no major illnesses. Six months before, during a preemployment physical examination, she was told she had hypertension, with a blood pressure of 150/95 mm Hg. At this visit the pressure is 155/100 mm Hg. She is prescribed a combination of lisinopril 10 mg and hydrochlorothiazide 12.5 mg. At the next visit the pressure is unchanged. The physical examination is unremarkable with no sign of identifiable hypertension (no abnormal appearance, no abdominal bruit). The following test results are reported in a workup for renal and endocrine abnormalities: urinalysis normal, serum Na 145, K 2.7, Cl 100, HCO_3 31, blood urea nitrogen (BUN) 13, creatinine 0.9, fasting glucose 110 mg/dL, 24-hour urine for metanephrines normal, 24-hour urine for free cortisol normal, plasma renin activity 0.6 ng/mL/h, serum aldosterone 35 ng/mL, aldosterone renin ratio 58.

Background

Hypertension and pregnancy have been related to each other in several very important patterns. These patterns are changing due to trends in the population of women who become pregnant, as many are now older than in the past. At one time the

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Table 32.1 Classification of hypertension in pregnancy

Hypertension within pregnancy
Preeclampsia/eclampsia syndromes
Transient hypertension in pregnancy without proteinuria
Chronic hypertension occurring before pregnancy
White-coat hypertension
Essential hypertension
Identifiable hypertension
Chronic renal disease
Renovascular hypertension
Primary aldosteronism
Cushing's syndrome
Pheochromocytoma

major focus on hypertension and pregnancy was the entity of preeclampsia, or toxemia of pregnancy, that is, the occurrence of an abrupt increase in blood pressure during pregnancy, together with proteinuria in a previously healthy woman with normal prepregnancy blood pressures. While that syndrome and its related diseases may still occur in as many as 5% of pregnancies, there are many more forms of hypertension to be considered because of greater emphasis on early detection and treatment of hypertension and recognition of prehypertension (blood pressures 120–139/80–89 mm Hg, with a high likelihood of becoming hypertensive). Table 32.1 lists the various disorders that may link hypertension and pregnancy and should be considered in assessment and treatment of the patient presented above. Since this patient's hypertension predates the onset of her pregnancy, the focus of this presentation is on the problems of hypertension before pregnancy and soon after pregnancy has occurred.

New Hypertension in Women with Child-Bearing Potential

Many women who are premenopausal have their blood pressures taken by a gynecologist or obstetrician, the usual primary caregivers for this population. Clinic pressures that are in the hypertensive range ($\geq$140/90 mm Hg) on a few occasions need not indicate that chronic hypertension is present. Measurement error and white-coat hypertension may often be found if supplemental pressures are taken by 24-hour ambulatory blood pressure monitoring or home blood pressure recording [1]. Thus, the first consideration in such patients is to determine their usual or average pressure as a crucial part of their assessment. Many will be found to have pressures that are in the high-normal range and above optimal levels, now called pre-hypertension [2].

Risk Profiles and Target Organ Damage

Concurrently with determination of average pressures is the need to assess overall risk for future cardiovascular disease with characterization of a risk profile.

Comprehensive assessment takes into account the presence or absence of smoking, diabetes, and lipid disorders. The family history should be defined with regard to first-degree relatives with diabetes, premature cardiovascular disease, renal disease, and familial hyperlipidemias. Target organ damage, particularly left ventricular enlargement or renal impairment, should be defined. All of these assessments can be made by the usual clinical methods.

Management of Hypertension at the Onset of Pregnancy

Many women with drug-treated hypertension and child-bearing potential become pregnant. They should be counseled that some medications may be harmful to the fetus, so their physician/provider should be informed of the pregnancy as soon as possible to change treatment appropriately. As blood pressure often falls during the first half of pregnancy, withdrawal of antihypertensive medication may often be safely done with surveillance to determine if any antihypertensive medication is needed. Strong evidence supports the fetal risk for angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Thiazide-type diuretics and beta-blockers (without alpha-blocking action) are suspected of potential harm for the fetus. Calcium blockers appear to be relatively risk free. The alpha-beta-blocker labetalol and α-methyldopa are generally favored for treatment of hypertension in pregnancy. For the case presented here, sequential withdrawal, lisinopril first, and then the diuretic, would be appropriate. Home blood pressure monitoring would be helpful to detect any trend to an increase in pressure that might require drug therapy. If the patient's average pressures rose to exceed 140/90 mm Hg, therapy with labetalol or α-methyldopa would be indicated. These patients should be referred for assessment by a perinatologist during this phase (<20 weeks) due to the high-risk state of the pregnancy, with increased likelihood of preeclampsia after 25 weeks.

What if clinical findings or results of tests indicate that identifiable hypertension is present? The less common disorders that cause hypertension, once called secondary hypertension, and now labeled as identifiable hypertension, include several conditions that can be included as endocrine hypertension. Failure to detect these disorders before onset of pregnancy or early in pregnancy (first trimester) may cause fetal impairment or loss and severe complications of pregnancy.

Identifiable Hypertension Before and During Pregnancy

Recent guidelines for management of hypertension emphasize treatment with lesser focus on a detailed search for identifiable causes (secondary hypertension), some of which may be curable. For those adults who do not have the potential for pregnancy, that is, men and postmenopausal women, this approach is justifiable, so a trial of drug treatment is often made and (with rare exception) identifiable hypertension is

only considered if a compelling clinical finding appears or the hypertension is resistant to treatment. For a woman with child-bearing potential, there is a compelling rationale for early detection of identifiable and reversible hypertension for three reasons. First, some antihypertensive medications must be avoided during pregnancy because of their risk for the developing fetus. Second, the accuracy of tests used to detect identifiable hypertension may be diminished during pregnancy so that it will be more difficult to include or exclude these conditions. Third, attempting to reverse the cause of hypertension by an intervention (surgery or an invasive intervention) might carry greater risk for both patients (mother and fetus) during pregnancy (especially after 25 weeks of gestation) than in the nonpregnant state. For these reasons, I favor a workup that considers identifiable hypertension for all women with new-onset hypertension who have child-bearing potential.

For the patient presented here, identifiable hypertension was considered despite the lack of clues to such conditions in the history and physical examination, which effectively ruled out pheochromocytoma and Cushing's syndrome. Chronic renal disease was easily excluded by the presence of a normal urinalysis and renal function (serum creatinine). However, the very low serum potassium concentration coupled with a metabolic alkalosis as reflected in the elevated serum bicarbonate shifted attention to the high likelihood of a mineralocorticoid excess syndrome, of which primary aldosteronism is the leading candidate. Further investigation of the renin-angiotensin-aldosterone system confirmed that the diagnosis was indeed primary aldosteronism, based on (1) the very low plasma renin activity (also making renal artery stenosis unlikely); (2) the elevated serum aldosterone concentration; and (3) a very high aldosterone to renin ratio (ARR), highly consistent with the presence of an aldosterone secreting adrenal adenoma, Conn's syndrome.

Primary Aldosteronism

Hypertension due to primary aldosteronism tends to be a disease of those >45 years of age with a predominance of women [3, 4]. While it may occur in women in the child-bearing age range, it more often is found after menopause. The clinical clues to primary aldosteronism are either hypokalemia or refractory hypertension [5, 6]. Otherwise, this disorder has no characteristic physical findings or specific features. It should be suspected even in diuretic-induced hypokalemia. A recent case-control study suggests that cardiovascular pathology is actually more like in hypertension associated with primary aldosteronism than essential hypertension [7]. The diagnosis of primary aldosteronism in nonpregnant women and men is based on the combination of a low plasma renin activity, increased plasma or urinary aldosterone levels, and an increased ARR [3, 8]. Once the biochemical diagnosis is made, imaging of the adrenal glands by high-resolution computed tomography (CT) scanning or magnetic resonance imaging (MRI) should be done. About 60% of patients with primary aldosteronism have macroadenomas found by CT. The gold-standard for

lateralizing adrenal aldosterone secretion is adrenal venous sampling, which should be performed if surgery is contemplated [9].

In pregnancy, assessment of the renin-angiotensin system control of aldosterone is altered by the hormonal status of human gestation. The limited experience of pregnancy with primary aldosteronism indicates that hypertension is nearly always present with hypokalemia. Plasma renin activity, however, may be normal or even increased, compared with suppression of plasma renin in nonpregnant patients. Plasma aldosterone levels are definitely increased [10]. In a recent case report with a summary of the literature of 29 reported cases worldwide of primary aldosterone found during pregnancy, the average age was 29±6 years (mean ± SD), far lower than the usual age of detection in nonpregnant patients. Proteinuria, suggestive of preeclampsia, was present in >50%. Intrauterine fetal death, abruption placenta, and small birth weight were often found [10]. The patient presented here had severe hypertension with hypokalemia (1.9 mEq/L) was treated medically after detection at 25 weeks, was delivered prematurely by cesarean section, and had a small-for-dates infant. During pregnancy her plasma renin activity was 2.2 ng/mL/h, well above the usual range for plasma renin activity (PRA) in nonpregnant patients with primary aldosteronism. After delivery, the PRA fell to a low level, with a very high plasma aldosterone level. A left adrenal tumor was found by CT scanning with lateralization of function by iodine-131-iodocholesterol scan. The patient was cured of hypertension and hypokalemia by laparoscopic left adrenalectomy; an adenoma was confirmed by pathology.

In summary, hypertension together with hypokalemia is the clue that should suggest primary aldosteronism in young women before pregnancy. Spironolactone might be effective as medical treatment, but there is risk for the fetus of abnormal sexual differentiation (feminization of male infants). The newer mineralocorticoid antagonist eplerenone may have greater specificity for treatment of primary aldosteronism with lesser effects on other steroid receptors [11], but there are no reports of its use in pregnancy so far. Curative adrenalectomy is feasible during the first 25 weeks of pregnancy due to the young age of the patients [4] and may reduce the likelihood of fetal loss and maternal morbidity as well.

Lessons Learned

1. Blood pressure often drops during the first trimester of pregnancy, and antihypertensive medications may often safely be withdrawn.
2. For a women of child-bearing potential a workup should be performed to diagnose identifiable hypertension.
3. Choice of antihypertensives during pregnancy must be carefully made to avoid those agents that pose potential harm to the developing fetus.
4. Renin levels during pregnancy in a woman with primary hyperaldosteronism may be normal or even increased, as compared with the suppression of plasma renin found in nonpregnant patients.

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Chapter 33
Hashimoto's Hypothyroidism During Pregnancy

Susan J. Mandel

Objectives

1. To understand levothyroxine (LT_4) dosage requirements and adjustment in hypothyroid women during pregnancy
2. To learn the potential adverse maternal and fetal outcomes associate with inadequate LT_4 therapy

Case Presentation

A 36-year-old woman who was diagnosed with hypothyroidism 3 years ago tells her endocrinologist that she wants to conceive in the next year. At that time of her diagnosis, her thyroid function tests were as follows: thyroid-stimulating hormone (TSH) 12 mIU/L (normal 0.5–5.0) and free thyroxine (FT_4) 1.0 ng/dL (normal 0.8–1.8). She was treated with levothyroxine (LT_4), 0.088 mg daily, and her serum TSH level returned to the normal reference range. Now, her serum TSH level is 4.1 mIU/L and her LT_4 dose is increased to 0.1 mg daily, with a repeat serum TSH level 2 months later of 0.7 mIU/L. She is instructed to notify her endocrinologist as soon as she finds out that she is pregnant so that a serum TSH level can be checked.

Four months later, after her menstrual cycle is 1 week late, a home pregnancy test is positive, and she checks her serum TSH level, which is 1.9 mIU/L. She is already separating ingestion of her prenatal vitamin and LT_4 by at least 4 hours. She is told to maintain the same LT_4 dosage and to recheck her serum TSH level 2 weeks later. At 7 weeks' gestation, the serum TSH level has risen to 6.9 mIU/L. Her LT_4 dosage is increased to 0.137 mg daily and she is instructed to recheck her serum TSH level in 4 weeks. At 11 weeks' gestation, the serum TSH concentration

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is 1.8 mIU/L and at 16 weeks' gestation it is 4.2 mIU/L. The LT_4 dose is increased to 0.15 mg/daily, and 4 weeks later, at 20 weeks' gestation, the serum TSH level is 0.6 mIU/L. At 26 weeks' gestation, the serum TSH concentration is 0.9 mIU/L, but at 33 weeks' gestation it increased to 5.7 mIU/L. However, further investigation reveals that she has developed an anemia, and her obstetrician prescribed a ferrous sulfate supplement. Although she has continued to separate ingestion of the prenatal vitamin from the LT_4, she is taking the ferrous sulfate at the same time as the LT_4 pill. She is instructed to separate intake of the iron pill and the LT_4 by 4 hours, and her serum TSH level at 37 weeks is 1.6 mIU/L. After an uneventful delivery of a healthy full-term infant, her endocrinologist reduces her LT_4 dose to 0.1 mg daily and at 6 weeks postpartum her serum TSH level is 1.8 mIU/L.

Normal Thyroid Physiology During Pregnancy

During normal gravid physiology, thyroid hormone synthesis is stimulated by several factors, with different relative influence at various gestational ages. Early in pregnancy, renal iodide clearance increases, potentially resulting in decreased iodide substrate for thyroid hormone synthesis. The high serum estrogen levels result in elevated serum thyroxine-binding globulin levels, in turn increasing the amount of protein bound thyroid hormone. In addition, serum human chorionic gonadotropin (HCG) concentrations increase throughout the first trimester. This protein has thyrotropic activity because of its shared α-subunit, resulting in stimulation of thyroid hormone production [1]. The placenta contains the type 3 deiodinase, which inactivates thyroxine (T_4) and triiodothyronine (T_3). As the placental mass grows, this may be a clinically relevant source for thyroid hormone metabolism. Finally, maternal T_4 crosses the placenta [2].

Thyroid function tests during pregnancy reflect the factors just described. Serum TSH levels decrease in the first trimester as a result of HCG stimulation of thyroid hormone synthesis. The 95% confidence intervals for first trimester serum TSH levels are 0.03 to 2.5 mIU/L and increase only slightly during the remainder of gestation. Therefore, this provides the rationale for both titrating LT_4 dosage to a TSH in the nonpregnant reference range but below 2.5 mIU/L in a woman contemplating pregnancy, and maintaining this target throughout gestation. In a woman with established primary hypothyroidism, LT_4 doses can be adjusted by measurement of the serum TSH alone [2, 3].

Fetal thyroid hormone synthesis begins around 12 weeks' gestation and requires adequate iodine concentrations. Fetal iodine originates from transplacental passage of maternal iodine. Therefore, like all pregnant women, LT_4-replaced hypothyroid women must take prenatal vitamins containing iodine. Currently, it is estimated that up to 60% of prenatal vitamins do not have iodine.

LT_4 Dosage Requirements During Pregnancy

In 10 studies, including over 300 hypothyroid pregnant women, the LT_4 dose needed to be increased during pregnancy in 57% of the women. Women with some residual thyroid gland reserve either may not need a dose increase or may require less of a dose increase than athyreotic women.

From published reports, the average LT_4 dose does need to be increased by 25% in 35% to 60% of hypothyroid women with Hashimoto's thyroiditis and by 45% in 70% to 100% of hypothyroid women after thyroidectomy or radioiodine ablation [2]. The median time for the increase in LT_4 dosage is reported to be 8 weeks' gestation, usually prior to the first antenatal obstetric visit [4]. Therefore, it is critical that the endocrinologist educate women about the change in LT_4 requirements during pregnancy. Some authors have suggested that a woman take an extra LT_4 pill as soon as she finds out that she is pregnant and check her serum TSH level [4]; others have advised LT_4 dosage modifications based on the TSH levels [2]. The increased LT_4 requirement plateaus after 20 weeks' gestation, so that further dosage adjustments may not be needed, although periodic TSH monitoring is still required [4]. Women must also be reminded that ingestion of prenatal vitamins, iron supplements, calcium supplements, and soy products should be separated by at least 4 hours from the LT_4 dose because of their potential for interference with LT_4 absorption. Postpartum, a woman may resume her prepregnancy LT_4 dose, and the serum TSH level should be checked 6 to 8 weeks later.

Maternal and Fetal Complications of Inadequate Maternal LT_4 Therapy

Hypothyroidism affects maternal gravid physiology. Most studies evaluating outcomes in hypothyroid pregnant women have been retrospective, but the general conclusion is that pregnancy complications are increased. The degree of increased risk is directly related to the degree of hypothyroidism. Reported complications include preeclampsia and pregnancy-induced hypertension, spontaneous abortion, fetal death, placental abruption, preterm delivery, and postpartum hemorrhage [2]. A recent prospective observational study demonstrated that even untreated subclinical hypothyroidism is associated with a threefold increase in placental abruption and a 1.8-fold increase in delivery before 34 weeks' gestation [5]. Appropriate LT_4 therapy to normalize the serum TSH levels may ameliorate the risk of complications.

Alterations in gravid physiology that accompany insufficiently treated maternal hypothyroidism may impair placental function and fetal somatic growth. Adjustment of maternal LT_4 dosage to normalize serum TSH levels may correct growth delay. In addition, inadequately treated maternal hypothyroidism may directly affect fetal neural development via decreased transplacental passage of maternal thyroid hormone, especially prior to fetal thyroid hormone production at 12 weeks' gestation. Normal fetal neurologic development requires thyroid hormone. Before fetal

thyroid hormone synthesis, transplacental passage of maternal T_4 is the sole source of nuclear T_3 in the fetal brain after intracellular deiodination. Compared to controls, the average IQ score was seven points lower in children born to women found retrospectively to be hypothyroid at 17 weeks' gestation and who therefore did not receive LT_4 therapy [6].

Lessons Learned

1. Optimize LT_4 dose prepregnancy (TSH 0.5–2.5 mU/L); treatment must be with LT_4, not with T_3 or T_4/T_3 combination therapy.
2. Check TSH as soon as the pregnancy test is positive. Median time for LT_4 dose increase is 8 weeks' gestation.
3. In the absence of trimester-specific normal ranges, maintain serum TSH level < 2.5 mIU/L during pregnancy.
4. Most LT_4-replaced hyothyroid women require a dosage increase during pregnancy. Magnitude of LT_4 dosage increase may depend on the etiology of maternal hypothyroidism:

a. Athyreotic (after ^{131}I ablation or thyroidectomy)	$\uparrow\sim 45\%$
b. Hashimoto's hypothyroidism	$\uparrow\sim 25\%$
c. Subclinical hypothyroidism	No change may be needed

5. Follow serum TSH level every 4 weeks in first half of gestation, but sooner if LT_4 dose adjustment is made.
6. Instruct women to separate ingestion of the LT_4 dose from prenatal vitamins containing iron, iron supplements, soy milk, or calcium supplements by at least 4 hours.
7. Ensure that prenatal vitamins contain iodine.
8. After delivery, reduce LT_4 dose to prepregnancy amount and recheck serum TSH level 6 weeks postpartum.

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Chapter 34
Type I Diabetes Mellitus During Pregnancy

Carol Levy and Gal Omry

Objectives

1. To understand the natural progression and treatment of type 1 diabetes during pregnancy and postpartum
2. To understand the hormonal changes throughout pregnancy and how they may affect blood sugar levels
3. To understand the adverse sequelae of poor or suboptimal glycemic control during pregnancy

Case Presentation

A 28-year-old woman diagnosed with type 1 diabetes mellitus 18 years prior, who is on an insulin pump, presents to her endocrinologist stating that she is planning a pregnancy. Her glycemic control has been suboptimal over recent years and she has background retinopathy, which has been stable and has not required laser treatment. She has no obvious neuropathy or nephropathy. Currently her insulin pump is set at basal rates such that her total daily basal dose is 14.2 units/24 hours, and she takes boluses of Lispro with each meal (4 to 10 units). Her blood pressure is stable and physical exam unremarkable. Her fasting blood sugars range from 140 to 180, and throughout the day her premeal values are 130 to 215. Her current hemoglobin A1c(HbA1c) is 7.8%.

She is instructed to refrain from getting pregnant until glycemic control improves, as documented by an A1c $<7\%$, and to start prenatal vitamins. She is also requested to maintain food and glucose records documenting fasting, premeal, 1 hour postmeal, bedtime, and 3 a.m. fingersticks for 1 to 2 weeks. She is referred for nutritional and carbohydrate counting counseling. Over the course of the next 3 to 4 weeks, insulin basals and boluses were adjusted according to pre- and postmeal sugars. The basal rate of insulin was increased to 16.6 units/24 hours, and premeal

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boluses were adjusted to an insulin to carbohydrate ratio of 1:10, with correction of 1:40 for hyperglycemia. Two months later, her A1c was 6.4%.

After 3 months, the patient notifies her endocrinologist that she is 3 weeks pregnant. Laboratory evaluation revealed an A1c of 6.1%, her retinopathy was stable, and there were no signs of nephropathy. The patient was instructed regarding the importance of maintaining optimal glycemic goals in pregnancy, that is, fasting blood levels <90 and 1-hour postprandial blood sugars of <120. The risks of hypoglycemia during the first trimester were discussed, as well as appropriate nutritional guidelines for both the prevention of ketosis and appropriate nutrition for the mother and fetus.

At 9 weeks' gestation the patient develops low fasting glucose levels and high postprandial sugars. She is instructed to decrease her overnight basal rate (total dose 15.5 units/24 hours basal) and increase her premeal insulin-carbohydrate ratio to 1:8. At 15 weeks' gestation (second trimester), she is normotensive and is exhibiting appropriate weight gain. Fasting glucose levels and postprandial values exceed the outlined goals. The basal rate, therefore, is increased to a total daily dose of 16.5 units and the insulin/carbohydrate ratio for different meals is adjusted as follows: breakfast 1:8, lunch 1:5, and dinner 1:6.

At 24 weeks, her hemoglobin A1c was 6.1% and she is normotensive with adequate weight gain. She exhibits no retinopathy or proteinuria. Fasting and postmeal blood sugars are elevated, and her insulin is adjusted as follows: basal rates were increased overnight (total daily basal now 17.1 units/24 hours) and premeal ratios were adjusted to breakfast 1:7, lunch 1:4, and dinner 1:5. At 26 weeks, she calls with complaints of abdominal pain, nausea, and fever with minimal solid food intake. She took no insulin boluses the prior day and glucose levels had been steadily increasing. Her morning sugar was 221 mg/dL with moderate urine ketones. She is able to drink fluids. She is instructed to take a correction dose using an algorithm of 1 unit of insulin for each 20 mg/dL of glucose decrement desired. Other instructions included to increase fluid intake and recheck her blood glucose in 1 hour to ensure the pump site is not occluded. Three hours later her glucose was 147 mg/dL, and urine ketones were "trace," but she still felt nauseous. She is instructed to take her insulin boluses after meals so that that she does not vomit before taking the bolus, thus preventing hypoglycemia. Ketones resolved and her glucose levels stabilized.

At 32 weeks she starts to undergo nonstress testing to assess placental function. An ultrasound reveals a fetal size in the 60th percentile without polyhydramnios. At 37 weeks, she started to note increased episodes of hypoglycemia in the 50- to 60-mg/dL range. Her nonstress tests were normal. She is reassured and instructed to decrease her bolus and basal insulin rate administrations.

At 39 weeks, she notes contractions. In the hospital, the obstetrician is instructed to discontinue the pump and an insulin drip is initiated with frequent blood glucose monitoring to maintain euglycemia (goal 70–110 mg/dL). She has a normal vaginal delivery and is instructed to resume her pump at 50% of her latest pregnancy doses for both basal and boluses.

At 2 weeks postpartum, the patient is breast-feeding. She notes variability in blood glucose levels and increased frequency of hypoglycemia after the baby is fed.

Her basal rates are decreased at breast-feeding by 50%, and she is instructed to decrease her mealtime bolus prior to breast-feeding or to take a snack to prevent hypoglycemia.

Physiology of Type 1 Diabetes Mellitus During Pregnancy

Optimization of glycemic control when planning a pregnancy is crucial. Hyperglycemia with an A1c>7% is associated with increased risk of fetal abnormalities and miscarriage in the first trimester, the time of organogenesis. Therefore, a target HbA1c <7% (ideally lower than 6%) should be attained prior to conception. Maintaining near-normal glucose levels reduces the risk of congenital malformations since hyperglycemia is associated with an increased risk of abnormalities in cardiac development, neural tube defects, as well as other organ abnormalities [1–3]. Additionally, patients should take prenatal vitamins containing folic acid to reduce the likelihood of neural tube defects Table 34.1).

Nutritional goals include carbohydrate intake accounting for 45% to 65% of total caloric intake, 25% to 35% of calories as fat (saturated fats should be limited to a maximum of 7% to 10%), and 15% to 20% of total calories as protein. Ideally, carbohydrates should be high in fiber. Snacks should be dosed based on the carbohydrate content.

Careful monitoring for complications of diabetes during pregnancy is critical. Both pregnancy and rapid correction of hyperglycemia can be associated with a worsening of baseline retinopathy. Consequently, patients with type 1 diabetes should undergo a dilated ophthalmologic exam prior to pregnancy, and patients should be examined each trimester. Proteinuria during pregnancy increases the risk of preeclampsia and eclampsia due to changes in glomerular filtration. Accordingly, 24-hour urine collections should be performed each trimester, with close blood pressure monitoring. Subjects with proteinuria may require referral to a nephrologist [4, 5].

First Trimester

During the first trimester, there is an increased risk of maternal hypoglycemia. This is due to increased utilization of glucose by the developing fetus, increased sensitivity to insulin, and an increased rate of metabolism. The etiology of the increased insulin sensitivity is not fully understood. Morning sickness and nausea, leading to decreased oral intake, may further exacerbate the risk of hypoglycemia. As the first trimester progresses, patients often need adjustments of insulin doses. Overall, basal rates of insulin infusion (or daily injections if not on an insulin pump) are adjusted according to fasting levels, and mealtime doses according to pre- and postmeal insulin blood glucose readings [5].

Table 34.1 Rules of management of type 1 diabetes mellitus in pregnancy

Preconception counseling

- Target A1c <6–7%
- Baseline ophthalmology exam
- Prenatal vitamins
- Frequent follow-up with physician/educator until target glycemic goals reached
- Contraception use until glucose goals attained

First trimester

- Target blood glucose
  - Fasting <90 mg/dL
  - 1-hour postprandial <120 mg/dL
- HbA1c, 24-hour urine collection for protein, ophthalmology exam
- Frequent contact with physician for blood glucose review and insulin adjustments
- Patient and provider should watch for hypoglycemia; insulin requirements may decrease due to increased insulin sensitivity

Second and third trimesters

- Target blood glucose: fasting <90 mg/dL and 1-hour postprandial <120 mg/dL
- Frequent contact with physician for blood glucose review and insulin adjustments
- HbA1c, 24-hour urine collection for protein, ophthalmology exam, and monitor blood pressure and weight gain
- As patients approach the third trimester, watch for increasing insulin resistance; insulin requirements will gradually increase

Peripartum/labor and delivery

- Insulin requirements may decrease due to placental breakdown, watch for increased hypoglycemia
- During labor, long-acting insulin or insulin pump should be discontinued; glucose levels should be managed with an insulin drip with target glucose levels of 70 to 110 mg/dL
- After labor and delivery, basal/bolus injections (or pump should be reinstituted) at one-half to two-thirds the final pregnancy requirements

Postpartum

- Patients should be warned that breast-feeding may be associated with hypoglycemia; basal insulin or premeal insulin may need to be adjusted, or patients may require a snack while breast-feeding
- A follow-up ophthalmology exam should be performed within 6 months of delivery

Second Trimester

During the second trimester, insulin requirements generally increase gradually. This is related to increased fetal requirements, increased maternal intake, and increasing insulin resistance. The insulin resistance is attributed to increased levels of estrogens, human placental lactogen, and an increase in free fatty acid levels [4, 5]. As such, patients need to speak with their endocrinologist frequently for appropriate management and insulin changes. Towards the end of the second trimester or early in he third trimester, patients undergo nonstress tests (NSTs) to assess placental function and fetal ultrasounds to evaluate for macrosomia and polyhydramnios, both of which are increased in pregnancies of mothers with diabetes.

Third Trimester

Insulin resistance continues to increase steadily throughout this trimester, and insulin requirements increase significantly. Hyperglycemia in the third trimester increases the risk of macrosomia, since the fetus responds to maternal hyperglycemia by producing more insulin. Increased insulin levels (via insulin-like growth factor effects) leads to accelerated fetal growth. Additionally, maternal hyperglycemia increases the risk of neonatal hypoglycemia due to increased fetal insulin overproduction [5]. Hyperglycemia also inhibits the maturation of fetal lungs and is associated with jaundice. Placental blood flow is also impaired by hyperglycemia, increasing the risk of inadequate perfusion to the fetus. Signs of fetal distress can be detected during nonstress testing, and rapid reductions in maternal insulin requirements suggest diminished placental capacity.

Peripartum

Insulin requirements continue to decrease throughout labor and delivery, and blood glucose levels may fluctuate due to decreased oral intake, increased stress, and increased energy expenditure. As long-acting insulins may be difficult to titrate, long-acting basal insulin injections, or the insulin pump, should be discontinued and an intravenous infusion of regular insulin initiated for labor and delivery. Intravenous insulin administration allows for frequent (hourly or as-needed) titration of insulin based on glucose levels. The effort of labor may necessitate significant reductions in the insulin infusion rate, the addition of dextrose, or possibly brief cessation of the insulin infusion.

Following labor and delivery, the prior method of diabetes management (pump or injection) may be resumed. As postpartum insulin sensitivity is often markedly increased (to levels greater than prepregnancy at times), decreases in insulin requirements are often quite significant. Generally, patients require 40% to 60% of the final pregnancy dose of insulin [4, 5].

Postpartum

Breast-feeding lowers blood glucose levels due to loss of maternal carbohydrate to the baby. To accommodate for glucose fluctuations, patients may decrease basal rates at times of breast-feeding, decrease mealtime bolus ratios when ready to breast-feed, or snack when breast-feeding. Breast-feeding is recommended for all patients postdelivery who are able, as it enhances transfer of maternal antibodies to the baby. Studies are currently ongoing to assess whether breast-feeding lowers the risk of development of type 1 diabetes in the offspring of parents with type 1 diabetes [4].

Lessons Learned

1. Tight glycemic targets are necessary for patients with type 1 diabetes mellitus prior to becoming pregnant.
2. Insulin and glucose management needs to be carefully monitored, as requirements often decrease in the first trimester and then gradually increase for the duration of the pregnancy.
3. Labor and delivery of patients with type 1 diabetes is best managed with intravenous insulin during labor and delivery and postpartum.
4. Postpartum, insulin sensitivity is frequently markedly increased. Patients typically required 40% to 60% of the final pregnancy dose of insulin.
5. Breast-feeding lowers blood glucose levels. Patients typically need to decrease basal insulin rates, or snack when breast-feeding, to prevent hypoglycemia.

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Questions

1. A patient with type 1 diabetes mellitus on an insulin pump during her second trimester reports the following blood glucose levels:

Fasting	1 hour post B	Pre-lunch	1 hour post L	Pre-dinner	1 hour post D	Bedtime
90	111	103	135	80	121	121
92	114	90	118	92	111	117
89	107	86	114	99	102	134
86	119	80	121	70	112	119
88	108	88	115	90	105	114

Her current insulin regimen is:

Time	Rate
00:00–03:00	0.5
03:00–06:00	0.4
06:00–10:00	0.8
10:00–16:00	0.8
16:00–00:00	0.6
Total daily dose (TDD)	15.5

Mealtime boluses; insulin/carbohydrate ratios:

Breakfast 1:8
Lunch 1:6
Dinner 1:6
Correction for hyperglycemia 1:40

What is the appropriate course of action?

A. No change is necessary, her blood glucose levels are at goal.
B. Decrease her basal rates by 0.1 to 0.2 units/h.
C. Increase her basal rates by 0.1 to 0.2 units/h and decrease her insulin/ carbohydrate ratios to: breakfast 1:9, lunch and dinner 1:5.
D. Increase her basal rates by 0.1 to 0.2 units/h. No change in mealtime boluses.

2. A 27-year-old woman with type 1 diabetes mellitus on an insulin pump in her first trimester of pregnancy is experiencing episodes of hypoglycemia. What is the appropriate course of action?

A. Increase insulin infusion rate.
B. Instruct her to eat chocolate when her blood glucose levels are low.
C. Instruct her to drink milk or to take 10 to 15 g of rapid-acting carbohydrates when her blood glucose levels are low.
D. Treat hypoglycemia and reduce appropriate basal rates or boluses to reduce the incidence of hypoglycemia.

3. Which is not a complication of hyperglycemia in the 3rd trimester?

A. Shoulder dystocia
B. Neonatal hypoglycemia
C. Impaired spinal cord and cardiac formation

D. Jaundice
E. Delayed lung maturity

4. Which of the following statements regarding levothyroxine (LT_4) treatment in pregnant hypothyroid women is TRUE:

   A. LT_4 dose requirements increase in the first trimester, but the dose can be reduced to prepregnancy levels after 20 weeks' gestation.
   B. Women diagnosed with mild subclinical hypothyroidism may not require a dosage increase.
   C. The mean time for LT_4 dosage increase is after the first trimester, when the fetal thyroid begins to function.
   D. The reference range for serum TSH level during pregnancy does not differ from the nonpregnant reference range.

5. During pregnancy, all of the following factors affect maternal thyroid hormone function EXCEPT:

   A. Deiodination of maternal T_4 by the placenta
   B. Decreased renal iodine loss
   C. Stimulation of thyroid hormone production by human chorionic gonadotropin (HCG)
   D. Increased serum thyroid binding globulin (TBG) levels

6. Inadequate maternal LT_4 therapy during pregnancy is associated with all of the following outcomes EXCEPT:

   A. Large-for-gestational-age babies
   B. Preeclampsia
   C. Preterm delivery
   D. Placental abruption

7. For a 30-year-old recently married woman with in-office blood pressure of 145/85 after two visits, no risk factors for cardiovascular disease, and no target organ damage, which is the most appropriate management?

   A. Initiate treatment with a hydrochlorothiazide
   B. Test for C reactive protein
   C. Instruct the patient in home blood pressure measurement
   D. Start a workup for identifiable hypertension

8. A 35-year-old woman is in the 3rd month of pregnancy and has been hypertensive for the past year; her pressures are unchanged. Workup is unremarkable except for a serum potassium of 2.9, sodium of 145 mEq/L, and HCO_3 of 28 mEq/L. Which test will be most misleading due to pregnancy?

   A. Plasma aldosterone
   B. Plasma renin activity
   C. Plasma deoxycorticosterone
   D. Plasma 18-hydroxycortisol

9. A young woman with fibromuscular dysplasia causing renovascular hypertension (bruit on examination) plans a pregnancy in the near future. Which of the following is true?

   A. Medical treatment with an angiotensin receptor blocker (ARB) will be effective and safe throughout pregnancy.
   B. Treatment with a calcium channel blocker is appropriate during pregnancy without need for intervention.
   C. Renal artery angioplasty is indicated before pregnancy or during the first half of pregnancy to minimize likelihood of preeclampsia during the THIRD trimester.

10. Which drug is the best choice for treatment of hypertension of a pregnant woman?

    A. Hydrochlorothiazide
    B. Labetalol
    C. Losartan
    D. Reserpine

11. A 40-year-old woman has been treated for hypertension with enalapril and hydrochlorothiazide. She has become pregnant within the past 10 weeks. Her blood pressure is 130/80. Which is the optimal management?

    A. Stop treatment and perform ambulatory blood pressure monitoring.
    B. Change treatment to labetalol.
    C. Change treatment to atenolol.
    D. Stop treatment and workup for identifiable hypertension.

Part XI
Type 1 Diabetes

Introduction

Åke Lernmark

Epidemiology

Type 1 diabetes is increasing worldwide and shows epidemic proportions in several countries or regions [1]. There is evidence to suggest that the annual increase in type 1 diabetes incidence may amount to 2% to 7% dependent on the country or region [1]. In a Swedish countrywide study in 1983 to 1998, it was found that the incidence of type 1 diabetes had not increased but rather shifted to a younger age at diagnosis—the 0- to 34-year age group [2]. In a similar study of Belgian patients up to 40 years of age, the rising incidence in children was largely restricted to boys under age 10, where the incidence more than doubled during the 15-year period [3]. At the same time obesity-related hyperglycemia appears to attain epidemic proportion [4]. It is controversial, however, to what extent an increase in body mass index increases the risk for type 1 diabetes [5]. The trend toward a younger age at onset is increasing the risk for ketoacidosis and cerebral edema in conjunction with the clinical onset of hyperglycemia.

Genetic Etiology

Type 1 diabetes can be diagnosed at any age. The genetic and environmental determinants as well as the clinical course are heterogeneous by age. The common pathway (Fig. XI.1) begins with genetic risk. It is remarkable that about 85% of newly diagnosed type 1 diabetes children or young adults have a first-degree relative (parent or sibling) with the disease [1]. The genetic factors represent primarily human leukocyte antigen (HLA) DR-DQ on chromosome 6 (Table XI.1). The HLA genetic factors may account for about 60% of the genetic risk for type 1 diabetes [4]. The HLA genotypes listed in Table XI.1 would typically account for about 90% of children and young adults developing diabetes. The

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Fig. XI.1 Type 1 diabetes pathophysiology. Children are born with genetic risk primarily conferred by HLA DR-DQ genetic factors on chromosome 6. Initiators are thought to trigger the development of islet autoimmunity, which is marked by autoantibodies against insulin, the 65-kd isoform of glutamic acid decarboxylase (GAD65) or IA-2. Genetic factors, virus infections, or diet may represent promoters of islet autoimmunity eventually resulting in hyperglycemia

DR4-DQA1*0301-DQB1*03021/DR3-DQA1* 0501-DQB1*0201 genotype (abbreviated DR4-DQ8/DR3-DQ2) is conferring the highest risk for type 1 diabetes in most countries. In North America and in Europe this high-risk genotype may be found among about 30% of the patients compared to 3% to 4% of the controls. The younger the patient, the higher the frequency of this genotype. The second highest risk genotype is DR4-DQA1*0301-DQB1*0302/DR4-DQA1*0301-DQB1*0302 (DR4-DQ8 homozygous), the frequency of which is 25% to 27% compared to about 3% to 4% among controls. These and the other HLA genotypes listed in Table XI.1 are therefore necessary but not sufficient for type 1 diabetes.

Table XI.1 Genetic factors affecting the risk of type 1 diabetes

Genetic factor	Chromosome	Contribution to risk	Reference
HLA DR-DQ genotypes	6p21	Major	[5]
DR4-DQA1*0301-DQB1*03021/DR3-DQA1* 0501-DQB1*0201			
DR4-DQA1*0301-DQB1*0302/DR4-DQA1*0301-DQB1*0302			
DR4-DQA1*0301-DQB1*03021/DR8-DQA1*0401-DQB1*0402			
DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201			
DR4-DQA1*0301-DQB1*03021/DR4-DQA1*0301-DQB1*0201			
DR4-DQA1*0301-DQB1*03021/DR12-DQA1*0101-DQB1*0501			
DR4-DQA1*0301-DQB1*03021/DR13-DQA1*0102-DQB1*0604			
DR4-DQA1*0301-DQB1*0302/DR4-DQA1*0301-DQB1*0304			
DR4-DQA1*0301-DQB1*03021/DR9-DQA1*0301-DQB1*0303			
DR3-DQA1*0501-DQB1*0201/DR9-DQA1*0301-DQB1*0303			
Non-HLA genetic factors		Minor	[5]
INS	11p15		
CTLA4	2q33		
PTPN22	1p13		
IL2RA	10p15		
IFIH1	2q24		
ITPR3	6p		
Non-HLA genetic regions		Minor	
Unknown	12q		
Unknown	16p		

Table XI.2 Virus implicated in the development of islet autoimmunity, type 1 diabetes, or both

Virus	Type	RNA/DNA
Coxsackie	Enterovirus	RNA
Echo	Enterovirus	RNA
Rubella	Rubivirus	RNA
Mumps	Paroxyvirus	RNA
Rota	Reovirus	RNA
Cytomegalovirus	Herpesvirus	DNA
Ljungan virus	Parechovirus	RNA

It is speculated that the interaction between these HLA genetic determinants and environmental factors such as certain virus may trigger islet autoimmunity (Fig. XI.1). Islet autoimmunity is marked by the appearance of islet autoantibodies (Table XI.2) to insulin (IAA), GAD65 (GADA) or IA-2 (IA-2A) [5]. The ability to develop these autoantibodies is related to the HLA genotype. Hence, IAA and IA-2A are more common among subjects who are positive for DR4-DQ8, while GADA is more likely to be found among DR3-DQ2–positive subjects.

Several non-HLA genetic factors (Table XI.1) have been identified either by association in case-control studies or by linkage analyses of affected sib-pairs [4]. The non-HLA genetic factors may contribute to age at onset or the presence of islet autoantibodies, increasing the risk of low-risk HLA DR-DQ genotypes. For example, IAA occurs more often in subjects with a high-risk INS genotype [5], while the genetic polymorphism of the *PTPN22* gene is increasing the risk for type 1 diabetes in subjects with low-risk HLA genotypes [4]. It will be important to determine to what extent the non-HLA genes contribute to islet autoimmunity, as may be the case for the *INS* gene [4], or represent promoters of the pathogenic process leading to hyperglycemia.

Etiologic Factors

Virus infection remains the major environmental candidate to trigger islet autoimmunity, onset of hyperglycemia, or both. Several viruses have been implicated (Table XI.2). The association between virus and type 1 diabetes is primarily based on studies carried out at the clinical diagnosis of type 1 diabetes [1]. Several authors are therefore questioning whether virus infections in conjunction with the onset of hyperglycemia rather represent a promoter phenomenon of islet autoimmunity than a trigger of type 1 diabetes. Longitudinal studies of children at genetic risk for type 1 diabetes, such as The Diabetes Autoimmunity Study in the Young (DAISY), The Baby Diabetes study (BABY DIAB), The Diabetes Prevention Project (DIPP), and The Environmental Determinants of Diabetes in the Young (TEDDY) [5], may identify virus infections resulting in islet autoimmunity as marked by the appearance of islet autoantibodies [5].

Table XI.3 Diagnostic thresholds for diabetes and lesser degrees of glucose dysregulation

Category	FPG	2-hour PG after OGTT
Normal	100 mg/dL (5.6 mmol/L)	140 mg/dL (7.8 mmol/L)
IFG	100–125 mg/dL (5.6–6.9 mmol/L)	–
IGT	–	140–199 mg/dL (7.8–11.0 mmol/L)
Diabetes*	126 mg/dL (7.0 mmol/L)	200 mg/dL (11.1 mmol/L)

Note: When both tests are performed, IFG or IGT should be diagnosed only if diabetes is not diagnosed by the other test.

*A diagnosis of diabetes needs to be confirmed on a separate day. The table is from [1].

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose.

Pathogenesis

The preclinical beta-cell autoimmunity marked by IAA, GADA, and IA-2A, alone or in combination, may be present for several years before the onset of hyperglycemia. Islet autoantibody-positive subjects have varying degree of beta-cell dysfunction, particularly in their first-phase insulin response to intravenous glucose [4]. The presence of islet autoantibodies predicts type 1 diabetes by the number of autoantibodies; three autoantibodies that are persistently positive represent the highest risk, higher than any autoantibody alone or characteristics such as isotype, subtype, or epitope-specificity [5]. The islet autoantibodies are standardized, and proficiency tests have been instituted. Islet autoantibodies are used to enroll subjects to immune intervention trials [5]. Islet autoantibodies are the first primary end point in the TEDDY observational cohort study in which newborns who are younger than 4 months and have high-risk HLA genotypes in the general population or are first-degree relatives of patients affected with type 1 diabetes GADA, in particular, may be important to the differential classification of diabetes in adults to distinguish type 2 from type 1 or autoimmune diabetes [5].

Diagnostic Criteria

The criteria to diagnose diabetes have remained the same with few modifications since the first recommendations were made in 1979 [1]. The diagnostic thresholds for fasting plasma glucose (FPG) and plasma glucose after a 75-g oral glucose tolerance test (OGTT) are summarized in (Table XI.3). Note also the thresholds for impaired fasting glucose (IFG) as well as impaired glucose tolerance (IGT). It is expected that an increasing number of subjects will be identified with any of the glycemic abnormalities shown in Table XI.3. There is considerable evidence that IFG, IGT, and, of course, diabetes are associated with increased morbidity including cardiovascular disease.

Classification of Diabetes

Once the diagnosis of hyperglycemia (IFG, IGT, or diabetes) has been made, the classification of disease is next. The classification of diabetes is complicated by the fact that symptoms—not defined etiologic, pathogenic, or pathophysiologic criteria—are used to classify the disease. In children, type 1 diabetes predominate. Type 1 diabetes is strongly associated with markers of autoimmune phenomena directed against the pancreatic beta-cells [3] and a loss of endogenous insulin production. In contrast to type 2 diabetes, type 1 diabetes is strongly associated with other organ-specific autoimmune disorders [3, 4]. Recent epidemiologic studies indicate that type 2 diabetes is rare among patients under 20 years of age. However, a major advance in molecular diagnosis has made it possible to classify diabetes into maturity-onset diabetes of the young (MODY), a dominantly inherited form of nonketotic diabetes [4]. MODY usually develops in childhood, adolescence, or young adulthood. However, despite the etiology, this disease is characterized by genetic and clinical heterogeneity. Type 2 diabetes genetic markers are beginning to be understood. Interestingly enough, most of the genetic factors identified so far seem to affect the beta-cell function [4]. Type 2 diabetes is strongly associated with obesity and an older age at onset, although current epidemiologic investigations suggest that also younger obese subjects may develop type 2 diabetes.

Future Directions

Current research efforts are focused on the identification of genetic and environmental determinants of the type 1 diabetes disease process and how they interact. The presentation of diabetes in children and adolescents is heterogeneous. Infants and preschool children, therefore, may be diagnosed at very different pathogenic stages. Children participating in screening studies for type 1 diabetes may be diagnosed by hyperglycemia. Diagnosis without the classic type 1 diabetes symptoms is possible, and ongoing and future studies will be important to establish possible beneficial effects on prognosis. Currently, after initiation of insulin replacement therapy, there is a transient, usually partial, remission. The remission, which is shorter in younger patients, is followed by complete insulin deficiency associated with acute and chronic complications and untimely death. Major research efforts, therefore, are focused on either preventing the development of hyperglycemia in islet autoantibody-positive subjects or intervening with the islet autoimmunity at the time of clinical diagnosis.

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Chapter 35
Type 1 Diabetes Onset with Ketoacidosis and Suspected Cerebral Edema

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The common pathway begins with preclinical beta-cell autoimmunity, which is associated with progressive defect of insulin secretion eventually followed by onset of hyperglycemia [1]. After initiation of insulin replacement therapy, there is a transient, usually partial, remission. The remission, which is shorter in younger patients, is followed by complete insulinopenia associated with acute and chronic complications and untimely death.

The criteria to diagnose diabetes have remained the same with few modifications since the first recommendations were made in 1979 [2]. The diagnostic thresholds for fasting plasma glucose (FPG) and plasma glucose after a 75-g oral glucose tolerance test (OGTT) are summarized in Table 35.1. Note also the thresholds for impaired fasting glucose (IFG) as well as impaired glucose tolerance (IGT). It is expected that an increasing number of subjects will be identified with any of the glycemic abnormalities shown in Table XI.3 in the introduction to Part XI.

Current research efforts are focused on the identification of genetic and environmental determinants of the type 1 diabetes disease process and how they interact. The presentation of diabetes in children and adolescents is heterogeneous. Infants and preschool children, therefore, may be diagnosed at very different pathogenic stages. Children participating in screening studies for type 1 diabetes such as DAISY, BABY DIAB, or DIPP, and most prominently in the TEDDY study, may be diagnosed by hyperglycemia [1]. Diagnosis without the classic type 1 diabetes symptoms is possible [1]. However, as more than 85% of newly diagnosed type 1 diabetes children do not have a parent or sibling with the disease, most infants of the general population are more likely to present with all the classic type 1 diabetes symptoms and also run the risk of developing cerebral edema [1, 3]. The case presented here is a child with hyperbilirubinemia who developed type 1 diabetes with ensuing ketoacidosis.

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Table 35.1 Gestational events increasing the risk for type 1 diabetes

Gestational event(s) increasing risk	Association with HLA or diabetes
Congenital rubella	Unknown
Gestational infections	
Enterovirus	Unknown
Blood group incompatibility	
ABO	Possibly HLA
Rh immunization	Unknown
Preeclampsia	Unknown
Increased relative birth weight	
Large for gestational age	HLA

Note: Association with HLA or diabetes suggests that the gestational phenomenon is primarily associated with either the HLA DR-DQ genotype conferring risk for type 1 diabetes or type 1 diabetes per se. Association with HLA indicates that many more individuals will experience the phenomenon than will develop type 1 diabetes.

Case Presentation

An 11-month-old boy is the first child of parents from Lebanon who are related to each other. The grandfather has type 2 diabetes. The boy presented in the neonatal period with hyperbilirubinemia. The maximum bilirubin was 580 μmol/L. The hyperbilirubinemia was treated with blood exchange and phototherapy. He was followed at the pediatric hematology section due to a mild hemolytic anemia of unknown cause and was treated with vitamins C and E.

The boy presented with increased thirst and polyuria. He had been vomiting for 3 days. The mother contacted the general practitioner, who believed it was gastroenteritis and sent the boy home. The mother returned to the general practitioner the next day, as the boy had become more tired and showed breathing problems. He was then admitted to the pediatric emergency unit due to suspected gastrointestinal disease.

How the Diagnosis Was Made

The boy was lethargic and dehydrated. He had Kussmaul breathing and there was a smell of acetone. When the diaper was removed, the boy urinated immediately. The urine sample was positive for glucose and ketones. Plasma glucose was 35 mmol/L, pH 6.95, Na 136 mmol/L, and K 4.7 mmol/L.

The boy was given buffered saline intravenously.

Intravenous insulin therapy was started with hourly controls of electrolytes and plasma glucose levels. After 24 hours he was more lethargic, and cerebral edema

was suspected. However, the boy improved overnight and was admitted to the pediatric ward the next day.

Serum insulin autoantibodies (IAAs) were 63 RU/mL (normal < 1). The human leukocyte antigen (HLA) genotype DQ8/X supports the classification of type 1 diabetes. About 27% of newly diagnosed Swedish type 1 diabetes children under the age of 18 have this HLA genotype.

Discussion

Although the onset of type 1 diabetes before 12 months of age is rare, when it happens it requires immediate attention because of the risk of cerebral edema. The fact that the parents were related is of interest, but the importance of their possible cousin marriage is unclear. Cousin marriages are common in the Middle East [1]. It is possible that the child was DQ8 homozygous, that is, had inherited the DQ8 haplotype from both the mother and the father. DQ8 homozygosity is the second highest HLA genotype for type 1 diabetes risk [3] and is present among Lebanese type 1 diabetes patients. However, Lebanon is not a high type 1 diabetes incidence area, and it is speculated that the genetic susceptibility in combination with environmental factors in Sweden may have triggered the disease in the patient. The early age at onset with positive IAA is consistent with recent observations [4]. The younger the patient, the more likely that IAA is present [3].

Epidemiologic studies have suggested that ABO incompatibility and hyperbilirubinemia are associated with an increased risk of type 1 diabetes [5]. The strongest association was found for ABO incompatibility and was a more common and also a stronger risk factor than Rh incompatibility [5]. Different perinatal events are associated with an increased risk of type 1 diabetes (Table 35.1). The effect of maternal–child blood group incompatibility is strong, but the true effect remain unexplained. It is important to distinguish maternal-child effects on islet autoimmunity (which may or may not lead to type 1 diabetes) from effects on hyperglycemia developing when the autoimmune process has killed a sufficient number of beta-cells.

It was recently reported in children with ABO immunization or hyperbilirubinemia that the prevalence of islet cell antibodies (ICA) was increased compared to controls not only in children with ABO immunization but also in newborn children with hyperbilirubinemia [5]. The prevalence of IA-2 autoantibodies, but not of GAD65 autoantibodies, was increased in children with ABO immunization compared to the hyperbilirubinemia group without incompatibility, or the controls [5]. These findings suggest that intrauterine factors may be associated with islet cell autoimmunity (Table 35.1). The mechanism, therefore, may be that hematologic incompatibility between the mother and the child is inducing islet autoimmunity. Further investigations of infants rapidly developing type 1 diabetes in studies such as TEDDY [3] will be critical to dissect the series of events leading to hyperglycemia from a triggering event, leading to the formation of islet autoantibodies (IAA is most common) and the onset of hyperglycemia.

Lesson Learned

Type 1 diabetes before 1 year of age is rare, and often develops rapidly. The symptoms are vague and may resemble breathing problems, gastroenteritis, or other gastrointestinal disease. It is important in children with unclear gastrointestinal symptoms to be generous with testing urine and blood for glucose. It is also more common that cerebral edema develops in these children, and therefore it is important to manage them carefully.

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Chapter 36
En Passant Diagnosis of Type 1 Diabetes in Infancy

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Objectives

The presentation of diabetes in children and adolescents is heterogeneous. The criteria to diagnose diabetes have remained the same with few modifications since the first recommendations were made in 1979 [1]. The diagnostic thresholds for fasting plasma glucose (FPG) and plasma glucose after a 75-g oral glucose tolerance test (OGTT) are summarized in Table XI.3 in the Introduction to Part XI. Note also the thresholds for impaired fasting glucose (IFG) as well as impaired glucose tolerance (IGT). It is expected that an increasing number of subjects will be identified with any of the glycemic abnormalities shown in Table IX.3. Diabetes is increasing worldwide. An important aspect is the obesity-related hyperglycemia, which may have attained epidemic proportion [2]. At the same time, there is evidence that autoimmune type 1 diabetes in children and adolescents is steadily increasing [3].

Once the diagnosis of hyperglycemia (IFG, IGT, or diabetes) has been made, it is critical to classify the disease. Diabetes in children and young adults is classified mostly as type 1. Alternative classifications include heterozygous gain-of-function mutations in the *KCJN11* gene encoding the Kir6.2 subunit of the K(ATP) channel found in approximately 47% of patients diagnosed with permanent diabetes at < 6 months of age [4]. In addition, major advances in molecular diagnosis have clarified the genetic background to maturity-onset diabetes of the young (MODY), a dominantly inherited form of nonketotic diabetes [2, 4]. MODY usually develops in childhood, adolescence, or young adulthood. However, despite how the genetic etiology is understood, this disease is characterized by genetic and clinical heterogeneity.

Type 1 diabetes is strongly associated with human leukocyte antigen (HLA) genetic factors [3] and markers of autoimmune phenomena associated with a loss of endogenous insulin production [5]. In addition, type 1 diabetes is strongly associated with other organ-specific autoimmune disorders [3]. Diagnosis of hyperglycemia

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is common among first-degree relatives of type 1 diabetes patients and such individuals are reported in studies such as The Diabetes Autoimmunity Study in the Young (DAISY), The Baby Diabetes study (BABY DIAB), The Diabetes Prevention Project (DIPP), and The Environmental Determinants of Diabetes in the Young (TEDDY) [3]. Childhood type 1 diabetes diagnosed through a screening and follow-up program has a less severe onset and a milder clinical course in the first year after diagnosis [3]. The objective of this case report is to analyze the beta-cell function in a younger sister of a type 1 diabetes patient.

Case Presentation

This 3-year-old girl presented with polyuria but no polydipsia or weight loss. Her older sister was diagnosed with type 1 diabetes 2 months earlier at 4½ years of age. There was a family history of hypothyroidism. Because the sister had diabetes, the parents checked the patient's plasma glucose level at home, and found it to be 13.9 mmol/L. They were advised by the pediatric clinic to measure the plasma glucose before and 2 hours after meals during 1 day. The patient had normal fasting plasma glucose levels, but plasma glucose after the evening meal was 15.0 mmol/L. She also had glucosuria. These observations prompted an intravenous glucose tolerance test (IVGTT) (Table 36.1). An OGTT could not be performed, as the patient refused to drink the glucose test solution.

The results of the IVGTT suggest a reduced first-phase insulin release (1 to 7 minutes). The expected C-peptide value after the glucagon infusion would have been at least 0.7 nmol/L.

Further analyses of blood samples showed that hemoglobin A1c(HbA1c) was 4.5% (normal 3.6–5.0), Islet Cell Antibodies (ICA) 116 Juvenile Diabetes Foundation-Units (JDF-U) (normal <1), GAD65 autoantibodies (GADA) 12 (normal < 35), IA-2 autoantibodies (IA-2A) 250 (normal < 6), and Insulin Autoantibodies (IAA) 0.59 (normal < 2). Hence, the patient had HbA1c within the normal range despite reduced insulin levels and the presence of two islet autoantibodies.

Thyroid parameters were normal and autoantibodies against gliadin and endomysium were negative. HLA-typing showed that the patient was a carrier of the type 1 diabetes high-risk genotype HLA-DQ2/8 (DR4–DQA1*0301–DQB1*03021/DR3–DQA1* 0501–DQB1*0201).

Table 36.1 Combined intravenous glucose tolerance and glucagon (at 90 minutes) tests (March 7, 2006)

	−10	0	1	3	5	7	10	30	50	70	90	96
P-glucose mmol/L	4.8	5.9	18.8	16.4	M	14.1	13.4	8.8	6.2	3.7	2.8	4.8
P-C-peptide nmol/L	0.30	0.29	0.41	0.36	M	0.37	0.40	0.31	0.38	0.35	0.31	0.56
P-insulin mU/L	1	3	6	4	M	3	4	3	3	2	2	8

k-value: 2.3% (> 1.0 is normal); M indicates a missing value.

Table 36.2 Intravenous glucose tolerance test (November 7, 2006)

	−10	0	1	3	5	7	10	30	50	70	90	96
P-glucose mmol/L	4.9	4.9	21.5	18.7	16.3	15.3	14.3	10.4	8.0	5.5	4.0	6.0
P-C-peptide nmol/L	0.17	0.14	0.20	0.17	M	0.19	0.20	0.23	0.17	0.24	0.23	0.56
P-insulin mU/L	1	1	2	2	2	2	2	1	1	2	< 1	7

k-value: 1.8% (> 1.0 is normal); M indicates a missing value.

How the Diagnosis Was Made

Because the patient's sister had diabetes, the patient was followed together with her sister at the pediatric clinic. She was well during the summer of 2006, but in October she had increased glucose level and glucosuria when tested at home.

A new IVGTT was performed in November (Table 36.2). The HbA1c had risen to 5.1%. Thyroid status was still normal and there were no autoantibodies against gliadin or endomysium. The ICA had risen to 286 JDF-U. Unfortunately, the GADA, IA-2A, and IAA were not measured. The presence of HLA-DQ2/8 and the presence of islet autoantibodies are consistent with autoimmune type 1 diabetes.

Discussion

Although the k-value was 1.8% and fasting blood glucose was normal (4.9 mmol/L), insulin and C-peptide values were remarkably low. Insulin treatment was initiated with a low dose (2 U per day) of Levemir once a day. In the end of November 2006 the patient was prescribed Novorapid before meals as the insulin requirement increased. The patient was out of remission after only 1 month on insulin treatment, even if the k-value was normal at diagnosis. The short remission period was not unexpected, as children at this young age are often found to rapidly lose their endogenous insulin production and may present without remission. We speculate that the patient was able to maintain a normal fasting blood glucose due to a high insulin sensitivity in conjunction with her remarkably low levels of insulin and c-peptide levels.

Awareness of a second hit of diabetes in families already affected by the disease varies. Several large studies of children at risk, such as DAISY, BABY DIAB, DIPP, and TEDDY [3], will continue to carry out nonsymptomatic diagnosis of diabetes. It was recently reported that childhood type 1 diabetes diagnosed through a screening and follow-up program has a less severe onset and a milder clinical course in the first year after diagnosis [3]. It remains to be determined if the early diagnosis of diabetes will improve the prognosis of type 1 diabetes.

Lesson Learned

Awareness of the diabetes diagnosis may result in very early detection. We believe that insulin treatment at the first presentation would have resulted in a longer remission period and better preserved C-peptide levels. The insulin and C-peptide values were low despite a normal k-value. Since the girl had type 1 diabetes, high-risk HLA, and more than one islet autoantibody as well as high plasma glucose levels after meals, a low dose of rapid-acting insulin at meal time would have been the treatment of choice.

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Multiple-Choice Questions

1. Diabetes is diagnosed at a fasting plasma glucose of:

   A. 6.9 mmol/L
   B. 7.0 mmol/L
   C. 7.8 mmol/L
   D. 11.1 mmol/L

2. An OGTT allows a diagnosis of diabetes if:

   A. The 2-hour P-glucose is > 26 mmol/L at a random test.
   B. The 2-hour P-glucose is > 11.1 mmol/L at two consecutive tests.
   C. The 2-hour P-glucose is > 11.1 mmol/L at the first tests.
   D. The fasting glucose is 7.8 mmol/L and the 2-hour P-glucose 11.1 mmol/L at a random test.

3. Type 1 diabetes is *strongly* associated with the HLA genotypes

   A. DQ 2/8
   B. DQ B1* 0602/0602
   C. DRB1*07/07
   D. B8/15

4. One of the following autoantibodies does not mark type 1 diabetes:

   A. GAD65 autoantibodies
   B. IA-2 autoantibodies
   C. Insulin autoantibodies
   D. Tissue transglutaminase autoantibodies

Chapter 37
Type 1 Diabetes and Comorbidity of Addison's Disease

Helena E. Larsson, Sten-A Ivarsson, and Åke Lernmark

Objectives

The criteria to diagnose diabetes have remained the same with few modifications since the first recommendations were made in 1979 [1]. Once the diagnosis of hyperglycemia (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], or diabetes) is made, the classification of the disease may be complicated. Type 1 diabetes is strongly associated with markers of autoimmune phenomena and a loss of endogenous insulin production, resulting in insulin dependency for life. In addition, type 1 diabetes is strongly associated with other organ-specific autoimmune disorders [2]. Major advances in molecular diagnosis make it also possible to classify diabetes into maturity-onset diabetes of the young (MODY), which is a dominantly inherited form of nonketotic diabetes. MODY usually develops in childhood, adolescence, or young adulthood. Also this disease is characterized by genetic and clinical heterogeneity. Neonatal diabetes may be due to heterozygous gain-of-function mutations in the *KCJN11*gene encoding the Kir6.2 subunit of the potassium adenosine triphosphate (K_{ATP}) channel and may be found in patients diagnosed with permanent diabetes at < 6 months of age [3]. These monogenic types of diabetes are not associated with autoimmune markers of type 1 diabetes.

More importantly, type 1 diabetes is also associated with other organ-specific autoimmune disorders (Table 37.1). First, about 10% of newly diagnosed type 1 diabetes patients develop celiac disease within 5 years of the clinical diagnosis of diabetes [2, 4]. Second, in newly diagnosed type 1 diabetes patients, thyroglobulin autoantibodies may be found among 33% compared to 14% of controls. Similarly, thyroid peroxidase autoantibodies may be found among 38% compared to 6% of controls (Ivarsson, unpublished observations). These thyroid autoantibodies are strong markers for Hashimoto's disease, a disorder that may develop among 20% to 30% of all type 1 diabetes patients. Other diseases of autoimmune character include

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Table 37.1 Organ-specific autoimmunity in type 1 diabetes

Organ-specific autoimmunity	Autoantibody marker
Celiac disease	Tissue transglutaminase
Hashimoto's disease	Thyroperoxidase Thyroglobulin
Atrophic gastritis	H^+,K^+-ATPase
Addison's disease	21-hydroxylase
Adrenal autoimmunity	Side chain cleavage enzyme 17α-hydroxylase
Vitiligo	Tyrosinase

vitiligo, atrophic gastritis, and Addison's disease. The present case report reveals the critical importance of considering Addison's disease as a comorbidity of type 1 diabetes.

Case Presentation

This patient was an 18-year-old man who developed type 1 diabetes at the age of 14. At the time a rather widespread vitiligo had also been noticed. There was no family history of diabetes. The patient had been treated with insulin and he was in satisfactory control.

Four months before admission, he had been anorectic, had developed weakness, and steadily lost weight. He had frequent hypoglycemic attacks despite a reduction in the insulin dosage. One month before admission, he was treated at another hospital due to a serious hypoglycemic attack with convulsions followed by mental confusion lasting for several days.

How the Diagnosis Was Made

On admission to the hospital, his general condition was satisfactory. He had no increased pigmentation of the skin, but widespread vitiligo. Blood pressure was 110/80, serum sodium (s-Na) 140 mmol/L, serum potassium (s-K) 5.6 mmol/L, and serum creatinine 88 μmol/L. Thyroid hormone levels were normal.

The plasma cortisol curve showed low levels of 70 nmol/L at 7 a.m. (normal 200–800), 60 nmol/L at 1 p.m. (normal 100–800), 50 nmol/L at 7 p.m. (normal 50–600), and 40 nmol/L at 1 a.m. (normal 20–400). p-ACTH was 126 pmol/L (normal 30 ± 2.6), p-aldosterone 0.02 nmol/L (normal 0.14–0.85), and p-renin 9.75 μmol/L (normal 2.1–4.0). Basal urinary cortisol excretion was undetectable (< 10 nmol/24 hours). Adrenal autoantibodies were not available.

The patient was diagnosed with adrenocortical insufficiency and successively treated with corticoid (about 15 mg hydrocortisone per m^2 body surface) substitution therapy. This was followed by an increase in insulin requirement from 28 U/day to 58 U/day.

Discussion

Type 1 diabetes has a number of comorbidities (Table 37.1). The most common is Hashimoto thyroiditis, which affects almost 20% to 30% of type 1 diabetes patients. At the diagnosis of type 1 diabetes, almost 40% of the patients have thyroperoxidase (TPO) and 33% thyroglobulin autoantibodies (Ivarsson, unpublished observations). Celiac disease is the second most common comorbidity [2, 4]. Although celiac disease is uncommon at the time of diagnosis of type 1 diabetes in children, recent studies demonstrate that about 10% develop celiac disease within 5 years of the diabetes diagnosis. Less common comorbid diseases include atrophic gastritis and Addison's disease.

Addison's disease is a relatively rare but curative cause of recurrent hypoglycemia in patients with type 1 diabetes. A low threshold for investigating patients with type 1 diabetes and recurrent hypoglycemia to detect Addison's disease has therefore been suggested [5]. Addison's disease is strongly associated with HLA DR3–DQ2, the second most common HLA haplotypes in type 1 diabetes. Autoantibodies against 21 hydroxylase (21OH), side-chain cleavage (SCC), and 17α-hydroxylase (17OH) are common in Addison's disease and autoimmune polyendocrine syndrome type II [2, 4]. It has been suggested that measurement of 21OH autoantibodies should be the first step in the immune assessment of patients with Addison's disease and individuals at risk for adrenal autoimmunity such as patients with type 1 diabetes. Due to their low prevalence in Addison's disease, measurement of SCC and 17OH autoantibodies should be indicated only for 21OHAb-negative patients and for those with premature ovarian failure [5].

Lesson Learned

The insulin requirement increases during puberty. When a patient presents with decreasing insulin requirement at this stage, it is important to rule out adrenocortical insufficiency.

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Multiple-Choice Questions

1. The most important genetic factor for type 1 diabetes is:

   A. HLA
   B. *KCJN11* gene
   C. Insulin gene
   D. Glucokinase gene

2. Vitiligo is a comorbidity of:

   A. MODY
   B. Type 1 diabetes
   C. Type 2 diabetes
   D. Impaired fasting glucose (IFG)

3. The following disorders occur with an increased frequency among patients with type 1 diabetes (several options may be correct):

   A. Hashimoto's thyroiditis
   B. Wilms' tumor
   C. Addison's disease
   D. Wegener's granulomatosis

4. Pair the following immune markers with their respective disease.

Autoantibody:	Disease:
A. IA-2	E. Atrophic gastritis
B. H^+K-ATPase	F. Vitiligo
C. Tyrosinase	G. Type 1 Diabetes
D. 21-hydroxylase	H. Addison's disease

Part XII
Type 2 Diabetes

Introduction

Barry J. Goldstein

The world is currently undergoing an epidemic of type 2 diabetes, largely associated with the burgeoning prevalence of overweight and obesity [1]. This crisis is emerging in developing countries where the population is recapitulating the metabolic effects of overfeeding and sedentary lifestyles. Obesity leads to insulin resistance and confers a dramatically increased risk profile for cardiovascular events, the major cause of morbidity and mortality in type 2 diabetes. Hyperglycemia is also clearly associated with microvascular complications of diabetes, and because of its high prevalence, type 2 diabetes is the most frequent cause of chronic renal failure and blindness.

Prevention of these chronic vascular complications is the major goal of diabetes management. Large clinical trials of the natural history and response to therapeutic interventions in type 2 diabetes, such as the United Kingdom Prospective Diabetes Study (UKPDS), have provided keen insight into the benefit of glycemic control in preventing especially the microvascular complications of type 2 diabetes [2]. These studies have led to the gradual tightening of the widely recommended glucose goals of therapy as well as other cardiovascular risk parameters from trials involving low-density lipoprotein (LDL) cholesterol and blood pressure lowering. The UKPDS results supported the benefit of lowering hemoglobin A1c levels to less than 7%. Ongoing trials, such as Action to Control Cardiovascular Risk in Diabetes (ACCORD) [3] are now evaluating the safety and efficacy of even more aggressive glucose reduction in type 2 diabetes so that the hemoglobin A1c falls below 6.5%. Consistent with these data, the American Diabetes Association recommendations for glycemic control are to achieve an A1c as close to normal as possible (representing normal fasting and postprandial glucose concentrations) while avoiding hypoglycemia [4].

The current armamentarium of therapeutics for managing hyperglycemia in diabetes arose from detailed investigations into the pathogenic mechanisms of the disease [5, 6]. Obesity is frequently associated with systemic resistance to the actions

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of insulin, due to a variety of interactions involving adipose tissue secretory products (free fatty acids and adipokines) and the accumulation of triglycerides in liver and muscle associated with mitochondrial dysfunction. In most obese subjects, insulin secretion is ramped up to cover the impairment of insulin signaling; however, a defect in islet beta-cell function is the trigger for inadequate insulin secretion, leading to the hyperglycemia of type 2 diabetes. Accordingly, the diabetes-susceptibility genes that have recently been identified are consistent with these metabolic abnormalities [6, 7].

The case scenarios that follow are derived from common patient experiences in the management of glycemia in type 2 diabetes. Oral therapies are targeted to reducing excessive hepatic glucose production (metformin), improving insulin sensitivity (thiazolidinediones), and enhancing insulin secretion (secretagogues). It is important to keep in mind that the clinical response to each of these interventions requires adequate beta-cell insulin response. Metformin and thiazolidinediones act on the underlying disease process in type 2 diabetes, and are not effective in type 1 diabetes, for example. With beta-cell inadequacy, the secretion enhancers also do not provide sufficient insulin release to effectively lower the blood glucose. The gradual loss of beta-cell function during the natural history of type 2 diabetes is one of the key findings of the UKPDS trial. This is also important to recognize clinically, as patients will need to be treated with increasing doses and early combinations of various therapies to maintain glucose targets.

Recent advances have also helped in the management of hyperglycemia in type 2 diabetes. Incretin signaling, for example, in which insulin secretion is enhanced by gastrointestinal delivery of carbohydrate due to the action of various gut hormones on islet cells and in the brain, has been recognized for many years to be deficient in type 2 diabetes. Preclinical and human studies of this important system have recently paid off with new pharmaceuticals becoming available for type 2 diabetes management. Exenatide, a mimetic of the incretin glucagon-like peptide 1 (GLP-1) with a longer half-life in the circulation, was approved for clinical use in 2005. Exenatide capitalizes on the multiple actions of GLP-1 in the body, as described in the following cases. Other approaches to increasing the levels of GLP-1 are likely to result in additional therapeutic modalities in the near future, including blocking the major enzymes that degrade GLP-1 in the circulation, with drugs that serve as dipeptidyl peptidase (DPP-4) inhibitors. Further research will most likely reveal other approaches to manage hyperglycemia and cardiovascular risk in type 2 diabetes, including lifestyle and pharmaceutical prevention strategies that successfully limit the development of obesity in the first place.

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Chapter 38
Exenatide in Type 2 Diabetes: Indications and Initiation

Vanita Treat and Serge Jabbour

Objective

To learn the indications for initiating exenatide (Byetta®) as part of the treatment of type 2 diabetes mellitus.

Case Presentation

A 46-year-old man with hypertension, dyslipidemia, and a 5-year history of type 2 diabetes is referred to us for better glycemic control. He is currently taking metformin 1 g twice a day and extended-release glipizide 5 mg twice a day, both of which he tolerates well. His other medications include atorvastatin 20 mg daily, ramipril 10 mg daily, and baby aspirin daily. His height is 5'8" and weight is 210 lb; he has difficulty losing weight, although he exercises for 1 hour three to four times per week. His blood glucose readings at home are running in the range of the mid-100s in the morning and mid-200s during the day; he rarely gets any readings below 60. He gets frequent eye exams and so far has no evidence of diabetic retinopathy, nor does he have any diabetic neuropathy or nephropathy.

Laboratory results show the following:

HbA1c: 7.8% (normal < 6%)
Serum creatinine: 0.8 mg/dL (normal 0.5–1.4)
Liver function tests: normal
Total cholesterol: 161 mg/dL; high-density lipoprotein (HDL) cholesterol: 37 mg/dL; low-density lipoprotein (LDL) cholesterol: 90 mg/dL; triglycerides: 172 mg/dL Thyroid-stimulating hormone (TSH): 0.7 μU/L (normal 0.4–5.5)
Spot urine microalbumin/creatinine ratio: 10 μg/mg (normal <30)

Is this patient a good candidate for exenatide?

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How the Diagnosis Was Made

Five years ago, the patient had routine testing, which revealed a fasting plasma glucose of 145 mg/dL. A repeat fasting plasma glucose a week later was 165 mg/dL, confirming the diagnosis of diabetes. According to the American Diabetes Association, the diagnosis of diabetes is made by laboratory criteria based on fasting plasma glucose, random plasma glucose, or glucose tolerance test.

Laboratory Diagnosis of Diabetes Mellitus

Fasting Glucose Criteria

- Fasting: no food intake for at least 8 hours.
- Normal plasma glucose is less than 100 mg/dL.
- Diabetes is diagnosed if the confirmed level is 126 or greater.
- A diagnosis of impaired fasting glucose is made if the fasting glucose is in an intermediate range (100 to 125 mg/dL).
    - Impaired fasting glucose (IFG) is a form of "prediabetes."

Random Glucose Criteria

- Random glucose >200 mg/dL on two occasions without regard to meals or time of day.
    - Usually associated with symptoms of diabetes.
    - Intermediate diagnoses (prediabetes) cannot be made on the basis of random glucose values.

Glucose Tolerance Test Criteria

- The oral glucose tolerance test (OGTT) is only rarely used to make the diagnosis of type 2 diabetes, because it is cumbersome to have a fasting patient drink 75 g of glucose in solution and have blood drawn 2 hours later.
- Oral glucose tolerance test (OGTT) criteria:
    - Glucose >200 mg/dL at 2 hours = diabetes
    - Glucose 140 to 200 mg/dL at 2 hours = impaired glucose tolerance (IGT)
        - IGT is a form of prediabetes
    - Glucose <140 mg/dL at 2 hours = normal glucose tolerance

In the absence of unequivocal hyperglycemia, these criteria (listed in the above three subsections) should be confirmed by repeat testing on a different day.

Lessons Learned

The Indications for Exenatide and How It Works

Type 2 diabetes is a condition characterized not only by insulin resistance and reduced beta-cell response, but also by inappropriately elevated glucagon, impaired secretion of incretin hormones, and accelerated gastric emptying [1, 2]. Many current therapies are available, though the use of several of these is restricted by side effects including weight gain, hypoglycemia, and edema [3]. Postprandial glucose levels are a key factor in the determination of the hemoglobin A1c value, especially as it approaches 7%.

Exenatide is a new class of drugs known as incretin mimetics, which improve glycemic control by mimicking the actions of glucagon-like peptide-1 (GLP-1), a natural incretin hormone secreted by the intestinal L-cells in response to a carbohydrate load. It acts on receptors in the pancreas, stomach, and liver to provide glucose homeostasis. Approximately 60% of postprandial insulin release is a result of incretins, which are decreased in type 2 diabetics [2]. Exenatide, a 39-amino-acid peptide derived from the salivary secretions of the Gila *(Heloderma suspectum)* monster, has a structure that overlaps with that of GLP-1 by 53% [3]. Like GLP-1, exenatide works through several mechanisms (Fig. 38.1). It enhances insulin secretion from the pancreas in response to elevated blood glucose, and it slows the release of glucagon after meals, thus improving glycemic control in the fasting state [3]. It also slows gastric emptying and reduces caloric intake, thereby markedly reducing postprandial glucose concentrations [3]. Fortunately, unlike GLP-1, exenatide is resistant to degradation by enzyme DPP-IV and thus has a longer duration of action than GLP-1 [3]. It has also been shown in some animal models to result in beta-cell proliferation and islet cell neogenesis [1].

Exenatide has primarily been studied as an adjuvant medication to those patients poorly controlled on one or two oral agents. It is initiated as a 5-μg dose b.i.d.

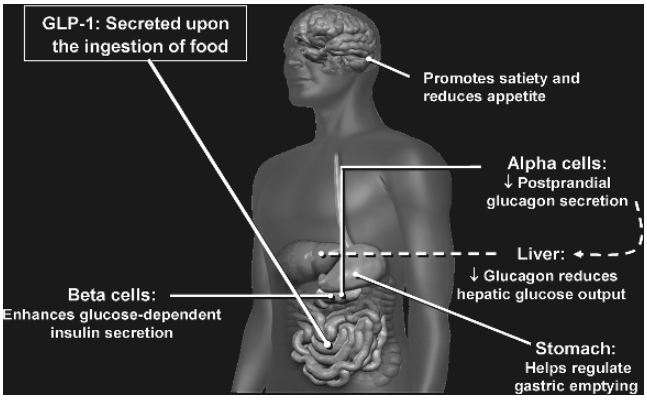

Fig. 38.1 Glucagon-like peptide 1 (GLP-1) modulates numerous functions in humans

for the first month and then titrated up if tolerated to a 10-μg b.i.d. dose. Three phase 3 trials have studied the effects of exenatide when added to sulfonylurea (SU) monotherapy, metformin monotherapy, a combination of both, or glitazone therapy. Each trial has shown an A1c decrease of about 0.8% to 1% at 30 weeks when compared to placebo in the 10-μg treatment arm [5]. Reductions in A1c were also seen, although less so, in the 5-μg treatment arm. Weight loss, a dose-dependent side effect, was also found to occur by the end of 30 weeks and ranged from 1.5 to 3 kg depending on the treatment arm [5]. This weight loss effect was not secondary to the nausea experienced by some patients, but mostly due to decreased caloric intake [4]. Extension studies have showed continuous weight loss and A1c reduction by the end of 2 years (weight loss averaging 12 lb over 2 years) [5].

Pharmacology

Exenatide follows first-order pharmacokinetics [2]. Its terminal half-life is 2.4 hours and can be detected up to 6 to 10 hours from the last dose [2]. It is thus recommended to leave at least 6 hours between doses when determining timing between administrations. Exenatide is predominantly renally excreted.

Indication/Dosage/Administration

Exenatide received Food and Drug Administration (FDA) approval in April 2005 as an adjunctive therapy for those type 2 diabetic patients taking metformin, a sulfonylurea (SU), or a combination of both and who have not yet achieved adequate glycemic control [2]. Exenatide is given as a subcutaneous injection in the thigh, abdomen, or upper arm. The medication is prepared in a prefilled pen. The starting dose is 5 μg twice a day up to 1 hour before meals [2]. This can be with breakfast and dinner or any two meals at least 6 hours apart. The dose is then titrated up to a 10-μg dose twice a day with meals if well tolerated [2]. Patients should skip the dose if the meal is missed or if administration prior to the meal is missed [2]. Patients can then resume administration with the next scheduled dose. Hypoglycemia should be monitored closely, especially when given in combination with an SU. Unlike an SU, exenatide does not result in increased insulin release when blood glucose levels are low [2]. The pen can be kept at room temperature between doses and should be disposed of 30 days after first use, so one pen should last 1 month [2]. A sustained-release formula, exenatide LAR, calls for weekly administration and is currently undergoing phase 2 trials.

Contraindications/Precautions/Drug Interactions/Side Effects

Exenatide is not indicated for type 1 diabetics or for treatment of diabetic ketoacidosis (DKA), as it is not insulin [1]. As mentioned previously, exenatide is indicated for use with SU, metformin, or a combination of the two. Use with glitazones has been studied but not FDA-approved yet. Use with insulin is

being studied. Avoidance is advised in those with renal disease (Cr clearance of <30 mL/min) because of a higher incidence of gastrointestinal side effects [1]. No adjustment of dose is needed in those with mild to moderate renal impairment (Cr clearance 30 to 80 mL/min) [1]. Exenatide should be avoided in those with severe gastrointestinal (GI) disease or gastroparesis as it has dose-related GI side effects. Therefore, when initiating therapy, titration is advised. Studies in pediatric patients or those with liver disease have not been conducted. It is pregnancy category C and can be present in breast milk [1].

Caution should be taken when used with a SU and close monitoring of hypoglycemia is advised. Most episodes of hypoglycemia have been mild to moderate, and oral carbohydrates result in resolution of symptoms. Hypoglycemia appeared to be dose-dependent in respect to both exenatide and the SU dose [1]. The hypoglycemia is due to the SU drug itself and not exenatide. The incidences of hypoglycemic episodes in metformin, 5 μg exenatide plus metformin, and 10 μg exenatide plus metformin groups were 5.3%, 4.5%, and 5.3%, respectively. In data summarized from three 30–week placebo-controlled clinical trials, the incidence of hypoglycemia with an SU alone, 5 μg exenatide plus an SU, and 10 μg exenatide plus an SU were 3.3%, 14.4%, and 35.7%, respectively. The incidence in the metformin and SU group, 5 μg plus metformin and SU group, and 10 μg exenatide plus metformin and SU group were 12.6%, 19.2%, and 27.8%, respectively [2]. So, clearly, there is an increased risk of hypoglycemia using exenatide with SU and therefore a dose adjustment of the SU is advised based on current blood glucose trends and hemoglobin A1c levels.

Exenatide slows gastric emptying, thus reducing the rate and extent of absorption of ceratin oral medications. Therefore, medications that require rapid gastrointestinal absorption or that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, should be taken at least 1 hour before exenatide injection [1].

The most common adverse event reported is mild to moderate nausea (44%), which again was found to be dose-dependent [1]. This nausea is transient in nature and dissipated over time with continued therapy [2]. This is predominantly why dose titration is used when initiating therapy. Other reported side effects include vomiting (13%), diarrhea (13%), feeling jittery (9%), dizziness (9%), headache (9%), and dyspepsia (6%) [1]. Nausea and vomiting were the two most common side effects leading to withdrawal of therapy [1].

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Multiple-Choice Questions

1. Exenatide works in all of the following mechanisms *except*:

   A. Slows gastric emptying
   B. Reduces caloric intake
   C. Increases the release of glucagon after meals
   D. Enhances insulin secretion from pancreatic beta-cells

   Answer: C.

2. Each of the following is correct *except*:

   A. Exenatide can be given up one hour before a meal.
   B. Exenatide has been approved for use with a sulfonylurea, metformin, combination of sulfonylurea and metformin, or with insulin.
   C. Exenatide can be administered in the arm, thigh, or abdomen.
   D. Exenatide comes from the salivary glands of the Gila monster.

   Answer: B.

3. The patient presented here is on metformin 1 g b.i.d., extended-release glipizide 5 mg b.i.d., and has an A1c of 7.8%. What should be done with the SU when considering the addition of exenatide in this patient?

   A. Keep the same dose, 5 mg b.i.d.
   B. Decrease the dose to 5 mg qd.
   C. Stop glipizide.

   Answer: B.

4. True or false: exenatide is resistant to DPP-IV enzyme breakdown and thus lasts longer in the body than GLP-1.

   Answer: True.

Chapter 39
Insulin Therapy in the Management of Diabetes Mellitus Type 2

Kevin Furlong and Intekhab Ahmed

Objective

To discuss the indications (when, why, and how) for initiation of insulin therapy in the management of diabetes mellitus type 2.

Case Presentation

A 58-year-old African-American woman who has had type 2 diabetes mellitus for the last eight years presented saying, "My blood sugars are staying high." At the time of diagnosis she presented with symptoms of polyuria, polydipsia, and weight loss. She was prescribed metformin 500 mg to be taken twice a day. A nutritional consult was also scheduled for the patient.

Due to gradually rising hemoglobin A1c values, into the 8% range, over the years she has tried to increase the dose of metformin, but this has been limited by diarrhea and upset stomach symptoms. She also tried rosiglitazone at some point, but discontinued it because of weight gain and mild peripheral edema. Glimepiride, first 2 mg per day, then gradually increasing to 8 mg per day, has helped her maintain good glycemic control in addition to the metformin 500 mg b.i.d. However, during the past 2 years, her A1c began to gradually rise above 8% and then above 9%. She has been compliant with her regimen, and has been trying to exercise (walking) and to watch her diet.

She checks her blood sugars frequently, and states that most of her fasting and postprandial blood sugars have been below 150 mg/dL, except that for the last 6 months her blood sugars have shown a progressive increase up to 350 mg/dL at random times. She denies any hospitalization secondary to hyperglycemia. These elevated blood sugars have also resulted in recurrence of polyuria, nocturia, and blurry vision. Her weight has remained stable over the past year

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The patient's medical history includes hypertension, and her surgical history includes a cesarean section and hysterectomy. Her mother had a history of type 2 diabetes, and her father had coronary artery disease with a myocardial infarction at age 50 and hypertension. Her brother has type 2 diabetes and obesity.

The patient does not smoke or drink alcohol, and has no history of illicit drug use. Her medications are metformin 500 mg b.i.d., enalapril 10 mg daily, and aspirin 81 mg daily. The review of symptoms include polyuria, polydipsia, nocturia, and blurry vision.

On physical examination, the patient's height is 5'3", her weight is 176 lb, blood pressure 118/62, and pulse 74 and regular in rate and rhythm. Acanthosis nigricans is seen at the back of the neck and axillae. There is no peripheral edema, and pulses are normal. There are no signs of Cushing's disease.

The lab findings are fasting blood glucose 260 mg/dL, and 2 hours post-breakfast 330 mg/dL. Hemoglobin A1c is 11.2%, Low-density lipoprotein 136 mg/dL, blood urea nitrogen/creatinine ratio 12:1.0.

How the Diagnosis Was Made

This patient was experiencing worsening control of her type 2 diabetes. Her age, body mass index (BMI), race, and response to prior therapy are consistent with a diagnosis of type 2 diabetes.

Lessons Learned

Why Insulin?

Diabetes is a progressive disease characterized by decreasing beta-cell function over time. The United Kingdom Prospective Diabetes Study (UKPDS) underscores the fact that glycemic control steadily deteriorates over time, and most patients eventually require insulin therapy for the control of their hyperglycemia. Unfortunately, most clinicians wait until beta-cell function has deteriorated to a significant degree before instituting insulin therapy. In fact, insulin therapy is started at a mean A1c of 10.4% in the United States. A recent study showed that reluctance to use insulin is much higher among U.S. physicians and acceptance of such intervention by their patients is lower when compared to other developed countries. However, there is now ample evidence indicating that loss of beta-cell function occurs early in the disease and early intervention with insulin not only may stabilize but also even spare beta-cell function. Moreover, early use of insulin is often necessary for the timely achievement of glycemic goals set forth by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE).

Despite this, it is often difficult for practitioners to initiate and implement insulin therapy. They face not only their own uncertainties and discomfort about initiating insulin, but also the patients' resistance. Some practitioners and patients view insulin therapy as a sign of failure and a last resort.

When to Start Insulin

Patients presenting with extreme hyperglycemia and symptoms such as polyuria, polydipsia, and weight loss should be started on insulin. These patients are in a state of glucose toxicity, which is characterized by impaired beta-cell function and increased insulin resistance. Oral agents do not work well in this setting and are unable to achieve the glycemic targets set forth by both the ADA and AACE.

What Insulin Regimen

Insulin regimens need to be tailored to the individual patient and to the clinical situation. A common initial approach for patients on maximized doses of oral agents is to add bedtime basal insulin in the form of neutral protamine Hagedorn (NPH) or glargine. In addition, some experts advocate a single injection of premixed insulin with the biggest meal of the day. One has to be cognizant of the potential interactions of these combinations. For example, insulin added to thiazolidinediones (TZDs) may result in unacceptable weight gain and fluid retention. Adding insulin to a sulfonylurea-based regimen can lower total daily insulin doses but can increase cost. Metformin is probably the best-suited agent to be used with insulin, since this combination causes less weight gain and fewer hypoglycemic events than insulin alone or insulin with sulfonylurea.

Patients presenting with extreme hyperglycemia need a more intensive insulin regimen. A basal-bolus regimen utilizing insulin glargine as the basal insulin and a rapid-acting analogue for prandial coverage may be appropriate for motivated patients. To be maximally effective, the patient has to be dedicated to carbohydrate counting and frequent blood glucose monitoring. This regimen is the closest to mimicking the normal physiology of insulin secretion and offers greater flexibility to the patient.

Premixed insulins are an option for patients who want convenience since they require fewer injections and glucose monitoring than with basal-bolus regimens. However, this convenience comes at a cost, because premixed insulins do not offer the flexibility in diet or lifestyle when compared to basal-bolus regimens. Patients have to eat consistent amounts of carbohydrates at consistent times of the day for these insulins to be maximally effective. Also, because the ratios of insulin are fixed, they do not offer dosing flexibility.

How to Start Insulin

Starting insulin doses can be weight based or fixed dose, with titration of doses to achieve glycemic control. A typical weight-based starting dose ranges from 0.15 to 0.6 units/kg/day based on the individual case. In our institution, we tend to use 0.5 units/kg/d as a starting point. Below are examples of how to start various regimens.

Basal-bolus therapy can be started based on the weight-based formula 0.5 units/kg/day. Approximately 50% of this dose should be given in the form of basal insulin and 50% as prandial boluses. Some experts recommend that the prandial doses be equivalent 0.1 U/kg/meal. To improve flexibility, patients are instructed how to count carbohydrates and given carbohydrate ratios to calculate prandial insulin doses. Initial carbohydrate ratios can be calculated by dividing 500 by the total daily insulin dose (TDD). In addition, correction doses to correct hyperglycemia (the correction factor or sensitivity index) can be estimated by dividing 1800 by TDD if using rapid acting analogues or by dividing 1500 by TDD if using regular insulin. These starting doses are then fine-tuned by the clinician based on the patient's response.

Premixed insulins can also be started by utilizing a weight-based formula of 0.5 units/kg/day, with two-thirds of this given as the a.m. dose and one third as the p.m. dose.

Alternatively, clinicians can start patients on low fixed doses and titrate the dose based on clinical response. A common approach for once daily basal insulin is to start with 10 units of NPH or glargine and titrate the dose based on fasting blood sugars. Similarly, one can start premixed insulin at 10 units twice daily before breakfast and dinner. There are dose titration tables available to assist the patient and clinician in obtaining glycemic control.

Why Insulin in This Case?

This patient has had a gradual deterioration of her diabetes control over the past several years, in spite of increasing doses of the sulfonylurea glimepiride. As noted above, data from the UKPDS clinical trial demonstrated clearly that the gradual worsening of hyperglycemia noted frequently in patients with type 2 diabetes is due to a progressive loss of beta-cell function and insulin supply. Some of this effect is due to the phenomenon of glucose toxicity, where the high glucose values impair the ability of the beta cell to sense glucose and secrete insulin properly. Additional effects, due to unknown genetic and beta-cell trophic factors are also playing a role.

Essentially all of the oral medications we currently use to treat diabetes require insulin to be provided by the pancreas to have their clinical effect; when the beta cells are unable to respond, the only therapeutic intervention is to provide that insulin by injection or inhalation therapy. Since the major drawback to inhaled insulin is that it only provides mealtime (prandial) coverage, injected insulin including an intermediate- or long-acting insulin component is required in this case. This

patient was reluctant to use multiple injections of insulin, so the decision was made to start the patient on premixed insulin in addition to discontinuing the glimepiride but maintaining her on oral metformin. Metformin can help with glycemic control, and also has been shown to reduce the weight gain often experienced by patients starting insulin therapy.

The initial insulin dosages were weight based and the patient was taught self-titration of insulin. She has been able to achieve and maintain the glycemic goals set forth by the ADA.

Suggested Readings

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Multiple-Choice Questions

1. In which patient with type 2 diabetes is it most appropriate to start insulin therapy?

   A. A 45-year-old man on 5 mg of extended-release glipizide a day with an average fasting capillary blood glucose of 166. The patient denies polyuria, polydipsia, or weight change.
   B. A patient with an A1c of 10.8 and average fasting capillary blood glucose exceeding 250 mg/dL with polyuria and polydipsia. The patient is currently taking metformin 1000 mg b.i.d., immediate-release glipizide 5 mg b.i.d., and pioglitazone 30 mg daily.
   C. A patient with 2-hour postprandial blood sugars exceeding 180 on metformin 1000 mg b.i.d.
   D. A 42-year-old sedentary patient with poor eating habits and no prior nutritional counseling who presents with a hemoglobin A1c of 9.2%.

2. An initial carbohydrate ratio can be estimated by using which formula?

   A. 1500 divided by the total daily dose of insulin
   B. 1800 divided by the total daily dose of insulin
   C. 1000 divided by the total daily dose of insulin
   D. 500 divided by the total daily dose of insulin

3. An initial weight based dose of insulin can be calculated by which of the following formulas?

   A. 0.1 units/kg/day
   B. 0.5 units/kg/day
   C. 1.0 units/kg/day
   D. 1.5 units/kg/day

4. Which of the following is a major drawback of the use of inhaled insulin in type 2 diabetes?

   A. It causes progressive lung damage.
   B. It is associated with frequent allergic reactions.
   C. It does not provide basal insulin coverage.
   D. It cannot be used with injected forms of insulin.
   E. It cannot be used with oral diabetes drugs.

Chapter 40
Treatment of Type 2 Diabetes Mellitus with Oral Agents

Jeremy J. Flood and Jeffrey L. Miller

Objective

To understand the goals for glycemic control and the mechanisms, benefits, disadvantages, and contraindications of oral agents for type 2 diabetes mellitus.

Case Presentation

A 56-year-old centrally obese African-American man with a history of hypertension and hypercholesterolemia presented for a follow-up office visit. He had been diagnosed with impaired fasting glucose 3 years earlier. At that time, he was counseled on the benefits of modest weight loss and regular physical activity. He had begun a diet and exercise program and lost 15 lb, but over the following 2 years his adherence declined and he gradually gained back the weight he had initially lost. At the follow-up visit, he noted increased frequency of urination and increased thirst.

On examination, the patient's height was 5'9" and his weight was 220 lb (100 kg, body mass index [BMI] 33). His blood pressure was 132/85. Funduscopic, cardiac, neurologic, and foot examinations were normal. He had no hepatomegaly.

Laboratory studies obtained after an 8-hour fast 1 week before his appointment included a plasma glucose of 184 mg/dL. The patient was asked to obtain another fasting plasma glucose level along with a hemoglobin A1c, fasting lipid profile, liver function tests, serum creatinine, and calculated GFR. He returned the following week having had the tests done. The results included a fasting plasma glucose of 192 mg/dL and an A1c of 9.5%. His low-density lipoprotein (LDL) was 118 mg/dL, his high-density lipoprotein (HDL) was 38 mg/dL, and his triglyceride level was 278 mg/dL. The remaining results were within normal limits.

The patient was informed of the diagnosis and implications of diabetes. Basic diabetes education was provided along with a referral to a diabetes educator for more extensive diabetes and nutrition education. He was provided a blood glucose

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monitor for self-monitoring of blood glucose and was advised to have an annual eye exam and regular foot examinations. The importance of weight loss and regular physical activity was reinforced. The patient was started on metformin 500 mg po b.i.d. and low-dose thiazolidinedione therapy after discussion of goals and side effects. He was told to increase his metformin to 1 g po b.i.d. after 1 week unless he experienced persistent gastrointestinal side effects on the starting dose. He was also started on aspirin 81 mg po qd, and antihypertensive and lipid-lowering therapies were intensified.

The patient returned 3 months later. Laboratory results included an A1c of 7.4%, LDL cholesterol 88 mg/dL, and urine microalbumin/creatinine ratio 12 μg/mg. His thiazolidinedione dose was increased and lifestyle modification was reinforced.

He returned 3 months later with an A1c of 7.2%. His weight had decreased to 217 lb. Liver function tests remained within normal limits. A low-dose secretagogue was added to his regimen.

After 6 months, the patient returned. His weight had increased to 221 lb, but his A1c was 6.4%. He reported an episode of hemoptysis, and due to a past smoking history, he was scheduled to undergo a contrast computed tomography (CT) scan of the chest. He was instructed to discontinue his metformin on the day of the scan and to have his serum creatinine measured 2 days after the scan. The scan was negative, and the serum creatinine remained normal, ruling out contrast-induced acute renal failure. The patient was therefore told to resume taking his metformin.

How the Diagnosis Was Made

The patient had two fasting plasma glucose levels greater than 126 mg/dL.

Lessons Learned

Goals for Glycemic Control

According to the American Diabetes Association, the goal for patients in general is an A1c <7%, but the goal for individual patients is an A1c as close to normal (<6%) as possible without significant hypoglycemia. The American College of Endocrinology, the American Association of Clinical Endocrinologists, and the European Union–International Diabetes Federation all recommend an A1c treatment target of <6.5%.

Mechanisms, Benefits, and Disadvantages of, and Contraindications to, Metformin

Metformin, the only biguanide available in most of the world, does not stimulate insulin secretion. Rather, it is considered an insulin sensitizer. Its primary effect is to reduce fasting blood glucose levels by reducing hepatic glucose production in the presence of insulin [1]. Within hepatocytes, metformin enhances the suppression of

gluconeogenesis by insulin and reduces glucagon-stimulated gluconeogenesis [2]. Additionally, metformin increases insulin-mediated uptake of glucose by peripheral tissues such as muscle and decreases fatty acid oxidation, thereby reducing substrate availability for gluconeogenesis. Metformin reduces postprandial glucose levels in addition to its primary reduction in fasting glucose levels [2]. Metformin therapy generally lowers the A1c by approximately 1 to 1.5 percentage points. The most frequent side effects are gastrointestinal, including abdominal discomfort, anorexia, diarrhea, nausea, and, rarely, a metallic taste. These side effects are generally mild and transient and may be dose-dependent.

A potentially life-threatening complication of metformin therapy, although rare, is lactic acidosis. Predisposing factors for lactic acidosis during metformin therapy include renal impairment (plasma creatinine values $\geq$1.5 mg/dL in men and $\geq$1.4 mg/dL in women), cardiac or respiratory insufficiency that is likely to cause central hypoxia or reduced peripheral perfusion (such as congestive heart failure), severe infection that could lead to decreased tissue perfusion, liver disease, and alcohol abuse [2, 3]. Metformin should be temporarily withheld in patients with acute illness and patients undergoing surgery or radiocontrast studies. These contraindications generally stem from an association of metformin with lactic acidosis, although a causative link in many of these contraindications is not well established.

Compared to other oral agents, metformin has several advantages. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated cardiovascular protective effects. Patients treated with metformin had reductions of 32% for any diabetes-related end point (microvascular and macrovascular), 42% for diabetes-related deaths, and 39% for myocardial infarction compared to those treated with conventional less-aggressive therapy. Patients receiving metformin had more impressive risk reductions in any diabetes-related end point and all-cause mortality than those receiving sulfonylurea or insulin with similar A1c improvement [3]. Additionally, metformin may cause modest weight loss, it is relatively unlikely to cause hypoglycemia, and it has salutary effects on plasma lipid levels. With long-term therapy, metformin produces a 10% to 20% reduction in plasma triglyceride levels due to decreased hepatic synthesis of very-low-density lipoprotein, a 5% to 10% decrease in plasma total cholesterol, and small increases in plasma high-density lipoprotein cholesterol (HDL) [2]. Its side effects are generally limited and mild, and it is inexpensive. For all of these reasons, metformin is generally considered the first-line oral agent for the treatment of type 2 diabetes [1]. Metformin can be started at 500 mg once or twice daily and increased to 1000 mg twice daily after 1 week if tolerated. If side effects are persistent, the dose can be increased more slowly. The maximum dose is 2550 mg daily.

Mechanisms, Benefits, and Disadvantages of, and Contraindications to, Thiazolidinediones

Rosiglitazone and pioglitazone are the two thiazolidinediones (TZDs) currently available. They are insulin sensitizers; they do not stimulate insulin secretion. They

activate the nuclear transcription factor peroxisome-proliferator–activated receptor γ (PPARγ) and thereby alter the transcription of a variety of genes that regulate carbohydrate and lipid metabolism. They decrease insulin resistance in peripheral tissues by increasing insulin-stimulated uptake of glucose by skeletal muscle; they also increase the sensitivity of adipose tissue and liver to endogenous and exogenous insulin and decrease lipolysis [1, 3].

The TZDs decrease fasting and postprandial blood glucose levels as well as free fatty acid levels [4]. They reduce A1c levels by 1 to 1.5 percentage points. The two TZDs have approximately equivalent effects on glycemia and body weight. While rosiglitazone is a pure PPARγ modulator, pioglitazone is a partial PPARα agonist, which likely accounts for its more beneficial effects on plasma lipids. Studies have shown that at maximal doses rosiglitazone increases plasma LDL cholesterol by 8% to 14% and may decrease triglycerides up to 19%, while pioglitazone has a negligible effect on LDL and decreases triglycerides by 14% to 26%. Both drugs raise HDL by about 10%, with some studies showing a slightly greater increase with pioglitazone [4]. These differences have been noted in patients who were not receiving statin therapy. Given that all patients with type 2 diabetes should generally be treated with statins, the clinical significance of these differences is unclear.

Thiazolidinedione therapy generally causes a dose-dependent 2- to 4-kg weight gain, partly due to fluid retention and peripheral edema and partly due to adipocyte proliferation [3]. Increased adiposity occurs, but with a redistribution from visceral to peripheral subcutaneous sites where the adipose tissue is associated with less insulin resistance [3]. New or worsened heart failure can occur, particularly in patients concurrently treated with insulin (possibly due to increased intravascular volume) [4]. Hepatotoxicity is very rare, but baseline hepatic function testing is recommended by the Food and Drug Administration with repeated testing based on clinical judgment [3]. Inconsequential anemia may infrequently occur [4]. TZDs are unlikely to cause hypoglycemia. Contraindications to TZD therapy include heart failure and significant renal and hepatic impairment.

Thiazolidinedione therapy produces favorable effects on insulin resistance, lipid levels, and adiposity distribution. Decreased rates of coronary artery in-stent restenosis and reduced progression of the carotid artery intima-media thickness have also been demonstrated, and studies are underway to evaluate theoretical cardiovascular benefits [4]. Because they offer potent glucose-lowering effects, the TZDs are a good choice for a second oral agent in the treatment of type 2 diabetes. They can be started with metformin as initial therapy as in the above example, particularly when metformin by itself would not be expected to reduce A1c levels adequately.

Mechanisms, Benefits, and Disadvantages of, and Contraindications to, Sulfonylureas and Meglitinides

Sulfonylureas and meglitinides stimulate the release of insulin from pancreatic beta-cells and are thus considered secretagogues. Sulfonylurea (SU) drugs are the

oldest oral diabetes medications. They work by binding to the SU receptor on the surface of pancreatic beta-cells. This binding effects a closure of voltage-dependent potassium adenosine triphosphate (K_{ATP}) channels, facilitating cell membrane depolarization, calcium entry into the cells, and insulin secretion [3]. The second-generation sulfonylureas currently used (e.g., glimepiride, glipizide, and glyburide) are more potent and probably safer than their first-generation counterparts but equally efficacious, producing an approximate 1.5 percentage point decrease in A1c [1, 3].

Sulfonylureas are generally well tolerated. Hypoglycemia is the most common side effect. The risk of hypoglycemia increases with the longer acting sulfonylureas (e.g., glyburide) and in elderly patients, patients with impaired renal function, and patients with irregular meal schedules. A weight gain of 2 to 5 kg is typical [3].

The meglitinides (nateglinide and repaglinide) have a mechanism of action similar to the sulfonylureas, binding to a different site within the SU receptor [1]. Their advantage is that they have short metabolic half-lives, producing brief episodic stimulation of insulin secretion. With mealtime administration, these agents reduce postprandial glucose elevations and convey a lower risk of hypoglycemia because less insulin is secreted several hours after meals. Furthermore, nateglinide has little stimulatory effect when given in the fasting state [3]. Repaglinide therapy decreases A1c levels by approximately 1.5 percentage points, while nateglinide therapy decreases A1c levels by approximately 0.6 to 1.0 percentage points [1, 3]. Weight gain from the meglitinides is similar to that from sulfonylureas [1].

In general, the sulfonylureas and meglitinides are metabolized by the liver and cleared by the kidney and must therefore be used with caution in patients with hepatic or renal impairment [3]. Glipizide is primarily excreted by the kidney as inactive metabolites, and only a small fraction of repaglinide is excreted by the kidneys; these drugs are therefore safer in the setting of renal failure.

These drugs provide no consistent additional benefits beyond improved glycemic control (e.g., on lipid levels or atherosclerosis). In contrast, by binding to cardiac tissue K_{ATP} channels, they may actually increase the risk of cardiac morbidity and mortality through several mechanisms such as reduced ischemic preconditioning [5]. Glimepiride is more selective for pancreatic beta-cell SU receptors than the other sulfonylureas and thus may confer less cardiac risk. Among the meglitinides, nateglinide has been shown to have no significant effect on myocardial K_{ATP} channels in animals, but repaglinide likely has no cardiovascular advantage over the sulfonylureas [5].

Because of the weight gain, risk of hypoglycemia, and cardiovascular concerns, the secretagogues are generally considered second- or third-line drugs for type 2 diabetes. In general, the glucose-lowering effect of these drugs plateaus after half the maximum recommended dose is reached [3]. Dosing schedules are variable and depend on the duration of action of each drug. Glimepiride and glyburide are given daily, glipizide is given twice daily or daily in an extended release formulation, and the meglitinides are given with each meal.

A New Oral Therapy Option: The Gliptins

The gliptins, the newest class of oral drugs for type 2 diabetes, are dipeptidyl peptidase IV (DPP-IV) inhibitors. DPP-IV is an enzyme that rapidly degrades incretin hormones: gastric inhibitory peptide (GIP), glucagon-like peptide 1 (GLP-1), and other bioactive peptides that affect glucose metabolism by promoting glucose-stimulated insulin secretion, lowering glucagon release, slowing gastric emptying, and suppressing appetite. Thus, the DPP-IV inhibitors augment these incretin effects, predominantly decreasing postprandial glucose levels, but also decreasing fasting glucose levels through the inhibition of glucagon release. Study results have been promising, with these drugs producing significant A1c reductions without weight gain, no significant side effects, and improved beta-cell function; animal studies have demonstrated increased beta-cell mass. The reported side effects are similar to those with placebo; the side effects listed in Table 40.1 were reported slightly more often than with placebo in clinical trials with sitagliptin. Sitagliptin was approved by the Food and Drug Administration in October 2006, and other drugs in this class are being tested and may be available soon.

Table 40.1 Oral medications for the treatment of type 2 diabetes mellitus

Class	Examples	Mechanism/actions	Major side effects/inconvenience
Biguanides	Metformin	Insulin sensitizer	Abdominal discomfort
		Reduce hepatic glucose production	Diarrhea
		Increase peripheral tissue glucose uptake	Lactic acidosis with predisposing conditions
Thiazolidinediones	Pioglitazone	Insulin sensitizer	Fluid retention
	Rosiglitazone	Activate PPARγ	Weight gain
		Increase skeletal muscle glucose uptake	Rare hepatotoxicity
		Decrease lipolysis	
Sulfonylureas	Glimepiride	Stimulate insulin release from beta-cells	Hypoglycemia
	Glipizide		Weight gain
	Glyburide		
Meglitinides	Nateglinide	Stimulate insulin release from beta-cells	need for frequent dosing
	Repaglinide		Weight gain
DPP-4 inhibitors	Sitagliptin	Limit postprandial insulin release	Upper respiratory infection
		Slow gastric emptying	Nasopharyngitis
		Suppress appetite	Headache

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Multiple-Choice Questions

1. In which of the following patients is metformin therapy appropriate?

   A. An 84-year-old woman with hypertension and normal creatinine clearance
   B. A 58-year-old man with chronic renal insufficiency with a stable creatinine of 1.5 mg/dL
   C. A 73-year-old woman on diuretic therapy for congestive heart failure
   D. A 62-year-old man inpatient with suspected septicemia

   Answer: A.

2. Which of the following statements about thiazolidinediones is correct?

   A. They often cause hypoglycemia when combined with metformin.
   B. They promote weight loss.
   C. They decrease visceral adiposity.
   D. They are safe to use in patients with New York Heart Association Class III heart failure.

   Answer: C.

3. Which of the following statements about secretagogues is correct?

   A. Nateglinide is as efficacious as metformin in reducing A1c levels.
   B. Glimepiride and nateglinide are safe to use in patients with renal failure.
   C. Weight gain is uncommon with meglitinide treatment.
   D. Most of the maximal efficacy of these drugs is conferred at half the maximal dose.

   Answer: D.

Part XIII
Lipid Abnormalities

Introduction

Neil J. Stone

Seek simplicity in all things, then distrust it.

Alfred North Whitehead

Three case histories with severe expressions of hyperlipidemia are presented in this section. Each case reveals important clinical clues that should prove useful to the careful reader when confronted with similar problems in the clinic. In Chapter 41, we see a man with premature coronary heart disease (CHD), diet resistant hypercholesterolemia and diagnostic tendon xanthomas of the extensor tendons of his hands, achilles tendons and tibial tuberosities. In Chapter 42, we meet a 21 year old man with recurrent bouts of pancreatitis, hypertriglyceridemia, often severe, and type 2 diabetes who presented with eruptive xanthomas on his elbows and buttocks. In Chapter 43, we meet a 57 year old markedly obese man with roughly equivalent raised concentrations of total cholesterol and triglycerides whose very low density lipoproteins were relatively cholesterol rich. These case histories not only reveal an underlying genetic disorder but as seen especially in cases 2 and 3 are illustrative of the importance of acquired causes of hyperlipidemia as well and how they impact management of genetic problems.

But these cases are about more than choosing the correct diagnosis. They also emphasize the important first step of translating hyperlipidemia to hyperlipoproteinemia. In the first case, the focus is on low density lipoprotein (LDL) cholesterol. The second case shifts to a consideration of hormonal abnormalities that lead to an excess of chylomicrons. The third case illustrates the importance of considering abnormal forms of triglyceride rich lipoproteins such as the cholesterol rich, beta-very low density lipoprotein (VLDL).

Finally, each case discusses the use of medications, often in combination, with the emphasis on understanding mechanism of action for the most effective treatment. This lies at the heart of successful multi-drug treatment of severe LDL cholesterol excess, chylomicronemia and VLDL excess as well as the accumulation of

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abnormal forms of VLDL. While these genetic disorders are not often seen in a busy endocrinology practice, they are important cases to understand so that they will not be missed, as effective treatment in each case depends on the recognition of the underlying abnormalities present.

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Chapter 41
Combination Drug Therapy in a Case of Severe Hypercholesterolemia

Conrad B. Blum

Objectives

1. To understand the clinical presentation and pathophysiology of severe hypercholesterolemia
2. To develop a rational combination drug regimen based on the mechanism of action of the varying drugs for this condition

Case Presentation

A 62-year-old man had been in good health until he developed exertional angina at the age of 42 in 1986. Evaluation at that time showed that he had sustained an apical myocardial infarction. Cardiac catheterization showed that he had severe three-vessel coronary artery disease including a complete occlusion of the left anterior descending artery, 95% stenosis of the circumflex artery, and 90% occlusion of the ramus intermedius. He was treated with coronary artery bypass surgery.

He had a family history of hypercholesterolemia and of premature coronary heart disease (CHD). His mother was hypercholesterolemic, a maternal uncle sustained a fatal myocardial infarction at age 45, and a maternal great uncle died at 55 of an acute myocardial infarction.

On physical examination, he was lean and weighed 124 lb (height 66 inches). Blood pressure was 135/80, heart rate 88/minute. He had intense corneal arcus. There were multiple tendon xanthomas involving extensor tendons of the hands, Achilles tendons, and tibial tuberosities. He had bilateral carotid bruits. There was a II/VI systolic murmur. The lungs and abdomen were normal.

A lipid profile obtained just prior to his cardiac surgery gave the following results: cholesterol 595 mg/dL, triglyceride 71 mg/dL, high-density lipoprotein

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(HDL) cholesterol 29 mg/dL, and low-density lipoprotein (LDL) cholesterol 552 mg/dL. Additional laboratory evaluation showed a fasting glucose 82 mg/dL and normal blood test results for testing of liver function, kidney function, and thyroid function. There was no proteinuria.

The patient was found to have familial hypercholesterolemia. At this time, 1986, the major medications available to reduce blood levels of LDL cholesterol were bile acid sequestrants (cholestyramine and colestipol) and nicotinic acid. Lovastatin, the first statin, was in experimental use. Ezetimibe had not yet been developed. Accordingly, treatment of hypercholesterolemia was initiated with the bile acid sequestrant in a dose of 20 g b.i.d. (Table 41.1). This caused total and LDL cholesterol to fall to 378 and 319 mg/dL. HDL cholesterol remained low. Because LDL cholesterol remained severely elevated, other drugs lowering LDL by different mechanisms were added to his regimen in stepwise fashion. With the addition of nicotinic acid 1.5 g three times daily, there was further improvement in LDL cholesterol to 287 mg/dL and an encouraging increase in HDL cholesterol to 38 mg/dL. In early 1987, lovastatin was obtained for the patient on a compassionate-use basis. With the addition of this medication in a dose that was gradually escalated to 40 mg twice daily, additional substantial reduction in LDL cholesterol was achieved. Subsequently, he was switched from lovastatin to the more potent atorvastatin 80 mg/d. This gave a further reduction in LDL cholesterol to 103 mg/dL. When ezetimibe became available in 2003, it was added. The four-drug regimen of atorvastatin, colestipol, nicotinic acid, and ezetimibe gave the following results in April 2003: cholesterol 122 mg/dL, HDL cholesterol 35 mg/dL, and LDL cholesterol 79 mg/dL. The only significant side effect of this regimen has been acute gout, a known side effect of nicotinic acid, which has occurred once every 2 years.

Table 41.1 Patient's history of lipid treatment

Date	Cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL-c (mg/dL)	LDL-c (mg/dL)	Treatment
08/02/86	595	71	29	552	Baseline with diet, no medication
10/07/86	378	133	32	319	Colestipol 20 g b.i.d.
11/13/86	360	174	38	287	Colestipol 20 g b.i.d. + nicotinic acid 1.5 g t.i.d.
10/11/87	192	47	42	141	Colestipol 20 g b.i.d.+ nicotinic acid 1.5 g t.i.d. + lovastatin 40 mg b.i.d.
09/17/97	148	55	34	103	Colestipol 20 g b.i.d. + nicotinic acid 1.5 g t.i.d. + atorvastatin 80 mg/d
04/08/03	122	39	35	79	Colestipol 20 g b.i.d. + nicotinic acid 1.5 g t.i.d. + atorvastatin 80 mg/d + ezetimibe 10 mg/d

There have been no anginal symptoms since his 1986 coronary artery surgery. Thallium stress testing in 2005 gave evidence of the apical infarction that was first identified in 1986. There was no evidence of ischemia. Repeated carotid ultrasound examinations have shown no deterioration over the past 20 years; there has been less than 70% stenosis bilaterally.

How the Diagnosis Was Made

The diagnosis of familial hypercholesterolemia (FH) was immediately suggested by the constellation of marked elevation of total and LDL cholesterol levels, multiple tendon xanthomas, intense corneal arcus, premature development of CHD, and a strong family history of hypercholesterolemia with premature CHD. This condition, whose heterozygous form occurs in about 0.2% of births, is caused by deficient or defective LDL receptors. As a consequence, the clearance of LDL from plasma is retarded, and high LDL levels accumulate in plasma. In making the diagnosis of FH, it was important to exclude elevations of LDL that are secondary to other health conditions such as nephrotic syndrome, hypothyroidism, or obstructive liver disease.

Tendon xanthomas are uncommon in patients with secondary hypercholesterolemia, although they can occur in the hypercholesterolemia associated with obstructive liver disease. Corneal arcus is a useful sign suggesting elevation of LDL cholesterol in young Caucasians; however, it loses specificity in older persons and in blacks.

Heterozygous FH, with half-normal levels of LDL receptors, usually causes total cholesterol levels in the range of 300 to 500 mg/dL and symptomatic CHD generally occurs between 30 and 50 years of age. The development of CHD in women lags that in men by about 10 years. In homozygous FH, when functioning LDL receptors are totally absent, total cholesterol levels range between 500 and 1000 mg/dL, and CHD generally presents by age 10. Until recent years, survival beyond age 20 has been extremely rare for those with homozygous FH.

In this patient the presenting cholesterol level was at the border between the range seen with heterozygous FH and that seen with homozygous FH. His condition is certainly heterozygous because he did not develop CHD until the fifth decade of life and because he responded superbly to drugs that act by stimulating LDL receptor activity (a bile acid sequestrant, statins, and ezetimibe).

At the lower end of the range of cholesterol levels seen with heterozygous FH, there can also be difficulties in making the diagnosis. Williams and colleagues [1] pointed out that in the general population only 4% of persons with a cholesterol level of 310 mg/dL will have FH; however, in the population of first-degree relatives of FH patients, 95% of those with a cholesterol level of 310 mg/dL will have FH. Thus, the total cholesterol level required for 98% specificity for a diagnosis of FH varies according to family history (Table 41.2).

Table 41.2 Total cholesterol level giving 98% specificity for diagnosis of familial hypercholesterolemia (FH)

	First-degree relative with FH	General population
Age (years)	Total cholesterol (mg/dL)	
<18	220	270
20	240	290
30	270	340
40+	290	360

Lessons Learned

The most important lesson to be learned from this patient is that intensive efforts to reduce LDL cholesterol utilizing a combination of drugs can be remarkably effective even in some of the most severely hypercholesterolemic patients. In these patients, such treatment can prevent the progression of CHD over many years. In this patient, the LDL cholesterol fell from a baseline of 552 mg/dL to a recent value of 79 mg/dL. Thus, even in the most severely affected patients, it may be possible to approach the stringent LDL target of 70 mg/dL; this LDL target is considered by the National Cholesterol Education Program to be an appropriate therapeutic option for very high risk patients [2].

Two major principles apply to the design of a combination drug regimen for intensive reduction of LDL levels:

1. The drugs used must individually reduce LDL levels.
2. They must do so by different mechanisms.

There are four major categories of drugs having LDL reduction as a major effect: statins, bile acid sequestrants, nicotinic acid, and ezetimibe, the inhibitor of cholesterol absorption. Each of these four has a different mechanism of action. However, the final common pathway for three of them (statins, bile acid sequestrants, and ezetimibe) involves stimulation of the clearance of LDL from plasma via the LDL receptor pathway. However, the mechanisms of action of these classes of drugs are sufficiently different that, when combined, they have additive effects on LDL reduction.

Statins have become the mainstay of LDL-reducing therapy because of their efficacy in lowering LDL levels, their tolerability, and a mountain of data demonstrating safety and CHD prevention [3]. These drugs are competitive inhibitors of hydroxymethylglutaryl coenzyme A reductase, the rate-limiting enzyme in biosynthesis of cholesterol. The consequence of inhibition of cholesterol biosynthesis is a reduced cholesterol concentration within the hepatocyte. A chain of homeostatic events is then activated to restore intrahepatic cholesterol levels. The end results of this chain are increased production of LDL receptors and enhanced clearance of LDL (and its cholesterol component) from plasma into the hepatocyte. A high hepatic extraction targets these drugs to the liver (Table 41.3). The reduction of LDL cholesterol at maximum dose ranges from approximately 34% to 60%. When LDL-lowering

Table 41.3 The statins: some characteristics

	Usual dose range (mg/d)	LDL reduction at maximum dose	Hepatic extraction (%)
Atorvastatin	10–80	58	>70
Fluvastatin	20–80	34	>68
Lovastatin	20–80	40	>69
Pravastatin	10–80	37	46
Rosuvastatin	5–40	57	60
Simvastatin	10–80	46	>79

medications are to be added sequentially, it is usually best to start with a statin because of the extremely well-documented safety and efficacy of these drugs.

Bile acid sequestrants (cholestyramine, colestipol, and colesevelam) also increase LDL clearance from plasma via the LDL receptor pathway. Just as the statins do, they cause the number of LDL receptors to increase in response to a reduced intrahepatic cholesterol concentration. The primary effect of the bile acid sequestrants is interruption of the enterohepatic circulation of bile acids. The consequent reduction in bile acid concentration leads to increased conversion of cholesterol to bile acids and a reduced intrahepatic cholesterol concentration. When a bile acid sequestrant is used, two homeostatic responses are activated to return intrahepatic cholesterol concentrations to normal. These involve [1] an increase in LDL receptor activity and [2] increased cholesterol biosynthesis. The increased cholesterol biosynthesis somewhat offsets the LDL-lowering effects of these drugs. However, combining a statin with a bile acid sequestrant blocks the increase in cholesterol biosynthesis. Thus, from a mechanistic perspective, the combination of a statin and bile acid sequestrant is very attractive. In a high dose of 20 to 24 g/day, cholestyramine reduces LDL cholesterol by nearly 30%. Such high doses are not often used because of gastrointestinal intolerance. The patient under discussion here, however, tolerated an equivalent high dose of colestipol (20 g twice daily) without difficulty. Colesevelam tends to have better gastrointestinal tolerability than the other two drugs in its class.

Ezetimibe, an inhibitor of cholesterol absorption, represents the third class of drug to act by enhancing the clearance of LDL from plasma via the LDL receptor pathway. By inhibiting intestinal cholesterol absorption it reduces the cholesterol concentration within hepatocytes. From this point, LDL receptor activity is stimulated in the same fashion as for the statins and bile acid sequestrants. The primary action of ezetimibe involves binding to an intestinal brush border protein, which may be a cholesterol influx transporter (Niemann-Pick C1-like 1). Thus, it is very specific in interfering with cholesterol absorption. It does not interfere with the absorption of fat-soluble vitamins or of fatty acids. When ezetimibe is used, we should remember that the most important dietary determinant of the plasma LDL level is saturated fat, not cholesterol; ezetimibe does not limit the absorption of saturated fatty acids. Thus, diet remains important regardless of whether a patient is taking ezetimibe. Ezetimibe, which reduces LDL cholesterol by 18% to 20% tends to be very well tolerated.

Nicotinic acid (niacin) is the fourth category of major LDL-reducing drugs. It is a B vitamin; in doses much higher than those required to prevent vitamin deficiency syndromes, it has beneficial effects of plasma lipoproteins. The related compound niacinamide (nicotinamide) prevents vitamin deficiency, but is devoid of lipid-altering effects. The lipid altering actions of nicotinic acid do not involve the LDL receptor pathway. Nicotinic acid binds to a G-protein–coupled receptor in adipocytes. This reduces cyclic adenosine monophosphate (AMP) levels, and, secondarily, reduces hormone-sensitive lipase in adipocytes. Hormone-sensitive lipase is the enzyme responsible for hydrolysis of triglyceride in adipose tissue. Thus, the reduced level of hormone-sensitive lipase limits mobilization of fatty acids from adipose tissue reducing the delivery of fatty acids to the liver. Because fatty acids are a major substrate and stimulus for production of very low density lipoprotein (VLDL), hepatic synthesis and secretion of VLDL fall. *Pari passu* with this, levels of LDL, the metabolic product of VLDL, also fall. Nicotinic acid has beneficial effects on plasma levels of all of the major atherogenic categories of lipoproteins. LDL, VLDL, remnants of VLDL, and lipoprotein (a) fall. Additionally, nicotinic acid is the most effective available drug for raising levels of HDL; HDL cholesterol levels can increase by 25% to 50% in response to treatment with nicotinic acid. LDL cholesterol levels tend to fall by 20% to 25%, and triglyceride levels fall by 20% to 50% in response to nicotinic acid.

Bothersome side effects are common with nicotinic acid. Cutaneous flushing occurs routinely; this is prostaglandin-mediated and can be blocked by prostaglandin inhibitors. Flushing is less prominent with long-acting preparations of nicotinic acid. Abdominal pain and heartburn lead to discontinuation of nicotinic acid in nearly one third of individuals. Nicotinic acid increases uric acid levels and occasionally causes acute gout, as it did in the case presented here. Pruritic dryness of the skin and acanthosis nigricans are also common effects of nicotinic acid. Drug-related hepatitis can occur; this is dose-related and occurs in about 3% of individuals treated with 3 g/day. Nicotinic acid can increase blood glucose levels. However, nicotinic acid has been just as effective in reducing CHD rates in diabetic patients as in nondiabetics [4].

Nicotinic acid is available in immediate-release and sustained-release forms. Flushing occurs more prominently with immediate-release forms of nicotinic acid. Sustained release form have been associated with markedly reduced flushing, but there is a potential to see more liver test abnormalities. One prescription form of nicotinic acid (Niaspan®) has been termed “extended release” and is said to have kinetics intermediate between the immediate release and the sustained release. However, there are no studies that sustain this claim.

Fibric acid derivatives (clofibrate, gemfibrozil, and fenofibrate) are much less effective in reducing LDL cholesterol than the other categories of lipid-altering medication. Thus, they will not usually have a role in combination drug regimens designed for maximal reduction of LDL cholesterol. Caution is warranted when a statin is used in combination with one of the fibric acid derivatives because of increased risk of myopathy; when this combination is used, fenofibrate is the preferred and safest of the fibric acid drugs available

in the United States [2]. Fenofibrate, in contrast to gemfibrozil and clofibrate, does not interfere with the metabolism of statins. Thus, the risk of myopathy is probably much less in fenofibrate-statin combinations than with other fibrate-statin combinations.

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Multiple-Choice Questions

1. Which of the following drugs for reducing LDL cholesterol does NOT act by enhancing the clearance of plasma LDL via the LDL receptor pathway?

   A. Simvastatin
   B. Cholestyramine
   C. Nicotinic acid
   D. Ezetimibe

   Answer: C.

2. Which of the following statements is true?

   A. Because ezetimibe interferes with cholesterol absorption, diet becomes relatively unimportant in management of hypercholesterolemic patients treated with this drug.
   B. Fenofibrate is the preferred fibric acid drug when a fibrate-statin combination is used.
   C. The fibric acid drugs (clofibrate, gemfibrozil, fenofibrate) can often be very helpful in combination regimens for maximum reduction of LDL cholesterol.
   D. Most individuals in the general population with a total cholesterol level of 310 mg/dL have familial hypercholesterolemia.

   Answer: B.

3. Which of the following statements is true:

   A. Because patients with heterozygous familial hypercholesterolemia have a deficiency of LDL receptors, drugs acting to reduce LDL cholesterol via the LDL receptor pathway are generally ineffective for these patients.
   B. Coronary heart disease tends to develop just as rapidly among women with familial hypercholesterolemia as among men with this condition.
   C. Tendon xanthomas suggest the presence of familial hypercholesterolemia in young Caucasian adults but not in elderly individuals or in blacks.
   D. In heterozygous familial hypercholesterolemia, coronary heart disease generally presents between the ages of 30 and 50 years.

   Answer: D.

Chapter 42
A Young Man with Abdominal Pain and Very High Triglycerides: The Chylomicronemia Syndrome

Molly C. Carr

Objective

1. To understand the differential diagnosis and management of the patient with chylomicronemia syndrome.
2. To understand the contribution of genetic and non-genetic factors in the assessment of hypertriglyceridemia.

Case Presentation

A 21-year-old man presented to the emergency department with a 2-day history of epigastric pain and dyspnea on exertion. The patient described his pain as a constant sharp mid-epigastric abdominal pain associated with nausea and diarrhea. He also reports changes in stool color (lighter than usual). He denies emesis, fever or chills, chest pain, or hypoglycemia.

The patient has an 8-year history of recurrent bouts of pancreatitis, hypertriglyceridemia, and type 2 diabetes. He developed pancreatitis initially at age 13 during an intensive care unit (ICU) admission, and since that time he has had frequent admissions for pancreatitis, as many as twice a month. He was diagnosed with diabetes at age 11 and insulin was initiated at age 13. He reports blood sugars that run between 200 and 500 mg/dL and his last hemoglobin A1c was 10.7%. Treadmill stress test and angiogram 5 years ago were negative.

The patient's height is 5'11", weight 264 lb, with a body mass index (BMI) of 38. His blood pressure was controlled at 121/68 mm Hg. Funduscopic exam revealed lipemia retinalis but not corneal arcus. He had eruptive xanthomas on his elbows and buttocks. Lungs were clear to auscultation bilaterally, without rhonchi, rales, or wheezes. Initial laboratory testing revealed a fasting serum total cholesterol 669 mg/dL, high-density lipoprotein (HDL) cholesterol 54 mg/dL, triglycerides 5867 mg/dL, and amylase 56 U/L (normal 20–115). The low-density

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lipoprotein (LDL) was not calculated, as triglycerides were greater than 400 mg/dL. Medications on admission included simvastatin 80 mg po qd, fenofibrate 145 mg po qd, ezetimibe 10 mg po qd, as well as pancreatic enzymes, insulin, pioglitazone, and a low-dose angiotensin-converting enzyme (ACE) inhibitor. The patient admitted to medication noncompliance. He was treated with restriction of oral intake, hydration, and analgesia, and his triglycerides dropped to 1040 mg/dL and stabilized at ~500 mg/dL after several days.

Clinical and Laboratory Characteristics of Chylomicronemia Syndrome

The diagnosis of chylomicronemia syndrome is made with elevated plasma triglyceride levels (>1000 mg/dL) and the presence of clinical symptoms, as there are no readily available laboratory tests that identify chylomicron particles in the plasma. Chylomicrons are triglyceride-rich lipoprotein particles secreted by the gut into the plasma after meals. Chylomicron particles are not typically present in fasting plasma as they are cleared within 8 hours after meals. Chylomicrons begin to appear in fasting plasma when triglyceride levels exceed 400 mg/dL and are always present in plasma when triglyceride levels exceed 1000 mg/dL.

Clinical manifestations of chylomicronemia syndrome arise when triglyceride levels exceed 2000 mg/dL and include lipemic plasma, acute pancreatitis, chronic abdominal pain, hepatosplenomegaly, steatosis (fatty liver), mild elevations in liver enzymes, dyspnea, eruptive xanthomas, lipemia retinalis, and neuropsychiatric symptoms. The clinical features improve with the reduction of plasma triglycerides. The most severe clinical manifestation of chylomicronemia syndrome is acute pancreatitis, as the diagnosis carries significant morbidity and mortality. It is estimated that 2% to 10% of pancreatitis cases are caused by chylomicronemia syndrome, and the artificially normal serum and urine amylase levels, due to assay interference by the plasma lipids, can make diagnosis difficult. The presence of lipemic plasma (with triglyceride levels >2000 mg/dL) is sufficient to make the diagnosis of chylomicronemia-induced pancreatitis. Abdominal pain in chylomicronemic patients can prompt the discontinuation of food intake prior to hospital admission, and some patients may present with triglycerides <1000 mg/dL.

Physical exam findings associated with chylomicronemia syndrome are variable and asymptomatic patients with triglyceride levels of 20,000 mg/dL have been described. Eruptive xanthomas are nontender, small, yellow papular skin lesions seen in patients with chronic chylomicronemia. These localized lipid deposits in the skin result from extravascular phagocytosis of chylomicrons by skin macrophages and are typically found on the elbows, knees, and buttocks. Eruptive xanthomas usually regress in size and number with triglyceride-lowering therapy, and the recurrence of xanthomas can indicate inadequate treatment. Lipemia retinalis appears on funduscopic exam as a pale pink appearance of retinal arterioles and venules caused by the scatter of light by large chylomicrons. There is no effect on the subject's

vision. Dyspnea has been noted in patients with severely elevated triglycerides. Neurologic sequelae of chylomicronemia include memory loss, dementia (reversible), depression, and peripheral neuropathy, but the mechanisms underlying these symptoms are unknown.

Lipemic plasma, seen in chylomicronemic patients, can interfere with several clinical assays and cause spurious results. Serum and urine amylase levels may be artificially normal even with severe pancreatitis due to assay interference by lipids and circulating lipase inhibitors. Artificially low levels of sodium (pseudohyponatremia), hemoglobin, and PO_2 as well as abnormal thyroid function tests are an artifact of assay interference by triglycerides.

Physiology of Triglyceride-Rich Particles

Triglyceride-rich particles originate from both the diet (chylomicrons) and from endogenous production in the liver (very low density lipoproteins [VLDL]). Chylomicrons are large lipoprotein particles that contain triglyceride, cholesterol, phospholipid, and apolipoproteins, primarily apolipoprotein (apo) B-48. They are synthesized postprandially in the intestinal mucosa and secreted into the bloodstream via the thoracic duct (exogenous pathway). Chylomicron particles start appearing in the bloodstream 1 to 3 hours after consuming a fatty meal, and most are cleared from the plasma within 8 hours. After a 12- to 14-hour fast, plasma does not usually contain any chylomicron particles. Once in the plasma, chylomicrons are acted on by the lipolytic enzyme lipoprotein lipase (LPL) and acquire apolipoprotein (apo) C-II (an activating cofactor of LPL). Lipoprotein lipase is a lipolytic enzyme that plays a key role in the lipolytic cascade by hydrolyzing triglycerides in triglyceride-rich particles (chylomicrons and VLDL). LPL is responsible for the conversion of chylomicrons to chylomicron remnant particles and a deficiency or reduction in LPL (see below) can lead to an accumulation of the chylomicron particles in the plasma. Chylomicron remnant particles are then cleared from the circulation via the liver with uptake mediated by apolipoprotein E (apo E).

Very low density lipoprotein particles (endogenous pathway) are made in the liver and processed in a similar fashion through the lipolytic cascade. Triglyceride in VLDL particles is hydrolyzed by LPL leading to the formation of intermediate-density lipoproteins (IDL) and then LDL particles, resulting in progressively smaller and more cholesterol-rich particles.

Etiology of Chylomicronemia Syndrome

It is important to recognize that chylomicronemia syndrome usually results from the coexistence of both a genetic (primary) and secondary form of hypertriglyceridemia. Common genetic disorders of triglyceride metabolism typically cause only moderate elevations in triglycerides (400 to 600 mg/dL). The exception to this rule is familial chylomicronemia syndrome (LPL deficiency), which is typically diagnosed

in childhood and no "second hit" is required. Recognizing the secondary (acquired) contributors to chylomicronemia syndrome is critical in the diagnosis and treatment of chylomicronemia syndrome.

Primary (Genetic) Causes of Hypertriglyceridemia

Familial combined hyperlipidemia (FCHL) is the most common genetic form of hyperlipidemia and is caused by an overproduction of apo B-containing lipid particles (VLDL, IDL, LDL) by the liver. Patients with FCHL present with elevated total and LDL cholesterol or hypertriglyceridemia, reduced HDL, and elevated plasma apo B (>90th percentile). The prevalence of FCHL was originally estimated at 0.5% to 2.0% of the population, but a recent study suggested a higher prevalence of 5.7%. In comparison to FCHL, familial hypertriglyceridemia (FHTG) is characterized by excess triglyceride synthesis but normal cholesterol production. Patients with familial hypertriglyceridemia present with elevated triglyceride levels and reduced HDL but normal plasma LDL and apo B levels.

Dysbetalipoproteinemia (also called remnant removal disease or type III hyperlipoproteinemia) is caused by the impaired clearance and accumulation of VLDL and chylomicron remnant particles. Patients with dysbetalipoproteinemia present with elevated total and LDL cholesterol or hypertriglyceridemia, and reduced HDL. Individuals with dysbetalipoproteinemia have defective apolipoprotein E, leading to the accumulation of remnant particles. The diagnosis can be confirmed by obtaining apo E genotype.

In comparison to the more common genetic disorders of triglyceride metabolism, familial chylomicronemia syndrome is quite rare (∼1 in 1,000,000) and can be the sole etiology of chylomicronemia syndrome. Genetic causes of familial chylomicronemia syndrome include deficient levels of lipoprotein lipase or apolipoprotein (apo) C-II (the activator of LPL) or rarely the presence of circulating LPL inhibitors. Patients with familial chylomicronemia syndrome typically present in infancy with severe hypertriglyceridemia and a low tolerance for dietary fat intake. Children with lipemic plasma and chronic abdominal pain should have lipoprotein lipase levels measured.

Secondary (Acquired) Causes of Hypertriglyceridemia

Genetic disorders alone are rarely the sole cause of chylomicronemia. The most common clinical scenario is the patient who has an underlying genetic disease and one or more secondary contributors that interact and predispose individuals to chylomicronemia syndrome. Common secondary contributors to hypertriglyceridemia include culprit medications, poorly controlled metabolic states, alcohol excess, and weight gain.

Medications that contribute to hypertriglyceridemia, in susceptible individuals, include oral estrogen, selective estrogen receptor modulators (tamoxifen and raloxifene), clomiphene, glucocorticoids, bile acid sequestrants, beta-blockers, diuretics (thiazide and loop), immunosuppressants (interferons, tacrolimus, cyclosporine), isotretinoin (Accutane®), protease inhibitors, and atypical antipsychotics. The ability of drugs to induce hypertriglyceridemia in susceptible individuals is not well recognized, as studies have found that most patients referred to lipid clinics with triglyceride-induced pancreatitis were still receiving culprit drugs.

Oral estrogen (but not transdermal) increases serum triglycerides, but in most cases the increased levels do not surpass the upper limit of normal. However, in susceptible women with baseline hypertriglyceridemia, oral estrogen therapy can cause chylomicronemia syndrome and pancreatitis that requires discontinuation of therapy. Bile acid sequestrants (resins) bind cholesterol in the gut lumen and are helpful in reducing LDL cholesterol levels, but patients with elevated triglycerides may have further increases in triglycerides during treatment with resins.

The common combination of poorly controlled diabetes and obesity are frequent contributors to chylomicronemia syndrome and can be difficult to treat, as illustrated in the case presented above. Disease states that can contribute to impaired triglyceride metabolism include hypothyroidism, renal failure and uremia, nephrotic syndrome, rapid weight gain, lipodystrophy, Cushing's syndrome, and acromegaly. Pregnant women with a history of chylomicronemia syndrome are at high risk for pancreatitis and require close follow-up, as pregnancy can worsen hypertriglyceridemia.

Management of Chylomicronemia Syndrome

The goal of therapy for chylomicronemia syndrome is to lower triglycerides to levels less than 1000 mg/dL, and the mainstay of management is a low fat diet. Dietary noncompliance is a common reason for treatment failure. Patients with chylomicronemia syndrome must be counseled on dietary fat restriction and weight loss, as most patients with hypertriglyceridemia are obese and weight loss is an essential feature of triglyceride management. In comparison to other heart healthy diets, patients with chylomicronemia syndrome must rigidly avoid all types of dietary fats (both saturated and unsaturated) by consuming a 0% to 15% of total calories from fat. Drugs that increase plasma triglycerides should be avoided in chylomicronemic patients. The patient with severe hypertriglyceridemia associated with alcoholic indiscretion should abstain from alcohol.

Patients with chronic chylomicronemia who do not respond to lifestyle intervention may require lipid-lowering therapy. Fibrates (gemfibrozil and fenofibrate) are lipid-lowering agents that increase lipolysis and enhance elimination of triglyceride-rich particles by activating LPL, reducing plasma triglycerides and increasing HDL cholesterol. The effects of fibrates on LDL cholesterol are variable and it is not unusual to see a rise in plasma LDL cholesterol after fibrate initiation in patients with triglycerides >500 mg/dL. Both fibrates carry a risk of liver toxicity, and

periodic monitoring of liver function tests is recommended for the duration of treatment. The drugs should be discontinued if liver enzyme levels persist above three times the normal limit. Fibrates also enhance the effects of coumarin anticoagulants and increase the risk of cholelithiasis. Combination therapy with fibrates and statins (hepatic hydroxymethylglutaryl coenzyme A [HMG-CoA]reductase inhibitors) is associated with increased risk of myopathy and rhabdomyolysis. Fibrate use is contraindicated in patients with severe liver or renal disease, in combination with cerivastatin (a statin), and in pregnant or nursing women.

In hospitalized patients with chylomicronemia and pancreatitis, supportive treatment for pancreatitis is usually adequate to lower triglycerides, including discontinuation of oral caloric intake, hydration, analgesia, and improved glycemic control. The use of plasmapheresis to remove chylomicrons from plasma is controversial. In most cases, triglyceride levels fall quickly by suspending food intake and reducing glucose levels. Insulin therapy has been recommended as an adjunct to supportive care, as insulin may increase LPL activity, but there is little data. If chylomicronemia syndrome is diagnosed, laboratory tests should include thyroid function tests, fasting glucose, liver function tests, and testing for proteinuria.

In conclusion, this case describes a young man with acute pancreatitis, type 2 diabetes, and chylomicronemia syndrome. Chylomicronemia syndrome-induced pancreatitis can be difficult to diagnose as both serum and urine amylase levels may be normal due to assay interference. In most cases, the etiology of chylomicronemia syndrome is multifactorial and related to both underlying genetic predisposition and exacerbating factors, including medications, poor glycemic control, obesity, and high fat diet. It would appear unlikely that this patient has an LPL gene mutation (familial chylomicronemia syndrome) as he has no early childhood history of lipemic plasma, hypertriglyceridemia, or abdominal pain after fatty meals. Successful treatment of this patient with chylomicronemia syndrome will require counseling on dietary fat restriction, weight loss, and improved glycemic control.

Suggested Readings

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Multiple-Choice Questions

1. Which two of the following tests would be helpful to diagnose a patient with a triglyceride level of 1500 mg/dL?

   A. LDL receptor genotyping
   B. Apo E genotype

C. Postheparin lipase activity
D. Apo B production rate

Answer: B and C.

2. A 55-year-old man with type 2 diabetes is referred to you for difficult to treat hyperlipidemia. Medications include metoprolol 50 mg b.i.d., aspirin 81 mg qd, glyburide 10 mg qd, and simvastatin 40 mg qd. Physical exam reveals central obesity. The fasting lipids are as follows: total cholesterol 350, triglycerides 1350, HDL 24, and hemoglobin A1c 9%. What's the best therapy to control his hyperlipidemia?

   A. Double simvastatin to 80 mg/day
   B. Add bile-acid resin to simvastatin
   C. Stop simvastatin, add fenofibrate, and control his diabetes.
   D. Stop simvastatin and control diabetes

   Answer: C

3. A 43-year-old woman with HIV infection has been treated with antiretroviral therapy, including a protease inhibitor, for 3 years. After seeing her lipid panel of total cholesterol 390, triglycerides 1700, and HDL 35, you recommend a low-fat diet (10% fat), but she returns 3 months alter with a similar lipid panel.
   Which medication would you start?

   A. Bile acid sequestrant
   B. Gemfibrozil
   C. Simvastatin
   D. Omega-3 fatty acids

   Answer: B.

Chapter 43
Roughly Equivalent Lipids in a Middle-Aged Obese Man at Risk for Coronary Disease

Stephen R. Crespin

Objectives

1. To understand how to suspect a genetic lipid disorder in patients with markedly elevated lipid values
2. To recognize an atherogenic dyslipidemia known as type III hyperlipoproteinemia or dysbetalipoproteinemia
3. To understand the key role of both genetic and nongenetic factors in the clinical presentation

Case Presentation

A 57-year-old, divorced, optical products salesman presents for endocrine consultation seeking treatment for morbid obesity. He is currently on no medication. He did, however, have a high coronary calcium score at a screening clinic and is concerned about both his cholesterol and whether he is at risk for coronary heart disease (CHD).

Family history showed that his father died at age 65 of a myocardial infarction. His mother is alive and well. He has one sister who is under treatment for hyperlipidemia, but her exact diagnosis is unknown. He also has a brother who has no known hyperlipidemia.

His past medical history was negative for significant illness, except as stated above. The social history showed that the patient was married and has one son, but the lipid status of his 18-year-old son is unknown. The review of systems was virtually asymptomatic except for shortness of breath on exertion.

His examination showed: height 5'6", weight 279 pounds, body mass index (BMI) 45, blood pressure 130/80, pulse 80 and regular. Except for the morbid obesity, the physical exam was essentially within normal limits. There were no

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planar xanthomas on the hands or tuberous xanthomas on the hands, elbows, or knees.

Laboratory data on the index visit disclosed the following (mg/dL):

Total cholesterol	324
Total triglycerides	359
High-density lipoprotein (HDL) cholesterol	65
Low-density lipoprotein (LDL) calculated	187
Nuclear magnetic resonance (NMR) lipid profile	119

The NMR profile showed the patient's concentration of intermediate-density lipoprotein (IDL) was in the 99th percentile. His concentration of small dense LDL was in the 90th percentile. Most of his HDL cholesterol was in the small HDL form.

Because of the discrepancy between his calculated LDL cholesterol and the LDL measurement by the NMR profile, an LDL by direct measurement using immunoassay was performed and this was also consistent with the LDL on the NMR profile. A fasting blood sugar, a comprehensive metabolic panel, a complete blood count, hemoglobin A1c and thyroid-stimulating hormone (TSH) were all within normal limits.

How the Diagnosis Was Made

His lipoprotein cholesterol was measured by ultracentrifugation (mg/dL):

Total cholesterol	157
Total triglycerides	152
VLDL triglyceride	106
VLDL cholesterol	45

Thus the ratio of cholesterol to triglycerides in his very low density lipoproteins (VLDL) was about 2 to 1, much higher than that normally seen in VLDL of normal composition where the ratio is usually five parts triglyceride to one part cholesterol. The ratio of his VLDL cholesterol to the total triglycerides was 0.296, consistent with type III hyperlipoproteinemia.

The patient was counseled about adhering to a 1500-calorie low-cholesterol diet, and was started on Lipitor 10 mg daily. A thallium stress test was negative. One month later he returned not having lost any weight, but taking atorvastatin 10 mg daily. On atorvastatin his lipid profile was as follows:

Total cholesterol	169 mg percent
Total triglycerides	145 mg percent
LDL calculated	75 mg percent
LDL direct (Quest Lab)	48 mg percent

The NMR lipid profile was as follows:

Total cholesterol	167 mg percent
Triglycerides	140 mg percent
HDL cholesterol	61 mg percent
LDL cholesterol	80 mg percent

The NMR profile showed a marked decrease in all LDL subfractions. Small dense LDL was now only in the 30th percentile, but the patient's IDL remained in the 99th percentile. Addition of fenofibrate to the patient's atorvastatin was proposed, but he declined this therapy because of concern over drug interaction. (Note: After some months the patient developed myalgias due to the atorvastatin. His lipids returned to their baseline values. He's now being considered for monotherapy with a fibrate.)

Lessons Learned

This patient did not present with the typical mixed dyslipidemia usually characterized by modest levels of LDL cholesterol combined with moderate elevation in serum triglycerides. The fact that he had a rather marked elevation of both total cholesterol and total triglycerides to about an equal degree, raised suspicion that he might have type III hyperlipoproteinemia. This was confirmed by ultracentrifugation, which revealed a large amount of cholesterol in his VLDL. Also, NMR lipoprotein analysis showed a very large amount of IDL.

Type III hyperlipoproteinemia, also known as dysbetalipoproteinemia, is a rare atherogenic dyslipoproteinemia, usually attributed to homozygosity of the apolipoprotein apoE2. ApoE is a protein constituent of chylomicrons, chylomicron remnants, VLDL, IDL, and HDL, and has a critical role in lipoprotein metabolism, serving as a ligand for the receptor-mediated clearance of these particles by hepatic lipoprotein receptors. It is a polymorphic protein, of which three common isoforms exist, designated apoE2, apoE3, and apoE4. ApoE3 is the most common isoform.

One percent of the population is the apoE2/E2 genotype, but only 0.01% of those with the genetic mutation actually express the hyperlipidemia. Therefore, type III hyperlipoproteinemia is a multifactorial disease because it usually requires additional genetic, hormonal, or environmental factors (in this case, the morbid obesity) for full phenotypic expression. Since there is impaired binding capacity of the apoE to the hepatic LDL receptors, there accumulates in the circulation, a cholesterol-enriched VLDL and large quantities of IDL, which is usually characterized by an equal amount of LDL and triglyceride. Chylomicron remnants also accumulate, and these lipoproteins usually predispose to premature atherosclerosis. Diagnostic laboratory criteria for type III hyperlipoproteinemia do include combined hypercholesterolemia and hypertriglyceridemia, as well as a ratio of VLDL cholesterol to total triglycerides exceeding 0.3. The normal ratio is 0.2. This disease is usually inherited as an autosomal recessive trait.

Clinical examination of a patient with type III hyperlipoproteinemia may reveal almost pathognomonic, flat, so-called planar xanthomas in the creases of the palms of the hands. Patients may also exhibit so-called tuberous xanthomas particularly about the elbows and knees, but do not generally exhibit cholesterol deposits in the tendons of the hands or Achilles tendons, which are commonly seen in familial hypercholesterolemia.

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Multiple-Choice Questions

1. What clinical features of a patient with combined hyperlipidemia should make one suspicious that he indeed has type III hyperlipoproteinemia?

   A. Family history of premature coronary disease
   B. Elevation of both cholesterol and triglycerides to an equal degree
   C. History of pancreatitis
   D. NASH Syndrome (Nonalcoholic steatohepatitis)

   Answer: B.

2. Treatment with a statin in this patient's case would be expected to:

   A. Raise HDL cholesterol by at least 20%.
   B. Reduce concentrations of apoB-containing lipoproteins.
   C. Enhance the conversion of small dense LDL particles to normal composition LDL.

   Answer: B.

3. Treatment with a fibrate in this patient's case would be expected to:

   A. Lower HDL cholesterol.
   B. Enhance the conversion of small dense LDL to normal composition LDL.
   C. Prevent the onset of diabetes mellitus.

   Answer: B.

4. The most serious clinical complication of type III hyperlipoproteinemia is:

   A. Diabetes mellitus
   B. Premature coronary artery disease
   C. Pancreatitis
   D. Sleep apnea

   Answer: B.

5. The most common apoE genotype in patients with type III hyperlipoproteinemia is:

   A. ApoE2/E2
   B. ApoE3/E3
   C. ApoE4/E4

   Answer: A.

Part XIV
Obesity and the Metabolic Syndrome

Introduction

Robert T. Yanagisawa and Derek LeRoith

Epidemic of Obesity

More than 30% of Americans are obese today, and the prevalence of obesity continues to rise at an epidemic proportion. There has been a 74% increase of obesity over the 10 years from 1991 to 2001 [1]. Such a rapid and widespread obesity epidemic is a reflection of the combination of excess caloric consumption with extra large portions of calorie-dense food and the sedentary lifestyle that we have become accustomed to in our present society. As a consequence, obesity threatens our future with a significant increase in the prevalence of diabetes and cardiovascular morbidity and mortality. Our predisposition to obesity-related metabolic conditions vary considerably, and therefore more individualized approaches are necessary to treat obesity. Some individuals are obese, yet they appear to be metabolically stable, while others develop many of the obesity-related metabolic complications, even with the same degree of obesity. Similar to other serious epidemic conditions, we must treat those obese individuals, with a high risk for metabolic complications, early and aggressively.

Endocrine Control of the Energy Balance System

Since the discovery of leptin in 1994, we have come to know that adipose tissue is a complex, and metabolically active endocrine gland. Obesity is defined as the presence of excess adipose tissue. This excess, particularly in the visceral compartment, is associated with an increased risk for the metabolic syndrome. Adipose tissue secretes a variety of bioactive peptides, known as adipokines, active both at the local and systemic level [2].

These signals from adipose tissue work in concert with the rest of the energy homeostasis system. As Kershaw and Flier [2] summarize eloquently in their review,

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energy homeostasis involves both long-term and short-term signals. Long-term afferent signals include leptin from adipose tissue and insulin from pancreatic beta-cells. Short-term, meal-related afferent signals from the gut include inhibitors of appetite such as Peptide YY_3-36 (PYY), glucagon-like peptide 1 (GLP-1), and cholecystokinin (CCK), and the stimulator of appetite such as ghrelin. These inputs are integrated within the brain, most importantly within the hypothalamic area, and then processed into satiety or hunger signals as efferent output. The efferent elements of this system include those regulating the intensity of hunger and subsequent food-seeking behavior. The efferent system also includes regulating the level of basal energy expenditure; energy expenditure is determined by physical activity and the levels of key circulating hormones such as insulin and glucocorticoids.

Since our survival used to be more acutely threatened by starvation than obesity, it comes as no surprise that the energy balance system is more robustly organized to respond to deficient energy intake and stores than to excess of energy. Our energy balance system is overwhelmed with the excess energy intake common in the present-day calorie-toxic environment. The system becomes more complicated when we take into account that our responses to food come not just from a simple hunger or satiety, but with more variety of senses such as mood, appearance, environment, and more.

The Present and Future of Obesity Management

A comprehensive approach should be taken to derive an individually appropriate treatment plan for obese patients. The intensity of therapy should be scaled based on patients' degree of obesity and coexisting metabolic risk factors. In the majority of cases, relatively small reductions in weight have a significant impact on obesity-related metabolic conditions, but some require further intervention. While more than two thirds of adults in the United States are either trying to lose weight or maintain their current weight, the majority struggle to lose any weight. One explanation is that only 17.5% were following the basic two key recommendations: eat fewer calories and increase physical activity [3].

There is no one dietary method that is effective for everyone, but in most cases, weight loss achieved closely approximates a mathematically estimated weight loss, by the difference between energy intake and energy requirement for the individual. There are more than 5000 successful long-term weight loss maintainers in the National Weight Control Registry, with an average weight loss of 30 kg for more than 5.5 years. They share three common behavioral strategies: (1) eating a diet low in fat, (2) frequent self-monitoring of body weight and food intake, and (3) high levels of regular physical activity (4). As we begin to understand some of the varied physiologic mechanisms relating to obesity, we will have more options to intervene. While we are far from curing obesity, we will discuss some of the specific and successful strategies toward approaching patients with obesity.

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Chapter 44
Metabolic Syndrome

Robert T. Yanagisawa and Derek LeRoith

Objectives

1. To review the criteria for metabolic syndrome and the obesity assessment according to the metabolic risk factors
2. To understand the benefit of weight loss and lifestyle modification
3. To review risk appropriate weight loss goals for individuals with metabolic syndrome

Case Presentation

A 45-year-old white woman presents with difficulty losing weight despite her diet and exercises program. She feels she is a setup for type 2 diabetes, which her mother developed when she was the patient's age. She states she was never very thin, but she has been gradually gaining weight over the last 10 years. She attributes her weight gain to decreased physical activity and stress-induced eating.

She has lost 15 to 20 lb on several occasions on various diet programs, but she stops following the diet when she does not see continued progress and then she regains her weight. The heaviest she ever weighed was 210 lb.

Her primary physician started her on amlodipine 10 mg daily for her hypertension this past year, but she is otherwise in good health. On physical exam, her blood pressure is controlled at 130/85 mm Hg. Her weight is 200 lb and height is 5'4". Her waist circumference is 38" and her hip circumference is 40"

She did not have any striae, bruising, or significant hirsutism. She had a normal cervical fat pad for her weight. Her abdomen was obese with weight distribution more typical of an android body shape. The remainder of her exam was unremarkable.Laboratory findings were notable for impaired fasting glucose with plasma glucose of 105 mg/dL, but her hemoglobin A1c (HgbA1c) was normal at 5.5%.

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A lipid profile reveals a total cholesterol of 198 mg/dL, the high-density lipoprotein (HDL) was low at 39 mg/dL, the triglycerides were high at 200 mg/dL, and a low-density lipoprotein (LDL) of 110 mg/dL. The thyroid-stimulating hormone (TSH) was normal at 1.6 μIU/mL, and the 24-hour urine free cortisol was 50 μg/24 hours.The patient wants to know what she can do to lose weight and reduce her risk of developing diabetes.

How the Diagnosis Was Made

Does the patient have obesity and obesity-associated metabolic syndrome? Let's calculate her body mass index (BMI) in order to evaluate her obesity and her metabolic risk. The BMI is a standard measure of degree of obesity and it is calculated using the patient's weight and height, as follows:

$$\begin{aligned} \text{BMI} &= \text{Weight (kg)/Height (m)}^2 \\ &= 704 \times \text{Weight (lb)/Height (in)}^2 \\ &= 34.3 \end{aligned}$$

To determine the appropriate risk of metabolic syndrome, we should use the risk-adjusted BMI, which takes the degree of central obesity into account. Waist measure or waist-to-hip ratio provides the measure of central obesity. The risk classification chart in Table 44.1 shows that by combining the patient's BMI and central obesity, she has as much metabolic risk as someone in class II obesity.

Central obesity is a major risk factor for metabolic syndrome. An android or an apple-shaped body weight distribution increases this risk compared to a gynoid or pear-shaped body weight distribution as it is associated with increased visceral adiposity (Fig. 44.1).

In addition to central obesity, the patient has three of the four features of metabolic syndrome [1] as defined by the International Diabetes Federation (IDF).

Table 44.1 Classification of overweight and obesity by BMI, waist circumference, and associated disease risk (risk for type 2 DM, HTN, and CVD)

	BMI	Obesity class	Waist circumference	
			< 40 for men < 35 for women	> 40 for men > 35 for women
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	Class I	High	Very high
Obesity	35.0–39.9	Class II	Very high	Very high
Morbid obesity	> 40.0	Class III	Extremely high	Extremely high

Adapted from the Practical Guide to the Identification. Evaluation, and Treatment of Overweight and Obesity in Adults (2000), NIH and NAASO

DM is diabetes, HTN is hypertension, CVD is coronary vascular disease, NIH is National Institutes of Health, NAASO is the North American Association for Study of Obesity.

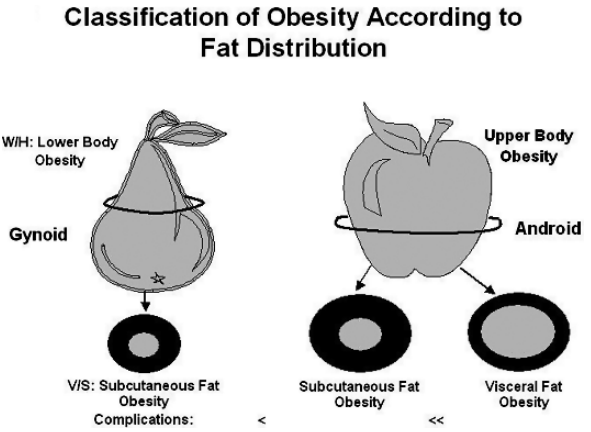

Fig. 44.1 Classification of obesity according to fat distribution W/H is waist hip ratio, V/S is visceral to subcutaneous adipose ratio

While the overall criteria of metabolic syndrome are similar (obesity, insulin resistance, dyslipidemia, and hypertension), different organizations define each point slightly differently. In the United States, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) criteria defines the cutoff for central obesity as 102 cm (40") for men and 88 cm (35") in women as above (NCEP ATP-III criteria is discussed in Case 45). The World Health Organization (WHO) also uses a waist/hip ratio as one of the criteria. Central obesity is defined as waist/hip ratio > 0.9 in males or > 0.85 in females. Also, there seems to be some ethnic variability on the degree of susceptibility to metabolic syndrome. Asians have increased risk even at a lower waist measures and cut off values of 90 cm for men and 80 cm in women should be used (Table 44.2).

So, what role does obesity play in metabolic syndrome? Obesity is a state of excess of body fat resulting in an increased level of free fatty acid (FFA). Increased levels of FFA contribute to inhibition of insulin-stimulated glucose utilization in

Table 44.2 The new International Diabetes Federation (IDF) consensus metabolic syndrome definition

Clinical features	Cutoff values
Central Obesity	$\geq$ 94 cm Europid men $\geq$ 80 cm Europid women (ethnicity-specific values)
Plus any 2 of the 4 following factors:	
1. Hypertriglyceridemia	$\geq$ 150 mg/dL or specific treatment for this lipid abnormality
2. Reduced HDL	$<$ 40 mg/dL men, $<$ 50 mg/dL women or specific treatment for this lipid abnormality
3. Elevated blood pressure	$\geq$ 130/85 mm Hg or treatment of previously diagnosed hypertension
4. Elevated plasma glucose	$\geq$ 100 mg/dL or previously diagnosed type 2 diabetes mellitus

1st International Congress. IDF; 2005; Berlin, Gemany.

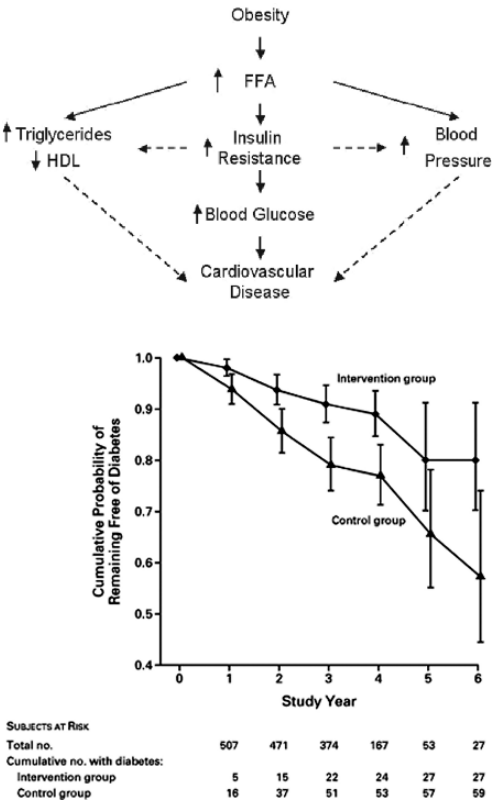

Fig. 44.2 The role of obesity

muscle and stimulation of hepatic glucose production. Visceral adipocytes are considered to be more lipolytically active than subcutaneous adipocytes and contribute to insulin resistance and its consequences [2] (Fig. 44.2).

While a 5% to 10% weight reduction is a significant [3] improvement, this may not be adequate for patients with significant obesity who are considered to be at high risk for cardiovascular disease (CVD). To take the weight management therapy one step further beyond the initial 5% to 10%, setting a mutually agreeable goal between the patient and the treating physician is important aspect of treating obesity. To set an appropriate goal for weight to reduce the risk of metabolic syndrome, physicians must inform patients of where they stand on the cardiovascular disease risk curve and what they need to do to reduce the risk to where it is more comparable to someone without significant obesity [4]. This is accomplished by reducing this patient's BMI from her initial 34 down to 27 or 28 (Fig. 44.3).

Setting the ideal body weight range as the appropriate goal is not realistic for someone with significant obesity. An overaggressive goal only leads to weight management failure. Many weight loss attempts fail because people do not transition well from the weight loss phase to the weight maintenance phase. Endocrine control

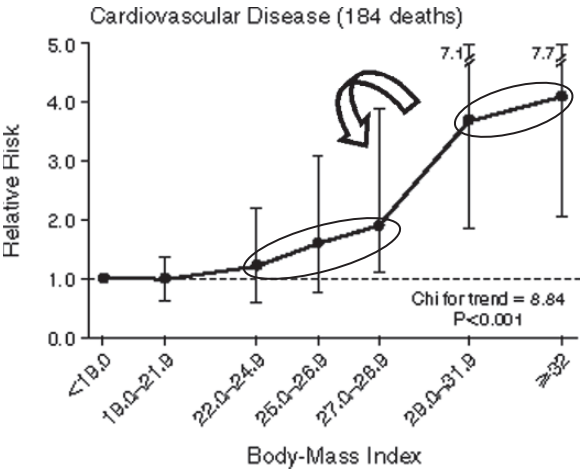

Fig. 44.3 Goals for risk reduction

of the energy balance system decreases basal energy expenditure with weight loss and counters the reduced body weight. Most people do not realize that they need to maintain both caloric restriction and exercises to increase their energy expenditure in order to maintain the weight loss.

Lessons Learned

1. Obesity is a state of excess body fat and accumulation of more lipolytically active visceral adipocytes. Resulting increased level of FFA contributes to the metabolic syndrome.
2. Metabolic risk of obesity is most commonly measured as both the degree of obesity (BMI) and regional fat distribution (waist and waist/hip ratio). Increased waist circumference or central obesity is an independent risk factor for metabolic syndrome.
3. Lifestyle modification intervention, even at the modest 5% to 10% total body weight reduction, has been clearly shown to have significant benefit of reducing the risk of metabolic syndrome.
4. The intensity of therapy and the appropriate goal weight should be based on the patients' metabolic risk.

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Multiple-Choice Questions

1. What is the BMI and the metabolic risk category for the case presented here?

   A. BMI 30 and increased metabolic risk
   B. BMI 34 and high metabolic risk
   C. BMI 34 and very high metabolic risk
   D. BMI 37 and very high metabolic risk
   E. BMI 37 and extremely high metabolic risk

   Answer: C. Explanation: The calculated BMI in choice A, D, and E are incorrect. The metabolic risk category in choice B is incorrect because by combining her BMI and central obesity, she has as much metabolic risk as someone in class II obesity.

2. What risk factors does she have for the metabolic syndrome?

   A. Central obesity
   B. Hypertriglyceridemia
   C. Reduced HDL
   D. Hypertension
   E. All of the above

   Answer: E. Explanation: Choices A to D are all determinants of metabolic syndrome. They are all part of the criteria set by the International Diabetes Federation (IDF) for the diagnosis of metabolic syndrome.

3. Considering her degree of obesity and metabolic syndrome, what is her appropriate weight loss goal to reduce her metabolic risks?

   A. Her metabolic risk is normal.
   B. Her metabolic risk cannot be reduced no matter what she does.
   C. Aim for the ideal body weight reaching BMI < 24.
   D. Start with 5% to 10% total body weight loss with a goal of reaching a BMI of 27 or 28.
   E. She needs a bariatric surgery for weight loss.

   Answer: D. Explanation: Choice A is incorrect, as her metabolic risk is very high. Risk stratification was discussed in question 1. Choice B is incorrect, as several weight management intervention studies have shown that obese individuals can significantly improve their metabolic risks by reducing weight. Choice C is incorrect, because setting the ideal body weight range as the appropriate

goal is not realistic for someone with a significant obesity. An overaggressive goal only leads to weight management failure. This patient does not meet the National Institutes of Health (NIH) criteria for surgical weight loss, and therefore choice E is incorrect. (See Case 46 for further details.)

Chapter 45
Polycystic Ovarian Syndrome

Michael Magnotti and Walter Futterweit

Objectives

1. To review the typical presentation of a patient with the polycystic ovarian syndrome (PCOS)
2. To examine the current diagnostic criteria for PCOS as well as the controversy surrounding these criteria
3. To learn about the link between PCOS and the metabolic syndrome
4. To understand the treatment options for PCOS
5. To discuss the long term complications of chronic PCOS

Case Presentation

A 22-year-old Caucasian woman is referred for evaluation of secondary amenorrhea. She reports menarche at age 13, followed by irregular menses for about 1 year. Her menses then became very regular until age 17. Since that time, she has been having irregular menses, often menstruating only once every 2 to 3 months. For the past 6 months she has had no menstrual periods at all, and after taking several home pregnancy tests that were negative, she presented to her internist. He confirmed that she was not pregnant with a urine β-human chorionic gonadotropin (β-HCG), and referred her for evaluation.

The patient currently takes no medications. She reports that at age 16 she weighed 140 lb, but gained about 40 pounds over the next 2 to 3 years. Her weight has been stable at 180 lb for the past few years. She notes some facial and abdominal hair growth as well as significant facial acne and excessive axillary perspiration. She has been married for 1 year and is not using any form of birth control at this time. In the future she and her husband plan on having children.

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On physical exam, she weighs 182 lb and is 66 inches tall, with a body mass index (BMI) of 29.4. Her waist circumference is 38 inches. Her blood pressure is 125/70 mm Hg and pulse is 72 beats per minute. She has notable acanthosis nigricans on the back of her neck and in her axillae bilaterally. There is a mild degree of hirsutism and a significant degree of acne vulgaris on the face. In addition, moderate hirsutism is present in the lower abdomen, with a male pattern hair distribution. There is no thyromegaly. Breast exam reveals the presence of some periareolar hair growth. Heart and lung exams are unremarkable. On abdominal exam, there is central adiposity without striae and there is no peripheral edema.

Laboratory evaluation reveals a mild microcytic anemia, normal chemistries, normal liver enzymes, and a fasting blood glucose of 85 mg/dL. Serum testosterone is 80 pmol/L, prolactin is 12 mIU/L, dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone, and 24-hour urinary free cortisol are all within normal limits. Lipid panel reveals a total cholesterol of 246 mg/dL, triglycerides of 190 mg/dL, high-density lipoprotein (HDL) of 42 mg/dL, and low-density lipoprotein (LDL) of 166 mg/dL. A standard 2-hour oral glucose tolerance test is performed, and her fasting glucose of 88 mg/dL rises to 180 mg/dL (after 2 hours). A liver ultrasound reveals moderate fatty infiltration without evidence of cirrhosis.

The patient is started on metformin 500 mg daily, which is titrated up over a few weeks to 1000 mg b.i.d. with meals. She is also advised to use an effective form of birth control until she desires to become pregnant. In addition, she receives extensive counseling on diet and exercise for weight loss and diabetes prevention.

How the Diagnosis Was Made

The diagnostic criteria for PCOS are the subject of continuing controversy. In 1990 after an international consensus conference, the National Institutes of Health (NIH) published the following criteria for the diagnosis of PCOS (all three are required):

1. Menstrual irregularity due to chronic anovulation
2. Evidence of clinical or biochemical hyperandrogenism (i.e., hirsutism, acne, or male-pattern alopecia)
3. Exclusion of other causes of hyperandrogenism and menstrual irregularity (i.e., hyperprolactinemia, Cushing's syndrome, androgen producing tumors of the ovary or adrenal gland, congenital adrenal hyperplasia)

These criteria were based mainly on expert opinion, with limited scientific evidence. They notably make no mention of the presence of polycystic ovaries on ultrasonography.

In the years after the release of the NIH criteria, it became apparent that there were women with normal menstrual cycles who had evidence of hyperandrogenism and polycystic ovaries on ultrasound and were therefore felt to have PCOS. However, they would not be classified as having PCOS by the NIH criteria because they

had normal menses. Therefore, in 2003 at a consensus conference in Rotterdam, the diagnostic criteria for PCOS were modified. These new criteria require the presence of two of the following three:

1. Oligo-ovulation (fewer than nine times per year) or anovulation
2. Clinical or biochemical evidence of hyperandrogenism
3. Polycystic ovaries (meeting specific criteria on transvaginal ultrasound)

The criteria also specify that other etiologies of hyperandrogenism and amenorrhea must be ruled out, as PCOS is a diagnosis of exclusion. A recent Position Paper by the Androgen Excess Society contends that hyperandrogenism, clinical or biochemical) as being the major criterion for distinguishing the PCOS from other etiologies manifesting oligo-amenorrhea, with the inclusion of polycystic ovaries on ultrasonography as a criterion. Similarly, they also require that other etiologies that may mimic PCOS be excluded in establishing the PCOS phenotype.

These several papers by established investigators' criteria were also not satisfactory to some experts in the field. According to a growing body of evidence, the appearance of polycystic ovaries on ultrasound can be demonstrated in many women who have causes of hyperandrogenism or amenorrhea other than PCOS, as well as in up to 23% of "normal" women. In fact, some investigators believe that the presence of a hyperandrogenic state may cause ovarian cyst formation, leading to the polycystic ovarian appearance on ultrasonography. Because of this, there continues to be controversy surrounding the inclusion of the polycystic ovarian morphology into the diagnostic criteria.

The pathogenesis of PCOS is not completely understood. In the normal ovary, the theca cells produce the androgens androstenedione and testosterone. These are converted to estrone and estradiol by aromatase activity in the granulosa cells. Androgen production by the theca cells is under the control of pituitary luteinizing hormone (LH) and the conversion to estrogens is under the control of follicle-stimulating hormone (FSH). LH and FSH production are in turn under the control of hypothalamic gonadotropin-releasing hormone (GnRH). It is the pulsatility of GnRH production that controls the relative amount of LH and FSH secreted by the pituitary. A rapid frequency of GnRH pulses favors the production of LH, and slower pulse frequency favors the production of FSH. It is theorized that women with PCOS have a more rapid GnRH pulsatility, causing a higher than normal ratio of LH to FSH production, thereby leading to higher than normal androgen production. However, as GnRH pulsatility is known to be affected by progesterone, it is unclear whether the abnormal GnRH pulsatility is a primary defect or is secondary to the lack of progesterone caused by anovulation.

The causative defect may also lie within the ovaries themselves. There is evidence from several studies that the theca cells in women with PCOS may be more efficient at producing androgens than those of normal women. Therefore, these ovaries would produce a greater amount of androgen in response to a given level of LH. This would then lead to the hyperandrogenic state of PCOS, and the changes in GnRH pulsatility would be secondary.

In addition, there is an association among the metabolic syndrome, hyperinsulinemia, and PCOS, and some studies report up to a 40% to 50% incidence of the metabolic syndrome (using Adult Treatment Panel III [ATP-III] criteria) in women with PCOS. These women also have a higher incidence of insulin resistance than normals, independent of their weight. Hyperinsulinemia often leads to the occurrence of acanthosis nigricans (darkening of skin most often on the back of the neck, in the axillae, and in the groin) as was noted in our patient. It also causes further stimulation of ovarian synthesis of androgens and suppression of hepatic production of sex hormone–binding globulin (SHBG), leading to an increase in free androgens. This in turn contributes to the hyperandrogenic phenotype that is typical of women with PCOS. Because of this phenomenon, treatment with insulin sensitizers (such as metformin, rosiglitazone, and pioglitazone) is often employed in an attempt to reverse the pathogenesis and return ovarian function to normal.

Because the metabolic syndrome has been linked to an increased risk of vascular disease (including myocardial infarction and stroke) as well as an increased risk of diabetes, the link between PCOS and the metabolic syndrome has significant health implications. Therefore, many groups recommend screening women with PCOS for the metabolic syndrome as well as for impaired glucose tolerance and diabetes. The Rotterdam consensus group recommends against specific testing for insulin resistance (because there is no one test that can accurately predict the presence of insulin resistance and because the presence of insulin resistance is not required to diagnose or treat PCOS). They do recommend screening all obese women with PCOS for the components of the metabolic syndrome and for impaired glucose tolerance and diabetes with the 2-hour oral glucose tolerance test (OGTT), as normal fasting glucose levels do not rule out impaired glucose tolerance. According to this group, there is insufficient evidence to recommend such screening for all nonobese women, but these women should certainly be screened if any additional risk factors are present. Despite this, some authorities recommend screening lean women with PCOS in the same way as obese women.

Treatment

When determining the appropriate treatment for a particular patient with PCOS, it is important to take the patient's major manifestations of the syndrome and his/her main treatment goals into account. In obese women, weight loss can be very effective in reversing many of the symptoms of PCOS. A 5% to 10% weight reduction can lead to a significant decrease in insulin resistance, and, in some patients, resumption of normal ovarian function and fertility. Weight loss can be accomplished with diet and exercise, medications, or bariatric surgery (in cases of morbid obesity).

In women with a preponderance of hyperandrogenic symptoms (such as hirsutism, acne, and alopecia) who do not desire pregnancy, oral contraceptive pills and/or spironolactone can be effective in reducing these symptoms. The most widely used form of the oral contraceptive pill (OCP) consists of two components, an

estrogen and a progestin. It is this combination OCP that is most useful in the treatment of PCOS. The estrogen component of the pill serves two main functions. First, it helps to inhibit pituitary production of LH, thereby decreasing ovarian androgen production. Second, estrogen stimulates hepatic production of SHBG, thus decreasing the amount of free androgen that is available to bind to its receptor. Both of these actions help to decrease the androgenic symptoms of the disorder. The progestin component allows the resumption of regular menses and protects the endometrium from the adverse effects of unopposed estrogen. However, as many of the synthetic progestins used in OCPs actually have proandrogenic effects, the specific choice of progestin can be important. The progestins norgestimate (found in Ortho-Cyclen, Ortho Tri-Cyclen, and their generic forms) and desogestrel (found in Mircette, Ortho-Cept, Cyclessa, Apri, Desogen, and Kariva) are essentially nonandrogenic, and the progestin drospirenone (found in Yasmin and Yaz) is actually antiandrogenic. Because of its antiandrogenic effects, drospirenone would seem to be the ideal progestin for the treatment of PCOS; however, there is no evidence from controlled trials to support this. When using drospirenone, potassium levels must be monitored because of its antimineralocorticoid effects.

Spironolactone is an antagonist of the mineralocorticoid receptor (potassium sparing diuretic) that is also able to antagonize the androgen receptor, furnishing it with utility in the treatment of PCOS. While it does not directly lead to increased fertility, it is teratogenic to a male fetus. Therefore, it is important to ensure that any female patient of reproductive age who is treated with spironolactone is placed on an effective form of contraception. This is often accomplished by using the oral contraceptive pill, because OCPs and spironolactone have synergistic antiandrogenic effects. However, any effective form of contraception would be acceptable. It is also essential to monitor potassium levels when using spironolactone. Cyproterone acetate is a more potent antiandrogen that is widely used in Europe for the treatment of hirsutism, but is not available in the United States at this time.

In women with the metabolic syndrome, impaired glucose tolerance, or overt diabetes, and those desiring fertility, insulin sensitizers can be very useful therapies. The biguanide metformin helps to improve insulin resistance mainly by decreasing hepatic gluconeogenesis. This leads to decreased insulin levels and therefore decreased ovarian androgen production and increased hepatic SHBG production (as discussed in the prior section). In some patients, that is enough to allow the resumption of normal menses and fertility. In addition, metformin has the added benefit of promoting mild weight loss in some insulin-resistant patients as well as potentially delaying or even preventing the onset of overt diabetes, and reducing the frequency of first trimester miscarriages in PCOS.

The thiazolidinediones (pioglitazone and rosiglitazone) are peroxisome-proliferator–activated receptor γ (PPARγ) receptor agonists that work primarily on the adipose tissue to improve insulin sensitivity. Initial studies with troglitazone and later with rosiglitazone and pioglitazone in women with PCOS have demonstrated a significant increase in ovulation, decrease in androgen levels, and increase in SHBG. However, the safety of these medications in pregnancy is unknown, limiting their use in women desiring fertility (pregnancy risk category C).

Finally, the natural history of PCOS is such that after the age of 30 to 35 many women notice a decrease in androgenic symptoms as well as a reduction of serum testosterone without any treatment. This may be due to age-related decreases in ovarian function leading to decreased efficiency of androgen production.

Long-Term Complications

Because women with PCOS frequently have oligo-ovulation or anovulation, they are chronically exposed to the effects of estrogen without progesterone. Recall that in women with normally functioning ovaries, estrogen produced during the first half of the cycle causes proliferation of the endometrium. After ovulation occurs, progesterone is made by the corpus luteum, decreasing proliferation and leading to differentiation of the endometrium in preparation for implantation. However, in a patient with PCOS who fails to ovulate, the endometrium is chronically exposed to the effects of estrogen without progesterone, causing a continued stimulus for proliferation and thereby an increased risk of endometrial cancer. This risk can be reduced by reintroducing the effects of progesterone, through the use of either combination oral contraceptive pills or insulin-sensitizing medications that cause the resumption of spontaneous ovulation. In addition, progesterone alone can be administered for 5 to 7 days of every month to induce menstrual bleeding and decrease risk of endometrial cancer.

There is also evidence that women with PCOS are at increased risk for nonalcoholic fatty liver disease. This condition consists of a spectrum of diseases ranging from hepatic steatosis to steatosis with inflammation and steatosis with fibrosis (also known as nonalcoholic steatohepatitis [NASH]). As it is one of the leading causes of cryptogenic cirrhosis and is potentially reversible if found early in its course, making the diagnosis of nonalcoholic fatty liver disease (NAFLD) before it is clinically evident may greatly decrease its morbidity and mortality. It is therefore especially important to pay close attention to high-risk populations. Evidence from three retrospective studies indicates an increased incidence of fatty liver disease in women with PCOS. It may be recognized by the presence of elevated liver chemistries on routine lab screening, but normal labs do not rule out NAFLD. In fact, one study demonstrated ultrasound evidence of fatty liver disease in over half of all women with PCOS, with only one in six of these women demonstrating elevated transaminases. Therefore, some physicians have advocated abdominal ultrasounds in all women with PCOS. But it remains unclear whether the women with evidence of fatty liver on ultrasound, but without elevated liver chemistries, will progress from simple fatty liver to NASH.

Lessons Learned

1. Patients with PCOS typically present with oligo- or amenorrhea and evidence of hyperandrogenism. Other causes of these symptoms must be excluded prior to making the diagnosis. The official diagnostic criteria remain controversial,

especially regarding the inclusion of the presence of typical polycystic ovarian cysts on ultrasound.
2. PCOS patients may be obese or lean and they may even have normal menses.
3. The metabolic syndrome is common in women with PCOS, and because of its health implications many (if not all) such women should be screened for its components as well as with a 2-hour oral glucose tolerance test.
4. The treatment of PCOS should be guided by the patient's symptoms and individual goals and should always include a discussion on family planning and the use of birth control.
5. Women with PCOS are at risk for developing many complications in addition to the metabolic syndrome, including vascular endothelial dysfunction, endometrial cancer, obstructive sleep apnea, and nonalcoholic fatty liver disease. They should be screened for these conditions in a proactive and aggressive manner. A recent Position Paper by the Androgen Excess Society contends that hyperandrogenism (clinical or biochemical) is the major criterion for distinguishing the PCOS from other etiologies manifesting oligo-amenorrhea, with the inclusion of polycystic ovaries on ultrasonography as a criterion. Similarly, they also require that other etiologies that may mimic PCOS be excluded in establishing the PCOS phenotype.

Suggested Readings

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Multiple-Choice Questions

1. Which of the following is true about the diagnosis of PCOS in this patient?

   A. This patient cannot have PCOS because she had normal menses for several years (prior to her current episode of amenorrhea).
   B. Because of the presence of amenorrhea and clinical evidence of hyperandrogenism, this patient most likely has PCOS.

C. This patient cannot have PCOS because she has a BMI of less than 30 and is therefore not obese.
D. The diagnosis of PCOS cannot be definitively made in this patient without a pelvic ultrasound to confirm the presence of ovarian cysts.

Answer: B. Explanation: The various diagnostic criteria for PCOS are reviewed above. However, no matter which set of criteria you utilize, it is clear that polycystic ovaries are not required to make the diagnosis of PCOS and therefore choice D is incorrect. Choice C is incorrect because none of the proposed diagnostic criteria require the presence of obesity. Although obesity is often associated with PCOS (at least 50% of women with PCOS are obese, particularly in the U.S.), there are clearly a significant number of lean women who meet the criteria for PCOS. Choice A is also incorrect because the presence of normal menses earlier in this patient's life certainly does not exclude the diagnosis of PCOS at the present time. The onset of PCOS is commonly either at the time of menarche or after a period of significant weight gain.

2. Which of the following is true about the diagnosis of the metabolic syndrome in this patient?

A. This patient has the metabolic syndrome because she has an elevated LDL, a low HDL, and a waist circumference greater than 35 inches.
B. This patient cannot have the metabolic syndrome because her BMI is not greater than 30.
C. This patient has the metabolic syndrome because she has elevated triglycerides, a low HDL, and a waist circumference of greater than 35 inches.
D. This patient cannot have the metabolic syndrome because her fasting blood glucose is normal.

Answer: C. Explanation: Using the 2005 National Cholesterol Education Program ATP-III criteria, the metabolic syndrome is defined as the presence of three of the following five criteria:

1. Waist circumference of greater than 35 inches in females or 40 inches in males
2. Triglycerides greater than 150 mg/dL or present drug therapy for hypertriglyceridemia
3. HDL less than 50 mg/dL in women or 40 mg/dL in men or present drug therapy for low HDL
4. Blood pressure greater than 130/85 mm Hg or present drug therapy for hypertension
5. Fasting plasma glucose of greater than 100 or the presence of diabetes

Based on these criteria, the patient described does have the metabolic syndrome and only answer choice C is correct. Neither BMI nor LDL levels are included in the current definition of the metabolic syndrome, so answers A and B are incorrect. Although fasting plasma glucose is included in the criteria, it is not

required to make the diagnosis if three of the other criteria are present (as in this case). Therefore, answer D is incorrect.

3. Which of the following treatment options would be reasonable for this patient, assuming she is sexually active but does not desire pregnancy at this time?

   A. Rosiglitazone alone
   B. Metformin alone
   C. Spironolactone alone
   D. Oral contraceptive pill plus metformin
   E. Any of the above would be reasonable treatments

   Answer: D. Explanation: Although all of the choices are reasonable options for the treatment of select patients with the polycystic ovarian syndrome, because this patient does not desire pregnancy, her treatment should include some form of contraception. It is important to remember that treatment of the insulin resistance of PCOS with metformin or a thiazolidinedione (TZD) (rosiglitazone or pioglitazone) may result in the resumption of normal ovarian function, normal ovulation, and therefore fertility. Thus, it is essential to discuss family planning with these patients prior to initiating treatment in order to prevent unwanted pregnancies. Because she does not desire pregnancy, choices A, B, and E are incorrect. Choice C is incorrect because spironolactone is teratogenic and therefore must never be given without an effective form of contraception (as will be discussed below).

4. Because she has PCOS, which of the following conditions is this patient at risk of developing?

   A. Vascular endothelial dysfunction
   B. Endometrial cancer
   C. Obstructive sleep apnea
   D. Fatty liver and/or non-alcoholic steatohepatitis
   E. All of the above

   Answer: E. Explanation: Patients with PCOS are at risk for a number of conditions, including all of those listed in the question and therefore choice E is correct. Several studies have demonstrated the presence of disorders of endothelial function and vascular compliance in women with PCOS. The degree of dysfunction is not fully accounted for by obesity alone, and there is evidence that it can be partially reversed by treatment with insulin sensitizers. There is also evidence to suggest a higher incidence of obstructive sleep apnea in patients with PCOS than can be explained by obesity alone. The reason for this remains unclear, but may also be related to insulin resistance.

Chapter 46
Bariatric Surgery

Robert T. Yanagisawa, Daniel Herron, and Derek LeRoith

Objectives

1. To review the appropriate patient criteria for weight loss surgery
2. To understand the appropriate diabetes management of patients undergoing bariatric surgery
3. To discuss the effect of gastric bypass surgery on insulin resistance

Case Presentation

A 45-year-old white man presented with morbid obesity. After his brother suffered a myocardial infarction, the patient realized he needed to take control of his health. His weight history revealed that he had gradually gained over 40 lb over the last 10 years. He had lost 10 to 15 lb on several attempts with diet and exercise programs, but he was unable to maintain his weight loss for more than 6 months. He was diagnosed with type 2 diabetes 2 years ago and he has been treated with a combination of glimepride, rosiglitazone, and metformin. He also suffers from a mixed dyslipidemia for which he takes simvastatin 40 mg daily. On a physical examination, he was morbidly obese. At 5'8" tall and 290 lb, he had a body mass index (BMI) of 44, with an android body weight distribution and a waist circumference of 48". He had no hepatosplenomegaly or any significant peripheral edema. His fasting glucoses ranged from 145 to 225 mg/dL and hemoglobin A1c (HgbA1c was 8.9%. He was evaluated by the multidisciplinary team, consisting of bariatric surgeons, endocrinologists, nutritionists, and psychiatrists who are all experts in a variety of bariatric procedures, and he was considered an appropriate candidate for surgical weigh loss. The patient was well informed regarding bariatric surgery and understood the importance of his lifelong adherence to nutritional management. His

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diabetes control was optimized preoperatively by starting a combination of basal and bolus insulin.

He underwent Roux-en-Y gastric bypass (RYGB) surgery, and his diabetes was controlled with a reduced basal insulin dose during his immediate postoperative period. Within 2 weeks of discharge from the hospital, he was able to discontinue all his insulin and maintained on rosiglitazone and metformin for his diabetes. Three months after surgery, his diabetes demonstrates remarkable improvement with an HgbA1c of 6.0%. His diabetes medications were discontinued. He takes nutritional supplements including calcium citrate with vitamin D, iron, and multivitamins.

How the Diagnosis Was Made

The best operations reduce body weight by 35% to 40%, with most of this effect being maintained for more than 10 years. According to National Institutes of Health (NIH) guidelines, bariatric surgery is indicated for patients with BMI >40 or those with BMI >35 plus one or more obesity-associated comorbidities such as diabetes or hypertension [1]. Among the variety of bariatric surgery procedures, RYGB appears to offer the best balance of effectiveness vs. risk, and it is the most widely used surgery for the morbidly obese people in the United States.

Roux-en-Y gastric bypass surgery is currently considered to be the "gold standard" bariatric operation. Performed most commonly though a laparoscopic approach, the surgery involves creation of a small gastric pouch with a Y-shaped intestinal reconstruction. It is a restrictive and mildly malabsorptive procedure (Fig. 46.1).

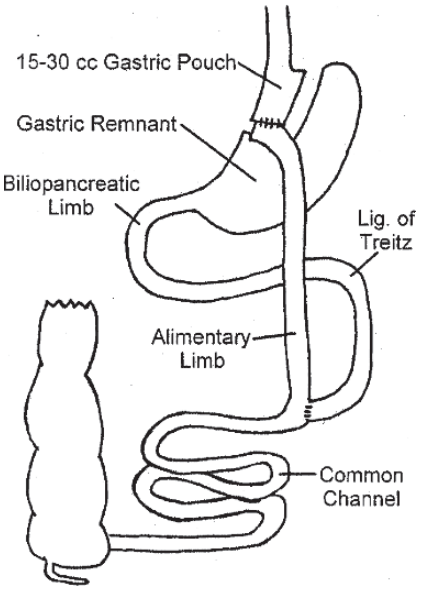

Fig. 46.1 Roux-en-Y Gastric Bypass (RYGB) surgery. Diagram courtesy of Dr. Daniel Herron

An appropriate preoperative screening includes prior history of failure to lose weight despite proper medical therapy. Patients must be educated regarding the bariatric procedure and the need for lifelong adherence to nutritional management. Glycemic control must be optimized in patients with diabetes prior to surgery in order to minimize the perioperative complications. Preoperatively, patients are more motivated to optimize their medical condition and endocrinologists can help manage their diabetes aggressively. Starting an insulin regimen is appropriate in order to optimize the glycemic control even in a relatively short period of time for patients preparing for the surgery. Perioperative tight glycemic control often requires some insulin coverage, but it must be adjusted accordingly to their insulin requirement (see below). Successful outcome after a surgical weight loss procedure depends on extensive patient counseling and multidisciplinary support postoperatively.

Bariatric surgery appears to be an effective option for the treatment of severe obesity, resulting in a long-term weight loss, an improved lifestyle, and, an amelioration in risk factors associated with obesity (Fig. 46.2).

The prospective controlled Swedish Obese Subjects Study involved obese subjects who underwent gastric surgery and contemporaneously matched, conventionally treated obese control subjects. One of the largest series, with 4047 subjects, it demonstrates the benefit of bariatric surgery for morbid obesity [2]. A significant number of patients with diabetes can recover with surgical weight loss, based on either the cutoff values or use of medication to treat diabetes. The mean changes in weight and risk factors were also more favorable among the subjects treated by gastric bypass than among those treated by banding or other form of surgical procedures.

The duration of diabetes since diagnosis seems to predict successful improvement of glycemic control postsurgery. The first-phase insulin response is typically disrupted early in the course of diabetes, and it improves to a near-normal level in patients who undergo gastric bypass surgery with diabetes of less than 3 to 5 years duration [3]. Recovery of the first-phase insulin response may be the best indicator of diabetes resolution in patients who have had gastric bypass surgery (Fig. 46.3).

The mechanisms underlying the effects of RYGB on body weight and glucose metabolism are still not completely understood, but we can predict the course of diabetes outcome with surgery. In the immediate postoperative period, patients are essentially fasting and resulting in the fast-induced alleviation of diabetes. Patients who are on significant doses of insulin preoperatively often only require a minimal basal insulin. Patients gradually tolerate their oral intake, but they continue to be in a state of negative energy balance, a condition that decreases glucose toxicity and improves ß-cell function. Eventually, a marked weight reduction with bariatric surgery allows patients to increase their level of physical activity. Increased physical activity coupled with decreased glucose load from small quantity of each meal after gastric bypass surgery leads to a dramatically improved diabetes control.

Cummings [4] hypothesizes more interesting possibilities of RYGB effect on glucose metabolism. Alterations in gut hormones release after RYGB may act in concert with the above mechanism to improve insulin secretion or action. Ghrelin, secreted by the stomach, exerts several diabetogenic effects including increased

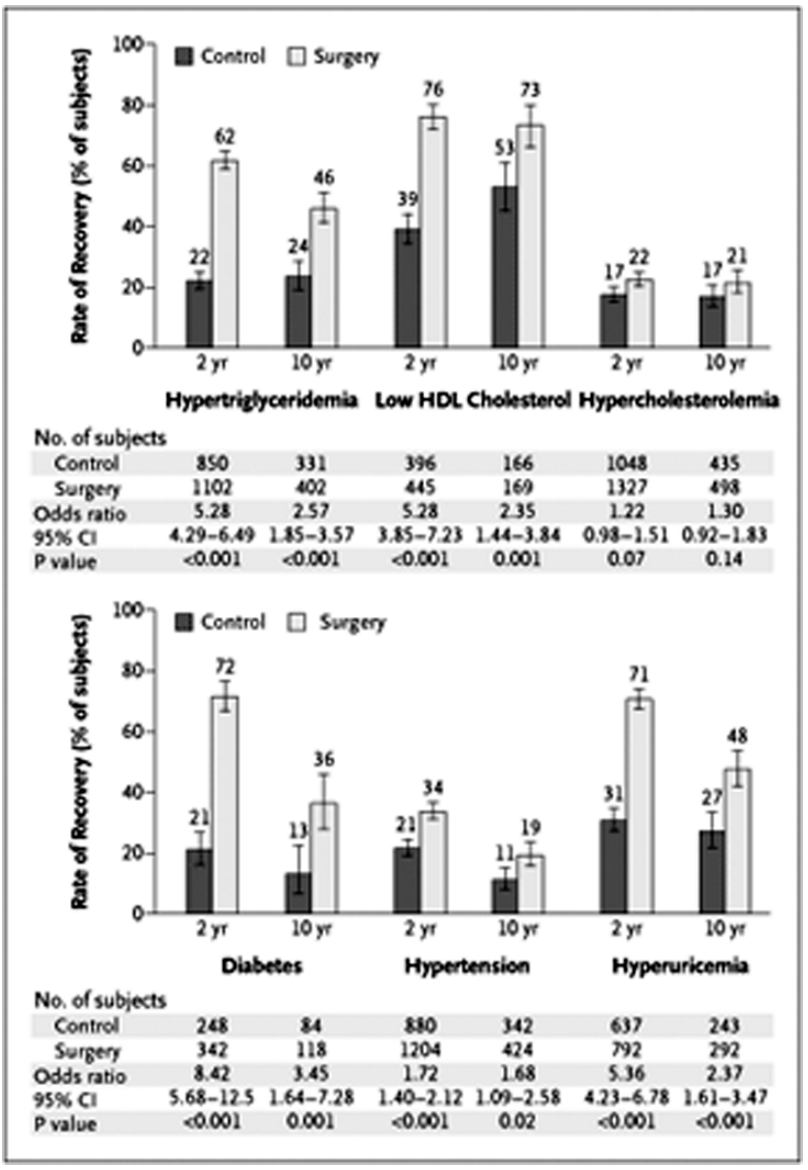

Fig. 46.2 Recovery from diabetes, lipid disturbances, hypertension, and hyperuricemia over 2 and 10 years in surgically treated subjects and their obese controls. Adapted from Sjöström et al. Lifestyle, Diabetes, and Cardiovascular Risk Factors 10 Years after Bariatric Surgery. NEJM 2004 351 (26):2683

levels of growth hormone (GH), cortisol, and epinephrine—three of the four classic counterregulatory hormones. Ghrelin levels are decreased after gastric bypass, resulting in an antidiabetogenic effect. The other effect of surgery is increased glucagon-like peptide 1 (GLP-1) secretion from bypassing part of the foregut and facilitated delivery of nutrients directly to the hindgut. GLP-1 is an incretin that stimulates insulin secretion in response to enteral nutrients. GLP-1 and peptide YY_{3-36} (PYY) also suppress gastrointestinal motility, gastric emptying, small intestinal transit, and food intake.

Patients with a relatively short duration of diabetes since diagnosis seem to have a better improvement of glycemic control post RYGB. While there is no standardized guidelines for the optimal timing to recommend patient with diabetes and obesity for bariatric surgery, these findings may call for an earlier referral of morbidly obese patients with diabetes to a surgical weight loss.

On the other hand, we must also understand nutritional consequences of surgical intervention for morbid obesity. While RYGB surgery should not cause severe malabsorptive problems postsurgery, patients will have a decreased absorption of protein, iron, calcium, and fat-soluble vitamins. Postoperatively, patients who have had RYGB surgery need to be periodically monitored for nutritional deficiency for the rest of their life.

Patients are instructed to eat at least 60 g of protein daily. Due to their limited gastric capacity, they usually require protein supplementation initially to be able to meet their nutritional goal. Chewable multivitamin and calcium supplementation is started on discharge from the surgery.

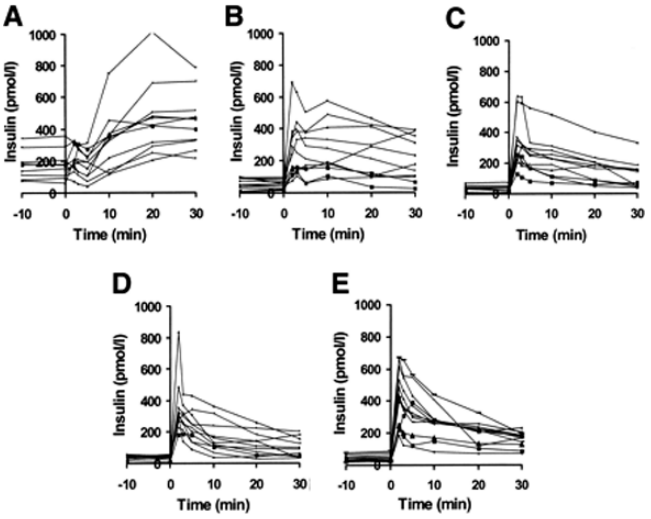

Fig. 46.3 Insulin response after intravenous glucose infusion in normal control subjects (*E*) and patients with type 2 diabetes, before gastric bypass (*A*), 3 months (*B*), 6 months (*C*), and 12 months (*D*) after gastric bypass. Adapted from Polyzogopoulou et al. Diabetes. 2003 May; 52(5): 1098–103.

After RYGB surgery, patients tend to have an increased parathyroid hormone (PTH) values, and one must avoid the development of overt secondary hyperparathyroidism from vitamin D deficiency. They need to be consistent with calcium with vitamin D. The goal is to maintain 25-OH vitamin D level above 25 and PTH level below 80 to 90. The amount required varies with extent of malabsorption, but typically 1000 to 1200 IU per day of vitamin D are required to maintain an adequate level.

While this patient may not require any hypoglycemic agents to control his diabetes, he must continue to avoid excess glucose and carbohydrate load. His small gastric pouch is likely to prevent him from eating large meals and hence creating a significant caloric deficit. However, despite RYGB surgery, he will be able to absorb simple sugars and still have a tendency for hyperglycemia. His success in ameliorating his diabetes depends on his success with his weight loss and his behavioral modification.

Lessons Learned

1. Bariatric surgery is an effective option for the treatment of severe obesity and obesity related metabolic risks for patients with BMI >40 or those with BMI >35 plus one or more obesity associated comorbidities.
2. Successful outcome of surgical weight loss depends on patient education and teamwork with the multidisciplinary team supporting the patient.
3. The duration of diabetes and strict behavioral modification predict successful improvement of the glycemic control postsurgery. Recovery of the first-phase insulin response improves to a near-normal level in patients who undergo gastric bypass surgery with diabetes of less than 3 to 5 years' duration.

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Multiple-Choice Questions

1. What makes the patient presented here an appropriate candidate for bariatric surgery?

A. BMI >40
B. Diabetes and other metabolic risk factors
C. Failed prior medical management to control his obesity
D. Ability to comply with his lifelong adherence to nutritional management
E. All of the above

Answer: E. Explanation: According to NIH guidelines for bariatric surgery, this patient meets BMI criteria (>40), but we should further evaluate him to see if he is an appropriate candidate for bariatric surgery. Choices B to D make him an appropriate surgical candidate.

2. What factors increase his likelihood of achieving his glycemic control post surgery?

A. Duration of his diabetes
B. Patient's ability to exercise with weight loss
C. Avoidance of his glucose toxicity
D. Decreased visceral adiposity
E. All of the above

Answer: E. Explanation: The short duration of his diabetes is an important indicator for improving his diabetes. The first-phase insulin response improves to a near-normal level in patients who undergo gastric bypass surgery with diabetes of less than 3 to 5 years duration. Choices B to D all help to improve his insulin resistance.

3. Postoperatively, what are the nutritional concerns for this patient?

A. Supplemental protein only if they develop signs of malabsorption.
B. Iron replacement only if they develop anemia.
C. Any excess calorie will not be absorbed so patients can eat ad lib and lose weight.
D. Calcium with vitamin D to prevent secondary hyperparathyroidism.
E. Patient does not need to follow his blood glucose any more.

Answer: D. Explanation: After RYGB surgery, patients will have a decreased absorption of protein, iron, calcium, and fat-soluble vitamins. Choices A and B are incorrect, as he will require these supplements to prevent malabsorptive complications. Choices C and E are incorrect, as he will be able to absorb simple sugars and still have a tendency for hyperglycemia. Choice D is correct and he needs his calcium, vitamin D, and PTH levels to be monitored.

Part XV
Puberty

Introduction

Donald Zimmerman

Puberty is a sequence of events comprising the transition from juvenile (or sexually immature) to adult (or sexually mature and fertile). The bodily changes that occur during puberty include the development of secondary sexual characteristics, such as growth of body hair, particularly in the pubic and axillary regions, growth of the penis and testes in boys, and growth of breasts in girls.

These changes have been divided into distinct stages by Tanner. The stages of development of pubic hair are as follows:

I. Short (no longer than hair over the hypogastrium), nonpigmented, fine, and straight
II. Longer than hypogastric hair and slightly pigmented, but still straight and fine
III. Curly, coarse, curly, pigmented but less dense and less extensive than in adults
IV. As dense as in adults but does not extend to medial thighs
V. Extends to medial thighs

The stages of breast development are as follows:

I. No visible or palpable breast tissue
II. Breast tissue detectable within the border of the areola
III. Breast tissue detectable outside the border of the areola but only slight enlargement of the papillae
IV. Protrusion of areola above plane of remaining breast; development of areolar structures (papillae and Montgomery follicles)
V. Areola and surrounding breast tissue on same plane; areolar structures (papillae and Montgomery follicles) mature

The stages of testicular development relate to testicular size:

I. < 4 mL (2.5 cm length)
II. 4 mL to 8 mL

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III. >8 to 10 mL
IV. >10 to 12 mL
V. >12 to 17 mL

The normal timing of puberty onset has been considered to be after 8 years of age in girls and after 9 years of age in boys. A large study by Herman-Giddens et al [1] showed that the mean age of breast development was 10.0 ± 1.7 years of age; 27.2% of African-American girls had pubertal changes before 8 years of age. The Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society changed the lower limit of pubertal onset to 7 years in Caucasian girls and 6 years in African-American girls. This guideline has generated much controversy because other large studies did not agree with the findings of Herman-Giddens and because a number of individuals with pathologic mechanisms of puberty and rapid pubertal progression would be overlooked. A number of practitioners study girls with pubertal onset between 7 and 8 years.

The conditions producing precocious puberty can be divided into those producing early activation of the hypothalamus and pituitary gland (elevated luteinizing hormone [LH], follicle-stimulating hormone [FSH], and sex steroids), those producing early activation of the gonads by gonadotropin-independent mechanisms (elevated sex steroids but suppressed levels of pituitary gonadotropins), and those producing secondary sexual characteristics without gonadal activation (adrenal and exogenous sex steroids).

Central Precocious Puberty

The differential diagnosis for central precocious puberty is as follows:

Early thelarche (normal variant)
Idiopathic
Brain tumor
Brain malformation (septo-optic dysplasia; hamartoma)
Brain injury
Hydrocephalus
Genetic/familial
Pituitary adenoma (gonadotropin-secreting)
Human chorionic gonadotropin (HCG)-secreting tumors in boys
Overlap syndrome (thyroid-stimulating hormone [TSH] stimulation of gonadotropin receptors in first-degree hypothyroidism)

Primary Gonadal Causes

Gonad tumors
Constitutive activation of LH receptors in boys (testitoxicosis)
McCune-Albright syndrome

Adrenal Causes

Early adrenarche (normal variant)
Adrenocorticotropin (ACTH) excess (pituitary/ectopic)
Mutations in steroidogenic enzymes/congenital adrenal hyperplasia
Adrenal tumors
Exogenous sex steroids

Normal Variants and Abnormal Conditions

Another important categorization of the causes of early puberty is the distinction between normal variants and abnormal conditions. Early thelarche is the early appearance of breast growth unassociated with other pubertal changes. It appears to result from mild, nonprogressive increased estradiol secretion. Early adrenarche is early secretion of adrenal androgens producing early appearance of pubic hair. Some individuals with early adrenarche have insulin resistance, some have static encephalopathy, and many have no obvious predisposing condition. Individuals with early thelarche and early adrenarche do not have marked acceleration of growth and do not have advancement of the bone age.

Treatment of early puberty is entirely dependent on the cause of the puberty. Tumors and other conditions that threaten health require specific treatments. Once these considerations are dealt with, central puberty is frequently treated with long-acting analogues of gonadotropin-releasing hormone (GnRH) that inhibit pituitary gonadotropin production through tachyphylaxis. Autonomous gonadal function (in testes with activating mutations of the LH receptor or gonads with activating mutations of the stimulatory guanosine triphosphate (GTP-binding protein) can be treated with inhibitors of sex steroid synthesis such as ketoconazole. Ovarian overproduction of estradiol in patients with constitutive activation may be treated with Tamoxifen. Adrenal steroid overproduction in congenital adrenal hyperplasia is treated with glucocorticoids (± mineralocorticoids, depending on the enzyme defect).

Delayed Puberty

Delayed puberty is defined as failure of pubertal development by 13 years in girls and by 14 years in boys. It is noteworthy that there is little controversy about the upper limit of normal pubertal onset. This is likely the result of very protracted puberty in many of the individuals who have early onset of puberty. The causes of delayed puberty are as follows:

1. Hypothalamic and pituitary causes
   Congenital/genetic: constitutional delay of growth and development (normal variant), Kallmann syndrome (includes anosmia; associated with mutations in

KAL1, FGF1, PROKR2, and *PROK2*), metastin receptor (*GPR54*) mutations, GnRH receptor mutations, *PROP-1* mutations, congenital adrenal hypoplasia (*DAX-1* mutations), septo-optic dysplasia, Bardet-Biedl syndrome, Prader-Willi syndrome
Tumors: brain or pituitary
Infiltration/deposition: histiocytosis, sarcoidosis, hemosiderosis
Energy metabolism/leptin: undernutrition (anorexia nervosa), increased energy expenditure, leptin deficiency
Brain trauma, brain irradiation, chemotherapy
Hypothyroidism
Hyperprolactinemia: pituitary tumor, tumors/infiltration/vascular abnormalities inhibiting blood flow through pituitary stalk, drugs (opiates, dopamine antagonists, antihypertensives), hypothyroidism, ectopic secretion
Chronic illness: especially renal insufficiency and hepatic insufficiency, inflammatory conditions
Drugs: marijuana, alcohol

2. Gonadal causes
Chromosomal/genetic: Turner syndrome (girls—absence or structural abnormalities of X chromosome), gonadal dysgenesis without Turner syndrome, Klinefelter syndrome (boys—two X chromosomes in addition to Y chromosome), Noonan syndrome, testosterone synthesis defects, inactivating mutations of LH and FSH receptors, trauma/torsion (including some cases of gonadal regression)
Infection: mumps, Coxsackie virus, HIV
Radiation/chemotherapy
Galactosemia
Autoimmune gonadal disease
Sex steroid insensitivity
Androgen insensitivity
Androgen excess (in females)
Adrenal androgens: tumors, Cushing disease, congenital adrenal hyperplasia
Ovarian androgens: tumors, polycystic ovary disease, hyperthecosis
Exogenous androgens

Delayed puberty may be the result of the normal variant—constitutional delay of growth and development. Individuals with delayed puberty due to constitutional delay frequently have a family history of constitutional delay. They typically have delayed bone age. The definitive diagnosis of constitutional delay cannot be established until puberty occurs. Many patients with hypogonadotropic hypogonadism are clinically similar to those with constitutional delay. However, individuals with hypogonadotropic hypogonadism frequently manifest eunuchoid proportions in the latter part of adolescence. These individuals have arm spans exceeding their height by more than 4 cm and have ratios of upper-to-lower body segments < 0.92 in young men and < 0.85 in women. The decision to replace sex steroid in patients who may have either condition need not await a definitive diagnosis. The usual approach is

to replace sex steroids and to suspend treatment at a later time to examine whether endogenous hormone production has supervened.

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Chapter 47
Amenorrhea

Liuska Pesce and Donald Zimmerman

Objectives

1. To recognize hypergonadotropic hypogonadism as part of the differential diagnosis of delayed puberty
2. To recognize premature ovarian failure as a cause of hypergonadrotropic hypogonadism
3. To recognize chemotherapy and cancer treatment modalities as etiologies of gonadal failure
4. To understand that it is hard to predict which patients will resume normal ovarian function after chemotherapy-induced failure

Case Presentation

A 16½-year-old girl presented with amenorrhea. She had experienced thelarche and pubarche at 10 years of age, followed by one episode of vaginal bleeding at 12 years old. At that time, she was diagnosed with rhabdomyosarcoma of the right hand. She was prescribed cyclophosphamide, vincristine, and dactinomycin. Three years later, rhabdomyosarcoma appeared in her right breast. Another course of treatment with chemotherapy was administered, which included cyclophosphamide, mesna, and tirapazamine.

She had been in remission from rhabdomyosarcoma for 1 year when she presented with amenorrhea. She had only had one menstrual period.

On physical examination, height was 151.7 cm (3rd to 10th percentiles), and weight was 53 kg (50th percentile). Breasts and pubic hair were in Tanner stage V. Her right breast showed a scar from tumor resection and later breast reconstruction. Her right hand was mildly atrophic and also had a scar from tumor resection. The rest of her physical exam was normal.

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Serum follicle-stimulating hormone (FSH) measured 66.3 mIU/mL (normal range: 1.5–9); luteinizing hormone (LH) measured 27.4 mIU/mL (normal range: 0.02–12); and estradiol measured 29 pg/mL (normal range for age: 40–410). There were normal circulating levels of thyroid-stimulating hormone (TSH) (0.911 mIU/mL) and prolactin (7.47 ng/mL).

How the Diagnosis Was Made

The diagnosis was hypergonadotropic hypogonadism secondary to chemotherapy-induced ovarian failure. Delayed puberty is defined as lack of onset of pubertal signs by the age of 13 years in girls and 14 years in boys, or as the lack of normal progression of puberty. Evaluation may be indicated if more than 5 years have elapsed between the first signs of puberty and menarche in girls, or completion of genital growth in boys [1].

Delayed puberty may be idiopathic or familial or due to a number of conditions resulting in undernutrition. However, absence or lack of progression of puberty may also be due to impaired gonadotropin secretion or due to gonadal failure [2].

The first approach in evaluating patients with delayed or lack of progression of puberty is to determine gonadotropin status. Elevated levels of gonadotropins indicate gonadal failure (hypergonadotropic hypogonadism).

Hypergonadotropic hypogonadism may be secondary to genetic, autoimmune, and infectious conditions, but also secondary to radiotherapy and chemotherapy [2, 3].

Advances in the management of cancer, with cytotoxic chemotherapy and radiotherapy, have improved cure rates of many young patients. For many of the malignancies affecting children and adolescents, survival rates exceed 60% and the mortality rate for childhood leukemia has decreased by more than 70% in the developed world (3–5). However, treatment is associated with significant morbidity and alterations in gonadal function are among the most common long-term effects of therapy [6].

Germinal epithelial damage resulting in oligospermia and azoospermia have long been recognized in the male. Although the ovary appears to be less vulnerable than the testis, ovarian failure is not uncommon following cytotoxic treatments [6], with reduced amounts of follicles and ovarian atrophy [5]. Since many of these patients are young, with expectations of normal reproductive life span, premature ovarian failure can impact their self-esteem and quality of life [5].

The effects of gonadotoxic effects of chemotherapy were first reported in patients treated with busulfan for chronic myeloid leukemia [6]. However, premature ovarian failure has been described with other drugs. Most of the available data are on patients treated for leukemia, lymphoma, and breast cancer. Most of the information available is on cyclophosphamide, methotrexate, and 5-fluorouracil [4].

The gonadal damage depends on the agent used, the dose, and the age of the patient. Younger patients appear to tolerate higher doses, and ovarian function starts again once treatment is suspended. The latent period before the reappearance of

normal menstruation is widely variable [4]. It is presumed than younger women are more resistant probably because of larger follicle stores prior to treatment [5].

Gonadal failure following chemotherapy in patients younger than 20 years has been estimated to be 13%, 50% in women 20 to 30 years old, and 100% in patients older than 30 years. Also, it has been noted than girls treated prior to menarche fail to start menarche while on therapy, but are able to have menarche shortly after cessation of the cytotoxic agents, while most of the girls who are started on treatment after menarche develop secondary amenorrhea [4].

Alkylating agents have been found impose the highest risk of ovarian failure, with cyclophosphamide having an odds ratio (OR) of 1.77 [5].

Even if women have normal cycles immediately following cessation of therapy, they may have premature menopause (42% may enter menopause by 31 years of age compared to 5% of controls) [6]. On the other hand, amenorrhea following chemotherapy does not necessarily imply permanent ovarian failure. A proportion of women may recover ovarian function, being able to have normal menses and fertility [5, 6]. Currently, there are no indicators allowing identification of this subgroup of patients, but it is more likely to occur in younger patients. However, inhibin A and B are being evaluated as possible markers of gonadotoxicity with promising results [3].

Gonadotropin-releasing hormone administered as adjuvant therapy together with chemotherapy, appears to protect adolescent girls from chemotherapy-associated gonadotoxicity manifested as hypergonadotropic amenorrhea. It also appears to prolong the fertility window by almost 10 years [3]. However, other studies have not support this beneficial effect [5].

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Multiple-Choice Questions

1. A 17-year-old girl presents to the clinic for the evaluation of primary amenorrhea. Which would be an important aspect of her clinical history?

   A. History of leukemia during infancy
   B. Short stature

C. History of delayed puberty in the family
D. All of the above
E. None of the above

Answer: D.

2. In the above patient, which of the following labs results would make you consider the diagnosis of ovarian failure?

A. FSH of 60 IU/L (normal 0.33–10.54)
B. Estradiol of 100 pg/ml (normal 40–410)
C. LH of < 0.2 IU/L (normal 0.69–7.15)
D. All of the above
E. None of the above

Answer: A.

3. Which of the following could explain premature ovarian failure in this 17-year-old girl?

A. Prolactinoma
B. Oophoritis
C. Chemotherapy
D. Hypogonadal hypogonadism
E. All of the above
F. B and C
G. None of the above
H. A and D

Answer: F.

4. Which of the following chemotherapeutic agents have been highly associated with premature ovarian failure?

A. Antibiotics
B. Antimetabolites
C. Plant alkaloids
D. Alkylating agents

Answer: D.

5. Which of the following patients could potentially have the worst fertility prognosis based on the current information we have on chemotherapy-induced premature ovarian failure?

A. A 7 years old currently being treated with cyclophosphamide
B. A 14 years old who had menarche at age 12 years, who completed treatment with cyclophosphamide three months ago, with amenorrhea for the last year
C. A 30 year old female who completed chemotherapy with cyclophosphamide 3 months ago and currently has normal menstrual cycles.
D. A and B

Answer: C.

Chapter 48
Early Puberty and Hyperthyroidism

Liuska Pesce and Donald Zimmerman

Objectives

1. To understand that gonadotropin-independent precocious puberty may be secondary to McCune-Albright syndrome
2. To understand that McCune-Albright syndrome is a sporadic syndrome, due to a postzygotic somatic mutation in the *GNAS1* gene, which is present only in the affected cells
3. To recognize that McCune-Albright syndrome is characterized by a variable clinical presentation

Case Presentation

This girl, age 3 years and 7 months, was the product of a normal full-term gestation. At the age of 9 months she was noted to have a bloody spot in her diaper. This event recurred the following day, and she was taken to see her primary pediatrician. Her pediatrician noted that she had enlarged breasts and a café-au-lait macule on her trunk. Circulating estradiol measured 7.9 ng/dL (normal <1.5), with prepubertal levels of luteinizing hormone (LH) (0.3 mIU/mL) and follicle-stimulating hormone (FSH) (0.03 mIU/mL). She also had a normal prolactin level (10.5 ng/mL). The bone age at chronologic age 9 months was advanced to $2\frac{1}{2}$ years. By age 2 years and 8 months, she was having vaginal bleeding every 4 to 5 months.

Physical examination at this time revealed the café-au-lait macule and Tanner III breasts and pubic hair. Free thyroxine (FT_4) measured 4.2 ng/dL (normal 0.8–2.2) with thyroid-stimulating hormone (TSH) suppressed to less than 0.01 mIU/mL. It was recommended that the patient be treated with the antithyroid medication propylthiouracil and with the aromatase inhibitor testolactone. The family elected not to proceed with these treatments.

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She presented to our clinic at the age of 3 years and 7 months. At this time, she had progressive breast development and was still having vaginal bleeding every 5 months. She did not have hirsutism, adult body odor, acne, or male-pattern baldness. She had dry hair and skin, but no temperature intolerance, constipation, or sleep disturbance. She had always been tall for her age. She had no breast discharge, headaches, vision disturbances, or symptoms of hypoglycemia.

On physical examination, height was 111.7 cm (3.5 standard deviations above the mean), and weight was 18.8 kg (between the 90th and 95th percentiles). Pulse was 150 and blood pressure was 134/61. A large café-au-lait macule extended over the right side of the trunk to the midline of the abdomen and to the midline of the back. It had irregular borders ("coast of Maine"). The thyroid gland was enlarged to twice normal size and was firm without nodules. Breasts were in late Tanner stage III, and pubic hair was in early Tanner stage II.

Sodium was 136 mEq/L, potassium was 4.2 mEq/L, chloride 110 mEq/L, and bicarbonate 21.7 mEq/L. Glucose was 92 mg/dL. BUN was 7 mg/dL, and creatinine was 0.3 mg/dL. Calcium was 9.5 mg/dL. Phosphorus was slightly low at 3.4 mg/dL. Liver function tests were normal except for total bilirubin mildly increased at 1.1 mg/dL, with a normal direct fraction of less than 0.1 mg/dL. Alkaline phosphatase was elevated at 594 IU/L.

The patient's gonadotropins were suppressed to less than 0.05 IU/L. Estradiol was elevated at 26 ng/dL (normal range for age: <1.5; normal range for Tanner stage III: 10–14.4). Total thyroxine was elevated at 14.1 μg/dL, and triiodothyronine measured 380.8 ng/dL (normal 119–218). The TSH was suppressed to less than 0.01 μIU/mL. Bone age was 10 years and 6 months at the chronologic age of 3 years and 7 months.

Bone survey revealed a ground-glass appearance in the right side of the mandible, some sclerotic changes in the base of the skull in the region of the maxilla, and lucent and sclerotic areas in both femoral necks, particularly on the right side. There was also a small lesion in the right mid-humerus, consistent with polyostotic fibrous dysplasia.

How the Diagnosis Was Made

The diagnosis was McCune-Albright syndrome (MAS). First described in 1937, this syndrome is characterized by the classic triad of polyostotic fibrous dysplasia, skin hyperpigmentation (café-au-lait spots), and endocrine dysfunction [1–3].

Although the most common endocrine dysfunction is gonadotropin-independent precocious puberty (also termed peripheral, incomplete, or pseudoprecocious puberty), other hyperfunctional endocrinopathies include hyperthyroidism, growth hormone excess, hyperprolactinemia, hyperparathyroidism, and hypercortisolism [3, 4].

Besides the fibrous dysplasia of the bone and the skin hyperpigmentation, other nonendocrine manifestations associated with this syndrome include hypophosphatemic rickets, hepatobiliary dysfunction, and cardiac disease [3–5].

Precocious puberty is the most common endocrinopathy in females with MAS, whereas it is uncommon in males (64–79% in girls vs. about 15% in boys). Half the girls show signs of puberty before the age of 4 years, frequently with menstrual bleeding and Tanner stage and bone age progression. Patients have ovarian follicular cysts leading to cycles with high estrogen levels accompanied by normal or suppressed gonadotropin levels [4]. In boys, clinical presentation may include enlargement of the testes, often with testicular microlithiasis [4]. In boys and girls, peripheral precocious puberty can precipitate central precocious puberty [4, 6]. This phenomenon also occurs in other settings such as androgen-secreting adrenal tumors, congenital adrenal hyperplasia, and prolonged exogenous sex steroid administration.

Treatment of precocious puberty in patients with MAS comprises blockade of sex steroid synthesis with ketoconazole, blockade of estrogen receptors with tamoxifen, or aromatase inhibition with letrozole in association with androgen receptor blockade with flutamide.

Hyperthyroidism is found in 2.7% to 21.9% of patients and is also more common in females. These patients tend to have elevated triiodothyronine (T_3) levels, but may have normal T_4 levels. The TSH is suppressed. Ultrasonography reveals nodules or cysts in approximately 35% of patients. Thyroid histology may include multinodular hyperplasia, colloid goiter, or follicular [4].

Growth hormone (GH) excess appears to be more frequent in males, with a prevalence of 4.4% to 37.7%. It usually manifests as acromegaly before the age of 20 years; some patients with early-onset develop gigantism. Approximately one third of the patients have microadenomas on magnetic resonance imaging (MRI) scans. Not all patients with microadenomas have elevated levels of insulin-like growth factor I (IGF-I) or of GH. Growth hormone excess in MAS appears to usually progress slowly. It seems to exacerbate craniofacial fibrous dysplasia [4]. Hyperprolactinemia frequently accompanies GH excess. Only half of hyperprolactinemic patients manifest galactorrhea or menstrual disorders on presentation [4].

Hypercortisolism in the setting of MAS also appears to be more frequent in boys, with prevalence ranging from 1.7% to 7.5%. It usually manifests very early in life as Cushing's syndrome, usually secondary to macronodular adrenal hyperplasia with autonomous cortisol production [4]. However, adrenocorticotropin (ACTH)-producing pituitary adenomas can occur as well [7]. Occasionally, nephrocalcinosis can be seen as well, which is postulated to be secondary to the effect of cortisol on bone turnover [4]. Hyperparathyroidism has been reported only in a few patients [4].

A number of nonendocrine manifestations occur in patients with MAS; fibrous dysplasia occurs in 46% to 98% of patients. The form associated with MAS is usually polyostotic (multiple lesions), but one third of patients may have a monostotic form [4]. Bone lesions are characterized by fibrous connective tissue with a characteristic whorled pattern, containing trabeculae of immature bone, and typically not bordered by osteoblasts. These are considered to be benign, developmental lesions, although rare malignant changes have been reported. Lesions originate from the marrow toward the cortical bone, which never seems eroded. As the disease progresses, the bone appears to contain a cyst [8].

Symptoms of fibrous dysplasia may begin in infancy, usually with recurrent fractures and bone deformities. The femur is the most commonly involved bone. Compression syndromes can occur, including chronic rhinitis, hearing loss, and blindness [4]. Bone fibrous dysplasia can be evaluated with conventional radiology; however, bone scintigraphy is indicated to monitor the spreading of lesions in the skeleton, for diagnostic purposes and to evaluate the extent of the disease. An MRI gives a better spatial resolution, being particularly indicated for surgical corrections and follow-up of monostotic lesions. It is also the best test to monitor for complications [8].

Café-au-lait spots are present in 53% to 92% of patients with MAS. The lesions follow Blaschko's lines and are described as having irregular borders such as the "coast of Maine" [4].

Approximately 50% of MAS patients have renal phosphate wasting. FGF23, a substance known to produce renal phosphate wasting in some patients with tumorigenic rickets, is elevated in MAS patients with renal phosphate wasting [4].

Hepatobiliary dysfunction has been noted, usually as neonatal jaundice with spontaneous regression. Also, nonprogressive elevation in liver enzymes has been observed [4, 5].

Cardiac disease ranges from tachycardia and hypertension to cardiomegaly and sudden infant death syndrome. Macroscopic findings are normal, making prediction of life-threatening events extremely difficult [4, 5].

McCune-Albright syndrome is a sporadic and heterogeneous disorder. Affected patients have somatic mutations in some of their tissues at codon 201 in exon 8 of the *GNAS1* gene. This gene encodes the α-subunit of the heterotrimeric guanosine triphosphate (GTP)-binding protein ($G_{S\alpha}$) [3, 4, 7]. These mutations usually cause the substitution for the normally encoded arginine, by either histidine or cysteine.

Upon hormone receptor interaction, Gsα binds GTP and activates adenylate cyclase. Guanosine triphosphatase (GTPase) activity inherent to the Gsα causes hydrolysis of GTP to guanosine diphosphate (GDP), terminating adenylate cyclase activation. The R201 mutation severely attenuates the Gsα GTPase activity, leading to constitutive activation of adenylate cyclase [7].

Because of the genetics of this disorder, the clinical presentation and prognosis of patients with MAS depends on the distribution of the affected cells [4, 5]. Also, the detection rate of the mutation is influenced by the presence of mosaicism and the unavailability of the affected tissues [7].

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Multiple-Choice Questions

1. Patients with McCune-Albright syndrome have endocrine overactivity and other manifestations because of an activating mutation in:

   A. Adenylate cyclase
   B. Protein kinase A regulatory subunit
   C. Alpha-subunit of stimulatory GTP-binding protein
   D. Hormone receptors
   E. Hormone secretory granules

   Answer: C. The constitutive overactivity results from inactivation of the mechanism for terminating the action of the stimulatory GTP-binding protein. The mechanism for terminating activity is a phosphatase that converts GTP to GDP.

2. Early puberty in McCune-Albright syndrome results from which of the following?

   A. Secretion of gonadotropins from pituitary microadenomas
   B. Adrenal sex steroid secretion
   C. Ectopic hormone secretion in fibrous dysplasia lesions
   D. Constitutive activation of gonadotropin receptor transducers
   E. Thyroid hormone excess

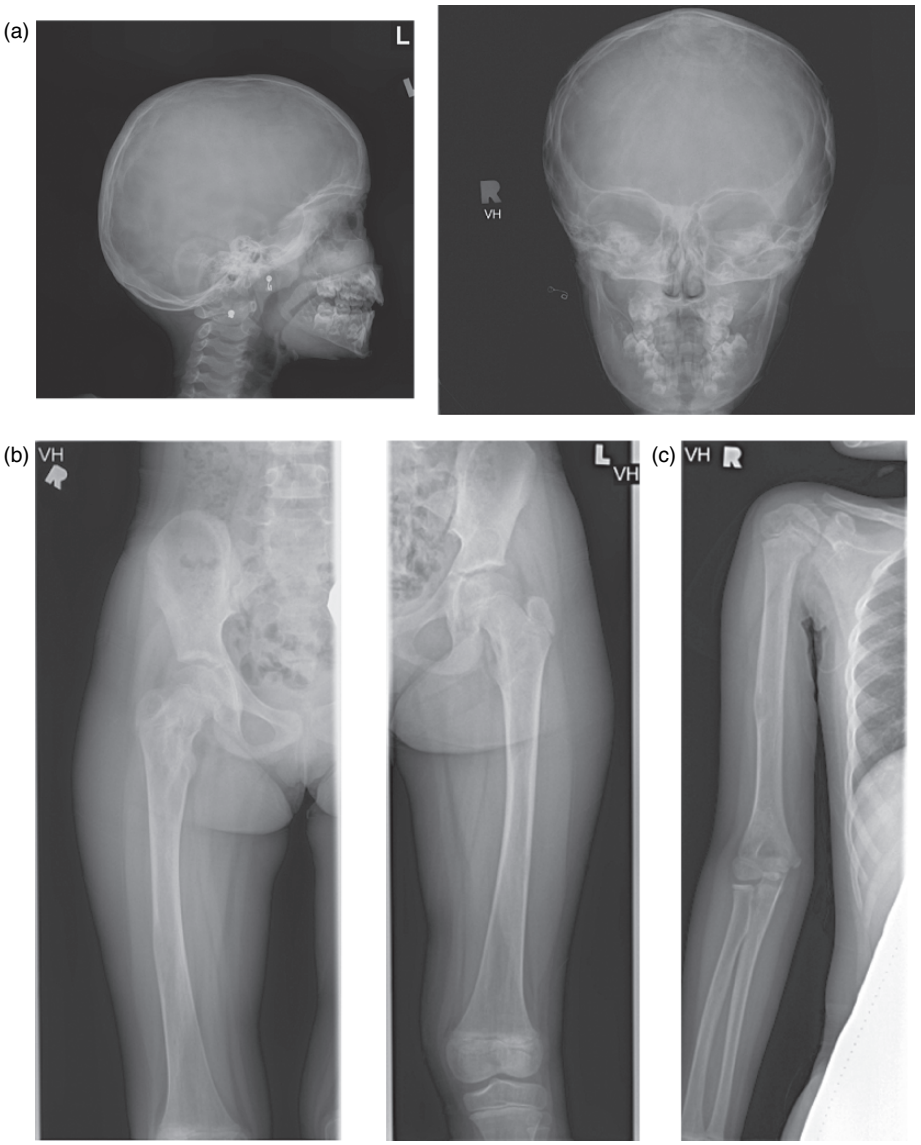
   Answer: D. Early puberty in McCune-Albright syndrome results from constitutive activation of the α-subunit of the stimulatory GTP-binding protein. This protein is a transducer of the activity of the gonadotropin receptors (as well as of a number of other receptors, such as the TSH receptor.)

3. Relatively good height prognosis in patients with McCune-Albright syndrome and precocious pubertal development may result from which of the following?

   A. Concurrent GH hypersecretion
   B. Protective effect of fibrous dysplasia on epiphyseal closure
   C. Protective effect of hyperthyroidism on epiphyseal closure

D. Protective effect of hypophosphatemia
E. Concurrent cortisol hypersecretion

Answer: A. Early puberty hastens the closure of the physes (growth centers of the bones), primarily through the action of estrogen. Closure of the physes causes



(a) Skull film showing ground-glass appearance right side of mandible and sclerosis in Maxillae. (b) Lucent and sclerotic areas both femoral necks. (c) Lesion of fibrous dysplasia right mid-humerus.

growth cessation. This accounts for the fact that children with early puberty stop growing earlier than do their peers. This often results in short stature, since growth stops at a time when the patients have not yet reached a height that is normal for adults. If growth is bolstered by oversecretion of growth hormone, then patients may achieve normal adult height despite early growth cessation.

4. Central precocious puberty in patients with McCune-Albright syndrome results from which of the following?

   A. Constitutively active transducers of GnRH receptor activity
   B. Humoral secretions from fibrous dysplasia lesions
   C. Hyperthyroidism in McCune Albright patients
   D. Cortisol hypersecretion
   E. Sex steroid hypersecretion

   Answer: E. The fact that early central puberty occurs in a number of conditions associated with elevated circulating levels of sex steroids (including McCune-Albright syndrome, adrenal tumors, gonadal tumors, congenital adrenal hyperplasia, and exogenous sex steroid administration) suggests that the mechanism relates to elevated circulating sex steroid levels themselves rather than to the specific mechanisms associated with each condition. It is likely that sex steroids are able to elicit positive hypothalamic-pituitary feedback in juveniles, which is similar to the positive feedback producing the midcycle gonadotropin surge in sexually mature women.

Chapter 49
Hypothalamic Hamartoma

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Objectives

1. To learn the manifestations of central precocious puberty
2. To be able to distinguish central precocious puberty from precocious pubertal changes caused by gonadal or adrenal sources

Case Presentation

This boy, age 4 years and 4 months, presented with precocious pubertal development. He had a significant increase in his growth velocity over the past 2 years. As an infant, he had been in the 50th percentile for length. From the age of 18 months, his length percentile steadily increased. At age 4 years and 4 months, he was wearing clothes appropriate in size for a 7-year-old boy. At age 3 years and 8 months, the patient developed pubic hair, increased oiliness of skin and hair, and aggressive behavior. At 4 years of age he developed acne over his nose and upper back, adult body odor, penile erections, and adult body odor.

He has not had headaches, seizures, or vision disturbance.
There is no family history of early puberty, pituitary, or thyroid disease.

On examination, height was 126.4 cm (5 standard deviations above the mean, 50th percentile for a boy of 7 years and 9 months). Weight 31.5 kg (3.8 standard deviations above the mean, 50th percentile for a 9-year-old boy). Acne was present over the bridge of the nose, forehead, and on the upper back. Hair was oily. The eyes were normal, as was the thyroid. The neurologic examination was normal. The penis was enlarged to 11.0 cm in length. The testes measured 4.5 cm in length (25 mL) bilaterally. Pubic hair was in Tanner stage III.

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Diagnostic Test Results

Bone age: chronologic age is 4 years and 4 months. The bone age (Greulich and Pyle) is estimated to be 9 years. One standard deviation for a male this age is 7.8 months.
Insulin-like growth factor I (IGF-I): 333.7 ng/mL (normal 58–209)
Insulin-like growth factor binding protein 3 (IGF-BP3): 2.7 mg/L (normal 0.8–3.0)
Human chorionic gonadotropin (HCG) quantitative: < 2 mIU/mL
Thyroid-stimulating hormone (TSH): 1.91 μIU/mL (normal 0.5–5.0)
Free thyroxine (FT_4): 1.53 ng/dL (normal 0.8–2.2)
Triiodothyronine: 177 ng/dL (normal 105–269)
Follicle-stimulating hormone (FSH): 1.6 mIU/L (normal 1–3.2)
Luteinizing hormone (LH): 1.56 mIU/mL (normal 0.07–0.3)
Testosterone: 280 ng/dL (within range for Tanner stage III–IV male; prepubertal range 3–10)
Prolactin: 39.6 ng/mL (normal 2–13)
Growth hormone: 0.71 ng/mL (normal 0.1–6)
Serum sodium: 139 mEq/L (normal 134–146)
Cortisol (in a.m.): 9.5 μg/dL (normal 3–21)

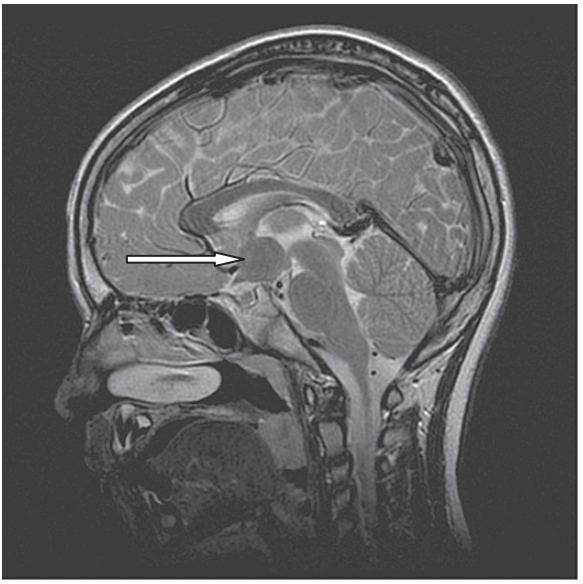

Fig. 49.1 Sagital view of T2-weighted magnetic-resonance scan of a 2.1 × 2.3 × 1.8 cm mass centered in the hypothalamus

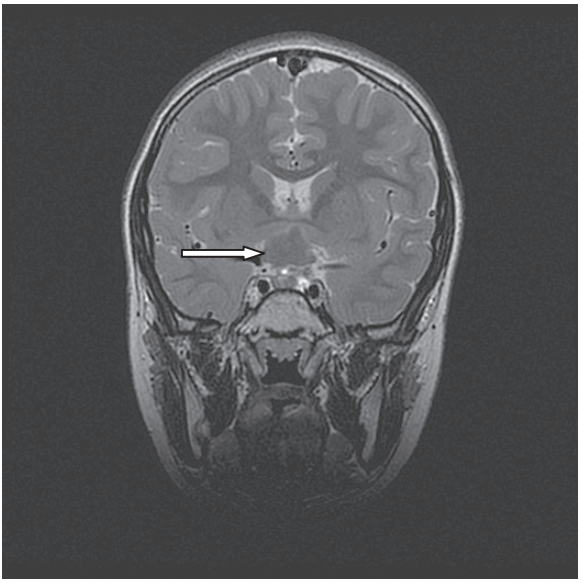

Fig. 49.2 Coronal view of T2-weighted magnetic-resonance scan of a 2.1 × 2.3 × 1.8 cm mass centered in the hypothalamus

Description

Large nonenhancing mass centered in the hypothalamus measuring 2.1 cm antero-posterior × 2.3 cm transverse × 1.8 cm craniocaudal

Diagnosis

Central precocious puberty.

Differential Diagnosis

See the section Central Precocious Puberty in the Introduction to Part XV for the differential diagnosis.

How the Diagnosis Was Made

Boys who start puberty before 9 years of age and girls who start before 7 to 8 years of age are thought to have early puberty. The tempo of puberty is also important. Thus, a girl who starts puberty at 7 years of age but who barely progresses with

advancement of secondary sexual characteristics and bone age might not need a thorough evaluation, while a girl who progresses rapidly may need a complete evaluation.

This young boy presents with central precocious puberty. The fact that both testes were enlarged suggests a hypothalamic-pituitary mechanism; the gonadotropins both stimulate gonadal activity and induce growth of gonads. Individuals with adrenal causes of pubertal development have prepubertal-size testes (less than 5 ml or 2.5 cm in length). When testicular tumors produce pubertal change, one testis is large while the other is small.

Pubertal gonadotropin levels associated with pubertal levels of testosterone and advanced bone age confirm a hypothalamic-pituitary cause for this patient's early puberty. The presence of a hypothalamic mass lesion on magnetic resonance imaging (MRI) scan points to the diagnosis of a brain tumor or to a brain malformation such as a hypothalamic hamartoma.

Hypothalamic hamartomas (HHs) are nonneoplastic, congenital malformations resembling the normal gray matter of the hypothalamus. In addition to central precocious puberty, gelastic or "laughing" seizures occur in a subset of affected individuals. Hamartomas are either embedded in the hypothalamus or attached to it by a stalk. There has not been a genetic anomaly identified. HH occurs equally in males and females. The neurons of HH resemble those in the normal tuber cinereum. Magnetic resonance imaging shows a noncalcified, nonenhancing solid mass that does not change size over time. The pathophysiology of the resulting precocious puberty caused by HH may be heterogeneous.

Often HH contain ectopic gonadotropin-releasing hormone (GnRH)-secreting cells, which may activate gonadotropins in the pituitary. GnRH-secreting neurons migrate to the arcuate nucleus and the prefrontal area of the hypothalamus from the olfactory placode within the area that becomes the nasal septum. Individuals with Kallmann syndrome have failure of migration of these neurons out of the olfactory placode. In Kallmann patients, GnRH-secreting neurons are identifiable within the nasal septum. The inability of GnRH-secreting neurons in the nasal septum to stimulate pituitary gonadotropin secretion results from the fact that there are few neurons secreting limited amounts of hormone into a high-flow system. By the time the systemic circulation reaches the pituitary gland, the concentration of GnRH is too low to elicit a response. The same number of cells located near capillaries coalescing to form the hypothalamic-pituitary portal system are able to produce quantities of GnRH that have higher concentration in the low-flow portal system; thus, the pituitary responds by secreting gonadotropins. When these GnRH-secreting neurons migrate into an ectopic region of the (forming a hamartoma), they are able to deliver GnRH into the portal system, producing pituitary gonadotropin secretion; however, they are not subject to the same regulation by neighboring neural and astroglial structures as are GnRH neurons in a eutopic position. Thus, these ectopic GnRH-secreting neurons become active prematurely, producing early puberty.

Some hypothalamic hamartomas do not contain GnRH-secreting neurons. Some of these masses produce transforming growth factor-α (TGF-α), a member of the

epidermal growth factor family. TGF-α is a known activator of GnRH by GnRH neurons. Thus, the proximity TGF-α–secreting hamartomas to eutopic GnRH neurons likely accounts for some instances of early puberty. It has also been hypothesized that HHs compress the hypothalamus and interfere with the normal inhibitory processes, which suppress gonadotropin secretion during childhood.

Hypothalamic hamartomas may be classified into parahypothalamic lesions attached to the floor of the third ventricle or suspended by a peduncle, or intrahypothalamic lesions, which involve the hypothalamus and distort the third ventricle. The parahypothalamic type is usually associated with central precocious puberty without seizures, while the intrahypothalamic type causes seizures, developmental delay, and, in about half the cases, precocious puberty.

Treatment

Treatment of precocious puberty caused by HH is with long-acting GnRH agonists. This medical therapy will suppress puberty by inducing tachyphylaxis at the level of pituitary gonadotropes, thereby inhibiting gonadotropin secretion. This treatment often causes regression in secondary sexual characteristics, slows the skeletal maturation rate, and improves the growth potential in children with HH. Once the GnRH agonist is withdrawn, puberty resumes. Often, attempted surgical removal of the hamartomas has been unsuccessful in halting the progression of central precocious puberty. For this reason, surgery is not recommended for control of early puberty in patients with parahypothalamic hamartomas. On the other hand, patients with intrahypothalamic hamartomas may have intractable seizures. Surgical intervention or radiosurgery should be considered in these patients for seizure control.

In summary, hypothalamic hamartomas are the most frequent type of central nervous system (CNS) mass to cause precocious puberty. It should be considered in the differential diagnosis of any child presenting with central precocious puberty. Hypothalamic hamartomas produce all the endocrine characteristics of normal puberty. They are nonprogressive lesions, and the treatment of choice is medical therapy with GnRH agonists to suppress puberty. Surgical treatment should be considered in cases of HH with intractable seizures.

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Multiple-Choice Questions

1. An 18-month-old boy presents with accelerated growth (bone age of 3 years), enlarged penis, pubic hair, adult body odor, and facial acne. Testes measure 1 to 2 mL bilaterally. He has an uncle who is short and infertile and had many genital surgeries as a child. Which diagnostic test will determine his diagnosis?

   A. MRI scan of the head
   B. GnRH stimulation test
   C. Adrenocorticotropin (ACTH) stimulation test
   D. Abdominal ultrasound
   E. HCG

   Answer: C. This boy likely has the non–salt-losing type of congenital adrenal hyperplasia in which he is missing the full enzymatic activity of 21-hydroxylase in his adrenal glands. If he were born with the salt-losing form of congenital adrenal hyperplasia, he would have presented by 2 to 3 weeks of life with adrenal crisis, dehydration, hyponatremia, and hyperkalemia. Therapy for this child consists of glucocorticoids and occasionally mineralocorticoids. Therapy is designed to suppress the hyperactive corticotropin-releasing hormone (CRH)-ACTH-adrenal access yet allow for optimal growth. In clinical management this is often difficult, and children must be monitored every 3 to 4 months to evaluate growth and measure serum androgen levels.
   An MRI scan of the head would be an appropriate diagnostic test if this child had evidence of central precocious puberty; his testes, however, are prepubertal. A GnRH stimulation test would produce a pubertal response in central precocious puberty, but is not helpful in diagnosing virilizing congenital adrenal hyperplasia. An abdominal ultrasound would be an appropriate diagnostic test if a virilizing adrenal tumor were suspected. Indeed, a testosterone-secreting adrenal tumor would produce a similar clinical scenario as above; however, there would not be a family history of disease. An HCG test would be positive in a boy with a chorionic gonadotropin-secreting tumor such as a hepatoblastoma. Often these boys have hepatomegaly on exam, and their testicles will be somewhat enlarged as HCG causes Leydig cell stimulation.

2. True or false: Idiopathic precocious puberty is more common in girls than boys.
   Answer: True. Idiopathic precocious puberty is a diagnosis of exclusion. MRI of the head should be performed in any child presenting with central precocious puberty. Boys, more often than girls, have a diagnosable neurologic disorder as the cause of their precocious puberty.

3. A 10-year-old boy presents with headaches and vision changes of 2 weeks' duration. He has had a recent growth spurt and appears to be in early puberty. Pubic hair is Tanner stage III and the testes measure 6 mL bilaterally. Also, he complains of polydipsia and polyuria over the past week. On computed tomography (CT) scan of his head, a mass is visualized in the tuber cinereum that extends

into the third ventricle. The mass contains calcifications and cystic lesions. What is this child's diagnosis?

A. Hypothalamic hamartoma
B. Craniopharyngioma
C. Langerhans cell histiocytosis
D. Optic glioma due to neurofibromatosis type 1

Answer: B. Hypothalamic hamartomas are congenital lesions and present with precocious puberty much earlier in childhood than age 10. Also, HHs do not cause headaches, vision changes, or diabetes insipidus. Craniopharyngioma is the most likely diagnosis from the above scenario. Craniopharyngiomas are the most common CNS tumor to cause endocrine abnormalities in addition to headaches and vision changes. Delayed growth and diabetes insipidus are the most common endocrinologic abnormalities at presentation. These are tumors of Rathke's pouch that originate in the pituitary stalk and spread to the suprasellar region. On CT scan, these tumors often contain calcifications and cystic lesions. Treatment consists of surgery and radiation therapy. Often, these patients have multiple endocrinology abnormalities following surgical resection. Langerhans cell histiocytosis often presents with diabetes insipidus and a thickened pituitary stalk, but these masses are not calcified or cystic. Finally, children with neurofibromatosis type 1 may develop a glioma that originates in the optic chiasm and invades the hypothalamus. These children have other manifestations of neurofibromatosis type 1 including multiple café-au-lait spots, Lisch nodules, axillary freckling, and neurofibromas. CNS tumors may arise and can cause precocious puberty or delayed puberty.

Chapter 50
Leydig Cell Adenoma

Courtney Finlayson, Reema Habiloy and Donald Zimmerman

Objective

To learn the manifestations and evaluation of gonadotropin independent precocious puberty in males.

Case Presentation

This boy, age 3 years and 9 months, was referred for precocious puberty. He had pubarche 6 months prior to presentation. His genitalia had always seemed to be larger than his older brother's genitalia; they had increased in size over the 4 to 6 months prior to presentation. He also had recent acceleration of growth in height. He did not have acne, adult body odor, breast enlargement, skin lesions or pigment abnormalities, headache, breast discharge, polyuria, or polydipsia. His energy had been normal. He had no prostration with intercurrent illness, orthostasis, salt craving, or symptoms of hypoglycemia.

The patient was the product of an uncomplicated, full-term gestation. One year prior to presenting with early puberty, he sustained a concussion after jumping out of his sister's crib; computed tomography of the head was negative.

The family history showed that the mother had menarche at 12 years of age, and the father's age at puberty was 13 years. The maternal grandmother had thyroid disease. There was no history of precocious puberty in the family.

On examination, height was 107.4 cm (95th percentile), and weight was 17.9 kg (75th to 90th percentile). The skin had no café-au-lait spots or other pigmentary abnormalities. The eye examination was normal. The thyroid was normal. Pubic hair was in Tanner stage II. The penis measured 9 cm in stretched length

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and 2.5 cm in diameter. The left testis had a volume of 2 to 3 mL and the right had a volume of 4 to 5 mL.

Diagnostic Test Results

Bone Age: chronologic age is 3 years and 9 months. According to standards of Greulich and Pyle, the bone age is 6 years. One standard deviation for a male this age is 6 months.
Testosterone: 179.7 ng/dL (normal < 10 ng/dL)
Follicle-stimulating hormone (FSH): 0.5 mIU/mL (normal 1–3.2)
Luteinizing hormone (LH): < 0.10 mIU/mL (normal 0.7–3)
Human chorionic gonadotropin (HCG): < 2 mIU/mL (normal < 2)
α-Fetoprotein (AFP): 4.9 ng/mL (normal 0–8.9)
Androstenedione: 28 ng/dL (normal 5–115)
Dehydroepiandrosterone sulfate (DHEAS): < 15 ng/dL (normal < 25)
17-hydroxyprogesterone: 26 ng/dL (normal 4–115)
Free thyroxine (FT_4): 1.53 (normal 0.8–2.2)
Thyroid-stimulating hormone (TSH): 3.69 (normal 0.5–5)

On testicular ultrasound, an area of multiple small round hypoechoic foci in the mid-testicle deep to the mediastinum (Fig. 50.1) indicates an ill-defined mass. The longest axis of the mass is approximately 1.29 cm. There is no evidence of epididymal abnormality or hydrocele

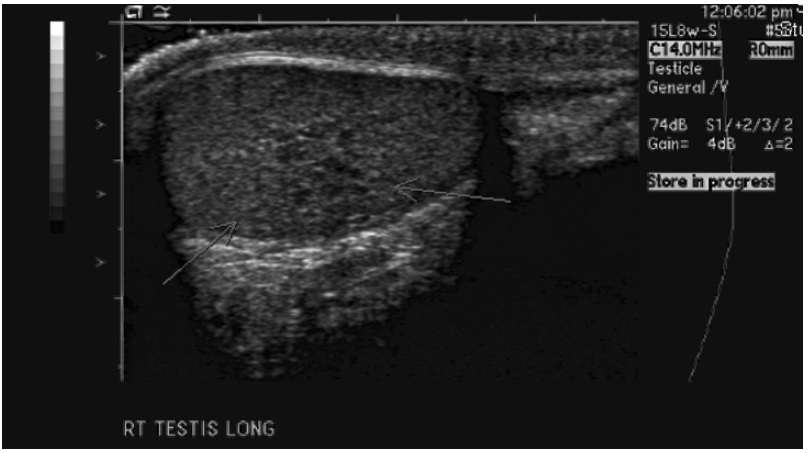

Fig. 50.1 An area of multiple small round hypoechoic foci in the mid-testicle deep to the mediastinum (arrows) indicates an ill-defined mass

Diagnosis

Gonadotropin-independent precocious puberty.

Differential Diagnosis

1. HCG-secreting tumors
2. Congenital adrenal hyperplasia
3. Virilizing adrenal neoplasm
4. Leydig cell adenoma
5. Familial testitoxicosis
6. McCune-Albright syndrome

How the Diagnosis Was Made

This boy presented with gonadotropin-independent precocious puberty: low gonadotropin levels, elevated testosterone, and advanced bone age. The asymmetry of his testicles led to the testicular ultrasound. The abnormal testicular ultrasound prompted surgery; a Leydig cell adenoma was removed.

Gonadotropin-independent precocious puberty is differentiated from gonadotropin-dependent precocious puberty by the gonadotropin levels, which are in the prepubertal range despite an elevated testosterone level. The differential diagnosis of gonadotropin-independent precocious puberty in boys includes HCG-secreting tumors, congenital adrenal hyperplasia, virilizing adrenal neoplasm, Leydig cell adenoma, McCune-Albright syndrome, and familial testitoxicosis.

Gonadotropin-secreting tumors may be hepatomas, hepatoblastomas, teratomas, yolk sac tumors, or germinomas. HCG is secreted by multinucleated tumor giant cells causing elevation of plasma HCG levels. In some cases, AFP is elevated as well. Congenital adrenal hyperplasia results from enzymatic deficiencies in cortisol synthesis. Decreased cortisol secretion results in increased pituitary secretion of adrenocorticotropin (ACTH). In turn, elevated ACTH levels produce increased size of the adrenal glands and increased production of cortisol precursors proximal to the step rendered inefficient by changed enzyme activity. Enzyme deficiencies associated with increased androgen production—and therefore with early male pubertal changes—include 21-hydroxylase or 11β-hydroxylase. Patients with these deficiencies have elevated plasma levels of 17-hydroxyprogesterone or 11-deoxycortisol, respectively. Adrenal tumors, including carcinomas or adenomas, secrete DHEA or DHEAS. Unlike congenital adrenal hyperplasia, in patients with adrenal tumors, these levels are not suppressed by glucocorticoid administration. McCune-Albright syndrome, which can affect males and females, is characterized by precocious puberty, café-au-lait spots, and polyostotic fibrous dysplasia. Patients may also have thyromegaly and thyrotoxicosis or hypophosphatemia. This condition results from activating mutations in the gene for the α-subunit of the stimulatory guanosine triphosphate (GTP)-binding protein. These activating mutations reflect somatic

rather than germ cell events; thus, some tissues are affected, and others are not. Familial testitoxicosis is caused by an activating mutation in the LH receptor, which leads to precocious puberty, often with clinical signs before the age of 4. This condition is manifest only in males, although it is transmitted with an autosomal dominant pattern of inheritance.

Leydig cell tumors (the abnormality detected in this child) are very rare. Testicular tumors occur in 2 per 100,000 males, and Leydig cell tumors constitute only 1% to 3% of those testicular tumors. Classically, patients present with precocious puberty, an isolated testicular mass, and elevated androstenedione. Leydig cell adenomas tend to present a bit later than familial testitoxicosis, at an average age of 5 to 9 years old. They are benign tumors that should be surgically removed, either by radical orchiectomy or testis-sparing surgery.

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Multiple-Choice Questions

1. A 3-year-old boy presents with enlarged penis and testes, pubic hair, and advanced bone age. Testes measure 4 to 5 mL bilaterally. His testosterone level is high, but his LH and FSH are low. His father recalls developing much earlier than other boys and is now 5 feet 4 inches tall. What is the most likely underlying defect causing this child's problem?

   A. 21-hydroxylase deficiency
   B. Activating mutation of LH receptor
   C. Leydig cell tumor
   D. HCG-producing germ cell tumor

   Answer: B. This boy has gonadotropin-independent precocious puberty. A heritable cause is likely, given the father's history of precocious puberty and short stature. The boy's testicular examination is symmetric, suggesting absence of a testicular tumor (although these may be detectable only on imaging studies). 21-Hydroxylase deficiency is less likely since the testicular size is pubertal. HCG overproduction may enlarge the testes to the degree seen in this patient. Neither Leydig cell tumors nor teratomas are heritable. To confirm the diagnosis, testing of the tissue and blood would have to be done to identify the mutation.

2. A 7-year-old boy presents with precocious puberty including Tanner stage III genitalia and pubic hair. He has had a recent growth spurt. Which set of clinical findings is not suggestive of gonadotropin-independent precocious puberty?

   A. Dry skin, thyromegaly, delayed relaxation phase of deep tendon reflexes, 25-mL testes, Tanner stage I pubic hair
   B. Café-au-lait pigmentation, limb deformity, thyromegaly, 10-mL testes, Tanner III stage pubic hair
   C. Unilateral testicular enlargement, Tanner stage III pubic hair
   D. Axillary freckling, small café-au-lait spots, pigmented spots of irises, 25-mL testes, Tanner stage III pubic hair
   E. General hyperpigmentation of the skin, 2-mL testes, orthostatic fall in blood pressure and rise in pulse, Tanner stage III pubic hair

   Answer: D. This patient has findings suggestive of neurofibromatosis (small café-au-lait spots, axillary freckling, pigmented spots on irises) and of central puberty (bilaterally enlarged testes.)

3. An 8-year-old boy presents with precocious puberty, an elevated testosterone level, and low FSH and LH. What imaging would you do if he were found to have elevated HCG levels as well?

   A. Magnetic resonance imaging (MRI) of the brain, abdominal and pelvic ultrasound, testicular ultrasound
   B. Abdominal and pelvic ultrasound
   C. Computed tomography (CT) of the brain and abdomen
   D. Testicular ultrasound

   Answer: A. HCG-secreting tumors can be found in many parts of the body. One could guide imaging by the presence of headache, which might suggest MRI of the brain to be done first, or hepatomegaly, which would lead to abdominal imaging first. In the absence of other localizing symptoms, however, multiple imaging modalities may be necessary.

Chapter 51
Prolactinoma

Jami Josefson and Donald Zimmerman

Objective

To learn the manifestations and evaluation of delayed puberty due to hyperprolactinemia.

Case Presentation

This girl, age 17 years and 3 months, presented for evaluation of primary amenorrhea. She had thelarche at 9 to 10 years of age and pubarche, and appearance of acne, adult body odor, and axillary hair at 12 years of age. She had not had menarche. She had a long history of obesity, with weight greater than the 97th percentile since the age of 3 years, height at the 50th to 90th percentiles, and weight for height greater than the 95th percentile. She did not have galactorrhea, hirsutism, male pattern hair loss, or lowering of the pitch of her voice.

She had normal temperature tolerance and energy. There had been no easy bruising, striae, or muscle weakness.

Her mother's age at menarche was 11 years old. A paternal aunt had menarche at 16 years of age. There was no family history of menstrual irregularity, infertility, hirsutism, pituitary tumors, kidney stones, hypercalcemia, or severe peptic ulcer disease.

On examination, height was 166.2 cm (50th to 75th percentile), and weight was 81 kg (90th to 95th percentile). Body mass index (BMI) was 29.3 kg/m^2. The skin had nonviolaceous striae over the abdomen and acanthosis nigricans of the neck and axillae. There was no hirsutism. The eye examination was normal, including visual fields by confrontation, extraocular movements, and ocular fundi. The thyroid gland was normal. Breasts were in Tanner stage V with no discharge. Pubic hair was in Tanner stage III. The clitoris and vagina were normal.

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Diagnostic Test Results

On magnetic resonance imaging (MRI) a large, 7.6 × 5.6 × 7.9 cm (craniocaudal and anteroposterior by transverse macrolobulated heterogeneous but predominantly T1 and T2 isointense enhancing mass was found (Fig. 51.1). It was centered within the sella but demonstrated extensive intracranial, skull base, and

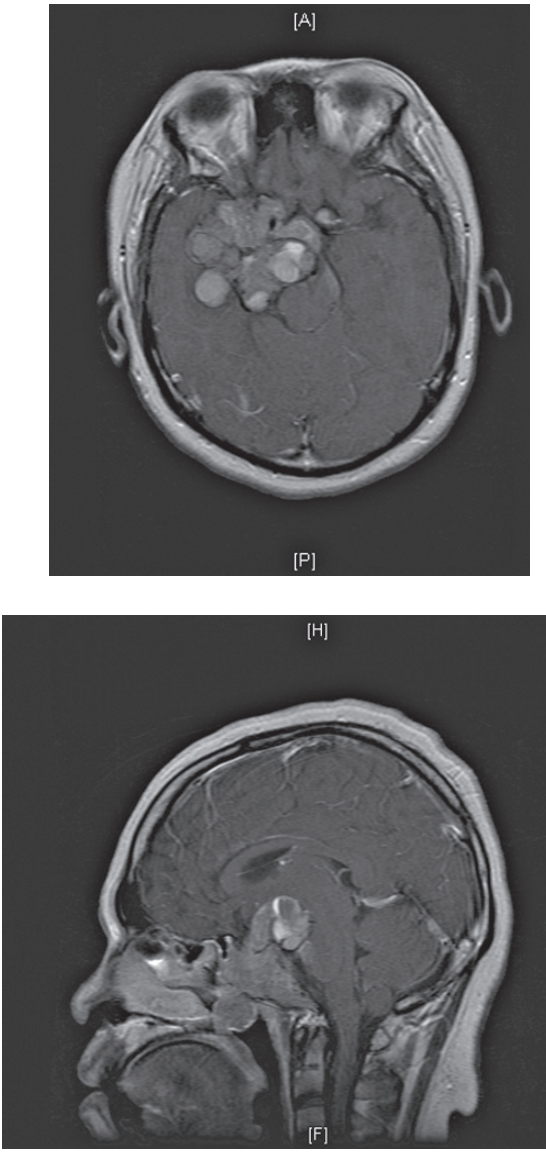

Fig. 51.1 Magnetic resonance imaging (MRI) shows a large, 7.6 × 5.6 × 7.9 cm (craniocaudal and anteroposterior by transverse) macrolobulated heterogeneous but predominantly T1 and T2 isointense enhancing mass

nasopharyngeal extension. The mass demonstrated multiple areas of hemorrhage and cystic change. It extensively involved both cavernous sinuses and encases both cavernous carotid arteries.

Laboratory

Follicle-stimulating hormone (FSH): 0.9 mIU/mL (normally menstruating females 1.5–33.4)
Luteinizing hormone (LH): 0.1 mIU/mL (normally menstruating females 0.5–76.3)
Thyroid-stimulating hormone (TSH): 1.339 μIU/mL (normal 0.7–5.7)
Free thyroxine (FT_4): 0.8 ng/dL (normal 0.6–2)
Prolactin: 164.9 ng/mL
Hemoglobin A1c: 5.5%
Chromosomes 46, XX
17-OH progesterone: 12 ng/dL
Testosterone, total: 33 ng/dL (normal 5–40)
Testosterone, free: 3.07% (normal for adult female 0.8–1.4%)
Testosterone, free dialysis: 10.1 pg/mL (normal 0.2–3.2)

Diagnosis

Primary amenorrhea

Differential Diagnosis

For the differential diagnosis, see the list in the section Delayed Puberty in the Introduction to Part XV. In addition to that list, pregnancy is in the differential for prolactinoma.

How the Diagnosis Was Made

The patient presented with primary amenorrhea. She had clinical signs of normal estrogen and androgen effects (breast development and pubic and axillary hair) and did not have evidence of androgen excess (hirsutism, male-pattern baldness, clitorimegaly, severe acne). There was no galactorrhea.

Her gonadotropins were not elevated, making primary hypogonadism unlikely. Human chorionic gonadotropin was normal, indicating that she was not pregnant. Total testosterone was normal, but free testosterone was elevated, raising the possibility of hyperandrogenism contributing to amenorrhea. Prolactin was elevated. The

high prolactin level prompted the magnetic resonance imaging (MRI) of the brain, which showed the prolactinoma.

Primary amenorrhea with estrogenization is differentiated from hypoestrogenic primary amenorrhea by the estrogen levels and clinical evidence of estrogenization, such as breast development. The differential diagnosis includes hypothalamic anovulation, pregnancy, obesity, undernutrition, Cushing's syndrome, hypothyroidism, drug abuse, chronic illness, and hyperprolactinemia.

Hypothalamic amenorrhea is a diagnosis of exclusion, which describes idiopathic hypothalamic anovulation. It is similar to the amenorrhea seen in athletes and in those with eating disorders, and is similar to psychogenic amenorrhea. Gonadotropin levels are typically high enough to allow for some pubertal development, but not high enough to induce ovulation.

Pregnancy is also a cause of primary amenorrhea, which must be ruled out by pregnancy test. Undernutrition, whether from anorexia nervosa or a chronic illness, may lead to primary amenorrhea. The mechanism in obesity is complex since there may be contributions from insulin-resistance–induced hyperandrogenism and from overproduction of estrogen by adipose tissue. Undernutrition alters the pulsatile pattern of gonadotropin-releasing hormone (GnRH) release, perhaps, in part, due to decreased levels of leptin. The excess glucocorticoids of Cushing's syndrome cause primary amenorrhea, mostly through their inhibition of GnRH. Hypothyroidism also decreases the secretion of gonadotropins. Drugs, including marijuana and alcohol, also suppress gonadotropin secretion leading to anovulation.

Hyperprolactinemia may be caused by prolactinomas, masses, or infiltration of the pituitary stalk (blocking the inhibitory effect of portal vein dopamine on pituitary prolactin secretion), ectopic secretion of prolactin by tumors, drugs, hypothyroidism, renal or liver failure, chest wall stimulation or irritation, and exercise and stress. Autoimmune conditions may be associated with hyperprolactinemia; however, a significant portion of these individuals with elevated prolactin levels have macroprolactinemia due to complexes of prolactin and antibodies to prolactin. Prolactinomas are usually microadenomas. However, macroadenomas, such as the tumor in the present patient, are not uncommon.

Hyperprolactinemia produces hypothalamic amenorrhea, often with only mildly decreased gonadotropins. Galactorrhea may or may not be present. Treatment starts with dopaminergic agonists such as bromocriptine and cabergoline. Often, these agents normalize prolactin levels and reduce tumor size. At times, these agents are ineffective, and treatment with transsphenoidal surgery or pituitary irradiation is required.

If a prolactinoma produces hypogonadotropic hypogonadism by mass effect, then control of hyperprolactinemia will not restore normal function of the hypothalamic-pituitary-gonadal axis. Under these circumstances, estrogen replacement should be provided with oral estrogens (estradiol or conjugated estrogens), transdermal estrogen, or parenteral estrogen. Since transdermal and parenteral estrogen avoid the first-pass effect at the liver, these routes may prevent adverse effects on lipid metabolism and on coagulation.

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Multiple-Choice Questions

1. A 13-year-old girl presents with Tanner stage I pubic hair and breast development and no menarche. Her height percentile has decreased over the last 3 years from the 30th percentile to 10th percentile. Her weight is at the 30th percentile. She complains of some fatigue and decreased appetite. What is the most likely etiology of her delayed puberty?

   A. Hypothyroidism
   B. Anorexia nervosa
   C. Isolated hypogonadotropic hypogonadism
   D. Crohn's disease

   Answer: A. She has poor growth, fatigue, decreased appetite, and delayed puberty, all of which can be explained by hypothyroidism. Although Crohn's disease is possible, it is not as likely as hypothyroidism because weight percentile has not declined along with height percentile. This child's maintenance of the weight percentile while the height percentile has decreased is not consistent with anorexia. Isolated hypogonadotropic hypogonadism would not usually present with a decrease in height.

2. A 17-year-old girl presents with primary amenorrhea. She has Tanner stage IV breasts and pubic hair. She reports breast development having started at age 10 and pubic hair at age 11. Her weight is less than the 5th percentile and her height is at the 50th percentile. She reports recent stress fractures, but no other medical problems. What is the most likely etiology of her delayed puberty?

   A. Hypogonadotropin hypogonadism
   B. Rheumatoid arthritis
   C. Anorexia nervosa
   D. Prolactinoma

   Answer: C. This patient presents with the female triad of undernutrition, stress fractures, and amenorrhea, which are suggestive of anorexia nervosa.

3. A 15-year-old boy presents with obesity and delayed puberty. His weight is greater than the 97th percentile and height is at the 10th percentile. Physical

exam shows red striae over his abdomen and flank and Tanner stage I pubic hair and genitalia. What tests are most likely to lend support to the etiology of his delayed puberty?

A. TSH, FT_4
B. Cholesterol panel and HgbA1c
C. Evening cortisol and ACTH level
D. Urine drug screen

Answer: C. Evening cortisol and ACTH level suggest the diagnosis of Cushing's syndrome. The patient is short and obese, rather than tall and obese, which is supportive of pathology rather than just overnutrition. The striae are also consistent with Cushing's syndrome and are not seen in hypothyroidism or drug abuse.

Chapter 52
Turner Syndrome

Jami Josefson and Donald Zimmerman

Objectives

1. To learn that Turner syndrome is a common form of primary hypogonadism
2. To learn the major components of Turner syndrome and its most common presentations: delayed puberty and short stature in girls

Case Presentation

The patient was the product of a full-term gestation and normal vaginal delivery. Her birth weight was 7 pounds. At age 2 years and 9 months, height was in the 25th percentile and weight was in the 10th percentile. By age 4 years and 8 months, height was in the 10th percentile and weight was between the 10th and 25th percentiles. Height standard deviation score fell to 2.7 standard deviations below the mean by the time of her presentation to a pediatric endocrinologist at age 9 years and 10 months. She had normal results of studies of urinalysis, complete blood count, erythrocyte sedimentation rate, blood chemistries, insulin-like growth factor I (IGF-I), IGF-BP3, thyroxine (T_4), and thyroid-stimulating hormone (TSH). Karyotype was 46X,i(X)(910). The follicle-stimulating hormone (FSH) measured 6.5 mIU/mL, (normal: 1–6) and luteinizing hormone (LH) measured 0.18 mIU/ml (normal: 0.02–0.3). Echocardiogram and ultrasound of the kidneys were normal. The patient presented to our clinic at age 10 years and 1 month for the assessment of her appropriateness of growth hormone treatment.

She had not had symptoms of dysfunction in the thyroid-stimulating hormone (TSH), antidiuretic hormone (ADH), adrenocorticotropin (ACTH), prolactin, or gonadotropin axes. She had not had gastrointestinal symptoms or headache or vision problems.

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Her father's height was 75 inches; mother's height was 66 inches. Her mother had menarche at 12 years of age and had hypothyroidism. Hypothyroidism had been present in the maternal grandmother and maternal-maternal great grandmother.

On examination, height was 120.8 cm (2.8 standard deviations below the mean). Weight was 21.8 kg (2.6 standard deviations below the mean). Blood pressure was 97/66; pulse was 98. The skin, eyes, ears, palatal arch, thyroid gland, neck, and abdomen were normal. The chest was clear. The heart had a 2/6 systolic ejection murmur at the left lower sternal border. There was cubitus valgum on the left and incomplete elbow extension on the right. The 4th and 5th metacarpals were short bilaterally. Deep tendon reflexes were normal. The spine was normal. Breasts and pubic hair were in Tanner stage 1.

Growth hormone treatment was started at age 10 years and 1 month. At the time of her most recent follow-up at age 13 years and 11 months, the patient's height was 2.7 standard deviations below the mean. Breasts were in Tanner stage 1, while pubic hair was in Tanner stage III. She had not had menarche.

Differential Diagnosis of Primary Amenorrhea

1. Abnormal genital structure such as mullerian agenesis/Mayer-Rokitansky-Kuster-Hauser syndrome
2. Hypogonadotropic hypogonadism
3. Constitutional growth delay
4. Prolactin excess
5. Autoimmune primary ovarian failure
6. Turner syndrome
7. Other forms of gonadal dysgenesis
8. Primary ovarian failure due to radiation, chemotherapy
9. Primary ovarian failure due to metabolic abnormalities (galactosemia, cystinosis)
10. LH receptor mutations

Turner syndrome (TS) is one of the most common sex chromosomal aneuploidies, occurring in approximately 1 of every 2000 to 3000 live female births. It results from an absence of one X chromosome (or part of the chromosome) leaving a 45 X karyotype or a karyotype with one normal/complete X chromosome and one abnormal/incomplete X chromosome. Approximately 50% of karyotypes of TS patients show this 45 X karyotype while 5% to 10% display a 46 XX karyotype with a significant part of the second X chromosome deleted. Additionally, many TS patients display some form of mosaicism (45 X, 46 XX) resulting from postzygotic nondisjunction. TS patients may also have some cells with Y chromosome material (45 X, 46 XY), and this may lead to some degree of masculinization and predisposes to gonadal tumors.

The Hypogonadism of Turner Syndrome

Numerous studies examining the relationship between the chromosomal karyotype and phenotypic characteristics have revealed a number of correlations. Regions of both the short and long arms of the X chromosomes appear to affect normal ovarian function. On the other hand, Turner patients with very distal deletions of the short arm of X (X_p deletions) may have normal ovarian function. Of particular note is the fact that some studies suggest there are normal numbers of germ cells in ovaries of Turner fetuses until 18 weeks' gestation. At this point, accelerated atresia occurs. Even adolescents with Turner syndrome have been recently found to have from 1.5 to 128 ovarian follicles per meter cubed (m^3). A corollary of these observations is the fact that 30% of Turner girls have some pubertal development, and 2% to 5% have spontaneous menses. The gonadal dysgenesis that occurs in most TS patients leads to streak ovaries and to hypoplastic uterus (the latter resulting from lack of estrogen). Elevated gonadotropins (FSH and LH) are indicative of ovarian failure. Ovarian failure requires treatment initially with low-dose estrogen. Subsequently, progesterone is added to ensure adequate shedding of the endometrium with menstrual flow and to achieve normal breast morphology. This therapy is necessary for both sexual maturation and the prevention of osteoporosis. While the majority of TS patients will not progress to spontaneous puberty, a proportion of patients will have onset of breast development to Tanner stage III or more and may have at least one menses. A very small proportion of TS patients (<10%) will continue to have menses into young adulthood, and there are case reports of TS patients achieving pregnancy and giving birth to healthy offspring.

Short stature appears to be the only characteristic present in virtually all TS patients. The *SHOX* gene (short stature homeobox-containing gene) is a pseudoautosomal gene located on the distal ends of the X and Y chromosome. It encodes a transcription factor responsible for a proportion of long-bone growth and therefore is thought to be the underlying gene deletion causing short stature in TS patients.

In addition to short stature, patients with TS manifest other skeletal growth disturbances such as short neck, abnormal upper-to-lower segment ratio, cubitus valgus, short metacarpals, increased risk of congenital hip dislocation, mandibular problems including micrognathia, high-arched palate, and scoliosis. Other physical features include lymphatic dysfunction, webbed neck, low posterior hairline, posteriorly rotated ears, edema of the hands and feet, strabismus, ptosis, and multiple pigmented nevi. Physiologic features include otitis media, gonadal failure, infertility, cardiovascular anomalies, hypertension, renal anomalies, and Hashimoto's thyroiditis with hypothyroidism. There are no pathognomonic features of TS; the one universal feature is short stature.

Most Turner's patients have normal intelligence, although approximately 10% will have significant developmental delays. There is an increased incidence of mental retardation in patients who have small ring X chromosomes. Additionally, patients with mosaicism tend to be less affected than those with the 45 X karyotype. Many patients will have subtle deficits in visual-spatial reasoning manifesting as difficulties with mathematics and nonverbal learning.

Once the diagnosis of TS is made, patients should receive coordinated care from a multidisciplinary team. Cardiovascular consultation and echocardiogram is warranted since 50% of TS patients have congenital heart defects. A renal sonogram to rule out a structural abnormality should be done. Additionally, patients should be monitored for hypertension regularly. TS patients are at higher risk of developing autoimmune disease such as Hashimoto's thyroiditis, celiac disease, inflammatory bowel disease, and juvenile rheumatoid arthritis. Carbohydrate intolerance occurs more frequently in TS patients. There is increased risk of both type 1 and type 2 diabetes mellitus.

Growth hormone therapy has been shown to safely increase growth velocity and final adult height in TS patients. Current guidelines suggest that growth hormone treatment should be initiated when the height of the TS patient falls below the 5th percentile of the normal curve. The decision of when to begin estrogen therapy for feminization is less clear. Studies have shown that once estrogen therapy is begun, epiphyseal fusion will occur in about 12 to 18 months, and growth of the long bones will stop. Estrogen treatment for sexual maturation should begin in a TS girl who has reached her target height while on growth hormone therapy or if growth is no longer being achieved on this therapy.

In summary, TS patients need lifelong endocrinology care. A smooth transition from pediatric endocrinology care to adult endocrinology care is a realistic goal.

Suggested Readings

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Multiple-Choice Questions

1. Patients with Turner syndrome have hypogonadism characterized by:

   A. Low gonadotropin levels and low levels of sex steroids
   B. High gonadotropin levels and low levels of sex steroids
   C. Normal levels of gonadotropins and estrogens but high levels of androgens
   D. High levels of androgens and estrogens and normal levels of gonadotropins
   E. High levels of gonadotropins and estrogens

   Answer: B. It is important to note that during childhood, Turner patients may have normal prepubertal levels of both sex steroids and gonadotropins.

2. Hypogonadism in Turner patients is associated with:

   A. Failure to form gonads
   B. Formation of gonads characteristic of males rather than of females
   C. Formation of ovaries that develop atretic follicles much earlier than do normal ovaries
   D. Formation of ovaries that are morphologically normal but functionally abnormal
   E. Formation of ovaries that undergo torsion in utero

   Answer: C. Another way to express this is that Turner patients develop early menopause—so early that it begins in the first half of gestation.

3. All of the following statements about sex steroid replacement in patients with Turner syndrome are true except:

   A. The timing of estrogen replacement may affect the timing of closure of the growth centers of the bones and therefore the adult height.
   B. The addition of progesterone to the estrogen regimen affects menstruation and breast development.
   C. In Turner syndrome, bone density is not significantly affected by introduction of estrogen replacement treatment.
   D. Occasional patients with Turner syndrome do not require sex steroid replacement.
   E. Many Turner syndrome patients who manifest some pubertal development still require sex steroid replacement.

   Answer: C. Patients with Turner syndrome may be at increased risk of osteoporosis. This predisposition is amplified by failure to treat with sex steroids.

4. Which of the following is not a feature of patients with Turner syndrome?

   A. Scoliosis
   B. Short stature
   C. Renal anomalies
   D. Congenital and acquired cardiovascular defects
   E. Prognathia

   Answer: E. Turner patients frequently have micrognathia and underdevelopment of bones at the cranial base.

Part XVI
Instructive Rarities

Introduction

Jeffrey I. Mechanick

One must preface any discussion of rarities in medicine by citing the impact of Bayes' theorem: that is, the rarer the disease, despite the availability of a highly accurate test, the less likely that a test can predict the presence of the disease. Rarities in endocrinology are no different from rarities in other areas of medicine and are also encumbered by other obstacles, such as (1) inadequate exposure during formal training, (2) less available pertinent knowledge and clinical evidence, and (3) a psychological scenario during a lengthy diagnostic process that can be discouraging for the physician and patient. Nevertheless, rarities do occur, and supporting clinical evidence is available, especially with easy-to-access computer databases. It is in this setting that instantiation of a proper management strategy by reviewing real-life case histories offers an educational experience comparable to substantiation of the strategy by theory and didactic teaching.

In Chapter 53, a woman presents with extreme and recalcitrant obesity in the setting of a hypothalamic disease. Obesity itself is very common, in fact too common, with nearly two thirds of all Americans being either overweight or obese. A great deal of attention has been devoted to understanding the role of hypothalamic integration of humoral and neural signals in the maintenance of a certain body composition. Unfortunately, there is no uniform approach to hypothalamic obesity that has proven efficacy. Here, the pivotal aspect is to recognize that the patient's obesity is not a common form that will respond to conventional intervention, and that an early and perhaps a more creative and diligent approach will be needed.

In Chapter 54, a man presents with osteoporosis and a skin rash suggestive of mastocytosis. The diagnosis of mastocytosis is confirmed by skin biopsy and histamine levels. Mastocytosis is a rare disease and not one that is intuitively associated with metabolic bone disease. It is the recognition of the rash that triggered consideration of a diagnosis of mastocytosis. Here, the pivotal aspect is to know the literature and be able to generate an appropriate differential diagnosis early in the evaluation.

In Chapter 55, a woman presents with virilization and an adrenal mass. The differential diagnosis is discussed and the diagnostic biochemical test—a serum

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testosterone level—is positive. Though the adrenal mass could be an incidentaloma and the testosterone level could be spurious or result from an ovarian source, the diagnostic and therapeutic procedure—a laparoscopic adrenalectomy—serves to confirm the diagnosis. Here, the pivotal aspect is to know what diagnostic procedure to perform.

Mastering the field of endocrinology must include exposure, both in real life and as part of an academic learning experience, to rare cases. Even though uncommon presentations of common disorders are more common than uncommon disorders, the successful endocrinologist knows the difference.

Chapter 53
Hypothalamic Damage and Obesity

Lalita Khaodhiar and Caroline M. Apovian

Objectives

1. To recognize the uncommon form of obesity caused by hypothalamic dysfunction
2. To review the pathophysiology of hypothalamic obesity
3. To discuss the available treatment options for hypothalamic obesity

Case Presentation

A 20-year-old Haitian woman was referred to the Nutrition and Weight Management Center for an evaluation and treatment of obesity. She was 154.2 cm (60.7 inches) tall and weighed 132.3 kg (291.13 lb). Two years earlier, she weighed approximately 68 kg (150 lb).

The patient's medical history was significant for her admission to the hospital 22 months earlier when she presented with sleepiness, weakness, blurred vision, headache, and 2 months of cold symptoms. She was found to have a serum sodium level of 116 mg/dL. She was deemed to have the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), possibly of a central origin. She was initially treated with fluid restriction and then with furosemide and sodium supplementation, which gradually normalized her serum sodium over the course of her hospitalization. She had a computed tomography (CT) scan of her brain, which showed no pituitary tumor. A magnetic resonance imaging (MRI) with gadolinium showed a T2 bright signal abnormality involving the left cerebral peduncle and left thalamus of unclear etiology. A lumbar puncture was performed. Her cerebrospinal fluid showed a white cell count of 24/mm^3 with 95% lymphocytes and three red blood cells, a protein level of 10 mg/dL, and glucose of 56 mg/dL. Mycobacterium and bacterial cultures were negative. Her repeated MRI a week later showed a slight increase in

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size of the brain lesion involving the left mamillary body and hypothalamus. She was transferred to another hospital for further workup and ultimately had a brain biopsy, which showed demyelination of the thalamus and hypothalamus believed to be from viral encephalitis.

Since then, she has experienced an increased appetite, poor impulse control, and poor short-term memory including being unaware of how much food she was eating or when she had eaten last. She had gained 13 kg (30 lb) while she was in a rehabilitation hospital for a year on a somewhat restricted diet. Since she returned home, she had gained more than 45 kg (100 lb) over a 6-month period. According to her father, she had been eating constantly with numerous trips to the refrigerator every day. For the past 2 months, her family has tried to control her caloric intake by decreasing the amount of fried food in the house as well as trying to prevent her from making frequent trips to the refrigerator. She was able to lose 2.7 kg (6 lb) from her maximum weight of 135 kg (297 lb). She did not exercise regularly. Her family recently obtained a treadmill but she refused to use it.

Her past medical history included positive tuberculin skin test (purified protein derivative [PPD]) 6 years earlier, for which she was treated with 6 months of isoniazid. She was recently diagnosed with type 2 diabetes mellitus and polycystic ovary syndrome. She is also being evaluated for obstructive sleep apnea. Her medications included atorvastatin, metformin, and modafinil.

Her family history was significant for a father with type 2 diabetes, which was controlled by diet. She had one sister with mild obesity, but no other extreme obesity in the family. She lived with her parents and her two brothers. Her mother did most of the cooking. The patient started college but dropped out since her illness. She denied tobacco, alcohol, or illicit drug use. Review of systems was significant for somnolence during the day, poor memory, and irregular periods.

On physical examination, the patient was 154.2 cm (60.7 inches) tall, weighed 132.3 kg (291 lb, 2 oz), and her body mass index (BMI) was 55.7. Her waist circumference was 142 cm (56 inches). She appeared in no acute distress, although she was intermittently sleepy and had difficulty maintaining wakefulness during the interview. The blood pressure was 94/70 mm Hg and the heart rate was 92 beats per minute. The eyes were equal and reactive to light and accommodation, and her extraocular movements were intact. Her neck showed no goiter or thyroid nodules. She had marked acanthosis nigricans. The lungs had no wheezes or crackles, and the heart sounds were normal. The abdomen appeared normal, although extremely obese, and was nontender with normoactive bowel sounds. Her sensory and motor neurologic exam was unremarkable. Her cranial nerves were intact. Her reflexes were trace but symmetrical.

A random measurement of blood glucose revealed a level of 71 mg/dL. The hemoglobin A1c was 6.0%. The thyroid-stimulating hormone (TSH) level was 3.31 μU/mL with the total thyroxine (T_4) of 10.5 μg/dL and total triiodothyronine (T_3) of 9.0 μg/dL. The a.m. serum cortisol level was 15.2 μg/dL with an adrenocorticotropic hormone (ACTH) level of 36 pg/mL. The prolactin level was 10.9 ng/mL. The serum follicle-stimulating hormone (FSH) level was 3.9 mIU/mL and the luteinizing hormone (LH) level was 6.5 mIU/mL. The serum estradiol level was < 37 pg/mL.

She was treated with therapeutic lifestyle changes (diet and exercise) as well as pharmacologic treatment (sibutramine). One year later, her weight was 132.8 kg (292.13 lb). She continued to eat constantly and had no regular exercise.

How the Diagnosis Was Made

Although hypothalamic damage is a rare cause of obesity, weight gain and obesity are not uncommon long-term problems in patients with hypothalamic damage. The true prevalence of hypothalamic obesity is not known and is probably underestimated partly because it may take several years to develop. In addition, this problem has been underrecognized by clinicians. Damage to the hypothalamus can result in hyperphagia, autonomic imbalance, a low metabolic rate, and various other problems that can contribute to weight gain and obesity [1]. In this case, the history of excessive body weight change after the hypothalamic disease along with the history of severe hyperphagia and food-seeking behavior were strong evidence supporting the diagnosis of hypothalamic obesity. Furthermore, hyperinsulinemia, physical inactivity, and hypersomnolence may have also played a role in her weight gain. It should also be noted that therapeutic lifestyle changes and sibutramine were not efficacious in this patient.

Lessons Learned

Both genetic syndromes and acquired structural damage to the hypothalamus can cause hypothalamic obesity. The most common causes of hypothalamic damage are space-occupying lesion such as tumors, aneurysms, and inflammatory and infiltrative diseases. In children and young adults, craniopharyngioma or its treatment with radiation or surgery is the most common cause of acquired hypothalamic obesity. The overall incidence of craniopharyngioma in the United States is only 0.13 per 100,000 person years, and up to 50% to 80% of children become obese after its surgical treatment [1]. In contrast, Prader-Willi syndrome (PWS) was considered the most common form of genetic disorder associated with hypothalamic obesity, even though recent data suggest that melanocortin-4 receptor mutation may be more common.

Pathophysiology of Hypothalamic Obesity

The hypothalamus is the integral part of many peripheral signals and neural pathways that control energy homeostasis and body weight [2]. Early studies showed that lesions of the ventromedial hypothalamus (VMH) resulted in hyperphagia and obesity; thus, the VMH was described as the brain satiety center. Recently, the concept of hypothalamic feeding and satiety centers has shifted to the specific neurotransmitters that control feeding behaviors and energy expenditure. The VMH

generally integrates information from the peripheral hormones leptin, insulin, and ghrelin. These hormones send information regarding meal size, nutrient composition, and adipocyte stores. The VMH then interprets this information into signals for feeding through neurons of the hypothalamic arcuate nucleus (ARC) that release neuropeptide Y (NPY) and agouti-related peptide, and also into signals for satiety through neurons releasing α-melanocyte stimulating hormone (αMSH) and cocaine-amphetamine regulated transcript. These neurons impact the activation of melanocortin-4 receptors (MC4-R). NPY is a potent central appetite stimulant that also inhibits thermogenesis. The ARC NPY neurons are stimulated by decreases in circulating leptin and insulin during starvation.

Causes of hypothalamic obesity are probably multifactorial. Several neuroendocrine mechanisms have been described. The contribution of each mechanism differs from one patient to another depending on the degree and distribution of hypothalamic damage. In addition, the extent of hypothalamic damage has been shown to correlate with the degree of obesity in children but not in adults [3].

Hyperphagia

Hyperphagia is often seen in patients with hypothalamic obesity, although not all patients exhibit this feature. Severe hyperphagia and food-seeking behavior can be antisocial and disruptive. In some cases, it can be as severe as in patients with leptin deficiency. Disruption of ARC function is likely to play a role in hyperphagia. Significant elevation of leptin levels has been observed in patients following surgical treatment for craniopharyngioma, suggesting that the loss of appetite control is probably involved in part by a loss of negative feedback by leptin on the ARC NPY neurons, which causes an increase in NPY release.

Autonomic Dysfunction

Studies showed that lesions to the VMH lead to reduced sympathetic nervous system activity and enhanced glucose-stimulated insulin secretion. This leads to the hypothesis that the damage to this area causes a disinhibition of vagal tone on the pancreatic β-cell, which initially leads to insulin hypersecretion, and eventually obesity.

Impaired energy expenditure and thermoregulation has also been described in hypothalamic obesity. Several regions of hypothalamus influence energy expenditure and the sleep-wake cycle. The ventromedial nuclei are important parts of the sympathetic nervous system, and when activated, the metabolic rate increases and lipolysis occurs. The medial hypothalamic leptin pathways also play a role as leptin increases energy expenditure through increased thermogenesis in brown adipose tissue. The preoptic anterior hypothalamus is an essential site of thermoregulation. Hypersomnolence, either secondary to obstructive sleep apnea or directly from disruptive neurohormonal mechanisms, can worsen weight gain through reduction of voluntary energy expenditure [4].

Management of Hypothalamic Obesity

Understanding the pathophysiology may help in establishing the treatment plan. Severe hyperphagia and physical inactivity are often obvious from the medical history. However, there are no absolute criteria for the diagnosis of hyperphagia, autonomic dysfunction, or decreased energy expenditure.

Behavioral Modification

Diet and exercise are the mainstay of obesity treatment. Although patients are not likely to achieve an ideal body weight, weight gain can be halted. Behavioral modification therapy for both patients and their families as well as the home environment are necessary, including close parental or household supervision of the patient to minimize the consumption of high caloric, high fat, or sugary foods and to restrict food seeking behavior.

Pharmacologic Treatment

In cases of severe hyperphagia, diet and exercise are often not effective. Data on medications for the treatment of hypothalamic obesity are limited, and in theory, the medications that work on the central nervous system, such as appetite suppressants as well as recombinant leptin therapy, may not be fully effective in the presence of hypothalamic damage (as in our patient). Orlistat has a limited role because it requires dietary adherence.

Surgery

There are few data on bariatric surgery in hypothalamic injury, and this treatment can be dangerous in the presence of severe hyperphagia. Gastric restrictive surgery in PWS patients has been associated with a high failure rate and with staple line rupture, although select cases of mild PWS have had successful outcomes. Case reports of malabsorptive procedures such as biliopancreatic diversion in hypothalamic injury have been shown to be have both successes and failures [5, 6].

Treatment of Hyperinsulinemia

Limitation of insulin release may be helpful in a subset of patients with hyperinsulinemia. The somatostatin analogue octreotide, which binds to the somatostatin receptor-5 on the pancreatic β-cell membrane, has been shown in a small randomized controlled study of children with hypothalamic obesity to suppress insulin levels, stabilize weight, and stabilize BMI [7]. However, there are no long-term data on this treatment. Other potential treatments for hyperinsulinemia include the use of low carbohydrate diets and selective pancreatic vagotomy.

Treatment of Decreased Energy Expenditure

Sympathomimetic drugs such as dextroamphetamine have been studied in five patients with hypothalamic obesity and poor attention, with the treatment stabilizing their weight gain, improving attention, and increasing overall physical activity [8]. There are no studies on other medications.

Hormonal Replacement

Although deficiencies of anterior pituitary hormones are probably not the main reason for weight gain after hypothalamic damage, anterior pituitary function should be assessed and treated as necessary. An increase in percent body fat is seen in patients with secondary hypothyroidism and hypogonadotrophic hypogonadism. Growth hormone therapy has been shown to improve body composition, linear growth, physical strength, and agility in PWS since these patients also have growth hormone (GH) deficiency [9]. GH use in adults with hypothalamic damage, however, has been associated with weight gain and obesity after the diagnosis [3].

In conclusion, weight gain is not uncommon in patients with structural hypothalamic damage. Several mechanisms may be involved, and identification of these mechanisms may help in the management plan. The available treatments, however, are usually of limited success in patients with severe obesity. It is thus important to identify patients at risk and start treatment early before severe obesity has developed.

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Multiple-Choice Questions

1. Which statement is correct?

   A. Hypothalamic obesity rarely occurs after hypothalamic damage.
   B. Hypothalamic obesity occurs in more than 90% of children and adult patients after the treatment for tumors of hypothalamic regions.
   C. Craniopharyngioma and its treatment are the most common causes of acquired hypothalamic damage in children and young adults.
   D. Prader-Willi syndrome is the most common cause of genetic disease associated with hypothalamic obesity.
   E. None of the above.

   Answer: C. Although hypothalamic damage is a rare cause of obesity, weight gain and obesity is not an uncommon long-term problem in patients with hypothalamic damage. In children and young adults, craniopharyngioma or its treatment with radiation or surgery is the most common cause of acquired hypothalamic obesity. The overall incidence of craniopharyngioma in the United States is only 0.13 per 100,000 person years and up to 50% to 80% of children become obese after its surgical treatment [1]. Prader-Willi syndrome (PWS) was considered the most common form of genetic disorder associated with hypothalamic obesity, but recent data suggest that melanocortin-4 receptor mutation may be more common.

2. What is (are) the mechanism(s) of weight gain in patients with hypothalamic damage.

   A. Hyperphagia
   B. Autonomic imbalance
   C. Leptin deficiency
   D. A and B
   E. A, B, and C

   Answer: D. Causes of hypothalamic obesity are probably multifactorial. Several mechanisms have been described including hyperphagia, autonomic imbalance, a low metabolic rate, hypersomnolence, and GH deficiency. Significant elevation of leptin levels has been observed in patients with hypothalamic obesity suggesting that the loss of appetite control is probably involved in part by a loss of negative feedback by leptin on the ARC NPY neurons.

3. Which one of the following endocrine defects is most likely seen in patients with acquired hypothalamic obesity?

   A. Insulin hypersecretion in response to glucose tolerance test
   B. GH deficiency
   C. Cortisol deficiency
   D. Secondary hypothyroidism
   E. Hypogonadotrophic hypogonadism

Answer: A. The damage to the VMH causes a disinhibition of vagal tone on the pancreatic β-cell, which initially leads to insulin hypersecretion and eventually obesity.

4. Which of these statements is false regarding the treatment of hypothalamic obesity?

A. Diet and exercise are often not effective.
B. The efficacy of appetite suppressants may be reduced.
C. Octreotide is the mainstay of long-term treatment.
D. Bariatric surgery is associated with high rates of failure and complications.
E. Treatment of GH deficiency may improve body composition.

Answer: C. The available obesity treatments including diet, exercise, pharmacotherapy, and surgery are usually of limited success in patients with severe hypothalamic obesity. Octreotide has been shown in a 6-month randomized controlled study of children with hypothalamic obesity to suppress insulin levels, stabilize weight, and stabilize BMI [7]. However, there are no long-term data on this treatment. Growth hormone therapy has been shown to improve body composition, linear growth, physical strength, and agility in PWS.

Chapter 54
Systemic Mastocytosis

Michael Kleerekoper and Luis Afonso

Objectives

1. To present a case of vertebral fractures in a young man
2. To review the clinical and biochemical evaluation leading to the correct secondary cause of bone loss and fractures

Case Presentation

A 34-year-old man felt a sudden "pop" in his back as he was lifting a bundle of wires in his usual occupation as an electrician. He had experienced similar episodes on two previous occasions, but neither was as severe. He gave a history of chronic back pain for 5 years, but this only minimally interfered with his employment. Six years prior to this presentation he was involved in a motor vehicle accident in which he sustained fractures of the pelvis, ribs, and second cervical vertebra. He had attributed his chronic back pain to that accident. He was certain that no other vertebral fractures had been sustained during that accident. Initial history was essentially unrevealing for possible causes of osteoporotic fracture. There was no family history of osteoporosis or fragility fractures, and he had normal thyroid and gonadal function by history. He had a 15-year smoking history at one pack per day, drank only moderately, and did not use other recreational drugs. He was on no chronic medication.

Physical examination revealed a maculopapular rash over the trunk and upper extremities. On the possibility that this was a manifestation of systemic mastocytosis, dermatographia was elicited and further history obtained. He stated that the rash had been present for about 4 years and was intensely pruritic at night or after a warm shower. He also complained of epigastric burning and dyspeptic symptoms that were aggravated in the supine position, but denied vomiting, abdominal cramps,

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or diarrhea. He denied any weight loss, although he had lost approximately 2 inches in height. He had experienced two episodes of unexplained (and unevaluated) syncope in the past. He denied any known drug allergies. He had used no medication for his rash.

The remainder of the physical examination included height 70.3 inches, weight 91.3 kg, and blood pressure 140/90 mm Hg without postural changes. There was a normal thoracic kyphosis but a slight decrease in the lumbar lordotic curve. There was no spinal or paraspinal tenderness and reasonable preservation of range of motion of the spine. There was normal abdominal examination without hepatosplenomegaly. Cardiac, lung, and neurologic exams were normal.

How the Diagnosis Was Made

The patient was evaluated by a dermatologist, who agreed with the clinical diagnosis of urticaria pigmentosa that was confirmed on skin biopsy. Urine excretion of histamine was elevated at 577 nmol/g (reference interval 0–321). This same 24-hour urine collection contained 419 mg calcium, 85.1 pmol pyridinoline/μmol creatinine (reference value <19). Serum bone-specific alkaline phosphatase was 31 μ/mL (reference interval 3–12) and serum osteocalcin 2.6 ng/mL (reference 3–13). Serum calcium was 8.8 mg/dL, inorganic phosphate 4.3 mg/dL, and intact parathyroid hormone (PTH) 16 pg/mL were normal, as were the liver enzymes. Hemoglobin 14.4 g/dL, white blood count (WBC) 6,800, platelets 208,000, neutrophils 69%, lymphocytes 23%, monocytes 6%, eosinophils 1%, and basophils 1%.

Spine radiographs revealed compression fractures of T12, L1, and L3 with diffuse osteopenia. No sclerotic lesions were seen. Bone mineral density was measured by dual-energy x-ray absorptiometry (DEXA). Only L3 and L4 could be evaluated in the lumbar spine because of the fractures, and the value of 0.66 g/cm^2 was 4.2 standard deviations (SD) below the mean for young men. In the radial midshaft (a measure of predominantly cortical bone), the value of 0.81 g/cm^2 was 0.2 SD below the mean for this age group.

Upper gastrointestinal endoscopy revealed esophagitis and duodenitis without ulceration. No biopsy was performed. Therapy was begun with astemizole and omeprazole with prompt relief of skin and gastrointestinal symptoms.

The patient was unable to resume his former work because of the back pain, and he was denied a disability claim because of the preexisting condition of osteoporosis. He has relied on supplies of medication from clinic resources and has been only intermittently on therapy. Every lapse in therapy had been associated with return of symptoms that were again relieved when he resumed therapy.

Lessons Learned

Osteoporosis occurring in men or in premenopausal women should always prompt a search for potentially treatable secondary causes of accelerated bone loss. This is

also the case when the severity of the disease is greater than can be accounted for by the patient's age, sex, and menopausal status. Indexes of disease severity include bone mineral density (BMD) below the reference interval adjusted for age, sex, ethnicity (Z score), or fragility fractures occurring at unusual sites. Often the cause is readily apparent, as in patients receiving chronic corticosteroid therapy, but in many cases the cause is far less obvious, requiring extensive laboratory investigation. This is the case for this 34-year-old man referred for evaluation of osteoporosis after he had sustained three vertebral compression fractures following trivial trauma.

This case illustrates quite dramatically the importance of obtaining a complete history and performing a comprehensive examination. The story of episodic profuse itching was not elicited initially but the diagnosis became very apparent when the patient disrobed and the typical rash of urticaria pigmentosa was observed. The dermatographia, skin biopsy, and elevated urine histamine quickly confirmed the diagnosis.

Systemic mastocytosis is a very uncommon secondary cause of osteoporosis in a young man in whom the diagnosis would not have been considered in the absence of the skin rash. However a recent systematic review [1] and an overview of the association between mast cells and bone remodeling [2] suggest an important role for mast cells in the pathogenesis of osteoporosis in the absence of mastocytosis. Whether it is appropriate to measure histamine in all cases of unexplained male osteoporosis can be debated. It is our recommendation that this be done. A simple clinical maneuver in the absence of other clinical manifestations of mastocytosis is to check for dermatographia in any patient examined for osteoporosis, although this has limited specificity. Chines et al [3] reported none of the four males in their series of 10 osteoporotic patients with systemic mastocytosis had skin lesions, and only two had any systemic manifestations. The report of Brumsen et al [2] of a specific evaluation for systemic mastocytosis in 1110 bone biopsies obtained from osteoporotic subjects revealed 12 cases previously unrecognized. Of the six males, only one had urticaria pigmentosa. Accordingly, it is reasonable to consider the diagnosis of mastocytosis in young males with osteoporosis-related fractures (they infrequently present prior to fracture) and obtain a measure of serum or urine histamine. Treatment should be directed at the underlying disease and may not require specific drug therapy for the osteoporosis. However in a case report by Brumsen et al [4] of a 10-year follow-up of a patient treated with alendronate, the skeletal disease improved while the mast cell activity continued unabated. There is no reason not to simultaneously treat both the underlying disease and the resultant osteoporosis with specific therapy for each.

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Multiple-Choice Questions

1. A 46-year-old man presents with fractures of the 10th and 12th thoracic vertebrae following a simple slip and fall at work. History and physical examination strongly suggests that this patient has previously unrecognized Klinefelter's syndrome. Which of the following laboratory tests is not indicated?

   A. Serum testosterone
   B. Serum gonadotrophins
   C. Urinary histamine
   D. Karyotype

   Answer: C. Male hypogonadism is a frequently overlooked cause of unexplained osteoporosis. In general, the clinical history and physical examination of men presenting with osteoporosis is not given enough attention because most men with gonadal dysfunction do not readily disclose this information. In Klinefelter's syndrome there is often mild gynecomastia, and the testes are small and firm. The karyotype is XXY, the testosterone is low and gonadotrophins elevated.

2. True or false: Skeletal complications of systemic mastocytosis only occur in men.

   Answer: False. Mastocytosis is more common in men but can certainly occur in women. There are many clinical presentations including abdominal pain, hepatomegaly, urticaria pigmentosa, and skeletal pain. The bone lesions may be either sclerotic or osteoporotic, and most patients have both lesions, which is an important clue to the diagnosis. The diagnosis is most easily made if the rash is present; skin biopsy provides a definitive diagnosis.

3. Osteoporosis secondary to systemic mastocytosis only responds to which of the following?

   A. Specific therapy for the mastocytosis
   B. Specific therapy for the osteoporosis
   C. Both of the above
   D. Neither therapeutic approach is effective and only symptomatic therapy should be given

Answer: C. Treatment for systemic mastocytosis should be directed toward the clinical presentation. Histamine blockers are effective for controlling the rash and many of the gastrointestinal symptoms. There is only anecdotal evidence that this helps the skeleton as well. There is no contraindication to specific therapy for osteoporosis. This has been shown to be effective long-term in one well-reported case, but that report also noted that this therapy had no effect on the underlying systemic disease.

Chapter 55
Testosteronoma

Kimberley E. Steele and Martha A. Zeiger

Objectives

1. To describe the evaluation of a patient who presents with hirsutism and virilization
2. To differentiate between a patient with an androgen-secreting tumor of the ovary or of the adrenal gland
3. To describe the indications for and approach to laparoscopic adrenalectomy

Case Presentation

A 42-year-old healthy African-American woman presented to her family physician with a chief complaint of increased facial, back, and abdominal hair. She also complained of acne on her back. All of these signs had been worsening over 1 year prior to presentation. Her medical history was otherwise unremarkable. She denied tobacco use and only consumed alcohol socially. She took no medications and had no known drug allergies. The patient was married with two children, both delivered by cesarean section. She denied any changes in her menstrual cycle. On physical examination, she was a healthy appearing female with notable virilizing features. These included excessive hair on her chin that required shaving, male pattern temporal balding with a receding hairline, excess hair over her mid-abdomen and upper back, as well as cystic acne overlying her shoulders and upper back. On abdominal exam, there were no obvious masses, and she had a well-healed lower midline abdominal incision.

The patient underwent a transvaginal and transabdominal ultrasound, which revealed normal ovaries, the presence of uterine fibroids, and a right adrenal mass that was $3 \times 3.5 \times 4$ cm in size. The following laboratory results were normal: a.m. serum cortisol 6 μg/dL (normal 3–22), a dexamethasone suppression test, serum aldosterone in an upright position 19.3 ng/dL (normal 5–30), plasma renin

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3.3 pg/mL (normal 1–6), 24-hour urine total catecholamines, vanillylmandelic acid (VMA) and metanephrines, dehydroepiandrosterone sulfate (DHEAS) 138 μg/dL (normal 32–240), and estradiol 60 pg/mL (normal 25–75 pg/ml). Abnormal test results included serum total testosterone 271 ng/dL (normal 14–76) and androstenedione 1130 ng/dL (normal <268). A computed tomography (CT) scan of the abdomen and pelvis confirmed a right adrenal mass measuring $3 \times 3.5 \times 4$ cm that was hypodense relative to liver (Fig. 55.1). This was nonspecific and malignancy could not be excluded.

The patient was taken to the operating room and underwent a laparoscopic right adrenalectomy. Intraoperatively, the right adrenal gland was enlarged with a 4 cm firm, fleshy mass (Fig. 55.2). The right adrenal vein was identified, isolated, and divided with endoclips. The right adrenal gland and tumor were removed intact and sent to pathology for permanent section. The patient tolerated the procedure well, and was discharged from the hospital on postoperative day one. Pathology confirmed an adrenal mass displacing normal adrenal tissue peripherally. Final pathology confirmed a right adrenal cortical adenoma measuring 4 cm in greatest diameter and weighing 32.5 g. The tumor was noted to be encapsulated and localized within the adrenal gland (Fig. 55.3a,b). There were no necrotic or mitotic figures identified. Immunostaining was positive for inhibin and melan A, and negative for S-100 protein (Fig. 55.3c–e). The cells had oncocytic features, and the immunostaining pattern was consistent with the diagnosis of a testosteronoma, which is a benign adrenal cortical testosterone-secreting adenoma.

How the Diagnosis Was Made

Hirsutism is defined as excessive terminal (androgen-dependent) hair growth on the face, chest, abdomen, back, and external genitalia in females. Virilization is an exaggeration of masculinizing features in female adults. Virilization is defined by the presence of clitoral enlargement, deepening of the voice, or temporal balding. Virilization in female children results in rapid growth and muscle development, acne, clitoral enlargement, as well as precocious puberty [1].

The initial approach to the woman presenting with hirsutism or other signs of masculinization includes a detailed history to establish the age of onset, the rate of progression of symptoms, medications, family history, and a menstrual history [2]. The differential diagnosis for hirsutism includes familial hirsutism and polycystic ovary syndrome, as well as uncommon etiologies, such as congenital adrenal hyperplasia, Cushing's syndrome, certain medications, and ovarian and adrenal tumors. Patients with familial hirsutism usually present during puberty. Polycystic ovary syndrome and congenital adrenal hyperplasia usually present with a gradual onset of hirsutism [3]. In contrast, androgen-secreting tumors, whether ovarian or adrenal in origin, usually present with a rapid onset of hirsutism [4].

Our patient presented at age 42 and her symptoms occurred over a span of only 1 year. Her symptoms included excessive hair growth in a male distribution, male

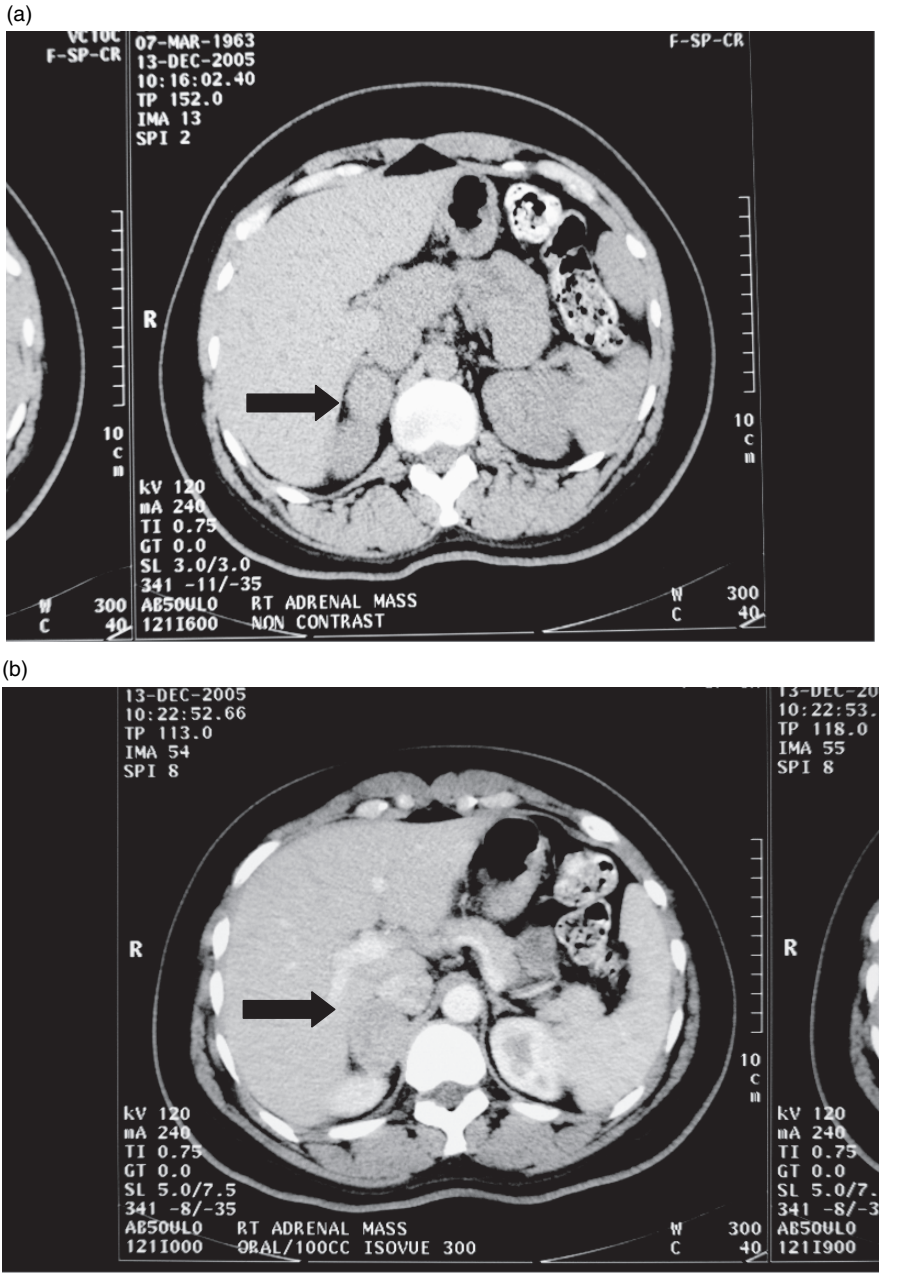

Fig. 55.1 Noncontrast (a) and contrast (b) of the abdomen showing right adrenal mass (arrow)

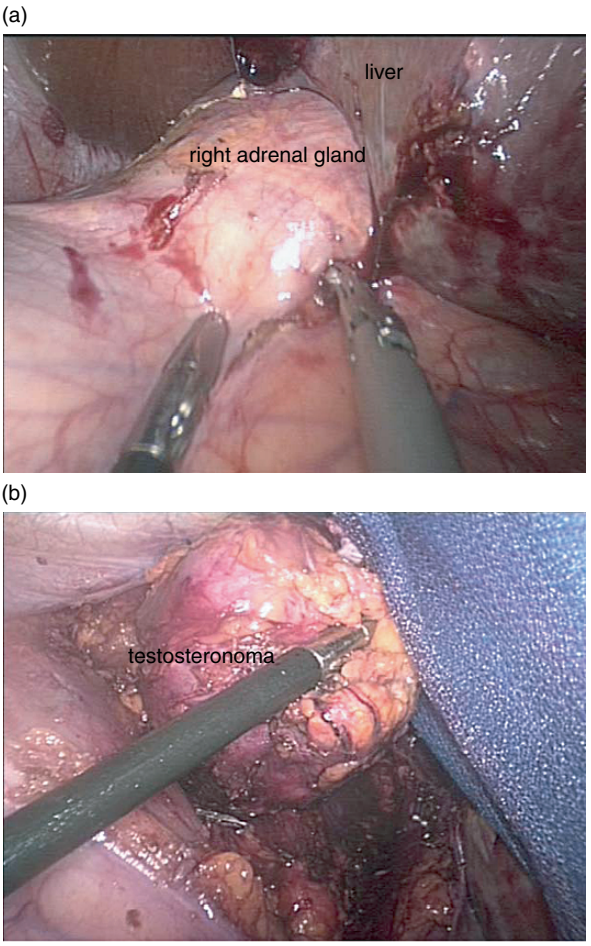

Fig. 55.2 Laparoscopic view of the testosteronoma of the right adrenal gland before (a) and after (b) dissection

pattern baldness, and acne. She was on no medications at the time, and reported no menstrual abnormalities. Thus, she presented with signs and symptoms consistent with virilization and suggestive of an androgen-secreting tumor of ovarian or adrenal origin.

Laboratory and Diagnostic Investigations

Androgen-secreting adrenal tumors can secrete excess testosterone, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), or androstenedione. Ovarian tumors usually do not secrete DHEA or androstenedione. A pure androgen-secreting

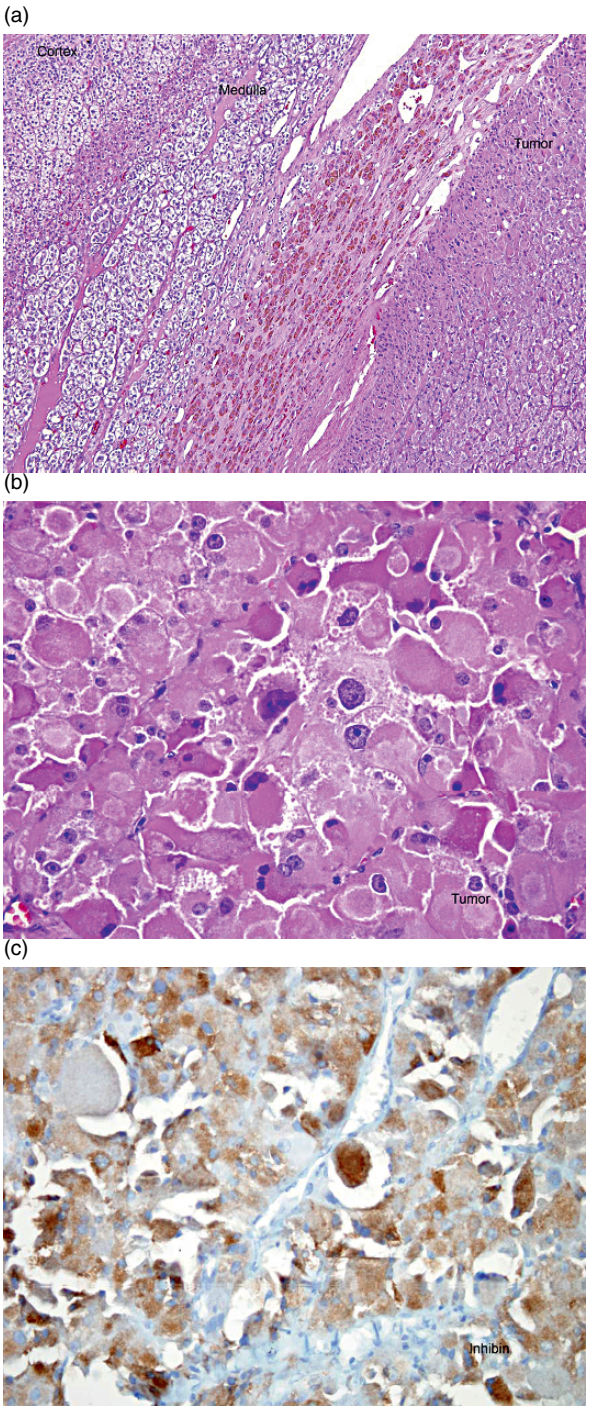

Fig. 55.3 (continued)

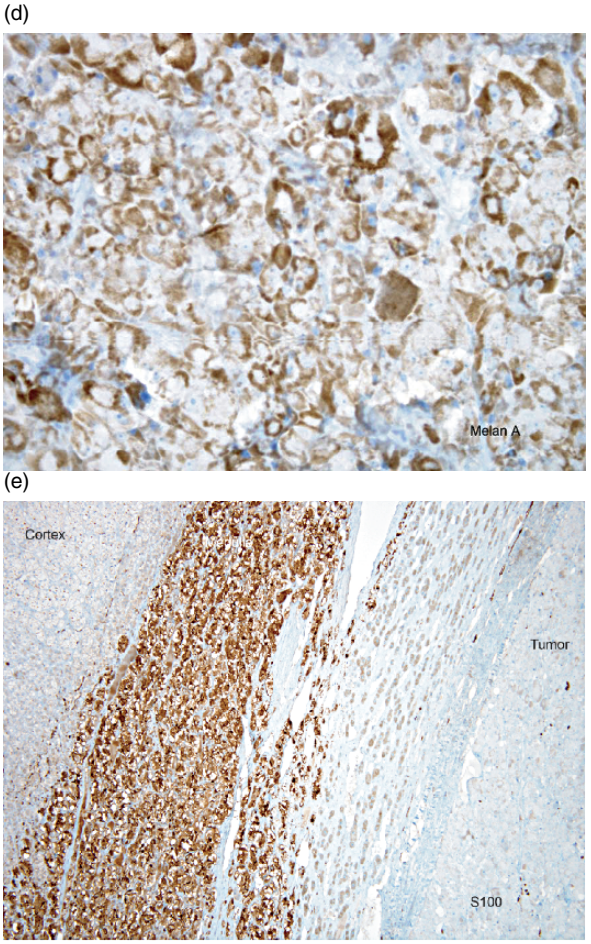

Fig. 55.3 Hematoxylin and eosin stain of testosteronoma and surrounding normal adrenal gland: (a) ×10 magnification; (b) ×40 magnification; (c) positive inhibin immunostaining of testosteronoma (×40 magnification); (d) positive Melan A immunostaining of testosteronoma (×40 magnification).(e) negative S 100 immunostaining of testosteronoma (×10 magnification)

adrenal tumor is usually benign. Adrenal tumors that concomitantly secrete corticosteroids are usually malignant. The most useful diagnostic test to differentiate adrenal from ovarian tumors is abdominal computed tomography (CT) scan.

Our patient was noted to have abnormally high testosterone and androstenedione levels. A pelvic exam and ultrasound were negative for ovarian pathology. Both ultrasound and CT scan of her abdomen and pelvis revealed a right adrenal mass with indeterminate radiographic characteristics. The lesion was less than 5 cm in greatest diameter, and neither adenopathy nor evidence of metastatic disease was seen. Following laparoscopic adrenalectomy, the tumor was pathologically identified as a benign testosterone-secreting adrenal adenoma.

Lessons Learned

1. Virilization implies the presence of hirsutism with exaggerated signs of masculinization, such as male pattern balding, acne, a deepening of the voice, increased muscle mass, breast atrophy, and clitoromegaly. While virilization is less common than hirsutism alone, its recognition is important because it can suggest the presence of an ovarian or adrenal tumor.
2. A rapid onset of hirsutism is concerning with an androgen-secreting ovarian or adrenal tumor. The most useful diagnostic test to differentiate adrenal from ovarian tumors is abdominal and pelvic CT scan.
3. Androgen-secreting adrenal tumors are extremely rare, with less than 100 cases reported in the literature. They are usually benign [5].
4. If there are no contraindications, androgen-secreting adrenal tumors can be removed safely by a laparoscopic approach.

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Multiple-Choice Questions

1. A 52-year-old Caucasian woman presents to your office with a chief complaint of excessive hair growth. Which of the following is least important to consider when obtaining a detailed history?

   A. Age of onset
   B. Progression of symptoms
   C. Tobacco history
   D. Medications
   E. Menstrual history

   Answer: C. There is no evidence to suggest that tobacco has any influence on the signs and symptoms of hirsutism or virilization.

2. A 38-year-old woman of European descent who works as a model is undergoing a yearly physical. On exam she has a clear complexion but excessive hair growth

on her face, lower back, areola, and inner thighs. She has normal menses and is on no medications. Her hirsutism could be secondary to:

A. Familial hirsutism
B. Polycystic ovarian syndrome
C. An ovarian tumor
D. An androgen-producing adrenal tumor
E. All of the above.

Answer: E. A detailed history, physical exam, and specific investigations are needed in order to make the proper diagnosis.

3. A 60-year-old African-American woman is referred to an endocrinologist for virilization. In determining the etiology, the best method to distinguish between an ovarian and an adrenal tumor is:

A. History and physical examination
B. Dexamethasone suppression test
C. Venous sampling
D. Radiologic techniques (abdominal ultrasound or computed tomography)
E. Nuclear medicine scan

Answer: D. Virilization in a female is less common than hirsutism alone; however, its recognition is important because it can suggest the presence of an ovarian or adrenal tumor. The best method to distinguish between the two sources are radiologic techniques including an abdominal and pelvic ultrasound or an abdominal and pelvic CT scan that can image both ovarian and adrenal pathology.

4. A 56-year-old woman who underwent a renal transplant 5 years ago complains to her physician that she has increased hair growth all over her body. Her last menstrual cycle was 2 years ago. Her medications consist only of her immunosuppressive regimen. The most likely cause of her excessive hair growth is:

A. Polycystic ovarian syndrome
B. Cyclosporine
C. An androgen secreting adrenal tumor
E. Familial hirsutism
E. Age.

Answer: B. This renal transplant patient has the classic signs of hirsutism caused by her immunosuppressive medication—cyclosporine.

5. An 18-year-old African-American woman presents to your clinic complaining of acne, facial hair requiring shaving, irregular menses, and temporal balding. She has no other medical or surgical history, and takes only oral contraceptives. Her abdomen is benign with no palpable masses. Her pelvic exam is normal. Laboratory studies show an elevated testosterone of 300 ng/dL, a DHEA level of 1200 mcg/dL, and a normal androstenedione level. Serum cortisol is normal. What is the most likely diagnosis?

A. Polycystic ovarian syndrome
B. An androgen-secreting adrenal tumor
C. An androgen-secreting ovarian tumor
D. A normal 18-year-old woman
E. Cushing's syndrome

Answer: B. This patient has classic signs of virilization. The differential should include an ovarian or adrenal source. She has no palpable pelvic masses on exam. However, the lab tests do reveal abnormally high testosterone and DHEA levels. Though she could have an ovarian source the most likely diagnosis is an androgen-secreting adrenal tumor. The next tests to be ordered should include a pelvic ultrasound and CT scan of the abdomen and pelvis.

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