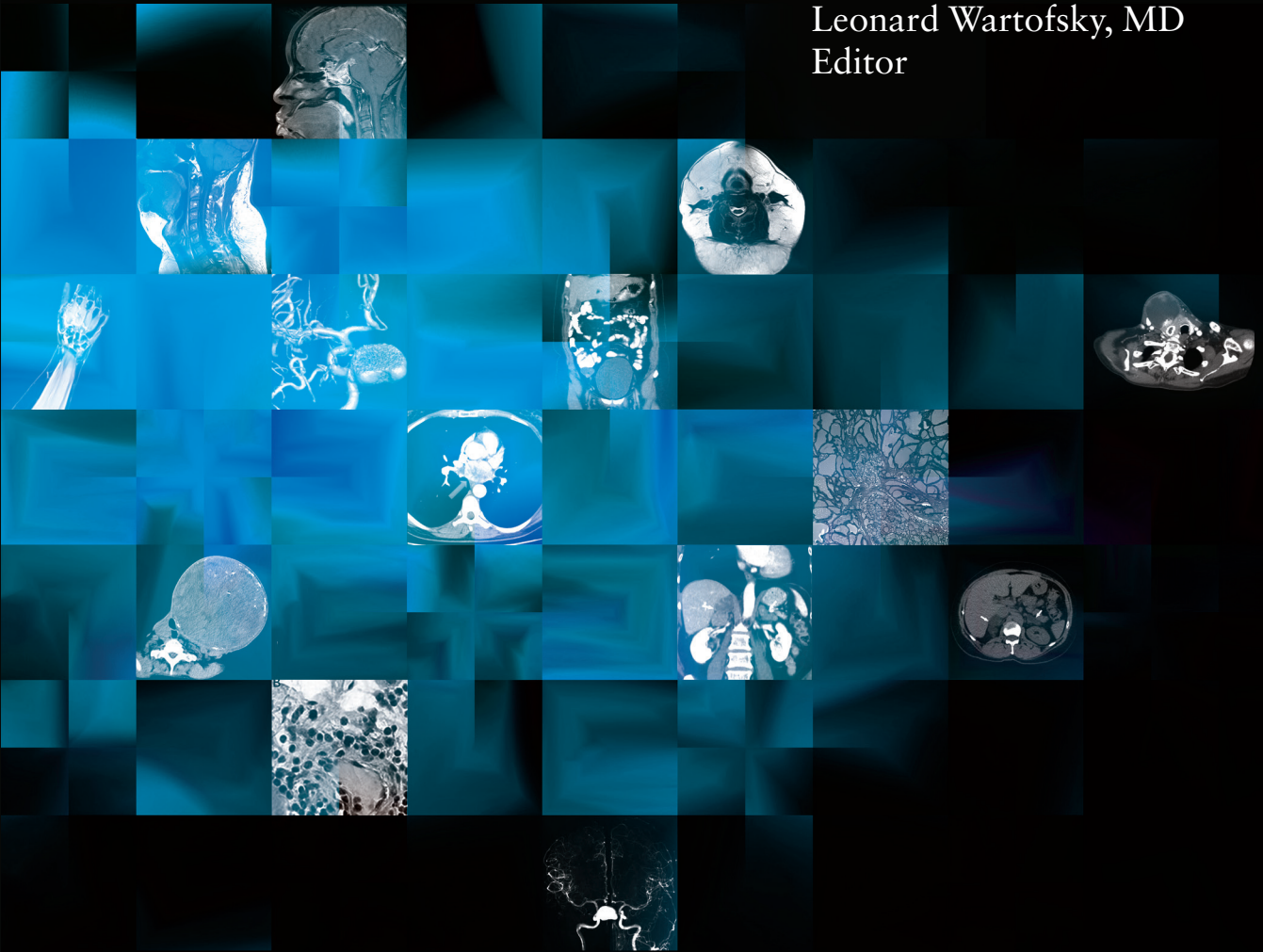


Endocrine Press

Diagnostic Dilemmas

IMAGES IN ENDOCRINOLOGY

Leonard Wartofsky, MD
Editor



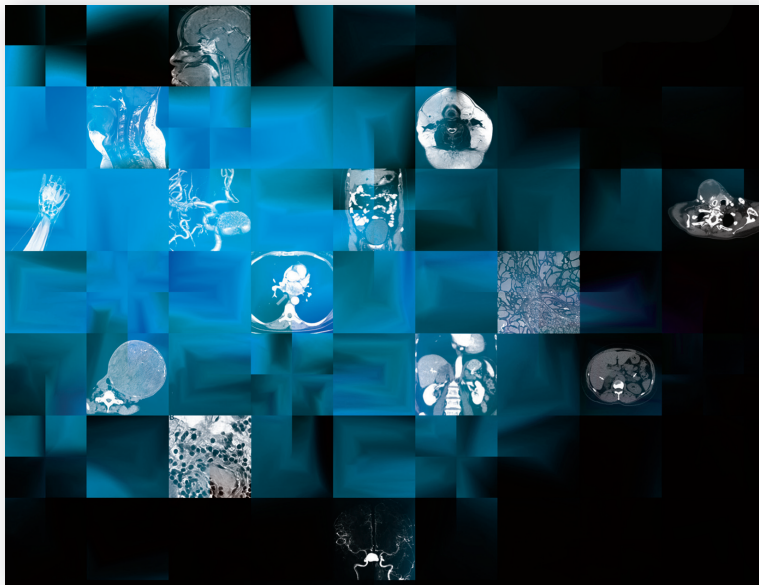
SECOND EDITION



THE
ENDOCRINE
SOCIETY®

Diagnostic Dilemmas

IMAGES IN ENDOCRINOLOGY



Leonard Wartofsky, MD
Editor



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Leonard Wartofsky, MD

DIAGNOSTIC DILEMMAS: IMAGES IN ENDOCRINOLOGY, 2ND EDITION

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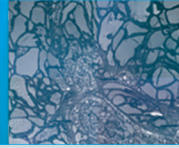
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Foreword



As an arguable generalization, internists have been considered the cognitive specialists in medicine. Indeed, I would take it a step further to characterize endocrinologists as being especially attracted to exercises like puzzles, thoughtful mind-twisting conundrums, and the diagnostic problem solving challenges typical of the CPC.* In this, the totally new second volume of “Diagnostic Dilemmas” from The Endocrine Society, previously published cases from the “Images in Endocrinology” series of *The Journal of Clinical Endocrinology and Metabolism* have been updated and reformatted to challenge and test the reader’s knowledge and ability to reach a diagnosis, in some instances of rare disorders or of unusual presentations of common endocrine disorders.

Each chapter is written to stand alone, and the chapters can be read at any time and in any sequence. This book will never go out of date for you can come back to the cases or “diagnostic dilemmas” again and again to re-test your diagnostic approach and the lessons learned. The chapters are punctuated by various classic reference articles, also from recent issues of the JCEM, including the latest guidelines or clinical review articles relevant to the cases being presented. The authors have been charged with updating their case presentations with expanded discussion where appropriate, updated reference citations, and a current status report on the patient’s outcome when last seen. As the case presentations unfold, you are asked to choose the best approach for each step of the way in multiple choice questions. All in all, this collection of entertaining and educational clinical cases will both engage and delight you. The volume is a perfect accompaniment for a long flight, and it can assuage your guilt while at the pool or beach and also impress that good looking person on the nearby blanket.

Leonard Wartofsky, MD

Editor-in-Chief

The Journal of Clinical Endocrinology and Metabolism

* Clinico-pathologic conference

1

A 28-year-old Woman with a Pain in the Neck

Marek Ruchala, MD, PhD and Ewelina Szczepanek-Parulska, MD, PhD

A 28-year-old woman presented with malaise, pain in the neck radiating to the right ear, and increased temperature up to 38°C. The patient reported an upper respiratory tract infection four weeks earlier. The right lobe of the thyroid gland was firm and painful on palpation, while the left lobe seemed normal in size and consistency. Laboratory tests revealed an increased erythrocyte sedimentation rate and C-reactive protein level; complete blood counts were normal. The TSH level was decreased, the free thyroxine level was slightly elevated, while the free triiodothyronine concentration was normal. Anti-thyroglobulin autoantibodies concentration was increased, while anti-thyroid peroxidase and anti-TSH receptor autoantibodies were normal (Table 1-1).

TABLE 1-1. Laboratory tests performed performed on admission.

Parameter	Value	Unit	Normal range
TSH	0.05	μIU/ml	0.27-4.2
FT4	22.27	pmol/l	11.5-21.0
FT3	6.22	pmol/l	3.95-6.8
ESR	85	mm/h	<12
CRP	92.9	mg/l	<5
TRAb	0.26	μIU/l	<2
TPOAb	10	IU/ml	0-34
TgAb	586	IU/ml	0-115

TSH: thyrotropin, FT4: free thyroxine level, FT3: free triiodothyronine, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TRAb: anti-TSH receptor antibodies, TPOAb: anti-thyroid peroxidase antibodies, TgAb: anti-thyroglobulin antibodies

A conventional ultrasound examination of the thyroid revealed unilateral enlargement of the thyroid, with an hypoechogenic lesion with diffuse margins located in the right lobe (Figure 1-1).

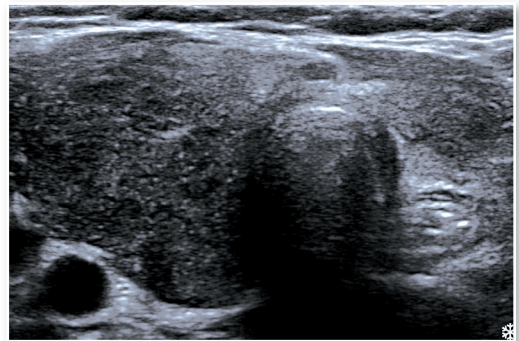


FIG. 1-1. Conventional ultrasonography of the neck (transverse section). Hypoechogenic lesion of ill-defined borders and enlargement of the right thyroid lobe.

Sonoelastography revealed significantly decreased elasticity of the lesion located in the right lobe, while the left lobe was characterized as having normal elastic properties (Figure 1-2).

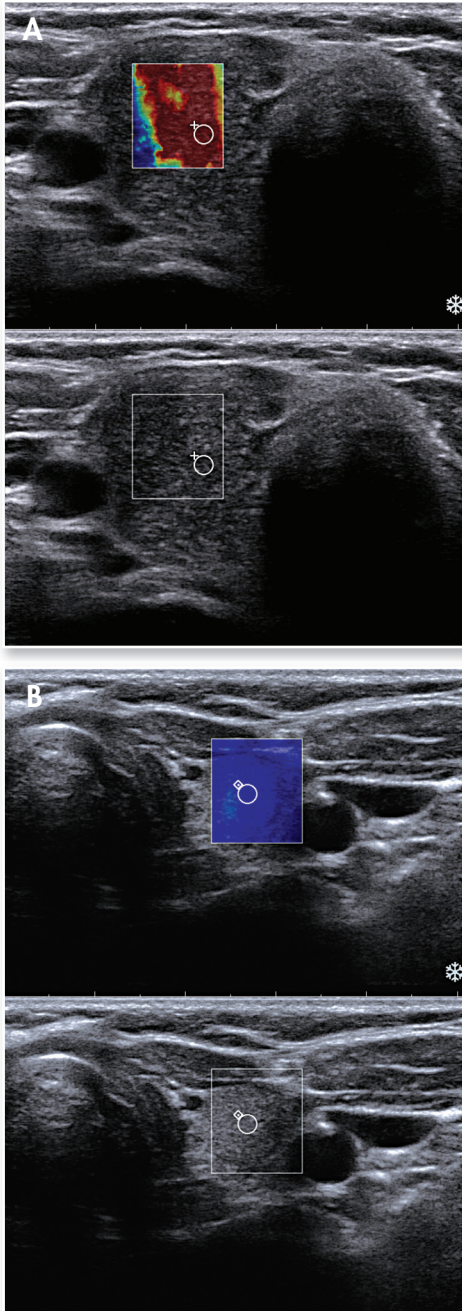


FIG. 1-2. Sonoelastographic examination. Decreased elasticity of the hypoechoic lesion located in the right lobe, presented in red (**A**). The left lobe presents with normal elasticity, expressed in blue (**B**). The pressure that needs to be applied to cause tissue distortion is expressed in kilopascals [kPa; 1 kPa = 0.145 pound per square inch (psi)] and is negatively correlated to tissue elasticity. The examination was performed with the Aixplorer equipment by Supersonic Imagine.

1. THE MOST LIKELY DIAGNOSIS IS:

- a. Thyroid cancer
- b. Acute thyroiditis
- c. Subacute thyroiditis
- d. Chronic thyroiditis
- e. Graves' disease

2. YOUR NEXT STEP IN DIAGNOSIS WOULD BE:

- a. Measurement of serum thyroglobulin level
- b. Measurement of serum calcitonin level
- c. Fine-needle aspiration biopsy
- d. Thyroid scintiscan
- e. The available information is sufficient to establish diagnosis

Fine-needle aspiration biopsy of the lesion in the right thyroid lobe was performed. On cytological examination, blood, inflammatory cells including multiple lymphocytes, histiocytes, a few single multinucleated giant cells and several groups of normal follicular cells were identified.

3. YOUR INTERPRETATION OF CYTOLOGICAL FINDINGS WOULD BE:

- a. Thyroid cancer
- b. Acute thyroiditis
- c. Subacute thyroiditis
- d. Chronic thyroiditis
- e. Graves' disease

Diagnosis

Subacute Granulomatous Thyroiditis.

Discussion

The cytological diagnosis was of a benign lesion consistent with subacute granulomatous thyroiditis. The patient

received NSAID (ibuprofen orally) at a daily dose of 1.0 gm. She took the medication for two days, but did not tolerate the therapy well and observed only minor improvement of symptoms. Hence, oral therapy with prednisone was initiated at a dose of 40 mg daily, gradually tapering by 5 mg every week. Only two days following the initiation of the therapy, gradual relief of symptoms was observed. Four weeks following the initiation of the therapy, the patient underwent repeat thyroid ultrasound examination and sonoelastography as well as laboratory tests. The patient reported almost complete remission of symptoms, with no malaise, normal temperature and no pain in the neck. Improvement in blood parameters was observed (TSH 0.064 μ IU/ml, FT4 19.23 pmol/l, ESR 34 mm/h, CRP 8 mg/l) (Figure 1-3).

On another follow-up visit, 10 weeks following the initiation of the therapy, the patient presented signs of complete clinical and biochemical remission (TSH 0.4 μ IU/

ml, ESR 6 mm/h, CRP 0.6 mg/l).

Clinically SAT often presents with decreased elasticity of the gland on physical examination, which is presumably associated with inflammatory infiltration of thyroid parenchyma. Patients may complain about malaise, fever and pain in the neck, radiating to the mandible, ear or occiput. Symptoms are often preceded by a viral infection, which may occur several weeks earlier. On conventional ultrasound examination, SAT presents with enlargement of the affected lobe (or lobes) in antero-posterior diameter, ill-defined regions of decreased echogenicity presenting different size and shapes with hypovascularization on Color Doppler examination. In laboratory tests, typical findings include an elevated ESR and CRP. Initial phase may be associated with destruction of thyroid follicles, which may result in transient clinical or subclinical thyrotoxicosis. The most typical course is to remission with no residual changes, although recurrences

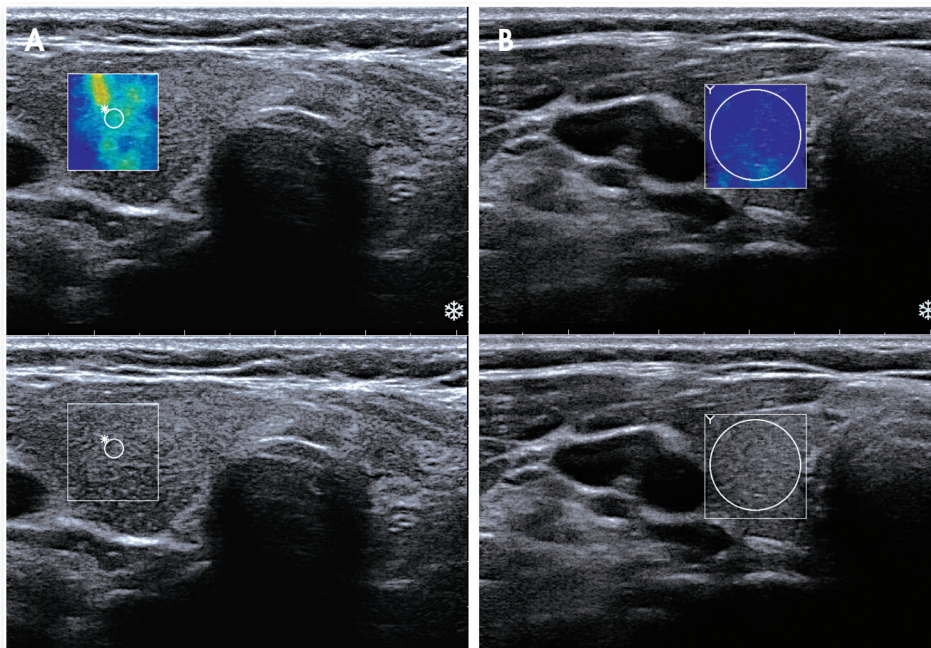


FIG. 1-3. Conventional ultrasonography and sonoelastography four weeks (A) and ten weeks (B) following the initiation of prednisone therapy.

are possible. Clinical examination, laboratory tests and conventional ultrasonography usually provide enough data to establish the diagnosis. However, sometimes additional procedures, *i.e.*, scintiscan, fine-needle aspiration biopsy, or newly applied sonoelastography, will be helpful.

Sonoelastography is a new ultrasound method which allows an unbiased and quantitative estimation of tissue elasticity (1). This technique has been used primarily for diagnostics of thyroid nodules, as decreased elasticity of a nodule is associated with increased risk of malignancy (2). However, it turned out to be useful also in assessment of patients with thyroiditis. The first report on potential utility of sonoelastography in SAT was published by Ruchala *et al.* in the JCEM in 2011 (3). A subsequent study on a larger group of subjects with SAT (18 patients) aimed to prospectively evaluate the sonoelastographic picture of the disease at baseline and during follow-up until full remission was achieved. In that study, SAT was found to be associated with profoundly decreased elasticity in the initial phase of the disease that is restored back to normal after remission (4).

Sonoelastography is becoming more widely used, is easy to perform and takes no more than a few more minutes longer than conventional ultrasonography. The technique has clear advantage over palpation, offering visualization of the degree of tissue stiffness in the dorsal parts of the thyroid, and the opportunity of monitoring evolution over time, with normalization of elastic properties being a marker of remission. These observations could be useful for more precise estimation of the best time point for reduction of medication dose. Moreover, sonoelastography might be useful in selection of potential target areas for biopsy, if indicated, and might be

helpful in patients with minimal changes on conventional ultrasonography. However, the changes in elasticity induced by SAT are not specific. Markedly decreased elasticity of the thyroid was observed in acute thyroiditis, Riedel thyroiditis and thyroid cancer (2, 4, 5), while autoimmune thyroid disease was found to be associated with minimally decreased elasticity of the gland (6, 7). Moreover, a weak association of thyroid elasticity with functional status has been observed (7). Sporea *et al.* also found subtle, but significant differences in thyroid elastic properties between Graves' disease and chronic autoimmune thyroiditis (6). However, the wide range of the results in both groups makes sonoelastography not an optimal modality for differentiation. Magri *et al.* reported that the degree of thyroid tissue stiffness positively correlates with anti-thyroid peroxidase autoantibody concentration (8). Decreased elasticity of the thyroid is positively linked to progression of Hashimoto thyroiditis and is reflected by the grade of fibrosis as thyroid stiffness was found to be higher in subjects with chronic autoimmune thyroiditis requiring L-thyroxin substitution than in euthyroid patients (8). Xie *et al.* also found the elasticity in patients with SAT to be decreased, similar to thyroid malignancy. As a consequence, sonoelastography may help differentiate between SAT and benign goiter, but will not predictably distinguish SAT from thyroid cancer (9).

Finally, it is important to note that changes of thyroid elasticity in thyroiditis might influence the stiffness estimation of coexisting thyroid nodules. It was reported that the presence of chronic autoimmune thyroiditis does not affect the interpretation of the sonoelastographic picture of thyroid nodules to a significant extent (8). However, it is probable that subacute or acute thyroiditis will more significantly disturb the elastic properties of the thyroid

parenchyma than will CAT and thereby affect the estimated nodule elasticity (4). Though studies on larger groups of subjects with SAT and concomitant focal lesions need to be performed, it seems prudent to delay assessment of the nodule elasticity until a complete remission from SAT or AT is achieved.

In conclusion, the initial phase of SAT is characteristically seen to have decreased elasticity of the affected region of the thyroid. Elastic properties of the gland parenchyma are restored to normal with remission. Thus, sonoelastography might be helpful in the initial diagnostic and differential diagnostic evaluation of the patient with neck pain and a thyroid mass, as well as for monitoring the course of the disease, especially in patients with a non-classical course.

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Answers:

- Question 1. c
Question 2. e
Question 3. c

2

A 20-year-old Woman with Hyperthyroidism

N. Stathatos, MD, R. Gaz, MD, P. M. Sadow, MD, D. S. Ross, MD, and G. H. Daniels, MD

A 20-year-old woman presented with a history of heat intolerance, tremors, and palpitations. At presentation, her thyroid gland was not enlarged and there were no palpable thyroid nodules. A 2-cm left, level III, cervical lymph node was palpated. Thyroid function tests confirmed hyperthyroidism due to Graves' disease: Thyroid-Stimulating Immunoglobulin (TSI), 4.7 IU/liter (normal, <1.3 IU/liter); Thyrotropin-Binding Inhibitory Immunoglobulin (TBII), 27 IU/liter (normal, <1.37 IU/liter), TSH < 0.01 μ IU/mL (normal, 0.40 - 5.00), T3 = 713 ng/dL (normal, 60–181), T4 = 14.7 μ g/dL (normal, 4.5–10.9).

1. THE NEXT STEP IN YOUR MANAGEMENT WOULD BE:

- Radioactive iodine treatment
- Neck ultrasound
- Initiation of methimazole treatment
- Surgical referral

An ultrasound of the neck revealed a heterogeneous, hypoechoic thyroid gland without any discrete nodules (Figure 2-1A and 2-1B). Blood flow was significantly increased throughout the thyroid gland (Figure 2-1C). An abnormal appearing left 2.0 x 1.8 x 1.4 cm lymph node (Figure 2-1D) in the region of the palpable lymph node was seen.

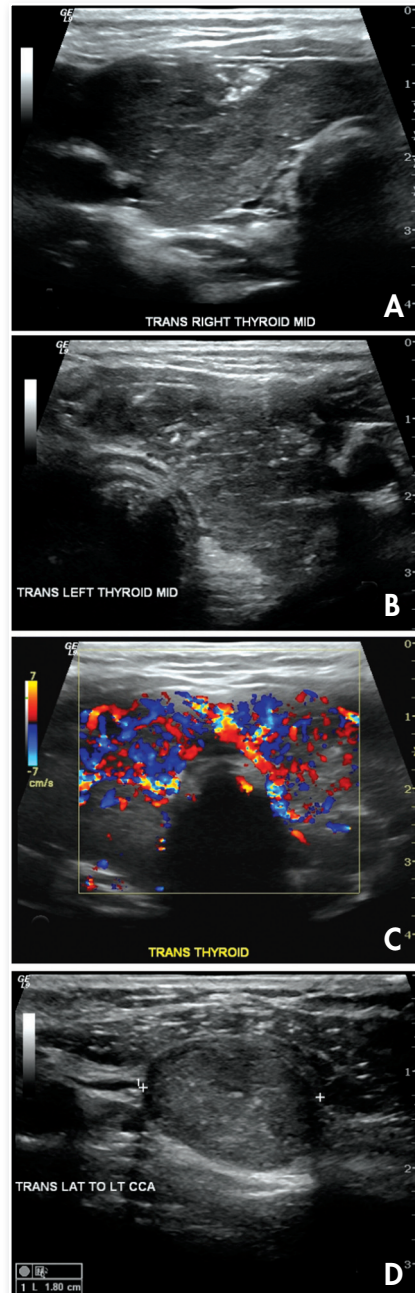


FIG. 2-1. **A.** Right lobe, **B.** Left lobe, **C.** Doppler flow, **D.** Left lateral level III lymph node.

2. BASED ON THE AVAILABLE INFORMATION, THE MOST LIKELY DIAGNOSIS IS:

- a. Graves' disease
- b. Thyroid lymphoma
- c. Thyroid cancer
- d. Graves' disease with concomitant thyroid cancer

A fine-needle aspiration of the lymph node revealed papillary thyroid cancer. Methimazole was prescribed. When the patient was euthyroid, a total thyroidectomy, a central neck and a left lateral neck dissection were performed. The final pathology revealed papillary thyroid carcinoma involving both lobes and the isthmus with a mixed growth pattern including papillary, follicular, and solid types. Several cervical lymph nodes were also found to be positive for metastatic thyroid cancer: 2 of 2 in level VI (central compartment), 3 of 11 in the left level II and 5 of 16 in the left levels III and IV. Diffuse hyperplasia, consistent with Graves' disease was also noted (Figure 2-2).

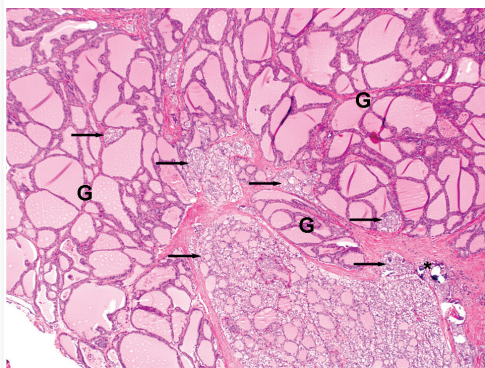


FIG. 2-2. Final histology showing classical papillary thyroid carcinoma (arrows) and papillary hyperplasia of the remaining parenchyma (G) (compatible with Graves' disease).

Two months after withdrawal of thyroid hormone, the patient's TSH was 0.09 $\mu\text{U}/\text{ml}$, free T4 was 0.6 ng/dl (7.72 pmol/liter;

normal = 0.9–1.8 ng/dl), and the total T3 was 77 ng/dl (1.18 nmol/liter; normal = 60–181 ng/dl).

3. GIVEN THE SUPPRESSED TSH, YOU WOULD:

- a. Tell the patient she must not have stopped taking her thyroid hormone
- b. Give recombinant human TSH to raise the serum TSH
- c. Tell the patient to remain off thyroid hormone for another 4 weeks
- d. Give the scanning dose of ^{131}I anyway

Twenty-four hours after 3 mCi ^{131}I , the overall uptake was 40%, with 4.38% uptake in the thyroid bed (Figure 2-3, arrow 1), mediastinal nodes (arrow 2), and diffusely in her lungs (arrow 3, right lung: 13.8%, left lung: 9.7%).

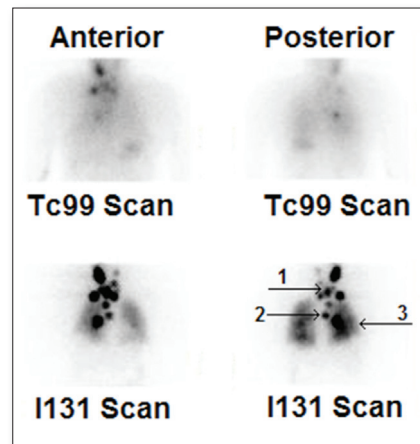


FIG. 2-3. Tc99scan obtained for localization. Arrow 1, Neck uptake; arrow 2, mediastinal metastasis; and arrow 3, pulmonary metastasis.

Based on the above scan, the patient was treated with 125 mCi of ^{131}I . Her thyroglobulin (Tg) was 163 ng/ml. Although technically this is a serum Tg with thyroid hormone suppression (as defined by the suppressed TSH), in fact, it is the equivalent of a Tg stimulated by

titers of TSH receptor antibodies. She was subsequently treated with levothyroxine in suppressive doses.

Diagnosis

Graves' Disease and Thyroid Cancer.

Discussion

There are two important questions concerning the association of Graves' disease and thyroid cancer: 1) Is the prevalence of thyroid cancer increased in patients with Graves' disease?; 2) Do TSH receptor antibodies stimulate thyroid cancer growth and function?

The literature concerning the prevalence of thyroid cancer in Graves' disease does not permit a firm conclusion. The reported prevalence of thyroid cancer in patients with Graves' disease ranges from 0.15 to 15% (1). It is likely that the different patient populations studied, whether or not ultrasonography was routinely used, and the choice of therapy all would influence the results of these studies. Given the relatively high prevalence of incidental papillary microcarcinomas, it is reasonable to assume that the more patients undergo surgery, the more likely one is to find papillary thyroid carcinoma. Graves' patients with thyroid nodules reportedly have a higher prevalence of thyroid cancer (2). This also likely reflects a selection bias, in that patients with thyroid nodules are more likely to undergo FNAB or have surgery recommended as an initial therapeutic option.

Well-differentiated thyroid carcinomas commonly express TSH receptors. Do TSH receptor antibodies cause these cancers to become more aggressive? Incidental papillary thyroid microcarcinoma in Graves' disease appears to have an excellent prognosis (3) whereas larger papillary thyroid carcinomas are reported to have a worse prognosis in Graves' disease (4). Whether TRAB

actually contribute to the aggressiveness of these cancers is uncertain, but stimulation of radioactive iodine uptake in the cancers has previously been shown (5).

The TSH remained suppressed in our patient despite the presence of hypothyroidism as determined by her free T4 concentration. The delayed recovery of a suppressed serum TSH after long-standing hyperthyroidism is well known (6). The surprise in our patient was the intense uptake in the lungs and mediastinal nodes despite a suppressed serum TSH. This stimulation is due to the presence of stimulatory TSH receptor antibodies, which increased iodine uptake by the papillary thyroid carcinoma (5). Although these stimulatory antibodies were beneficial to this patient by permitting radioactive iodine therapy despite a suppressed serum TSH, they have the potential to be harmful by stimulating thyroid cancer growth via TSH receptor stimulation (5). A fully suppressed serum TSH seems to confer a survival in stage III and IV well-differentiated thyroid cancer (7). In our patient, TSH receptor antibodies are the equivalent of elevated serum TSH. There is currently no way to inhibit the production of TSH receptor antibodies although small molecule inhibitors are being developed (8).

Clinical Course

The patient received a second 125 mCi dose of ¹³¹I after dosimetry, 1 year after her original treatment. Interestingly, the titers of the thyrotropin receptor antibodies have decreased (TSI, Figure 2-4A) or disappeared (TBII, Figure 2-4B), although the clinical significance of this finding is not clear.

Subsequent Follow-up on the Patient

Although she still has detectable disease in the neck and the lungs, she has responded well with significantly reduced uptake in

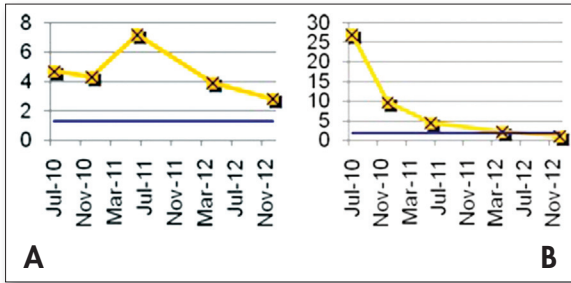


FIG. 2-4. **A.** TSI titers, **B.** TBII titers over time.

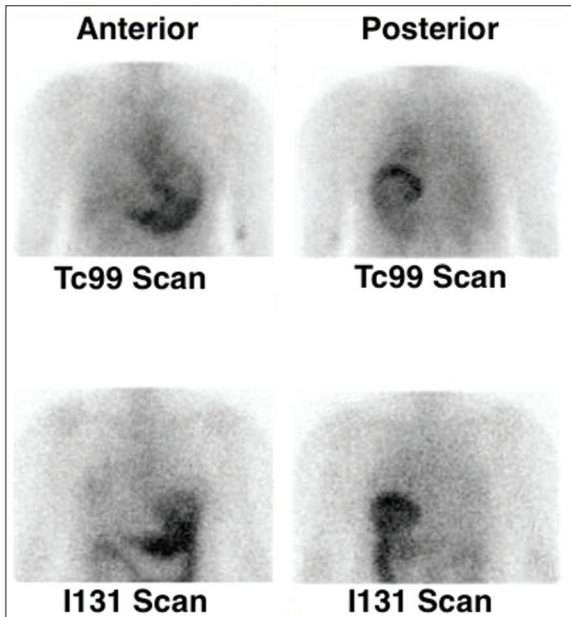


FIG. 2-5: Diagnostic whole body scan (10 mCi of ¹³¹I) 1 year after the second treatment with radioactive iodine.

all known involved areas, as evidenced by a 10 mCi whole body scan (higher scanning dose used to maximize visualization of metastatic disease) 1 year after her second treatment: Thyroid bed: 0.12%, right lung: 1.8%, left lung: 1.3% (Figure 2-5). Her stimulated thyroglobulin was 8.8 ng/dL at that time. She is now scheduled for a third I131 treatment.

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Answers:

- Question 1. b
 Question 2. d
 Question 3. d

3

An 80-year-old Woman with a Giant Goiter

Léa M. Z. Maciel, MD, Patrícia K. R. Magalhães, MD, Edson G. Soares, MD, Patrícia M. Gomes, MD, Francisco V. Mello Filho, MD, Luiz C. Conti-Freitas, MD

An 80-year-old woman was referred with a 40-year history of a slowly enlarging anterior neck mass. She had no compressive symptoms, history of trauma, previous fine-needle aspiration biopsy (FNA) or other neck procedures. There was no family history of thyroid diseases. Physical examination showed a giant (circumference: 50 cm) painless goiter (Figure 3-1). Serum thyrotropin (TSH = 1.97 mIU/L; normal range= 0.4-4.0) and free thyroxine (Free T4 = 18.0 pmol/L; normal range=10.3-24.5) levels were normal and no antithyroid antibodies were detected. Cervical ultrasound revealed a right thyroid lobe with normal size and a heterogeneous thyroid mass measuring approximately 15.0 x 16.5 x 18.0 cm (volume = 2347 cm³), with calcifications in the left thyroid lobe. Computed tomography (Figure 3-2) showed a large

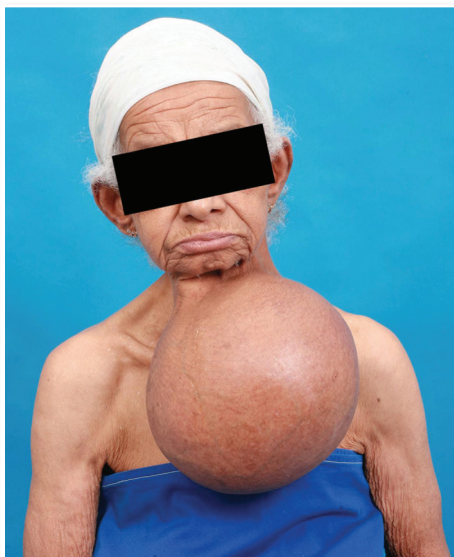


FIG. 3-1. Picture of the patient.



FIG. 3-2. Axial non-contrast-enhanced computed tomography of the neck.

solid mass (16 x 16 x 17 cm) with multiple peripheral calcifications in the left lobe of the thyroid, with deviation of the trachea and cervical structures to the right side. No abnormal findings in the right lobe of the thyroid were found, and surrounding lymph nodes were not detected.

1. THE MOST LIKELY DIAGNOSIS IS:

- Endemic Goiter
- Congenital Hypothyroidism due to Dysmorphogenesis
- Papillary Thyroid Carcinoma
- Thyroid Hemangioma
- Thyroid Lymphoma

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Chest x-ray
- Radioiodine scan
- Serum thyroglobulin
- Fine needle aspiration
- None of above

A fine-needle aspiration biopsy guided by ultrasound of the left thyroid lobe mass was performed. Macroscopically, the aspiration yielded hemorrhagic smears. Microscopically, there was a low cellularity, consisting of macrophages and occasional lymphocytes, amid widely hemorrhagic background. Thus, a cytologic examination was inconclusive.

3. THE BEST APPROACH AT THIS TIME WOULD BE:

- a. Magnetic resonance imaging (MRI)
- b. Single-photon emission computed tomography (SPECT)
- c. Digital subtraction angiography (DSA)
- d. Red blood cell (RBC) scan
- e. Any of the above

MRI, SPECT, DSA and RBC scan are useful in the differential diagnosis of hemangioma. However, biopsy is required to make a definitive diagnosis.

A left-side hemithyroidectomy was performed and a 22 x 21 x 17 cm encapsulated mass weighing 2,800g with foci of hemorrhage and calcification was removed (Figure 3-3A). Histological analysis showed extensive ischemic necrosis, with sparse calcification. In areas of viable tissue, there was a benign vascular lesion formed by large and congested vessels covered with flat endothelium without atypia. Some thyroid follicles were observed only in the periphery of the nodule (Figure 3-3 B and C). The definitive diagnosis of a cavernous hemangioma of the thyroid was made.

Diagnosis

Primary Cavernous Hemangioma of Thyroid.

Discussion

Hemangiomas are an extremely rare category of thyroid nodules which often escape preoperative diagnosis. In most

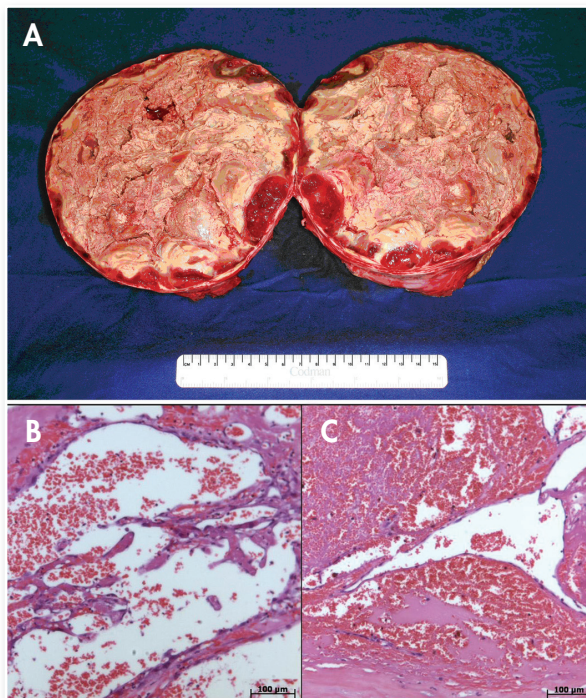


FIG. 3-3. **A**, Macroscopic view of the thyroid hemangioma. **B** and **C**, Histology: benign encapsulated vascular tumor consisting of irregular, dilated, and anastomosed vascular structures of thin wall covered with flattened epithelium. (hematoxylin and eosin x 100).

TABLE 3-1. Demographic and clinical characteristics of patients with thyroid hemangioma.

Patient	Country	Sex	Age at diagnosis (years)	Location (thyroid lobe)	Size (cm)	Reference
1	USA	M	56	Left	7.5 x 3 x 2	Pickleman <i>et al.</i> , 1975 (4)
2	India	M	53	Right	6 x 3.5	Pendse & Porwal, 1998 (5)
3	India	M	53	Right	4 x 4	Kumar <i>et al.</i> , 2000 (2)
4	Spain	F	48	Left	5 x 4	Rios <i>et al.</i> , 2001 (6)
5	Spain	F	63	Left	5 x 3	Rios <i>et al.</i> , 2001 (6)
6	Japan	M	21	Right	5.5 x 3 x 2	Kano <i>et al.</i> , 2005 (7)
7	Korea	M	66	Left	17 x 16.5	Lee <i>et al.</i> , 2007 (8)
8	India	M	25	Left	4.9 x 4.4	Datta <i>et al.</i> , 2008 (9)
9	Greece	M	78	Right	4 x 4	Michalopoulos <i>et al.</i> , 2010 (10)
10	Switzerland	F	84	Left	4	Gutzeit <i>et al.</i> , 2011 (11)
11	Brazil	F	80	Left	22 x 21 x 17	Maciel <i>et al.</i> , 2011 (12)

F: female, M: male

cases, a hemangioma of the thyroid gland is secondary to trauma or fine-needle aspiration biopsy and they may be considered as a development of vascular proliferation which follows the organization of a hematoma (1). Primary thyroid hemangiomas are infrequent and they are a developmental anomaly resulting from the inability of the angioblastic mesenchyma to form canals (2). These benign congenital vascular malformations are usually asymptomatic neck masses, but can cause compressive symptoms. The differential diagnosis is quite difficult and is based on histological findings. On ultrasound examination, the hemangioma presents as a hypoechoic area within the thyroid gland, without specific, distinct characteristics. There are also no pathognomonic findings on computed tomography scan. Even experienced radiologists may find this lesion difficult to diagnose. Coarse calcifications and phlebolith, when present, are suggested as a reliable sign of the presence of a hemangioma (3), but calcifications may also be present in benign goiters and in

malignancy. More specific studies such as magnetic resonance imaging, single photon angiography and red blood cell scans may improve diagnostic ability. In most cases, cytological analysis of material collected by fine-needle aspiration shows only a large amount of blood, resulting in an inconclusive diagnosis. At present, most of the reported cases had the diagnosis confirmed only after pathologic examination of a surgical specimen. Surgical resection is indicated when there are compressive symptoms or with a specific diagnosis. There are only 11 cases of primary thyroid hemangioma reported in the literature. These cases have had male predominance with variable age at diagnosis and clinical features (Table 3-1).

In conclusion, this is a description of a giant primary cavernous hemangioma of the thyroid gland, probably the largest one described so far.

Subsequent Follow-up on the Patient

The patient had no complications after surgery, with normal thyroid function, and three years later remains asymptomatic.

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Answers

Question 1. d

Question 2. d

Question 3. e

4

A 63-year-old Woman with a Painful Goiter

Fritz-Line Vélayoudom-Céphise, MD, PhD

A 63-year-old woman was admitted for a painful goiter. She had no medical history, except a renal carcinoma. She developed pulmonary metastases 2 years after diagnosis. Administration of sunitinib (50 mg/d) included six repeated cycles with 4 weeks of treatment followed by 2 weeks without treatment. A swollen and painful neck appeared 5 months after initiation of treatment with sunitinib. The patient had no signs of thyrotoxicosis but had an irregular goiter. TSH was suppressed (0.06 mU/liter; normal, 0.27–4.20), with elevated free T₄ (131 pmol/liter; normal, 12.0–22.0) and free T₃ (9.2 pmol/liter; normal, 3.5–6.5).

1. THE MOST LIKELY DIAGNOSIS IS:

- Diffuse lipomatosis of the thyroid
- Graves' disease
- Thyroiditis
- Thyroid lymphoma
- Hashimoto thyroiditis

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- No further exploration
- Antithyroid antibodies
- Thyroid ultrasonography
- Contrast computed tomography
- (¹²³I) scintigraphy

Antithyroid antibodies were absent. C-reactive protein level was 3.27 mg/ml (normal, <5), sedimentation rate was 35 mm/h (normal, 0–20), and thyroglobulin level was 42.3 ng/ml (normal, 2.5–30). Ultrasonography confirmed goiter (65 cm³) and precise structure of the thyroid (Figure 4-1).

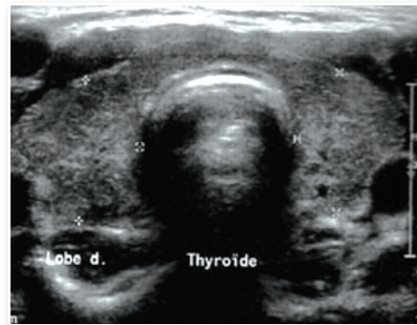


FIG. 4-1. Ultrasonography showed heterogeneous thyroid compatible with thyroiditis.

3. YOUR INTERPRETATION OF THE IMAGING FINDINGS:

- Hashimoto thyroiditis
- Amyloidosis of the thyroid
- Lipomatosis of the thyroid
- Autoimmune thyroiditis
- Destructive thyroiditis linked to sunitinib

Neck and chest contrast computed tomography (CT) was performed for the assessment of kidney cancer and revealed an unusual aspect of the thyroid [36 Hounsfield unit (HU) density] (Figure 4-2).

Beta-blockers were started. After 10 days, free T₄ and free T₃ decreased (7.91 and 1.78 pmol/liter, respectively),

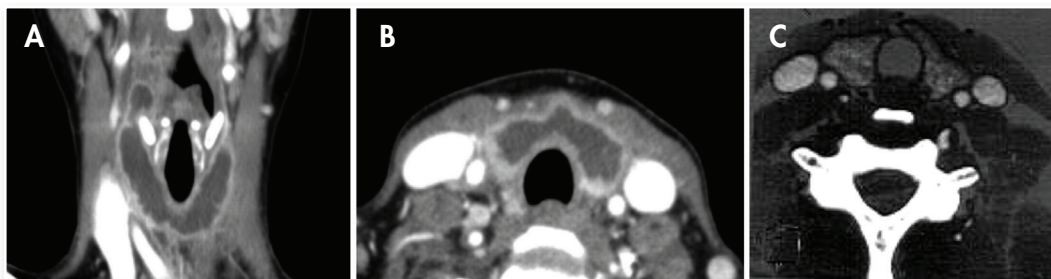


FIG. 4-2. CT scan revealed hypodensity in the central area of thyroid contrasting with normal aspect of the thyroid around **A**: coronal cut of thyroid and **B**: axial cut of thyroid). Density of normal thyroid is high due to rich content of iodine (70 HU) and increases up to 100 HU after contrast **C**: a contrast-enhanced CT normal thyroid gland from a different patient).

TSH increased (17.31 mU/liter), thyroid peroxidase antibodies became positive (81 U/ml; normal, <60), sedimentation rate was 24 mm/h, and thyroglobulin was 27.9 ng/ml.

Ultrasonography of the thyroid was unchanged. L-Thyroxine was required (75 μ g/d) and normalized thyroid function.

Diagnosis

Destructive Thyroiditis Linked to Sunitinib.

Discussion

Sunitinib is a tyrosine kinase inhibitor with antiangiogenic and antiproliferative effects (1). This molecule is one of the first-line treatments of advanced renal carcinoma (2). Several reported side effects of sunitinib have involved thyroid dysfunction, but the mechanisms remain unclear.

Hyperthyroidism has been reported in 25% of patients preceding hypothyroidism and associated with shrinkage of thyroid volume (3-5).

Several hypotheses have been discussed to explain thyroid dysfunction after sunitinib treatment: the blocking of iodine uptake (6), a destructive thyroiditis with follicular cells apoptosis (7), the inhibition of thyroid peroxidase activity (1) and most recently, alterations in T_4/T_3 metabolism

and thyroid capillary regression (8). Several reviews have suggested that an increased thyroglobulin level, decreased iodine uptake and cytological data point to a destructive thyroiditis without autoimmune mechanisms (6, 9, 10).

Overall, the availability of thyroid imaging in this situation remains scant, especially during the phase of thyrotoxicosis. In our patient's presentation, a thyroid cytotoxic or ischemic effect of sunitinib could explain the transient thyrotoxicosis and the CT scan appearance of the thyroid. This situation was reported for the first time by Velayoudom-Cephise *et al* in the JCEM (11) from which the above case has been abstracted. The authors suggest that early and continuous monitoring of patients treated with sunitinib is warranted to detect and avoid thyroid dysfunction. Conceivably, CT imaging could help to define the mechanism of the thyroiditis.

Subsequent Follow-up on the Patient

When last seen in 2012, the patient adhered to a regimen of thyroxine treatment and thyroid function was preserved, with a normal TSH of 1.74 mU/liter, and decreased thyroid peroxidase antibodies (38 U/ml). The thyroid gland was reduced on ultrasonography and poorly visualized on CT imaging (Figure 4-3).

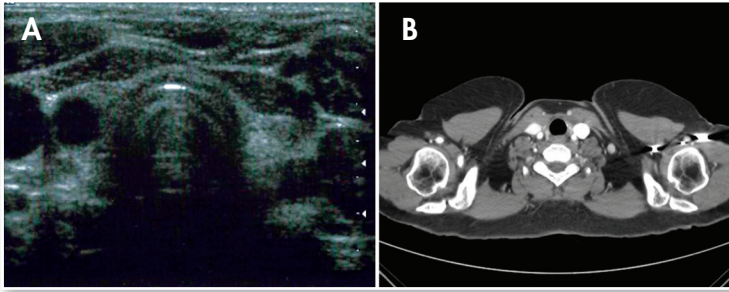


FIG. 4-3. **A:** Thyroid ultrasonography performed 2 years after diagnosis showing a shrinkage of thyroid volume. **B:** CT showing a poorly visualized thyroid gland.

Acknowledgments

Cédric Sénéchal from the department of Urology (University Hospital of Pointe-à-Pitre), Louis Thionville and Maud Kawamura, radiologists, for the picture of the normal thyroid CT scan and the monitoring pictures of the patient.

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Answers:

- Question 1. c
 Question 2. b, c
 Question 3. e

5

A Child with a Lump in the Neck

Maria Segni, MD

A 4-year-old girl came to our clinic with the complaint of a lump of more than 2 cm in the left side of the neck. (Figure 5-1A)



FIG. 5-1A. The neck at first observation.

1. THE MOST LIKELY DIAGNOSIS IS:

- Congenital mass (*i.e.* branchial cleft cyst)
- Inflammatory mass (*i.e.*, Bacterial/viral/mycobacterial *etc*)
- A benign neoplasm (*i.e.* lipoma, neurofibroma, thyroid adenoma)
- A malignant neoplasm (Lymphoma, rhabdomyosarcoma, neuroblastoma)
- A hemorrhage

About 1 month earlier she had an upper respiratory infection with fever (39° C), and was treated with amoxicillin for 1 week. Fifteen days later, she was admitted to a different institution for a left anterior neck mass. The mass was painful, tender, and the overlying skin was erythematous and warm. She presented

with fever (39° C) and leukocytosis (white blood cells, 22,100; neutrophils 85%), and she was treated with iv ampicillin and gentamycin for a week.

On our initial examination, she presented with a firm, painless lump of more than 2 cm in the left side of the neck (Figure 5-1A).

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Neck ultrasound
- Fine needle aspiration (FNA) and culture
- Neck and mediastinum magnetic resonance imaging (MRI)
- Neck and mediastinum computed tomography
- Thyroid scan
- Barium esophagogram

On ultrasonography (Figure 5-2A), the left lobe of thyroid was enlarged, and the parenchyma looked altered, with a large irregular hypoechoic area and effacement of the planes between the prethyroid muscles and the perithyroidal soft tissues. Adjacent to the lump, a hypoechoic area was found in the soft tissue, which was presumed to be an abscess (*arrow*).

An MRI of the neck and mediastinum confirmed a mass involving the entire left side of the thyroid, with effacement of the planes between prethyroid muscles and soft tissues surrounding the left lobe. The trachea was shifted to the right. Inflammatory markers were normal (erythrocyte sedimentation rate, C-reactive protein), white blood cell count was 7,820 with neutrophils of 39%. Serum thyroid

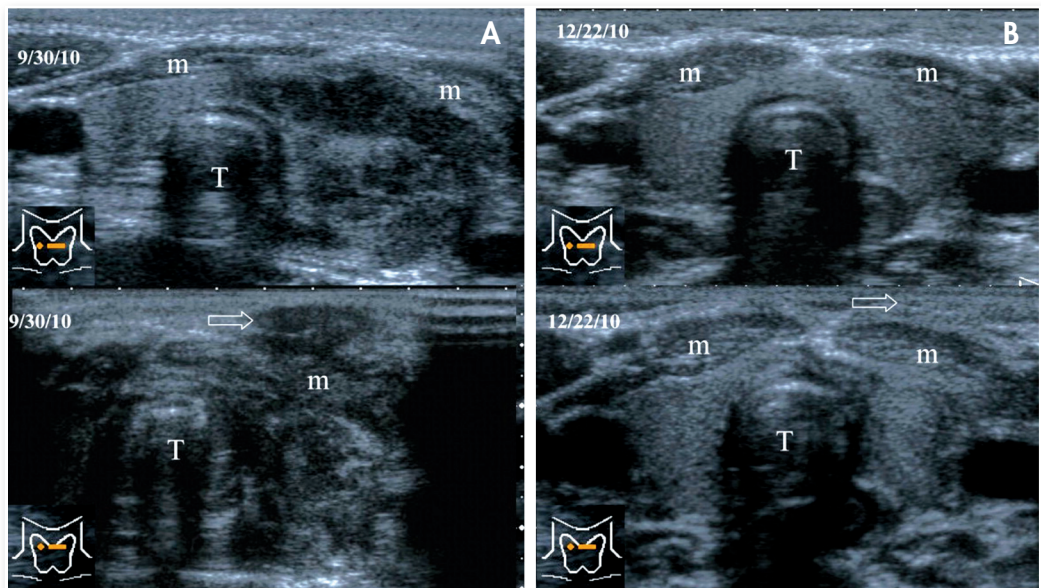


FIG. 5-2. Transverse thyroid ultrasound. T, Trachea; m, prethyroid muscles. Bottom panels, Transverse thyroid section including the sc tissues below the lump. Top panels, Transverse thyroid section including the soft tissues behind the thyroid. **A**, First observation. Adjacent to the lump, a hypoechoic area in the soft tissue, presumably an abscess (*arrow*). **B**, Recovery of the thyroid parenchyma as well as muscles and soft tissues after treatment. The hypoechoic area was substituted with hyperechoic tissue (*arrow*).

3. ACUTE SUPPURATIVE THYROIDITIS IN CHILDREN IS:

- a. Common
- b. Very rare
- c. Mostly due to anaerobes
- d. Mostly due to aerobes
- e. Any infective etiology is possible

function tests were all within normal limits.

All serological tests including tuberculosis, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *treponema pallidum*, *Salmonella typhi* O, H, and paratyphi A-O, B-O, A-H, B-H, and *Proteus OXK* and OXK were negative.

Because of the previous antibiotic treatment and need of sedation, we decided to avoid FNA and the child was treated non-invasively with amoxicillin and clavulanic acid (100 mg/kg/d per os) for 55 days. Ultrasonograms were carried out every ten days to monitor the efficacy of



FIG. 5-1B. The neck after treatment.

the treatment. The lump had completely disappeared at the end of the antibiotic treatment (Figure 5-1B). The ultrasound (Figure 5-2B) demonstrates nearly normal thyroid parenchyma as well as normal muscles and soft tissues. The hypoechoic area previously identified had been replaced by hyperechoic tissue (*arrow*).

After 30 months of follow-up, the child is well and thyroid function is normal. Thyroid ultrasound shows a small hypoechoic area with calcifications as a “scar” in the area of the previous abscess.

Diagnosis

Acute Suppurative Thyroiditis.

Discussion

Acute suppurative thyroiditis (AST) is uncommon in children (1). The thyroid gland is thought to have intrinsic resistance to infection because of its high iodine and hydrogen peroxide content, rich vascularization, lymphatic drainage and capsule encasement. AST occurs more commonly in the left lobe and the presence of remnants of the third or fourth branchial pouch as pyriform sinus fistulae can act as a viaduct for spread of bacterial from the pharynx to the thyroid. AST is usually due to bacterial agents, both aerobic or anaerobic, but many other etiologies are known (1). AST is a potentially life-threatening endocrine emergency. The management of this condition has recently been reviewed (2–4), and the optimal treatment is still debated. Surgery is the traditional treatment of this condition, but nonsurgical management has also been proposed (5). Imaging is fundamental for the diagnosis of this condition (6).

This case illustrates a successful conservative approach monitored by ultrasonography in a 4-year-old girl. Thyroid ultrasound in this young child was also essential to monitor the progressive resolution of the abscess during 55 days of antibiotic therapy. Thereafter, we performed ultrasound every ten days, and more invasive procedures were avoided. After 30 months of follow-up, she is well, and thyroid function is normal. A transnasal laryngoscopy to evaluate a possible pyriform sinus fistula is planned if a recurrence occurs.

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Answers:

- Question 1. b
Question 2. a
Question 3. b

6

A 29-year-old Woman with Episodic Thyroid Enlargement

Takao Ando, MD, PhD, Kan Nakamura, MD, PhD, Mariko Ogata, MD, Toshiro Usa, MD, PhD, and Atsushi Kawakami, MD, PhD

A 29-year-old woman presented with visible thyroid swelling. The swelling was painless and accompanied by additional symptoms including palpitations, shortness of breath, and headaches that occurred every few days and had developed a year earlier. Her thyroid gland could not be seen when she did not have these symptoms (Figure 6-1). Her thyroid function tests were all within reference range and the thyroid gland appeared normal on ultrasound performed when the patient was asymptomatic.

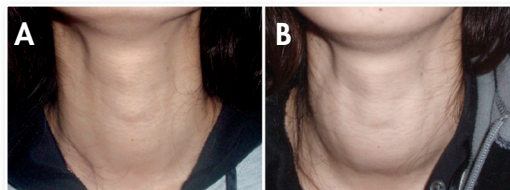


FIG. 6-1. Overt paroxysmal thyroid swelling. Photos of the patient taken without swelling (**A**) and during a spell (**B**). Note that the thyroid gland swelling is apparent during the spell.

1. THE MOST LIKELY DIAGNOSIS IS:

- Subacute thyroiditis
- Painless thyroiditis
- Graves' disease
- Anaplastic thyroid carcinoma
- None of the above

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Fine needle aspiration of the thyroid gland
- Thyroid magnetic resonance imaging (MRI)
- Thyroid autoantibodies
- Abdominal computed tomography (CT) scan
- Echocardiography

Total body CT scan revealed a left adrenal tumor with heterogeneous enhancement, suggesting pheochromocytoma (Figure 6-2A). Plasma catecholamine levels were unremarkable when the patient was asymptomatic. During symptomatic spells, she was hypertensive (180/100 mmHg) and tachycardic (100 bpm) with high plasma epinephrine (417 pg/ml; normal <100 pg/ml) and norepinephrine (2665 pg/ml; normal 100 to 450 pg/ml). The left adrenal tumor showed positive ^{123}I -MIBG accumulation, confirming pheochromocytoma (Figure 6-2B).

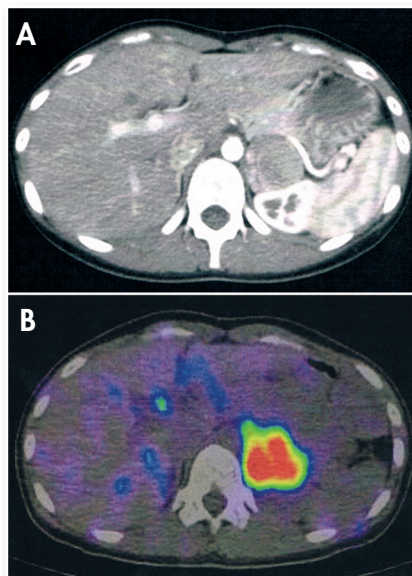


FIG. 6-2. Left adrenal pheochromocytoma. Contrast-enhanced CT showed a left adrenal tumor with heterogeneous enhancement (**A**). The tumor clearly accumulated ^{123}I -MIBG (**B**).

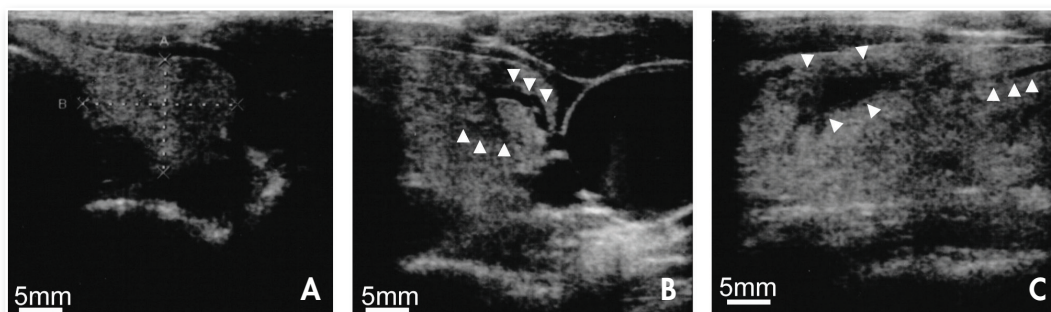


FIG. 6-3. Paroxysmal thyroid swelling detected by ultrasound. The left thyroid lobe thickened from 12.5 mm without swelling (A) to 20.2 mm during a spell (B). Hypoechoic areas, as indicated by arrow heads, are apparent during a spell (B and C).

Ultrasonography of the thyroid gland performed during a symptomatic episode showed a transient (lasting <15 to 60 minutes) thickening of the thyroid (Figure 6-3). Multiple intrathyroidal hypoechoic areas were reproducibly found only during an episode and some hypoechoic areas showed blood flow, while others did not. Thyroid function tests (TSH, free T₃, and free T₄) taken before, during, and the day after the episode were unremarkable.

The patient underwent left adrenalectomy, and the histological findings of the adrenal tumor were consistent with pheochromocytoma.

3. YOUR INTERPRETATION OF THE THYROID FINDINGS IN THE PATIENT WITH PHEOCHROMOCYTOMA:

- Destructive thyroiditis
- Medullary thyroid carcinoma
- Thyroid metastasis of pheochromocytoma
- Graves' disease
- None of the above.

Diagnosis

Paroxysmal Thyroid Swelling.

Discussion

Paroxysmal thyroid swelling (PTS) in pheochromocytoma is a clinical condition

of visible or palpable thyroid swelling that develops acutely with catecholamine release from a pheochromocytoma and disappears shortly thereafter. PTS was first described in 1937 (1), but has been only rarely reported and nearly forgotten for some 30 years (2, 3). PTS had not been studied by imaging modalities until a recent report by Nakamura *et al.* in the JCEM in 2011 (4). PTS appears as a thickening of the thyroid caused by multiple hypoechoic areas, suggesting focal edemas, presumably related to increased blood flow.

The reported cases of pheochromocytoma showing PTS, including ours, are norepinephrine-secreting. Although the precise mechanisms of the occurrence of PTS remain unknown, it has been shown that the thyroid gland is enlarged upon the intravenous injection of norepinephrine, but not epinephrine (5). It has been suggested that PTS might be mediated by the carotid sinus nerve because this nerve seems to regulate thyroid blood flow (2). It is not known why only a few patients with norepinephrine-secreting pheochromocytoma develop PTS, nor why only the thyroid gland becomes enlarged while other organs apparently do not.

It has been shown that individuals suffering pheochromocytoma spells may develop the potentially fatal complication

of non-cardiogenic pulmonary edema, which can be reproduced in humans by the injection of norepinephrine (6). Capillary hypertension in the lung has been suggested to be a cause of interstitial pulmonary edema, a finding based on experiments in which animals were injected with excessive epinephrine (7). Although to the best of our knowledge, the coexistence of PTS and non-cardiogenic pulmonary edema in a single individual with pheochromocytoma has never been reported, these two manifestations of pheochromocytoma might share some of the same pathogenesis.

Of the variety of pathological conditions affecting the thyroid gland, including autoimmunity, tumors, infiltrative disorders, *etc.*, none has been associated with episodic thyroid enlargement. Transient thyroid swelling can be seen upon mechanical irritation, such as that in aspiration biopsy, and this can be easily differentiated from PTS. We believe PTS is highly specific to pheochromocytoma.

In conclusion, the physical finding of PTS seems unique to predominantly norepinephrine-producing pheochromocytoma. Even though PTS is a rare manifestation of pheochromocytoma, it can be an important clue for diagnosis. Therefore, physicians should be aware of this rare sign of the disease and look for it when performing a workup for pheochromocytoma.

Subsequent Follow-up on the Patient

At the time of writing, it has been almost two years since the patient underwent left adrenalectomy, and she has not experienced another symptomatic episode or PTS since the procedure.

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Answers:

Question 1. e

Question 2. d

Question 3. e

7

A 60-year-old Woman with Osteoporosis and Goiter

Robert Pichler, MD, PhD

A 60-year-old woman presented with osteoporosis and atraumatic fractures of the spine and ribs in the neurological hospital in Linz, Upper Austria. CT of the spine showed multiple fractures from T8 to L2 (Figure 7-1). She had a clinical history of bipolar affective disorder and cognitive decline, but the actual medical complaint was of lumbar pain. Treatment for her osteoporosis already included bisphosphonates, vitamin D, and calcium.

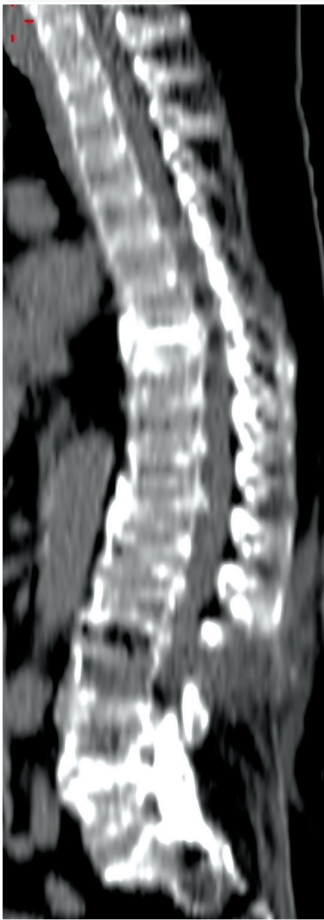


FIG. 7-1. CT of the spine showed multiple fractures from T8 to L2

1. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Bone densitometry
- Change treatment for osteoporosis
- Search for cancer and/or bone metastasis
- Reevaluate clinical history for falls
- Endocrine evaluation of secondary osteoporosis

Densitometric measurement of the hip (T score = -1.7) and distal radius (T score = -1.9) revealed osteopenia, but measurement at the lumbar spine was not feasible. Endocrine evaluation for secondary osteoporosis showed low TSH (0.17 μ U/ml) under prophylactic levothyroxine treatment (75 μ g/d) for multinodular goiter and ACTH-dependent hypercortisolism. Clinical evaluation revealed obesity (weight, 75 kg, for 150 cm height), arterial hypertension, and diabetes mellitus.

ACTH was elevated at 106 pg/ml, whereas morning serum cortisol (22 μ g/dl) was still in the normal range. Cortisol measured in 24-h urine was highly elevated at 502 μ g/d (normal range, 40–158 μ g/d). Dexamethasone suppression test with 1, 4, and 8 mg failed to suppress either plasma ACTH or cortisol in serum and/or 24-h urine (ACTH, >45 pg/ml; and cortisol, >20 μ g/dl and >400 μ g/d in all tests). Brain magnetic resonance imaging showed mild cortical atrophy and revealed no pituitary abnormality.

2. YOUR NEXT DIAGNOSTIC PROCEDURE WOULD BE:

- a. Petrosal sinus catheterization
- b. Whole body FDG PET-CT
- c. CT of thorax and abdomen
- d. Thyroid scan
- e. Search for a neuroendocrine tumor (e.g., DOPA-PET)

Petrosal sinus catheterization was not available in the federal state of Upper Austria, and had to be deferred. Whole body fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) was done in May 2009 for tumor screening to detect a possible ectopic source of ACTH. A single nodule of the right thyroid lobe proved to be FDG avid (Figure 7-2). Additionally, the CT detected a lesion of the right kidney with a diameter of 2 cm that did not accumulate FDG.

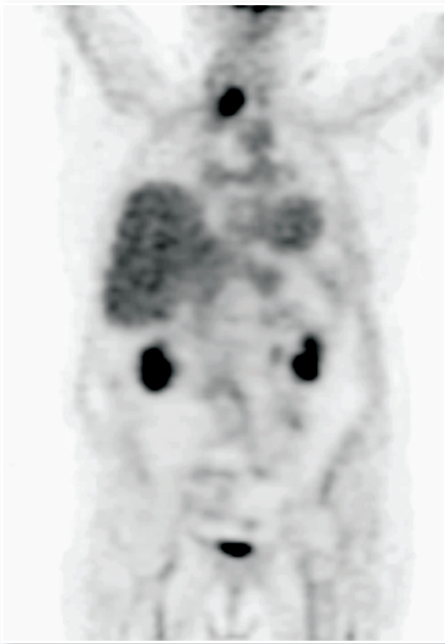


FIG. 7-2. FDG PET showed a single nodule of the right thyroid lobe with a diameter of 1.5 cm to be FDG-avid with a standard uptake value of 5.7. Otherwise, whole body imaging showed physiological FDG uptake.

An earlier thyroid evaluation was available from March 2009 that had been performed in a regional institute in the “Salzkammergut” in Upper Austria. The FDG-avid lesion was noted to be a cold nodule by Technetium-scintiscan, and fine-needle-aspiration cytology had shown oncocyctic transformation of thyrocytes. Serum calcitonin screening had been negative in the patient.

3. THE MOST LIKELY DIAGNOSIS IS:

- a. Cushing’s disease (pituitary origin)
- b. Cancer-related Cushing’s syndrome
- c. Ectopic ACTH production
- d. Erroneous laboratory values - no hypercortisolism
- e. Adrenal hypercortisolism

We recommended thyroid surgery as the next step, and a near-total resection of the thyroid took place in June 2009. The surgical pathology revealed multinodular goiter with no malignant lesion identified. The suspicious nodule was considered to be an oncocyctic adenoma.

In July 2009, the lesion of the right kidney was resected and proved to be a clear cell carcinoma (pT1aG2). At follow-up evaluation 6 months later, tumor progression or metastasis was excluded, and thyroid function was normal with substitution of 100 mcg levothyroxine/day. The last endocrinological check in our hospital showed normal morning values of serum cortisol (22 µg/dl) and plasma ACTH (33 pg/ml).

Immunohistochemistry was positive for ACTH on the thyroid oncocyctic nodule which showed positive intracytoplasmatic ACTH (Figure 7-3) that was not seen on any other thyroid tissue. The oncocyctic nodule was therefore considered to be the source of the patient’s ectopic Cushing syndrome. Immunohistochemical

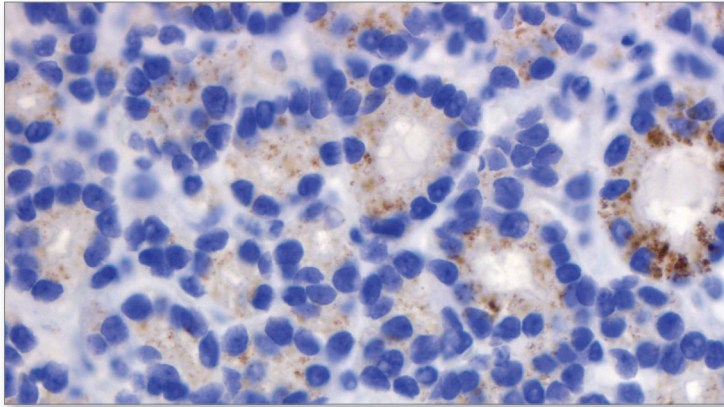


FIG. 7-3. A thyroid adenoma expressing ACTH: There is a well-demarcated microfollicular growth pattern, exhibiting ACTH immunoreactivity. ACTH immunostaining in the tumor appears brown. Small capillaries show no positive staining pattern as an internal control.

analysis of the adenoma was negative for thyroglobulin and calcitonin, whereas the surrounding thyroid parenchyma was thyroglobulin positive. The renal tumor exhibited no ACTH expression.

At clinical follow-up in June 2011, the patient presented with improved mobility and mood. Persistent hypercortisolism was excluded by a normal morning value of serum cortisol (3 µg/dl) after 1mg dexamethasone overnight suppression test. In October 2012, the patient had a bone scan which excluded bone metastasis, and no recent vertebral fractures were noted.

Diagnosis

Cushing Syndrome due to Ectopic ACTH Secretion by an Oncocytic Thyroid Nodule.

Discussion

About 10% of ACTH-dependent Cushing syndrome is caused by ectopic ACTH secretion, typically from tumors of neuroendocrine origin. Most common is bronchial carcinoid, but thymic and pancreatic carcinoid also occur. In regard to the thyroid, medullary thyroid carcinoma has been described to co-secrete hormonally active ACTH (1–4). To our knowledge, this is the first published case report of ectopic ACTH secretion by a benign thyroid nodule (5). The case also demonstrates the utility of FDG PET/CT to detect an endocrinologically active lesion (6).

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Answers:

- Question 1. e
 Question 2. a
 Question 3. c

8

A 40-year-old Woman with a Goiter

J.P.H. van Wijk, MD, PhD, and P.M.J. Zelissen, MD, PhD

A 40-year-old woman was referred to the hospital with a 4-year history of a goiter. During the last year, she complained of slowly progressive obstructive symptoms. On physical examination, she had a large multinodular goiter. Laboratory evaluation revealed slightly low TSH (0,15 mIU/L, normal 0,35-5,0 mIU/L), normal free T₄ (16,1 pmol/L, normal 10-22 pmol/L) and normal total T₃ (2,9 nmol/L, normal 1,0-3,0 nmol/L). Ultrasound of the neck showed bilateral enlarged thyroid lobes with multiple nodules, but no cervical lymphadenopathy.

1. THE MOST LIKELY DIAGNOSIS IS:

- Multinodular goiter
- Thyroid carcinoma
- Graves' disease
- Hashimoto thyroiditis

2. YOUR NEXT STEP IN THE DIAGNOSTIC WORK-UP WOULD BE:

- Radioactive iodine scan
- Computed tomography scan
- Fine needle aspiration (FNA) cytology of (a) dominant or suspected nodule(s)
- Both computed tomography scan and FNA cytology

Ultrasound-guided FNA cytology of a dominant nodule in the right thyroid lobe was performed. The FNA report described normal thyroid cells without evidence of malignancy. Computed tomography, performed to evaluate tracheal diameter, showed a goiter slightly narrowing the airway. There was no retrosternal extension of the goiter. She was diagnosed with subclinical hyperthyroidism and obstructive symptoms due to a multinodular goiter. Because of the risk of further thyroid growth and progressive tracheal compression, subtotal thyroidectomy was performed. Histopathological examination revealed a multinodular goiter with localization of a follicular carcinoma (2 cm) in the left thyroid lobe (Figure 8-1). Subsequently, completion thyroidectomy was performed (no malignancy) and the patient was treated with 3700 MBq radioactive iodine. Posttherapy whole body scintigraphy after recombinant human TSH revealed uptake in the thyroid bed and, to our surprise, also in the right ovary (Figure 8-2). Stimulated serum thyroglobulin was 3.0 µg/L.

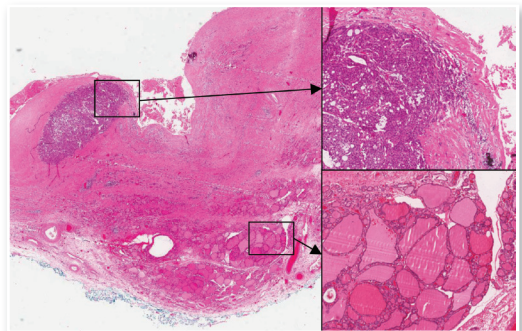


FIG. 8-1. Fragment of subtotal thyroidectomy with normal thyroid tissue (detail lower right corner) and follicular thyroid carcinoma (detail upper right corner).



FIG. 8-2. Scintigraphic image (Cobalt-57 flood source behind patient) demonstrating focal intense iodine uptake in the right ovary (arrow). There is also residual thyroid bed uptake and normal physiological uptake in the salivary glands.

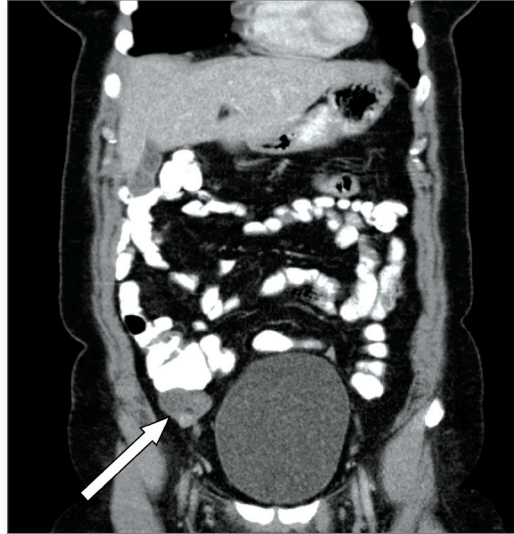


FIG. 8-3. Non-contrast-enhanced abdominal computed tomography in coronal view showed an enlarged right ovary with variable density.

3. THE DIFFERENTIAL DIAGNOSIS OF SCINTIGRAPHIC IODINE UPTAKE IN THE RIGHT OVARY IN THIS PATIENT INCLUDES:

- Ovarian metastasis of follicular thyroid carcinoma
- Ovarian teratoma (*e.g.*, struma ovarii)
- Thyroid carcinoma arising in struma ovarii
- False-positive uptake on whole-body scintigraphy
- All of the above

4. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Therapy with 5500 MBq radioactive iodine
- Follow-up of serum thyroglobulin in 6 months
- Abdominal computed tomography
- Surgical resection of the right ovary

Abdominal computed tomography showed an enlarged right ovary with variable density (4,5 cm), suggestive for mature teratoma (Figure 8-3).

Laparoscopic salpingo-oophorectomy was performed. Histopathological examination confirmed the diagnosis benign cystic ovarian teratoma with localization of normal thyroid tissue (< 10%, Figure 8-4). There was no cytonuclear atypia or vascular invasion. Immunohistochemical markers were positive for thyroglobulin. Three months after surgery, basal serum thyroglobulin fell below 0.20 µg/L. The patient had no symptoms.

Diagnosis

Benign Ovarian Teratoma.

Discussion

There are four major entities to consider in the differential diagnosis of a woman who presents with scintigraphic iodine uptake in the right ovary after total thyroidectomy and radioactive iodine ablation for follicular thyroid carcinoma: ovarian teratoma (*e.g.*, struma ovarii), thyroid

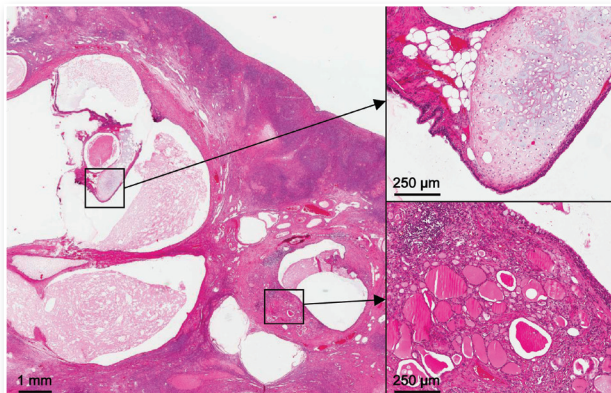


FIG. 8-4. Mature teratoma consisting of multiple cysts lined by respiratory type epithelium and goblet cells. Surrounding these cysts, some lymphoid tissue was present, as well as cartilage (detail upper right corner), mineralized bone and multiple benign thyroid follicles lined by monolayered cuboidal epithelium and filled with colloid (detail lower right corner).

carcinoma arising in struma ovarii, metastatic thyroid carcinoma, and false-positive radioactive iodine uptake. False-positive radioactive iodine uptake has been rarely reported in several medical conditions (1, 2), but was considered unlikely in our patient. A computerized tomographic scan showed an ovarian mass, and subsequent salpingo-oophorectomy revealed a mature teratoma containing small amounts of normal thyroid tissue.

Mature teratomas account for 20% of all ovarian tumours (3-5). Approximately 20% of mature teratomas contain thyroid tissue (3-5). For a teratoma to be classified as struma ovarii, it must contain more than 50% thyroid tissue. Most of the cases of struma ovarii are incidental findings that are diagnosed in patients having surgery for an ovarian mass. It is usually a benign condition although malignant transformation has been observed (4, 5). The differentiation of malignant from benign struma ovarii rests solely upon histopathological features. However, both clinically and pathologically, it can be difficult to distinguish benign thyroid tissue from highly differentiated thyroid cancer. Histopathological features of thyroid carcinoma can be extremely focal and subtle and can escape detection by an unaware pathologist.

Follicular thyroid carcinoma is known

for its propensity for vascular invasion and subsequent distant metastases (6), most commonly in bones and the lungs. Abdominal spread of follicular thyroid carcinoma is uncommon as there have been only a few cases documenting ovarian spread of primary differentiated thyroid carcinoma (7, 8). In these cases, there were initial problems in the distinction of the ovarian neoplasm from a malignant struma ovarii (7, 8). In our patient, the possibility of both struma ovarii and ovarian spread of follicular thyroid carcinoma were considered. Laparoscopic salpingo-oophorectomy was performed, and histopathological findings were consistent with the diagnosis of benign cystic ovarian teratoma with localization of normal thyroid tissue. There was no histopathological evidence of thyroid carcinoma. Furthermore, the presence of other teratomatous elements helped to distinguish from ovarian involvement as a metastatic disease.

In conclusion, we present a case of scintigraphic iodine uptake in the right ovary after total thyroidectomy and radioactive iodine ablation for follicular thyroid carcinoma. Fortunately, a mature teratoma containing normal thyroid tissue was detected and laparoscopically removed. However, when other teratomatous elements are not identified, the possibility of spread from a (prior)

thyroid neoplasm should always be considered.

Subsequent Follow-up on the Patient

When last seen in 2012, the patient had no symptoms. Recombinant human TSH stimulated serum thyroglobulin was < 0.20 µg/L indicating cure of her follicular thyroid carcinoma.

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Answers:

- Question 1. a
Question 2. d
Question 3. e
Question 4. c

9

A 76-year-old Woman with a Neck Mass

Pratima Kumar, MD, FACE

A 76-year-old woman with no past significant medical history presented with a neck mass that had enlarged rapidly over the past eight months. She denied hoarseness of her voice, dysphagia, or dyspnea but did report a ten-pound weight loss. Serum TSH was 1.24 μ IU/ml. Computed tomography of the neck was performed to evaluate the mass (Figure 9-1).



FIG 9-1. CT of the neck showed a 7.9 cm lobulated mass.

1. THE MOST LIKELY DIAGNOSIS IS:

- Papillary thyroid carcinoma
- Primary thyroid lymphoma
- Medullary thyroid carcinoma
- Anaplastic thyroid carcinoma
- Squamous cell carcinoma

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Thyroid ultrasound
- Magnetic resonance imaging (MRI) of the neck
- Radioiodine uptake and scan
- Fine needle aspiration
- Positron emission tomography (PET) scan

Fine-needle aspiration was performed (Figure 9-2).

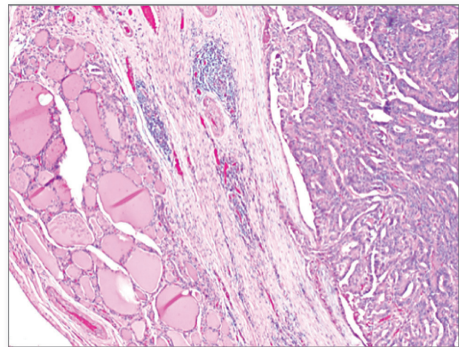


FIG 9-2. Fine-needle aspiration cytology.

3. YOUR INTERPRETATION OF THE CYTOLOGIC FINDINGS:

- Squamous cell carcinoma
- Medullary thyroid carcinoma
- Papillary thyroid carcinoma with poorly differentiated component
- Follicular thyroid carcinoma
- None of the above

Fine needle aspiration revealed undifferentiated carcinoma with spindled cells present anterior to a papillary thyroid

carcinoma. Within 1 month, the mass had markedly increased in size and was eroding through the skin (Figure 9-3).



FIG 9-3. Erosion of anaplastic thyroid cancer through the skin.

Diagnosis

Anaplastic Thyroid Carcinoma with Cutaneous Extension.

Discussion

Undifferentiated or anaplastic thyroid carcinoma (ATC) is an uncommon aggressive malignancy that is invariably fatal with a mean survival time of less than 6 months from the time of diagnosis (1). Although it accounts for only 1-2% of all thyroid malignancies, it is responsible for 14-39% of thyroid carcinoma deaths (2). It may arise *de novo* but usually results from anaplastic transformation of a pre-existing well differentiated thyroid cancer (3). It can present as a rapidly enlarging neck mass. Anaplastic thyroid cells have lost the ability to synthesize thyroglobulin and thus have negative immunohistochemical staining for thyroglobulin (3,4). The tumor typically presents in the fifth to seventh decade of life with a female preponderance (5).

Distant metastases of anaplastic thyroid carcinoma are usually localized to the lungs, bone and brain (5). Dahl *et al.* (6) reviewed the English literature since 1964, and noted that among 43 cases of thyroid carcinoma that metastasized to

the skin, 41% were papillary, 28% were follicular, 15% were medullary, and 15% were anaplastic carcinomas. However, cutaneous extension of anaplastic thyroid carcinoma with uncontrolled tumor overgrowth as seen in our patient as an initial presentation is uncommon.

There is no standardized treatment protocol for ATC since it is unclear whether therapy prolongs survival (7, 8). All anaplastic thyroid carcinomas are classified as stage IV tumors due to their aggressive nature. Multimodality treatment including surgery, chemotherapy and radiotherapy have all been used though they add little to the overall poor prognosis. On review of novel molecular-targeted therapies, Kojic *et al.* concluded that advancements in genotyping, molecular targeting and antiangiogenic drugs might expand future treatment for anaplastic carcinoma (8).

In conclusion, diagnosis of anaplastic thyroid cancer should be considered when there is a rapid growth of a thyroid mass in an elderly patient as seen in our patient.

Subsequent Follow-up on the Patient

The patient underwent a radical wide excision of neck skin and soft tissue, total thyroidectomy with central compartment and right modified radical neck dissection. Pathology showed 4.5-cm papillary and 6-cm anaplastic thyroid carcinoma (ATC) with direct extension into the skin and sternocleidomastoid muscle with metastases to nine lymph nodes. There was no evidence of distant metastasis. The tumor stained negative for thyroglobulin, calcitonin, chromogranin, cytokeratin-7, and cytokeratin-20 but positive for thyroid transcription factor-1. The patient received postoperative palliative external beam radiotherapy and two courses of adjuvant palliative chemotherapy with paclitaxel but declined any further treatment. She died four months after surgery.

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Answers:

Question 1. d

Question 2. d

Question 3. c

A 47-year-old Man with Ultimobranchial Body Remnants (Solid Cell Nests) and Hashimoto Thyroiditis

B. Biondi, MD, C. Bellevicine, MD, S. Ippolito, MD, D. Arpaia, MD, and G. Troncone, MD

A 47-year-old man was admitted to our ambulatory center for an enlargement of the right lobe of the thyroid gland. Neck ultrasonography (US) revealed a nodule of 3.0 cm in the right lobe without evidence of nodular disease in the left lobe.

1. THE NEXT STEPS IN PATIENT WITH THYROID NODULE:

- a. TSH and FT3, FT4 plasma levels
- b. Serum thyroid auto-antibodies (AbTg and AbTPO)
- c. Serum Calcitonin
- d. Fine needle aspiration
- e. Computed tomography

Thyroid function was normal and calcitonin levels were within the normal range. Thyroid autoantibodies were increased.

The ultrasound guided- fine-needle aspiration biopsy (FNAB) of the nodule showed benign-appearing follicular cells, colloid, and scattered Hurthle cells, and was interpreted to be consistent with a benign hyperplastic nodule (1, 2). Computed tomography (CT) showed slight compression of the airway. Therefore, the patient was referred to surgery and underwent a right lobectomy. The surgical pathology described a heavy lymphoplasmacytic background with occasional germinal center formations as observed in Hashimoto thyroiditis, and a microscopic (<1 cm) follicular proliferation of epithelial thyroid cells

whose nuclei displayed membrane irregularity and chromatin clearing with occasional grooves. The findings were consistent with the diagnosis of a follicular variant of papillary microcarcinoma. A completion total thyroidectomy was performed at the Federico II University of Naples. The complete set of slides from both surgeries was reviewed by expert pathologists in the field of thyroid disease.

Histology review

On slide review, the histology showed that the thyroid parenchyma was engulfed by many lymphoplasmacytic cells with a variable degree of interlobular fibrosis and occasional formation of germinal centers; moreover, oncocytic metaplasia of follicular epithelium was also noted (Figure 10-1). This latter feature overlapped with the original description of Hashimoto thyroiditis. In a background of inflammatory cells were detected several clusters of polygonal to oval epithelial cells with elongated nuclei. These clusters were merged with a small cyst filled with eosinophilic material and lined by flattened epithelium (Figure 10-2A). Furthermore, small round to oval “fret-like” groups of elongated cells with centrally located oval nuclei and scanty eosinophilic cytoplasm surrounded by a collection of lymphocytes were also observed (Figure 10-2B). The nuclei of these epithelial clusters featured some worrisome aspects for malignancy, *e.g.*, chromatin clearing and nuclear membrane irregularity with occasional

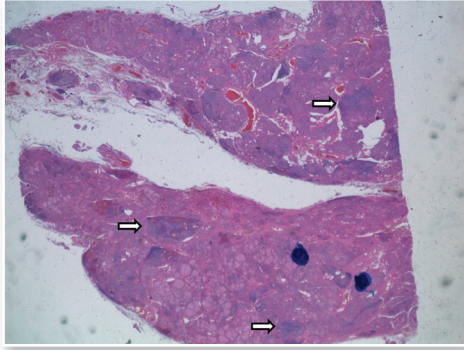


FIG. 10-1. A whole slide macro-photography showing the thyroid parenchyma heavily infiltrated by lymphocytes, which result as bluish aggregates (arrows) on this hematoxylin and eosin stained specimen. The pen marks on lower right, indicate the area magnified in the next image.

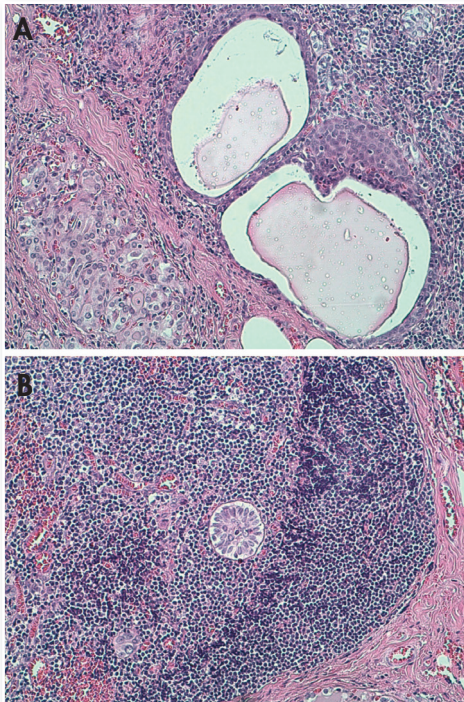


FIG. 10-2. At higher magnification, within a background of Hashimoto thyroiditis, solid-cystic aggregates (A) and floret-like formations (B) can be noted (magnification x20).

grooves and cup-shaped nuclei (Figure 10-3). These features may overlap with those of papillary thyroid carcinoma and could be the basis for the original misdiagnosis of a papillary microcarcinoma.

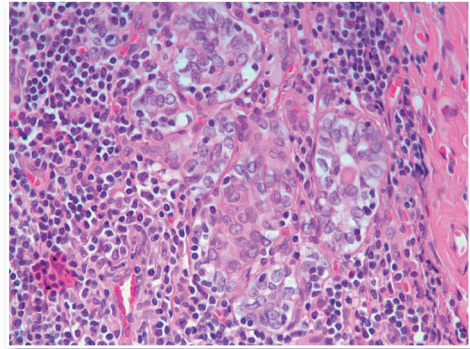


FIG.10-3. In this picture, the nuclear details described in the text can be observed. Chromatin clearing, membrane irregularities and grooves led to the original mistaken diagnosis of papillary microcarcinoma (magnification x40).

The morphological details described above were consistent with solid cell nests (SCNs) in a background of Hashimoto thyroiditis. In fact, SCNs (ultimobranchial body remnants) represent a major pitfall in the differential diagnosis of papillary thyroid carcinoma, especially in the background of thyroiditis (2).

2. THE MOST FREQUENT DIFFERENTIAL DIAGNOSIS OF SOLID CELL NESTS IS:

- a. Papillary thyroid microcarcinoma
- b. Squamous metaplasia of follicular thyroid cells
- c. Primary or metastatic squamous cell carcinoma
- d. Thyroglossal cyst
- e. C-cell hyperplasia
- f. Medullary microcarcinoma

p63, a p53-homologue nuclear transcription factor, is consistently expressed in basal/stem cells of several multilayered epithelia, and represents a reliable immunohistochemical marker of SCNs. With immunostaining for p63 we observed a strong nuclear signal in the SCNs, confirming our morphological interpretation and ruling out the original diagnosis (Figure 10-4) (4).

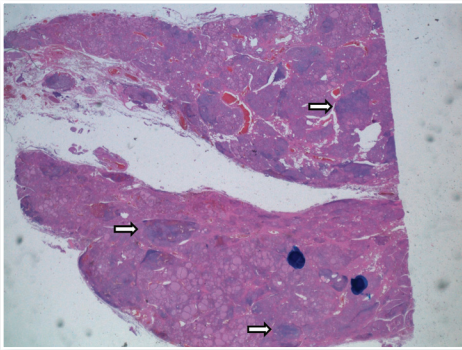


FIG.10-4. Immunohistochemistry for p63 showed a strong nuclear signal confirming our morphological interpretation of SCNs.

Diagnosis

Solid Cell Nests of the Thyroid.

Discussion

Solid cell nests of the thyroid gland are embryonic remnants of endodermal origin from the ultimobranchial pouches (5). SCNs represent a group of polygonal to ovoid cells with elongated nuclei, finely granular chromatin, which may often show small nuclear grooves measuring 0.1 mm or less in diameter. Cells with round nuclei and clear cytoplasm may be present (3). On the basis of different morphological appearance, four different types of SCNs have been reported. Type 1 SCNs are composed of small oval or round groups of elongated or spindle shaped cells with centrally oval to enlarged nuclei and irregular nuclear envelope, and inconspicuous nucleoli with occasional nuclear grooves called “main cells”

(floret-like features). Type 2 SCNs have large polygonal cells with abundant cytoplasm and distinct cell boundaries (epidermoid-like features). Type 3 SCNs are characterized by a cystic structure lined by flattened or large polygonal cells, and Type 4 SCNs are composed of structures lined by main cells and follicular epithelium (3).

The distinction of SCNs from other benign (squamous metaplasia, thyroglossal cyst, C-cell hyperplasia) or malignant (primary or metastatic squamous cell carcinoma, papillary microcarcinoma, medullary carcinoma) entities can be difficult. In particular, SCNs associated with Hashimoto thyroiditis could be confused with papillary thyroid carcinomas.

The correct diagnosis of SCNs can be reached by careful analysis of tissue morphology and selected ancillary staining (3- 7). SCNs are strongly positive for p63, weak positive for TTF-1 and negative for thyroglobulin, HBME-1, calcitonin and galectin-3 (3-7).

On the contrary, papillary thyroid microcarcinomas are strongly positive for thyroglobulin, TTF-1, HBME-1, while calcitonin and chromogranin are negative. p63 is not expressed in normal and neoplastic lesions of follicular and C cell origin and its positivity represent the most reliable immunohistochemical marker for the diagnosis of SCNs (5).

Subsequent Follow-up on the Patient

After the thyroidectomy was performed, replacement therapy with levo-thyroxine was started.

During the patient’s follow-up for 2 years he has remained euthyroid during L-thyroxine therapy. Neck ultrasound is negative for residual thyroid tissue and recurrences. Thyroid auto-antibodies have been progressively decreasing. The patient appears to be very healthy and is

asymptomatic. We believe that recognition of the correct diagnosis avoided what would have been unnecessary treatment.

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Answers:

Question 1. d

Question 2. a

Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline

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Objective: *The aim was to update the guidelines for the management of thyroid dysfunction during pregnancy and postpartum published previously in 2007. A summary of changes between the 2007 and 2012 version is identified in the Supplemental Data (published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>).*

Evidence: *This evidence-based guideline was developed according to the U.S. Preventive Service Task Force, grading items level A, B, C, D, or I, on the basis of the strength of evidence and magnitude of net benefit (benefits minus harms) as well as the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.*

Consensus Process: *The guideline was developed through a series of e-mails, conference calls, and one face-to-face meeting. An initial draft was prepared by the Task Force, with the help of a*

medical writer, and reviewed and commented on by members of The Endocrine Society, Asia and Oceania Thyroid Association, and the Latin American Thyroid Society. A second draft was reviewed and approved by The Endocrine Society Council. At each stage of review, the Task Force received written comments and incorporated substantive changes.

Conclusions: *Practice guidelines are presented for diagnosis and treatment of patients with thyroid-related medical issues just before and during pregnancy and in the postpartum interval. These include evidence-based approaches to assessing the cause of the condition, treating it, and managing hypothyroidism, hyperthyroidism, gestational hyperthyroidism, thyroid autoimmunity, thyroid tumors, iodine nutrition, postpartum thyroiditis, and screening for thyroid disease. Indications and side effects of therapeutic agents used in treatment are also presented. (J Clin Endocrinol Metab 97: 2543–2565, 2012)*

Summary of Recommendations

1.0. Management of hypothyroidism: maternal and fetal aspects

1.1. We recommend caution in the interpretation of serum free T₄ levels during pregnancy and that each laboratory establish trimester-specific reference ranges for pregnant women if using a free T₄ assay. The nonpregnant total T₄ range (5-12 µg/dl or 50-150 nmol/liter) can be adapted in the second and third trimesters by multiplying this range by 1.5-fold. Alternatively, the free T₄ index (“adjusted T₄”) appears to be a reliable assay during pregnancy. U.S. Preventive Service Task Force (USPSTF) recommendation level: B; evidence, fair (GRADE 2|⊕⊕○○).

1.2.1. Overt maternal hypothyroidism is known to have serious adverse effects on the fetus. Therefore, maternal hypothyroidism should be avoided. For overt hypothyroidism: USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○).

1.2.2. Subclinical hypothyroidism (SCH; serum TSH concentration above the upper limit of the trimester-specific reference range with a normal free T₄) may be associated with an adverse outcome for both the mother and offspring, as documented in antibody-positive women. In retrospective studies, T₄ treatment improved obstetrical outcome, but it has not been proved to modify long-term neurological development in the offspring. However, given that the potential benefits outweigh the potential risks, the panel recommends T₄ replacement in women with SCH who are thyroid peroxidase antibody positive (TPO-Ab+). For obstetrical outcome: USPSTF recommendation level, B; evidence, fair (2|⊕⊕○○); for neurological outcome, USPSTF recommendation level, I; evidence, poor (2|○○○○). The panel also recommends T₄ replacement

in women with SCH who are TPO-Ab negative (TPO-Ab-). For obstetrical outcome: USPSTF recommendation level, C; evidence, fair (2|⊕⊕○○); for neurological outcome: USPSTF recommendation level, I; evidence, poor (2|○○○○).

1.2.3. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T₄ dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, poor (2|⊕○○○).

1.2.4. The T₄ dose usually needs to be incremented by 4 to 6 wk gestation and may require a 30% or more increase in dosage. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

1.2.5. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. T₄ dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 mIU/liter (in an assay using the International Standard) in the first trimester (or 3 mIU/liter in second and third trimesters) or to trimester-specific TSH ranges. Thyroid function tests should be remeasured within 30-40 d and then every 4-6 wk. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

1.2.6. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored every 4-6 wk for elevation of TSH above the normal range for pregnancy. USPSTF recommendation level: A; evidence, fair (1|⊕⊕⊕○).

1.2.7. After delivery, most hypothyroid women need to decrease the T₄ dosage they received during pregnancy to the prepregnancy dose. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

2.0. Management of hyperthyroidism: maternal and fetal aspects

2.1. Management of maternal hyperthyroidism: maternal aspects

2.1.1. If a subnormal serum TSH concentration is detected during gestation, hyperthyroidism must be distinguished from both normal physiology of pregnancy and gestational thyrotoxicosis because of the adverse effects of overt hyperthyroidism on the mother and fetus. Differentiation of Graves' disease from gestational thyrotoxicosis is supported by the presence of clinical evidence of autoimmunity, a typical goiter, and presence of TSH receptor antibodies (TRAb). TPO-Ab may be present in either case. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○).

2.1.2. For overt hyperthyroidism due to Graves' disease or thyroid nodules, antithyroid drug (ATD) therapy should be either initiated (before pregnancy if possible, and for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T₄ at or just above the upper limit of the nonpregnant reference range, USPSTF recommendation level: B; evidence, fair (1|⊕⊕○○), or to maintain total T₄ at 1.5 times the upper limit of the normal reference range or the free T₄ index in the upper limit of the normal reference range. USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

2.1.3. Propylthiouracil (PTU), if available, is recommended as the first-line drug for treatment of hyperthyroidism during the first trimester of pregnancy because of the possible association of methimazole (MMI) with specific congenital abnormalities that occur during first trimester organogenesis. MMI may also be prescribed if PTU is not available or if a patient cannot tolerate or has an

adverse response to PTU. MMI 10 mg is considered to be approximately equal to 100-150 mg of PTU. Recent analyses reported by the U.S. Food and Drug Administration (FDA) indicate that PTU may rarely be associated with severe liver toxicity. For this reason we recommend that clinicians change treatment of patients from PTU to MMI after the completion of the first trimester. Available data indicate that MMI and PTU are equally efficacious in the treatment of pregnant women. Practitioners should use their clinical judgment in choosing the ATD therapy, including the potential difficulties involved in switching patients from one drug to another. If switching from PTU to MMI, thyroid function should be assessed after 2 wk and then at 2- to 4-wk intervals. USPSTF recommendation level: B; evidence, fair (1|⊕⊕○○). Although liver toxicity may appear abruptly, it is reasonable to monitor liver function in pregnant women on PTU every 3-4 wk and to encourage patients to promptly report any new symptoms. USPSTF recommendation level: C; evidence, poor (2|⊕○○○).

2.1.4. Subtotal thyroidectomy may be indicated during pregnancy as therapy for maternal Graves' disease if: 1) a patient has a severe adverse reaction to ATD therapy; 2) persistently high doses of ATD are required (over 30 mg/d of MMI or 450 mg/d of PTU); or 3) a patient is nonadherent to ATD therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester. USPSTF recommendation level: C; evidence, fair (2|⊕○○○).

2.1.5. There is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome, and treatment could potentially adversely affect fetal outcome. USPSTF recommendation level: C; evidence, fair (2|⊕○○○).

2.2. Management of maternal hyperthyroidism: fetal aspects

2.2.1. Because thyroid receptor antibodies (thyroid receptor stimulating, binding, or inhibiting antibodies) freely cross the placenta and can stimulate the fetal thyroid, these antibodies should be measured by 22 wk gestational age in mothers with: 1) current Graves' disease; or 2) a history of Graves' disease and treatment with ^{131}I or thyroidectomy before pregnancy; or 3) a previous neonate with Graves' disease; or 4) previously elevated TRAb. Women who have a negative TRAb and do not require ATD have a very low risk of fetal or neonatal thyroid dysfunction. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○).

2.2.2. ^{131}I should not be given to a woman who is or may be pregnant. If inadvertently treated, the patient should be promptly informed of the radiation danger to the fetus, including thyroid destruction if treated after the 12th week of gestation. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○). There are no data for or against recommending termination of pregnancy after ^{131}I exposure. USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

2.2.3. In women with TRAb or thyroid-stimulating Ig elevated at least 2- to 3-fold the normal level and in women treated with ATD, maternal free T_4 and fetal thyroid dysfunction should be screened for during the fetal anatomy ultrasound done in the 18th-22nd week and repeated every 4-6 wk or as clinically indicated. Evidence of fetal thyroid dysfunction could include thyroid enlargement, growth restriction, hydrops, presence of goiter, advanced bone age, tachycardia, or cardiac failure. If fetal hyperthyroidism is diagnosed and thought to endanger the pregnancy, treatment using MMI or PTU should be given with frequent clinical, laboratory,

and ultrasound monitoring. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○).

2.2.4. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical and sonographic data and the information gained would change the treatment. USPSTF recommendation level: B; evidence, fair (2|⊕○○○).

2.2.5. All newborns of mothers with Graves' disease (except those with negative TRAb and not requiring ATD) should be evaluated by a medical care provider for thyroid dysfunction and treated if necessary. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○).

3.0. Gestational hyperemesis and hyperthyroidism

3.1. Thyroid function tests (TSH, total T_4 , or free T_4 index, or free T_4) and TRAb should be measured in patients with hyperemesis gravidarum (5% weight loss, dehydration, and ketonuria) and clinical features of hyperthyroidism. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

3.2. Most women with hyperemesis gravidarum, clinical hyperthyroidism, suppressed TSH, and elevated free T_4 do not require ATD treatment. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕). Clinical judgment should be followed in women who appear significantly thyrotoxic or who have in addition serum total T_3 values above the reference range for pregnancy. Beta blockers such as metoprolol may be helpful and may be used with obstetrical agreement. USPSTF recommendation level: B; evidence, poor (2|⊕○○○).

3.3. Women with hyperemesis gravidarum and diagnosed to have Graves' hyperthyroidism (free T_4 above the reference range or total $\text{T}_4 > 150\%$ of top

normal pregnancy value, TSH < 0.01 μ IU/liter, and presence of TRAb) will require ATD treatment, as clinically necessary. USPSTF recommendation level: A; evidence, good (1| $\oplus\oplus\oplus$).

4.0. Autoimmune thyroid disease and miscarriage

4.1. A positive association exists between the presence of thyroid antibodies and pregnancy loss. Universal screening for antithyroid antibodies, and possible treatment, cannot be recommended at this time. As of January 2011, only one randomized interventional trial has suggested a decrease in the first trimester miscarriage rate in euthyroid antibody-positive women, but treatment duration was very brief before the outcome of interest. However, because women with elevated anti-TPO antibodies are at increased risk for progression of hypothyroidism, if identified such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy. USPSTF recommendation level: C; evidence, fair (2| $\oplus\circ\circ\circ$).

5.0. Thyroid nodules and cancer

5.1. Fine-needle aspiration (FNA) cytology should be performed for predominantly solid thyroid nodules larger than 1 cm discovered in pregnancy. Women with nodules 5 mm to 1 cm in size should be considered for FNA if they have a high-risk history or suspicious findings on ultrasound, and women with complex nodules 1.5 to 2 cm or larger should also receive an FNA. During the last weeks of pregnancy, FNA can reasonably be delayed until after delivery. Ultrasound-guided FNA is likely to have an advantage for maximizing adequate sampling. USPSTF recommendation level: B; evidence, fair (1| $\oplus\oplus\oplus\circ$).

5.2. When nodules discovered in the

first or early second trimester are found to be malignant or highly suspicious on cytopathological analysis, to exhibit rapid growth, or to be accompanied by pathological neck adenopathy, pregnancy need not be interrupted, but surgery should be offered in the second trimester. Women found to have cytology indicative of papillary cancer or follicular neoplasm without evidence of advanced disease and who prefer to wait until the postpartum period for definitive surgery may be reassured that most well-differentiated thyroid cancers are slow growing and that delaying surgical treatment until soon after delivery is unlikely to change disease-specific survival. USPSTF recommendation level: B; evidence, fair (1| $\oplus\oplus\circ\circ$).

5.3. It is appropriate to administer thyroid hormone to achieve a suppressed but detectable TSH in pregnant women with a previously treated thyroid cancer, in those with an FNA positive for or suspicious for cancer, or in those who elect to delay surgical treatment until postpartum. High-risk patients may benefit more than low-risk patients from a greater degree of TSH suppression. The free T₄ or total T₄ levels should ideally not be increased above the normal range for pregnancy. USPSTF recommendation level: I; evidence, poor (2| $\oplus\circ\circ\circ$).

5.4. Radioactive iodine (RAI) with ¹³¹I should not be given to women who are breastfeeding or for at least 4 wk after nursing has ceased. USPSTF recommendation level: A; evidence, good (1| $\oplus\oplus\oplus\oplus$). Furthermore, pregnancy should be avoided for 6 months to 1 yr in women with thyroid cancer who receive therapeutic RAI doses to ensure stability of thyroid function and confirm remission of thyroid cancer. USPSTF recommendation level: B; evidence, fair (1| $\oplus\oplus\circ\circ$).

6.0. Iodine nutrition during pregnancy

6.1. Women in the childbearing age should have an average iodine intake of 150 µg/d. As long as possible before pregnancy and during pregnancy and breastfeeding, women should increase their daily iodine intake to 250 µg on average. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

6.2. Iodine intake during pregnancy and breastfeeding should not exceed twice the daily recommended nutrient intake (RNI) for iodine, i.e. 500 µg iodine per day. USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

6.3. Although not advised as a part of normal clinical practice, the adequacy of the iodine intake during pregnancy can be assessed by measuring urinary iodine concentration (UIC) in a representative cohort of the population. UIC should ideally range between 150 and 250 µg/liter. If there is significant concern, the caregiver should assay TSH and thyroid hormone levels. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

6.4. To reach the daily recommended nutrient intake for iodine, multiple means must be considered, tailored to the iodine intake level in a given population. Different situations must therefore be distinguished: 1) countries with iodine sufficiency and/or with a well-established universal salt iodization (USI) program; 2) countries without a USI program or with an established USI program where the coverage is known to be only partial; and 3) remote areas with no accessible USI program and difficult socioeconomic conditions. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

6.5. We recommend that once-daily prenatal vitamins contain 150-200 µg iodine and that this be in the form of potassium iodide or iodate, the content of which is verified to ensure that all pregnant

women taking prenatal vitamins are protected from iodine deficiency. Ideally, supplementation should be started before conception. Preparations containing iron supplements should be separated from thyroid hormone administration by at least 4 h. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

6.6. We recommend that breastfeeding women maintain a daily intake of 250 µg of iodine to ensure that breast milk provides 100 µg iodine per day to the infant. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

7.0. Postpartum thyroiditis

7.1. There are insufficient data to recommend screening of all women for postpartum thyroiditis (PPT). USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

7.2. Women known to be TPO-Ab+ should have TSH measured at 6-12 wk gestation and at 6 months postpartum, or as clinically indicated. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

7.3. Because the prevalence of PPT in women with type 1 diabetes, Graves' disease in remission, and chronic viral hepatitis is greater than in the general population, screening by TSH is recommended at 3 and 6 months postpartum. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

7.4. Women with a history of PPT have a markedly increased risk of developing permanent primary hypothyroidism in the 5- to 10-yr period after the episode of PPT. An annual TSH level should be performed in these women. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

7.5. Asymptomatic women with PPT who have a TSH above the reference range but less than 10 mIU/liter and who are not planning a subsequent pregnancy do not

necessarily require intervention but should, if untreated, be remonitored in 4-8 wk. When a TSH above the reference range continues, women should be treated with levothyroxine. Symptomatic women and women with a TSH above normal and who are attempting pregnancy should be treated with levothyroxine. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

7.6. There is insufficient evidence to conclude whether an association exists between postpartum depression (PPD) and either PPT or thyroid antibody positivity (in women who did not develop PPT). USPSTF recommendation level: I; evidence, poor (2|⊕○○○). However, because hypothyroidism is a potentially reversible cause of depression, women with PPD should be screened for hypothyroidism and appropriately treated. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

8.0. Screening for thyroid dysfunction during pregnancy

8.1a. Universal screening of healthy women for thyroid dysfunction before pregnancy is not recommended. USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

8.1b. However, caregivers should identify individuals at “high risk” for thyroid illness (see Table 1) on the basis of their medical history, physical exam, or prior biochemical data. When such individuals are identified, prenatal measurement of serum TSH is recommended. If it is above 2.5 mIU/liter, the test should be confirmed by repeat assay. Although no randomized controlled trials are available to guide a response, the committee believes it is appropriate to give low-dose T₄ treatment to bring TSH below 2.5 mIU/liter. This treatment can be discontinued if the woman does not become pregnant or postpartum. USPSTF

recommendation level: I; evidence, poor (2|⊕○○○).

TABLE 1: Recommended patient profiles for targeted thyroid disease case finding in women seeking pregnancy or newly pregnant

Women over age 30 yr
Women with a family history or autoimmune thyroid disease or hypothyroidism
Women with a goiter
Women with thyroid antibodies, primarily thyroid peroxidase antibodies
Women with symptoms or clinical signs suggestive of thyroid hypofunction
Women with type 1 DM or other autoimmune disorders
Women with infertility
Women with a prior history of miscarriage or preterm delivery
Women with prior therapeutic head or neck irradiation or prior thyroid surgery
Women currently receiving levothyroxine replacement
Women living in a region with presumed iodine deficiency

8.2a. All women considering pregnancy with known thyroid dysfunction and receiving levothyroxine should be tested for abnormal TSH concentrations before pregnancy. USPSTF recommendation level: B; evidence, fair (1|⊕⊕○○).

8.2b. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T₄ dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, fair (2|⊕⊕○○).

8.2c. All women receiving levothyroxine should be verbally screened prenatally to assess their understanding of changing levothyroxine requirements after conception. These women should be counseled to contact a physician or medical professional immediately upon

a missed menstrual cycle or suspicion of pregnancy to check their serum TSH level. An additional recommendation may be to increase their levothyroxine dose by 30%, which is often two additional tablets per week (nine tablets per week instead of seven tablets), until their serum TSH can be checked. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

8.3a. Universal screening for the presence of anti-TPO antibodies either before or during pregnancy is not recommended. USPSTF recommendation level: C; evidence, fair (2|⊕○○○).

8.3b. However, women with elevated anti-TPO antibodies are at increased risk for miscarriage, preterm delivery, progression of hypothyroidism, and PPT. Therefore, if identified, such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy. USPSTF recommendation level: C; evidence, fair (1|⊕⊕○○) (see also Section 8.5).

8.4a. The committee could not reach agreement with regard to screening recommendations for all newly pregnant women. Two versions are therefore presented.

8.4a1. Some members recommended screening of all pregnant women for serum TSH abnormalities by the ninth week or at the time of their first visit. USPSTF recommendation level: C; evidence, fair (2|⊕⊕○○) (Authors supporting: L.D.G., J.R., J.H.L., N.A., C.J.E.).

8.4a2. Some members recommended neither for nor against universal screening of all pregnant women for TSH abnormalities at the time of their first visit. These members strongly support aggressive case finding to identify and test high-risk women (Table 1) for elevated TSH concentrations by the ninth week or at the time of their first visit before and during pregnancy, and they recognize that

in some situations ascertainment of the individual's risk status may not be feasible. In such cases, and where the local practice environment is appropriate, testing of all women by wk 9 of pregnancy or at the first prenatal visit is reasonable. USPSTF recommendation level: I; evidence, poor (2|⊕○○○) (Authors supporting: M.A., E.K.A., J.M., L.B., S.S., S.J.M., D.L., R.H.C.).

8.4b. If serum TSH is greater than 2.5 mIU/liter at the time of testing (or > 3.0 mIU/liter in the second trimester), levothyroxine therapy should be instituted. For overt hypothyroidism, USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕); for SCH and obstetrical outcome, USPSTF recommendation level: C; evidence, fair (2|⊕⊕○○); and for SCH and neurological outcome, USPSTF recommendation level: C; evidence, poor (2|⊕○○○).

8.4c. If TSH concentration is 2.5-10 mIU/liter, a starting levothyroxine dose of 50 µg/d or more is recommended. Other thyroid preparations (such as T₃) are not recommended. USPSTF recommendation level: C; evidence, fair (2|⊕⊕○○).

8.5. Women at high risk for PPT in the postpartum months should be screened via assessment of serum TSH. These high-risk groups include: 1) women known to be TPO-Ab+; 2) women with type 1 diabetes; and 3) women with a prior history of PPT. Screening should occur at 6-12 wk postpartum. Women with Graves' disease who enter remission during pregnancy should be screened for recurrence by TSH assay at 3-6 months. USPSTF recommendation level: C; evidence, poor (2|⊕○○○) (see also Section 7).

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed thyroid dysfunction during pregnancy a priority

area in need of practice guidelines and appointed a task force to formulate evidence-based recommendations. The task force followed the approach of the U.S. Preventive Service Task Force and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to evaluate the strength of each recommendation and the quality of the evidence. The task force used the best available research evidence to develop the recommendations. In the USPSTF system, the strength of a recommendation is graded A, B, C, D, or I (if insufficient), and evidence is graded good, fair, or poor. In the GRADE system strong recommendations use the number 1, and weak recommendations use the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that panelists considered in making the recommendation; in some instances, there are remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated.

This guideline is concerned with the management of pregnant women who may have a variety of known or undisclosed thyroid conditions, such as hypothyroidism and hyperthyroidism, the presence of thyroid autoantibodies, the presence of nodules, or inadequate iodine nutrition. Pregnancy may affect the course of

these thyroid disorders, and conversely, thyroid diseases may affect the course of pregnancy. Moreover, the thyroid disorders (and their management) may affect both the pregnant woman and the developing fetus. Finally, pregnant women may be under the care of multiple health care professionals, including obstetricians, nurse midwives, family practitioners, endocrinologists, and/or internists, making the development of guidelines all the more critical.

An international task force was created under the auspices of The Endocrine Society to review the best evidence in the field and develop evidence-based guidelines, and a report was issued in 2007. Because of advances in the field, the committee was reconvened in 2009. The current task force also includes members of the Asia and Oceania Thyroid Association and the Latin American Thyroid Society.

The task force undertook a review of all material on these topics published in English during the past two decades, or earlier at the working group's discretion. We concentrated on original reports and largely excluded reviews from our references. At present, with the exception of studies on iodide nutrition, only a few prospective, randomized intervention trials have been published in this area. We are aware of large-scale prospective intervention trials that are ongoing. Nevertheless, in the past decade many high-quality studies have modified older dogmas and profoundly changed the ways in which these patients are managed.

Thyroid problems during pregnancy encompass at least eight different conditions, and we have therefore divided our report into the following sections:

1. Management of hypothyroidism:
maternal and fetal aspects
2. Management of hyperthyroidism:
maternal and fetal aspects

3. Gestational hyperemesis and hyperthyroidism
4. Autoimmune thyroid disease and miscarriage
5. Thyroid nodules and cancer
6. Iodine nutrition during pregnancy
7. Postpartum thyroiditis
8. Screening for thyroid dysfunction during pregnancy

The material herein is a condensed and abstracted version of the full report, which is published online at <http://www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm>; <http://www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm>. Each subsection provides recommendations followed by an abbreviated examination of evidence. Each recommendation is followed by a statement of strength of the recommendation and quality of the evidence. We have indicated the specific bibliographic citations on which each recommendation is based.

1.0. Management of hypothyroidism during pregnancy: maternal and fetal aspects

Recommendations

1.1. We recommend caution in the interpretation of serum free T₄ levels during pregnancy and that each laboratory establish trimester-specific reference ranges for pregnant women if using a free T₄ assay. The nonpregnant total T₄ range (5-12 µg/dl or 50-150 nmol/liter) can be adapted in the second and third trimesters by multiplying this range by 1.5-fold. Alternatively, the free T₄ index (“adjusted T₄”) appears to be a reliable assay during pregnancy. USPSTF recommendation level: B; evidence, fair (GRADE 2|⊕⊕○○) (1,2,3).

1.2.1. Overt maternal hypothyroidism is known to have serious adverse effects on

the fetus (4,5,6,7,8). Therefore maternal hypothyroidism should be avoided. For overt hypothyroidism: USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○).

1.2.2. SCH (serum TSH concentration above the upper limit of the trimester-specific reference range with a normal free T₄) may be associated with an adverse outcome for both the mother and offspring. In retrospective studies, and in prospective studies on women with SCH and TPO-Ab+, T₄ treatment improved obstetrical outcome, but it has not been proved to modify long-term neurological development in the offspring. However, given that the potential benefits outweigh the potential risks, the panel recommends T₄ replacement in women with SCH. For obstetrical outcome: USPSTF recommendation level, C; evidence, fair (2|⊕○○○) (4,5,6,7,8,9); for neurological outcome: USPSTF recommendation level, I; evidence, poor (2|○○○○) (4,5,6,7, 9).

1.2.3. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T₄ dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, poor (2|⊕○○○) (1,10,11,12).

1.2.4. The T₄ dose usually needs to be incremented by 4 to 6 wk gestation and may require a 30% or more increase in dosage. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (12,13,14,15).

1.2.5. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. T₄ dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 mIU/liter (in an assay using the International Standard) in the first trimester (or 3 mIU/liter in second and

third trimesters) or to trimester-specific TSH ranges. Thyroid function tests should be remeasured within 30-40 d and then every 4-6 wk. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (3, 11, 16, 17).

1.2.6. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored for elevation of TSH above the normal range for pregnancy every 4-6 wk. USPSTF recommendation level: A; evidence, fair (1|⊕⊕⊕○) (12,14).

1.2.7. After delivery, most hypothyroid women need to decrease the T₄ dosage they received during pregnancy to the prepregnancy dose. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (18).

1.1.-1.2.7. Background and evidence

Overt hypothyroidism occurs in 0.3-0.5% of pregnancies, and SCH occurs in 2-3%. Thyroid autoantibodies are found in 5-15% of women during childbearing age, and chronic autoimmune thyroiditis is the main cause of hypothyroidism, apart from iodine deficiency (19). Other causes include radioiodine ablation or surgery for hyperthyroidism, thyroid tumor surgery, congenital hypothyroidism, and rarely, lymphocytic hypophysitis.

Hypothyroid women are more likely to experience infertility, and they have an increased prevalence of abortion, anemia, gestational hypertension, placental abruption, and postpartum hemorrhage (4,5,6,7,8,9). Untreated maternal overt hypothyroidism is associated with adverse neonatal outcomes including premature birth, low birth weight, and neonatal respiratory distress. There may be more fetal and perinatal death, and gestational hypertension may also contribute to the overall increase in neonatal risks. Women with gestational SCH were found in one

study to have more preterm deliveries (20), and the offspring have more admissions to neonatal intensive care and an increased rate of respiratory distress syndrome (4). Even maternal TSH levels in the upper normal range are associated with increased fetal loss, as compared with lower “normal” levels (11).

Thyroid hormone contributes critically to normal fetal brain development (21). In moderate and severe iodine deficiency, there is significant childhood IQ reduction, preventable by gestational iodine supplementation. In iodine-sufficient areas, there is also a significantly increased risk of impairment in neuropsychological developmental indices, IQ scores, and school learning abilities in the offspring of hypothyroid mothers. A study in the United States showed that children born to untreated hypothyroid women had an IQ score seven points below the mean IQ of children born to healthy women (6). Children born to untreated hypothyroid mothers were three times more likely to have IQ that were 1 sd below the mean of controls. Early maternal low free T₄ has been associated with a lower developmental index in children at 10 months of age, and children born to mothers with prolonged low T₄ (until wk 24 or later) showed an 8- to 10-point deficit for motor and mental development (22). If free T₄ recovered spontaneously to normal later in gestation, infants had a normal development, suggesting that prolonged low T₄ was needed to impair fetal neural development. A recent study by Henrichs *et al.* (23) confirmed the adverse effects of maternal free T₄ levels in the lowest 10% of the normal range on early childhood cognitive development.

Diagnosis.

Hypothyroidism may be suggested by cold sensitivity, fatigue, or dry skin or it may go

unnoticed. Because many women remain asymptomatic, particular attention is required from obstetrical care providers for careful diagnosis and, if appropriate, thyroid function evaluation at the first prenatal clinic attendance. Only thyroid function tests confirm the diagnosis.

Total serum T₄ rises rapidly during the first trimester to roughly 150% of the nonpregnant range because of estrogen-induced elevation of T₄ binding globulin. Serum TSH elevation suggests primary hypothyroidism. Thyroid autoantibody titers [TPO-Ab or thyroglobulin (TG) antibodies] confirm an autoimmune origin (12). Serum TSH values are normally lowered, particularly near the end of the first trimester, because of the thyrotropic activity of elevated circulating human chorionic gonadotropin (hCG) concentrations. In the first trimester, the “normal” range is reduced to 0.1-2.5 mIU/liter (2, 24). Thus, a serum TSH within the classical reference range (0.4-4.0 mIU/liter) might be misdiagnosed as “normal” in women who have a slight TSH elevation, or hyperthyroidism may be wrongly suspected in normal women who have a blunted serum TSH.

Serum T₄ distinguishes between SCH and overt hypothyroidism, if normal, or clearly below normal for gestational age, respectively. Reference ranges provided by the manufacturers of most free T₄ measurement kits have been established using pools of nonpregnant normal sera, and such reference ranges are not valid during pregnancy. If free T₄ is the only test available, pregnancy-specific reference ranges should be established for each assay. The nonpregnant total T₄ range (5-12 µg/dl or 50-150 nmol/liter) can be adapted in the second and third trimesters by multiplying this range by 1.5-fold. Alternatively, the free T₄ index (“adjusted T₄”) appears to be a reliable assay during pregnancy.

Treatment.

Levothyroxine is the treatment of choice for maternal hypothyroidism, assuming adequate iodine nutrition (14).

Hypothyroid pregnant women require larger levothyroxine doses than do nonpregnant patients. Women receiving T₄ antenatally usually should increase their dosage by 4-6 wk gestation to 30-50% above preconception dosage (14,15). The increment is greater in women without residual functional thyroid tissue (*e.g.* radioiodine ablation, total thyroidectomy) than in those with residual thyroid tissue (*e.g.* Hashimoto’s thyroiditis) (15). When serum TSH is first checked during pregnancy, the average increments of levothyroxine needed are 25-50 µg/d for serum TSH levels between 5 and 10 mIU/liter, 50-75 µg/d for serum TSH between 10 and 20 mIU/liter, and 75-100 µg/d for those with a serum TSH above 20 mIU/liter.

Management of a pregnant woman with normal TSH for pregnancy, but with thyroid hormone level by reliable assay below the pregnancy and trimester normal range on repeat assay, is controversial and requires further study (22,23). However, in the opinion of the committee, partial replacement therapy may be initiated at the discretion of the caregiver, with continued monitoring.

2.0. Management of hyperthyroidism: maternal and fetal aspects

Recommendations

2.1. Management of maternal hyperthyroidism: maternal aspects

2.1.1. If a subnormal serum TSH concentration is detected during gestation, hyperthyroidism must be distinguished from both normal physiology of pregnancy and gestational thyrotoxicosis because of the adverse effects of overt hyperthyroidism on the mother and fetus.

Differentiation of Graves' disease from gestational thyrotoxicosis is supported by the presence of clinical evidence of autoimmune thyroid disease, a typical goiter, and the presence of TRAb. TPO-Ab may be present in either case. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○) (24,25,26).

2.1.2. For overt hyperthyroidism due to Graves' disease or thyroid nodules, ATD therapy should be either initiated (before pregnancy if possible, and for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T₄ at the upper limit of the nonpregnant reference range. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○); or to maintain total T₄ at 1.5 times the upper limit of the normal reference range, or the free T₄ index in the upper limit of the normal reference range. USPSTF recommendation level: I; evidence, poor (2|⊕○○○) (27).

2.1.3. PTU, if available, is recommended as the first-line drug for treatment of hyperthyroidism during the first trimester of pregnancy, because of the possible association of MMI with specific congenital abnormalities that occur during first trimester organogenesis. MMI may also be prescribed if PTU is not available or if a patient cannot tolerate or has an adverse response to PTU. MMI 10 mg is considered to be approximately equal to 100-150 mg of PTU. Recent analyses reported by the FDA indicate that PTU may rarely be associated with severe liver toxicity. For this reason, we recommend that clinicians change treatment of patients from PTU to MMI after the completion of the first trimester. Available data indicate that MMI and PTU are equally efficacious in the treatment of pregnant women. Practitioners should use their clinical judgment in choosing the ATD therapy, including the potential difficulties involved in switching patients from one

drug to another. If switching from PTU to MMI, thyroid function should be assessed after 2 wk and then at 2- to 4-wk intervals. USPSTF recommendation level: B; evidence, fair (1|⊕⊕○○). Although liver toxicity may appear abruptly, it is reasonable to monitor liver function in pregnant women on PTU every 3-4 wk and to encourage patients to promptly report any new symptoms. USPSTF recommendation level: C; evidence, poor (2|⊕○○○) (28,29,30,31,32,33,34).

2.1.4. Subtotal thyroidectomy may be indicated during pregnancy as therapy for maternal Graves' disease if: 1) a patient has a severe adverse reaction to ATD therapy; 2) persistently high doses of ATD are required (over 30 mg/d of MMI or 450 mg/d of PTU); or 3) a patient is nonadherent to ATD therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester. USPSTF recommendation level: C; evidence, fair (2|⊕○○○) (35,36,37).

2.1.5. There is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome, and treatment could potentially adversely affect fetal outcome. USPSTF recommendation level: C; evidence, fair (2|⊕○○○) (27,38).

2.2. Management of maternal hyperthyroidism: fetal aspects

2.2.1. Because thyroid receptor antibodies (thyroid receptor stimulating, binding, or inhibiting antibodies) freely cross the placenta and can stimulate the fetal thyroid, these antibodies should be measured by 22 wk gestational age in mothers with: 1) current Graves' disease; or 2) a history of Graves' disease and treatment with ¹³¹I or thyroidectomy before pregnancy; or 3) a previous neonate with Graves' disease; or 4) previously elevated TRAb. Women who have a negative TRAb and do not require ATD have a very low

risk of fetal or neonatal thyroid dysfunction. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○) (39,40,41,42).

2.2.2. ¹³¹I should not be given to a woman who is or may be pregnant. If inadvertently treated, the patient should be promptly informed of the radiation danger to the fetus, including thyroid destruction if treated after the 12th week of gestation. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○). There are no data for or against recommending termination of pregnancy after ¹³¹I exposure. USPSTF recommendation level: I; evidence, poor (2|⊕○○○) (43,44,45,46,47).

2.2.3. In women with TRAb or thyroid-stimulating Ig elevated at least 2- to 3-fold the normal level, and in women treated with ATD, maternal free T₄ and fetal thyroid dysfunction should be screened for during the fetal anatomy ultrasound (18th-22nd wk) and repeated every 4-6 wk or as clinically indicated. Evidence of fetal thyroid dysfunction could include thyroid enlargement, growth restriction, hydrops, presence of goiter, advanced bone age, tachycardia, or cardiac failure. If fetal hyperthyroidism is diagnosed and thought to endanger the pregnancy, treatment using MMI or PTU should be given with frequent clinical, laboratory, and ultrasound monitoring. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○) (39,41,48,49,50).

2.2.4. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical and sonographic data, and the information gained would change the treatment. USPSTF recommendation level: B; evidence, fair (2|⊕○○○) (41,51,52,53,54,55,56).

2.2.5. All newborns of mothers with Graves' disease (except those with negative TRAb and not requiring

ATD) should be evaluated by a medical care provider for thyroid dysfunction and treated if necessary. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○) (40, 48, 52).

2.1.1-2.2.5. Background and evidence

The prevalence of hyperthyroidism in pregnancy ranges from 0.1 to 0.4%, with Graves' disease accounting for 85% of cases (28, 57, 58). The activity level of Graves' disease may fluctuate during gestation, with exacerbation during the first trimester and improvement by late gestation. Hyperthyroidism of Graves' disease may be aggravated by high levels of hCG in the first trimester.

Because nonspecific symptoms of hyperthyroidism may be mimicked by normal pregnancy, the presence of a goiter, especially with a bruit or thrill, may point to a diagnosis of true Graves' disease. Thyroid function tests must be interpreted in the context of the normal gestational changes of decreased serum TSH and increased T₄ and T₃ levels.

Patients suspected of having hyperthyroidism require measurement of serum TSH, T₄ or free T₄, T₃ levels, and TRAb. However, interpretation of thyroid function tests must be made in relation to the hCG-mediated decrease in serum TSH levels and the increase in T₄ binding globulin concentrations that occur during pregnancy (59,60,61). In the normal pregnant woman, TSH levels typically are suppressed in the mid to late first trimester.

Fetal hyperthyroidism due to the transplacental passage of maternal TSH receptor stimulating antibody (TRAb) levels is rare (0.01% of pregnancies), but it should be considered in any woman with a past or current history of Graves' disease and may require treatment with maternal antithyroid medications.

Maternal hyperthyroidism is associated with both gestational and

fetal risks that are related to the disease itself and/or to the medical treatment of the disease. Inadequately treated maternal thyrotoxicosis is associated with an increased risk of medically indicated preterm delivery, intrauterine growth restriction and low birth weight, preeclampsia, congestive heart failure, and fetal death (62). In addition, overtreatment of the mother with thioamides can result in iatrogenic fetal hypothyroidism (51), but undertreatment of maternal hyperthyroidism may lead to central congenital hypothyroidism (63,64).

Fetal hyperthyroidism can be associated with intrauterine growth restriction, fetal tachycardia, fetal goiter, advanced bone age, fetal hydrops, preterm delivery, and fetal death (40,41,42, 53, 56, 65). The diagnosis is suggested by any of these signs or abnormalities. Maternal TRAb levels able to induce fetal hyperthyroidism are usually over three times the upper normal limit.

PTU and MMI or its derivative carbimazole are the mainstays of treatment. Recently, the Adverse Event Reporting System of the FDA has focused attention on the relation between hepatotoxicity and PTU (29). This finding has led to a recommendation that PTU use in pregnancy be limited to the first trimester, and then treatment be switched to MMI. Use of MMI during the first trimester has been associated with a possible embryopathy.

3.0 Gestational hyperemesis and hyperthyroidism

Recommendations

3.1. Thyroid function tests (TSH, total T₄, or free T₄ index, or free T₄) and TRAb should be measured in patients with hyperemesis gravidarum (5% weight loss, dehydration, and ketonuria) and clinical features of hyperthyroidism. USPSTF

recommendation level: B; evidence, fair (2|⊕⊕○○) (24,27,66,67,68).

3.2. Most women with hyperemesis gravidarum, clinical hyperthyroidism, suppressed TSH, and elevated free T₄ do not require ATD treatment. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕). Clinical judgment should be followed in women who appear significantly thyrotoxic or who have in addition serum total T₃ values above the reference range for pregnancy. Beta blockers such as metoprolol may be helpful and may be used with obstetrical agreement. USPSTF recommendation level: B; evidence, poor (2|⊕○○○) (13,25,26, 66-68).

3.3. Women with hyperemesis gravidarum and diagnosed to have Graves' hyperthyroidism (free T₄ above the reference range or total T₄ > 150% of top normal pregnancy value, TSH < 0.01 mIU/liter, and presence of TRAb) will require ATD treatment, as clinically necessary. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (13, 25, 26, 66-68).

3.1-3.3 Background and evidence

Gestational hyperthyroidism (GH), also referred as gestational thyrotoxicosis or gestational transient thyrotoxicosis, is defined as transient hyperthyroidism, limited to the first half of pregnancy, characterized by elevated serum free T₄ and suppressed or undetectable serum TSH, in the absence of thyroid autoimmunity. GH is typically associated with hyperemesis gravidarum, defined as severe vomiting in early pregnancy that causes more than 5% weight loss, dehydration, and ketonuria and occurs in 0.5-10 cases per 1000 pregnancies. The etiology of thyroid stimulation is thought to be hCG itself, or molecular variant proteins related to hCG. Multiple gestation is another recognized cause of GH. Very

high elevations of hCG occurring in patients with hydatidiform mole or choriocarcinoma are often associated with clinical hyperthyroidism. TSHR mutations with functional hypersensitivity to hCG have also been recognized as a rare cause of severe GH. Other isolated rare cases of GH, such as hyperplacentosis and hyperreactio luteinalis, have been reported. The condition can cause severe morbidity and may require frequent visits to the emergency room or admission to the hospital for management of dehydration, electrolyte abnormalities, psychological support, and occasionally parenteral nutrition (25,26).

In women with GH, the serum TSH is suppressed or undetectable; serum total T₄ and free T₄ are elevated, but the free T₃ is elevated less frequently. Women with hyperemesis and elevated thyroid hormone levels most commonly do not have other clinical evidence of Graves' disease and lack the TSH receptor antibodies typically present in Graves' disease. A small portion of these patients have clinical hyperthyroidism. Clinical symptoms of hyperthyroidism antedating pregnancy, the presence of goiter, ophthalmopathy, and laboratory evidence of autoimmunity favor the diagnosis of Graves' hyperthyroidism. Because many common signs and symptoms of hyperthyroidism may be mimicked by normal pregnancy, the clinical challenge is to differentiate these disorders (13,25,26, 66-68). There is disagreement as to whether thyroid hormone should be measured in all pregnancies with hyperemesis, or only when clinical features of hyperthyroidism are present. Some authorities suggest that measurement of thyroid function tests may safely be limited to those women with clinical evidence suggestive of hyperthyroidism.

There is no clear evidence in the medical literature that patients diagnosed

with GH have benefited from antithyroid therapy, but only a few patients have been reported who received ATD for a few weeks. The available data indicate that most women with hyperemesis, with no or mild clinical evidence of hyperthyroidism, suppressed TSH, and elevated free T₄, remit spontaneously. No clear data are available to support the use of ATD in the management of women with GH, but clinical judgment should be followed in women with clear signs of hyperthyroidism and elevated free T₄ and free T₃, or total T₃ above the normal pregnancy range (13,25,26,66,67,68).

4.0. Autoimmune thyroid disease and miscarriage

Recommendations

4.1. A positive association exists between the presence of thyroid antibodies and pregnancy loss. Universal screening for antithyroid antibodies, and possible treatment, cannot be recommended at this time. As of January 2011, only one randomized interventional trial has suggested a decrease in the first trimester miscarriage rate in euthyroid antibody-positive women, but treatment duration was very brief before the outcome of interest. However, because women with elevated anti-TPO antibodies are at increased risk for progression of hypothyroidism, if identified such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy. USPSTF recommendation level: C; evidence, fair (2|⊕○○) (69,70,71,72).

4.1. Background and evidence

A 2- to 5-fold increased risk of miscarriage has been found in unselected populations of euthyroid women with autoimmune thyroid disease (70). Most but not all

studies have also demonstrated an association between thyroid antibodies and recurrent miscarriage in euthyroid patients (69,71). However, the data are imperfect because the timing of sample collection for thyroid antibody measurement was not always specified, the prevalence of thyroid antibodies varied widely, and studies measured TPO-Ab or TGAb or both. In some of these reports, thyroid antibodies may simply serve as a marker for generalized autoimmune disease. TSH levels have been found slightly but significantly higher (within the normal range) in euthyroid women with thyroid autoimmunity than in those women without it. In some of these studies, women with thyroid antibodies were older than those without antibodies.

The data are less clear on the miscarriage rate in infertile patients undergoing assisted reproductive technology, according to the presence or absence of thyroid antibodies. Half of the studies find that the presence of thyroid antibodies is associated with a 2-fold increased risk for spontaneous miscarriage in euthyroid women undergoing in vitro fertilization (73,74). No significant difference was found in the other studies, but in some a trend toward a higher miscarriage rate was noticed in the thyroid antibody-positive women. The largest series, although retrospective, failed to demonstrate an adverse effect on miscarriage rates in antibody-positive vs. antibody-negative women undergoing assisted reproductive technology (73). It is not possible to draw a definitive conclusion based on available data.

Treatment

Negro *et al.* (72) performed a prospective, randomized trial of 984 unselected women who were screened for TPO antibody positivity and thyroid function tests on their first obstetrical visit. The 115 women

who were TPO-Ab+ were divided into two groups: group A (n = 57) included TPO-Ab+ women treated with levothyroxine; group B (n = 58) included TPO-Ab+ women who received no levothyroxine intervention. Group C (n = 869) consisted of all TPO-Ab- women, none of whom received levothyroxine. The first trimester miscarriage rate was significantly lower in groups A (3.5%) and C (2.4%) than in group B (13.8%) ($P < 0.05$). However, the mean gestational age at the time of miscarriage was 8.5 wk, and treatment on average did not start until 10.5 wk gestation (40% on treatment by 8 wk and 79% by 12 wk). It should also be taken into account that TSH levels during pregnancy were significantly higher, whereas free T4 levels were significantly lower (although in the normal range) in group B than in group C.

In a retrospective study in Belgium, 42 TPO-Ab+ patients received levothyroxine treatment during pregnancy, and their evolution was compared with 709 TPO-Ab- women. No significant differences in the obstetrical complications rate were observed between the groups, but early miscarriages were not investigated in this study. A further limitation to this study is that a TPO-Ab+ group without levothyroxine treatment was not included (75).

Regarding medical intervention in thyroid antibody-positive women with recurrent abortion, the studies reviewed demonstrate that T4 or iv Ig treatments may decrease the miscarriage rate (64, 65,66,67,68,69,70,71,72,73,74, 75, 78). However, many of these women had evidence of other autoimmunity, and limitations in the design of each study preclude any conclusion regarding the efficacy of medical intervention.

A single study has evaluated the impact of T₄ therapy in euthyroid antibody-positive infertile women who underwent assisted reproduction techniques (73).

Although the miscarriage rate was lower in women who received T₄ (33%) than in those who did not (52%), this difference failed to reach statistical significance (a failing that may have been secondary to the small sample size).

Women with recurrent pregnancy loss are reported to have lower selenium levels in hair and in red blood cells (77). Selenium substitution and treatment with selenomethionine may decrease TPO-Ab levels in euthyroid subjects (78). Large randomized studies are needed to assess the contribution of selenium in the etiology of recurrent pregnancy loss and the potential benefits of its supplementation.

Besides the risk of miscarriages, thyroid autoimmunity may be correlated with a higher frequency of preterm deliveries (between 2- and 3-fold higher than in pregnancy without thyroid antibodies) and low birth weight. According to a study by Negro *et al.* (72) in Italy, the preterm delivery rate was higher (22.4%) in TPO-Ab+ women without treatment than in TPO-Ab+ women on levothyroxine treatment (7%) or in TPO-Ab- women (8.2%) ($P < 0.05$), although the gestational age at delivery was not specified between the groups.

Recently, 9247 singleton pregnancies were prospectively studied in Finland. Perinatal mortality was 2- to 3-fold greater in women who were TPO-Ab+ or TG antibody positive in the first trimester as compared with those who were antibody negative, but most of these infants were also born preterm (79).

Intellectual and motor development score evaluations were performed at 25-30 months of age on the children from 34 euthyroid mothers with elevated titers of TPO-Ab at 16-20 wk gestation. The mean intelligence score was 10 points lower and the mean motor score 9 points lower than those of the controls ($P = 0.001$ and $P < 0.001$, respectively) (80).

More studies are necessary to confirm whether thyroid autoimmunity could be considered a risk factor for impaired neurodevelopment, independent of the thyroid function.

5.0 Thyroid nodules and cancer

Recommendations

5.1. FNA cytology should be performed for predominantly solid thyroid nodules greater than 1 cm discovered in pregnancy. Women with nodules 5 mm to 1 cm in size should be considered for FNA if they have a high-risk history or suspicious findings on ultrasound, and women with complex nodules 1.5-2 cm or larger should also receive an FNA. During the last weeks of pregnancy, FNA can reasonably be delayed until after delivery. Ultrasound-guided FNA is likely to have an advantage for maximizing adequate sampling. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕○) (81,82,83,84).

5.2. When nodules discovered in the first or early second trimester are found to be malignant or highly suspicious on cytopathological analysis, to exhibit rapid growth, or to be accompanied by pathological neck adenopathy, pregnancy need not be interrupted, but surgery should be offered in the second trimester. Women found to have cytology indicative of papillary cancer or follicular neoplasm without evidence of advanced disease and who prefer to wait until the postpartum period for definitive surgery may be reassured that most well-differentiated thyroid cancers are slow growing and that delaying surgical treatment until soon after delivery is unlikely to change disease-specific survival. USPSTF recommendation level: B; evidence, fair (1|⊕⊕○○) (75,83,84,85).

5.3. It is appropriate to administer thyroid hormone to achieve a suppressed but detectable TSH in pregnant women

with a previously treated thyroid cancer, in those with an FNA positive for or suspicious for cancer, or in those who elect to delay surgical treatment until postpartum. High-risk patients may benefit more than low risk patients from a greater degree of TSH suppression. The free T₄ or total T₄ levels should ideally not be increased above the normal range for pregnancy. USPSTF recommendation level: I; evidence, poor (⊕○○○) (86).

5.4. RAI with ¹³¹I should not be given to women who are breastfeeding or for at least 4 wk after nursing has ceased. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕). Furthermore, pregnancy should be avoided for 6 months to 1 yr in women with thyroid cancer who receive therapeutic RAI doses to ensure stability of thyroid function and confirm remission of thyroid cancer. USPSTF recommendation level: B; evidence, fair (1|⊕○○○) (87,88,89).

5.1-5.4 Background and evidence

There is biological plausibility that pregnancy could promote the onset of growth of a benign or malignant nodule due to a pregnancy-induced relative iodine deficiency, the thyroid-stimulating effect of hCG, and high estrogen levels. Only data from areas of mild iodine insufficiency are available and suggest that nodules may be more prevalent in pregnant women and that the volume may increase in gestation (82). Several retrospective studies reported a malignancy rate of about 15%, with one exceptional study finding of 50% (90), and these limited data suggest that the malignancy rate is either similar to or possibly greater than that seen in the general population.

The diagnostic evaluation of a single thyroid nodule or a nodule found in a multinodular goiter discovered during pregnancy should be similar to that of nonpregnant patients (75,91) and

relies primarily on the results of thyroid ultrasound and FNA biopsy. Nodules suspected to be hyperfunctioning may await further assessment with a radionuclide scan until postpartum. For the rare nodule causing severe hyperthyroidism, ATD treatment and operation may be advisable. Evaluating the nodule during pregnancy is often helpful to the mother in making decisions regarding breastfeeding and the potential need for postpartum adjunctive therapy with radioiodine after surgical removal of a cancer.

There is no clear evidence that pregnancy worsens the survival from well-differentiated thyroid cancer found during an existing pregnancy (75,92). However, if the result of FNA is consistent with or highly suggestive of papillary, follicular, anaplastic, or medullary carcinoma, or has suspicious sonographic characteristics, surgery should be offered in the second trimester. During the first trimester, there is concern over the possible teratogenic effects on the fetus, and surgery of any type is associated with increased early fetal loss (93). Surgery in the third trimester is associated with a higher incidence of preterm labor. Fetal loss or significant complications are rare in the second trimester (93). There is some evidence that thyroid cancers discovered during pregnancy have a greater chance of recurrence when defined by increasing serum markers of TG or TG antibodies (94). However, operation for papillary cancer may be postponed with little increased risk until after delivery if the patient is hesitant to undergo surgery during pregnancy (75,91,92,93), and there are no data that surgery undergone during pregnancy as compared with immediately postpartum affects survival.

If a nodule suspicious of cancer is discovered in the third trimester, further workup and treatment can be delayed

until after delivery unless the nodule is rapidly growing or associated with a poor prognosis. Exogenously administered thyroid hormone is recommended for suspicious or malignant nodules to achieve a suppressed TSH with a free T₄ or total T₄ in the upper normal range for pregnancy to avoid both maternal and fetal complications.

Several series have examined the natural history of cancer recurrence in women who became pregnant after receiving successful treatment for thyroid cancer, and in all studies there was no evidence that thyroid cancer was adversely influenced by the pregnancy (95). Monitoring with TG is recommended for women who have received RAI, and women may be maintained on suppressive doses of T₄ that do not cause overt hyperthyroidism.

Multiple studies have indicated that prior treatment with ¹³¹I does not appear to affect subsequent pregnancy outcomes including infertility, congenital malformations, miscarriages, stillbirths, prematurity, low birth weight, infant mortality, the rate of nonthyroidal malignancy in the offspring, or intellectual development (96). However, nursing women should not be offered ¹³¹I therapy because of the concentration of isotope in the lactating breast and transfer of the isotope to the infant. Conception should be avoided for at least 1 yr after ¹³¹I ablative treatment to confirm remission of thyroid cancer and stability of thyroid function tests (87).

6.0. Iodine nutrition during pregnancy

Recommendations

6.1. Women in the childbearing age should have an average iodine intake of 150 µg/d. As long as possible before pregnancy and during pregnancy and breastfeeding,

women should increase their daily iodine intake to 250 µg on average. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (59,97,98,99).

6.2. Iodine intake during pregnancy and breastfeeding should not exceed twice the daily RNI for iodine, *i.e.* 500 µg iodine per day. USPSTF recommendation level: I; evidence, poor (2|⊕○○○) (59,97,98,99).

6.3. Although not advised as a part of normal clinical practice, the adequacy of the iodine intake during pregnancy can be assessed by measuring UIC in a representative cohort of the population. UIC should ideally range between 150 and 250 µg/liter. If there is significant concern, the caregiver should assay TSH and thyroid hormone levels. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

6.4. To reach the daily recommended nutrient intake for iodine, multiple means must be considered, tailored to the iodine intake level in a given population. Different situations must therefore be distinguished: 1) countries with iodine sufficiency and/or with a well-established USI program; 2) countries without a USI program or with an established USI program where the coverage is known to be only partial; and 3) remote areas with no accessible USI program and difficult socioeconomic conditions. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (100,101,102,103,104).

6.5. We recommend that once-daily prenatal vitamins should contain 150-200 µg iodine and that this be in the form of potassium iodide or iodate, the content of which is verified to ensure that all pregnant women taking prenatal vitamins are protected from iodine deficiency. Ideally, supplementation should be started before conception. Preparations containing iron supplements should be separated from thyroid hormone administration by at least 4 h. USPSTF recommendation level: B;

evidence, fair (2|⊕⊕○○) (105).

6.6 We recommend that breastfeeding women maintain a daily intake of 250 µg of iodine to ensure that breast milk provides 100 µg iodine per day to the infant. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○).

6.1.-6.6. Background and evidence

Iodine is essential for the synthesis of T₄, a critical hormone for fetal brain development. Maternal T₄ is the only source of hormone before the development of the fetal thyroid at 13-15 wk gestation; maternal iodine is still required for fetal thyroid hormone synthesis thereafter. During pregnancy, thyroid hormone synthesis increases by 20-40%, compensating for estrogen-induced T₄ binding globulin and increased iodine clearance. Therefore, maternal iodine intake must be increased during pregnancy. Iodine stores should be replete at conception with an iodine intake of more than 150 µg/d (97).

Worldwide, iodine deficiency is the leading cause of preventable fetal brain damage (98,106). Severe iodine deficiency causes endemic goiter, hypothyroidism, cretinism, decreased fertility, miscarriage, increased infant mortality, trophoblastic or embryonic fetal disorders, and mental retardation (99). Even mild to moderate iodine deficiency during pregnancy can lead to increased TSH levels and may cause both maternal and fetal goiter (98). Mild maternal subclinical or overt hypothyroidism due to iodide deficiency may result in intellectual deficit and/or neuropsychomotor deficits in offspring. These problems may be prevented if iodine supplementation is started in early pregnancy (100).

Breastfed infants are dependent upon maternal iodine intake. The mammary gland concentrates iodine, and breast milk supplies 100 µg/d to the infant.

Mothers should continue to have an intake of 250 µg iodide per day during lactation. A World Health Organization expert panel (97) recommended iodine intake of 200-300 µg/d in pregnant and breastfeeding women, based on population studies, noting prevention of maternal hypothyroidism and goiter and fetal goiter.

Environmental iodine varies widely geographically, as does iodine supplementation of food, salt, or oil. The best parameter to evaluate the adequacy of iodine nutrition in a population is urinary iodine excretion (UIE). During pregnancy, the UIE should be 150-250 µg/d (97,100). Although UIE is useful for health population studies, it is not a valid diagnostic criterion in individuals.

The prevalence of iodine deficiency (UIE < 100 µg/d) ranges from 11% in North and South America to 42% in some parts of Africa, and as high as 50% in some parts of Europe and China (107). Recent surveys of iodine nutrition in pregnant women are limited, and a global estimate of the prevalence of iodine deficiency in pregnancy is not possible (105). More recent surveys of urinary iodine in limited geographical areas continue to reveal significant numbers of women with suboptimal iodine nutrition, defined as urinary iodine less than 150 µg/liter during pregnancy, even in areas where iodization of salt has been implemented (97, 105).

In the United States, overall urinary iodine declined substantially from the 1970s to the 1990s, but stabilized at 168 µg/liter in 2002 and 160 µg/liter in 2002-2004. Concomitantly, the mean urinary iodine in pregnant women in the United States decreased from 327 µg/liter to 140 µg/liter from 1971-1974 to 1988-1994, with an increase in the prevalence of moderately low urine iodine concentrations (<50 µg/liter) from 0.6 to 1.9% (108). The most recent National Health and Nutrition

Examination Survey data for pregnant women in the United States note stability of median urinary iodine in pregnancy from 141 µg/liter (1988-1994), 173 µg/liter (2001-2002), and 181 µg/liter (2003-2004), but with a substantial number of women still having low urine iodine (21% < 100 µg/liter and 4.7% < 50 µg/liter) at the most recent report (97,108,109).

In an individual pregnant woman, the best surrogate to determine iodine sufficiency is maternal thyroid function. Iodine restriction during pregnancy results in reduction of free T₄ and increases in TSH, TG, T₃/T₄ ratio, and thyroid volume, with goiter formation in both the mother and fetus. However, Hollowell and Haddow (99) found no evidence of low T₄ or high (>4.5 mIU/liter) TSH values in a small sample of U.S. pregnant women with urinary iodine less than 50 µg/liter.

The recommended method for correcting iodine deficiency worldwide is USI, but in some countries where USI cannot be implemented, massive annual doses of slow-release iodinated oil are given to children and to women in the reproductive age group. Four hundred milligrams of oral iodine will cover the thyroidal needs for an adult for about a 1-yr period (99).

Fortification should begin as soon as possible in a pregnant woman, ideally no later than the first trimester to allow rapid adaptation to the increased needs of pregnancy. It is important to note that even in a population judged to be iodine sufficient, individual women may have inadequate iodine intake before and during pregnancy, thus emphasizing the need for routine supplementation of all pregnant women with adequate iodine in the form of prenatal vitamins. Women should be counseled to take prenatal supplements containing the RNI for pregnancy and to ascertain that their vitamin preparations in fact do contain adequate amounts of

iodine. Supplementation should begin as soon as pregnancy is confirmed.

Excess iodine intake may, paradoxically, lead to an increase in hypothyroidism in subjects at risk for autoimmune thyroid disease and to hyperthyroidism, particularly when iodine is newly introduced in populations with previous iodine deficiency and multinodular goiters. Excess iodine is empirically defined as double the RNI (110).

7.0. Postpartum thyroiditis

Recommendations

7.1. There are insufficient data to recommend screening of all women for PPT. USPSTF recommendation level: I; evidence, poor (2|⊕○○○) (111,112).

7.2. Women known to be TPO-Ab+ should have TSH measured at 6-12 wk gestation and at 6 months postpartum, or as clinically indicated. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○) (112,113,114,115,116).

7.3. Because the prevalence of PPT in women with type 1 diabetes, Graves' disease in remission, and chronic viral hepatitis is greater than in the general population, screening by TSH is recommended at 3 and 6 months postpartum. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

7.4. Women with a history of PPT have a markedly increased risk of developing permanent primary hypothyroidism in the 5- to 10-yr period after the episode of PPT. An annual TSH level should be performed in these women. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○) (113,117-119).

7.5. Asymptomatic women with PPT who have a TSH above the reference range but less than 10 mIU/liter and who are not planning a subsequent pregnancy do not necessarily require intervention, but should, if untreated, be remonitored in 4-8 wk. When a TSH above the reference

range continues, women should be treated with levothyroxine. Symptomatic women and women with a TSH above normal and who are attempting pregnancy should be treated with levothyroxine. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○) (112).

7.6. There is insufficient evidence to conclude whether an association exists between PPD and either PPT or thyroid antibody positivity (in women who did not develop PPT). USPSTF recommendation level: I; evidence, poor (2|⊕○○○). However, because hypothyroidism is a potentially reversible cause of depression, women with PPD should be screened for hypothyroidism and appropriately treated. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○) (120,121,122,123,124,125,126).

7.1.-7.6. Background and evidence

PPT is the occurrence of thyrotoxicosis, hypothyroidism, or thyrotoxicosis followed by hypothyroidism in the first year postpartum in women who were without clinically evident thyroid disease before pregnancy. It is believed to be caused by an autoimmunity-induced discharge of preformed hormone from the thyroid. PPT occurs almost exclusively in women who are thyroid antibody positive.

Prevalence in unselected populations.

The reported prevalence of PPT varies globally, and the mean prevalence in prospective studies in iodine-sufficient areas in which at least two thirds of the cohort was followed for at least 5 months postpartum is approximately 7% (127). Incidence is affected by genetic influences and iodine intake.

Prevalence in women with type 1 diabetes mellitus (DM).

The prevalence of TPO antibodies in patients with type 1 DM reported in the

Familial Autoimmune and Diabetes Study was 26.6%. In accord with this, the incidence of PPT in women with type 1 DM is higher than in an unselected population, with a range of 18-25% (114).

Predictors of PPT.

PPT is caused by the immunological perturbations that occur during pregnancy and postpartum. Some of the immunological abnormalities are observed before the onset of thyroid dysfunction (128). Among these, TPO-Ab positivity is the most useful marker for the prediction of postpartum thyroid dysfunction (129). From 40-60% of women with positive TPO-Ab in early pregnancy develop postpartum thyroid dysfunction (112,123). The majority of mothers with high titers of antibody develop postpartum thyroid dysfunction (129).

Thyrotoxic symptoms of women with PPT.

The thyrotoxic phase of PPT occurs between 1 and 6 months postpartum (most commonly at 3 months) and usually lasts only 1-2 months. It is important to differentiate between the thyrotoxic phase of PPT and Graves' disease presenting *de novo* in the postpartum period. Symptoms during the thyrotoxic phase of PPT tend to be milder than during hyperthyroidism due to Graves' disease. Furthermore, 95% of women with Graves' disease are TSH receptor antibody positive. In contrast to Graves' disease, PPT is characterized by decreased RAI uptake (measurement of ¹³¹I uptake is contraindicated in lactating women). From 20-30% of patients who develop PPT have only thyrotoxic symptoms. Fatigue, palpitations, weight loss, heat intolerance, nervousness, anxiety, and irritability are more prevalent in women with PPT than in euthyroid women (129). The frequency of asymptomatic hyperthyroidism among patients with PPT is approximately 30% (112).

Hypothyroid symptoms of women with PPT.

The hypothyroid phase of PPT usually occurs between 3 and 8 months (most commonly at 6 months). Approximately 40-45% of women who develop only the hypothyroid phase of PPT will experience symptoms, whereas 25-35% of women who develop hypothyroidism after the hyperthyroid phase will experience hypothyroid symptoms (130).

Hypothyroidism tends to happen earlier when preceded by thyrotoxicosis than when it occurs alone. The hypothyroid phase usually lasts 4-6 months. In systematic studies, fatigue, loss of concentration, poor memory, constipation, and possibly depression were most frequently experienced (128,129).

Association of PPT with PPD.

The incidence of PPD in nonselected populations using Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revision (DSMIII-R) criteria appears to be approximately 10% (120). Several studies have addressed whether there is an association between PPD and positive thyroid antibody status alone, in addition to the possible association between PPD and women who have PPT with thyroid dysfunction. At present, reported studies have not revealed a consistent association between PPD and either PPT or the presence of thyroid antibody positivity in euthyroid women postpartum.

Optimal treatment for PPT.

There have been no controlled studies evaluating the optimal treatment for PPT. In the thyrotoxic phase of PPT, intervention with propranolol was recommended for women with symptoms of palpitations, fatigue, heat intolerance, and/or nervousness. Treatment decisions for women in the hypothyroid phase of

PPT depend on both the degree of hypothyroidism and whether the woman is attempting pregnancy. Asymptomatic women who are not planning a subsequent pregnancy and whose TSH level is between 4 and 10 mIU/liter do not necessarily require intervention and should, if untreated, be reevaluated in 4-8 wk. When a TSH above the reference range continues postpartum, women should be treated with levothyroxine. Women with a TSH between 4 and 10 mIU/liter who are either symptomatic or attempting to become pregnant should be treated with T₄.

Follow-up for women with PPT.

Postpartum thyroid dysfunction is typically transient in nature, with the majority of women returning to euthyroidism by the end of the first postpartum year. However, even after recovery from hypothyroidism, abnormalities in ultrasonography and/or iodide perchlorate discharge tests persist, reflecting underlying chronic autoimmune thyroiditis. It is therefore not surprising that a small percentage of women never recover from the initial hypothyroid phase, and 20-64% of women develop permanent hypothyroidism during long-term follow-up (117, 119).

8.0. Screening for thyroid dysfunction during pregnancy

Recommendations

8.1a. Universal screening of healthy women for thyroid dysfunction before pregnancy is not recommended. USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

8.1b. However, caregivers should identify individuals at “high risk” for thyroid illness (Table 1) on the basis of their medical history, physical exam, or prior biochemical data. When such individuals are identified,

prenatal measurement of serum TSH is recommended. If it is above 2.5 mIU/liter, the test should be confirmed by repeat assay. Although no randomized controlled trials are available to guide a response, the committee believes it is appropriate to give low-dose T₄ treatment to bring TSH below 2.5 mIU/liter. This treatment can be discontinued if the woman does not become pregnant or postpartum. USPSTF recommendation level: I; evidence, poor (2|⊕○○○) (22, 131-133).

8.2a. All women considering pregnancy with known thyroid dysfunction and receiving levothyroxine should be tested for abnormal TSH concentrations before pregnancy. USPSTF recommendation level: B; evidence, fair (1|⊕○○○) (134, 135).

8.2b. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T₄ dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, fair (2|⊕○○○) (132,133,134, 136).

8.2c. All women receiving levothyroxine should be verbally screened prenatally to assess their understanding of changing levothyroxine requirements after conception. These women should be counseled to contact a physician or medical professional immediately upon a missed menstrual cycle or suspicion of pregnancy to check their serum TSH level. An additional recommendation may be to increase their levothyroxine dose by 30%, which is often two additional tablets per week (nine tablets per week instead of seven tablets), until their serum TSH can be checked. USPSTF recommendation level: B; evidence, fair (2|⊕○○○) (12,13,14, 135).

8.3a. Universal screening for the presence of anti-TPO antibodies either before or during pregnancy is not recommended. USPSTF recommendation level: C; evidence, fair (2|⊕○○○).

8.3b. However, women with elevated anti-TPO antibodies are at increased risk for miscarriage, preterm delivery, progression of hypothyroidism, and PPT. Therefore, if identified, such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy. USPSTF recommendation level: C; evidence, fair (1|⊕○○○) (72, 132) (see also Section 8.5).

8.4a. The committee could not reach agreement with regard to screening recommendations for all *newly pregnant* women. Two versions are therefore presented.

8.4a1. Some members recommended screening of all pregnant women for serum TSH abnormalities by the ninth week or at the time of their first visit. USPSTF recommendation level: C; evidence, fair (2|⊕○○○) (6,9,22,72,137) (Authors supporting: L.D.G., J.R., J.H.L., N.A., C.J.E.).

8.4a2. Some members recommended neither for nor against universal screening of all pregnant women for TSH abnormalities at the time of their first visit. These members strongly support aggressive case finding to identify and test high-risk women (Table 1) for elevated TSH concentrations by the ninth week or at the time of their first visit before or during pregnancy, and they recognize that in some situations ascertainment of the individual's risk status may not be feasible. In such cases, and where the local practice environment is appropriate, testing of all women by wk 9 of pregnancy or at the first prenatal visit is reasonable. USPSTF recommendation level: I; evidence, poor (2|⊕○○○) (72,80,137,138) (Authors supporting: M.A., E.K.A., J.M., L.B., S.S., S.J.M., D.L., R.H.C.).

8.4b. If serum TSH is greater than 2.5 mIU/liter at the time of testing (or >3.0 mIU/liter in the second trimester),

levothyroxine therapy should be instituted. For overt hypothyroidism, USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕); for SCH and obstetrical outcome, USPSTF recommendation level: C; evidence, fair (2|⊕⊕○○); and for SCH and obstetrical outcome, USPSTF recommendation level: C; evidence, poor (2|⊕○○○) (4,5, 9, 131, 137).

8.4c. If TSH concentration is 2.5-10 mIU/liter, a starting levothyroxine dose of 50 µg/d or more is recommended. Other thyroid preparations (such as T₃) are not recommended. USPSTF recommendation level: C; evidence, fair (2|⊕⊕○○) (135).

8.5. Women at high risk for PPT in the postpartum months should be screened via assessment of serum TSH. These high-risk groups include: 1) women known to be TPO Ab+; 2) women with type 1 diabetes; and 3) women with a prior history of PPT. Screening should occur at 6-12 wk postpartum. Women with Graves' disease who enter remission during pregnancy should be screened for recurrence by TSH assay at 3-6 months. USPSTF recommendation level: C; evidence, poor (2|⊕○○○) (112,113,114) (see also Section 7).

8.1-8.5. Background and evidence

Thyroid dysfunction (hypothyroidism, hyperthyroidism, and thyroid autoimmunity) during pregnancy can result in serious complications for both mother and infant (4,6,9,131,137). For women with undiagnosed thyroid disease, a screening test may identify dysfunction, allowing the institution of interventions such as levothyroxine therapy. The multitude of adverse outcomes linked to untreated thyroid disease during pregnancy (particularly relating to hypothyroidism) leads to consideration of the potential benefit and costs of screening for thyroid dysfunction before or during pregnancy.

The frequency of thyroid disease during

pregnancy and postpartum is sufficient to support consideration for screening to detect abnormal TSH concentrations (19,131,137). Overt hypothyroidism occurs in 0.3-0.5% of pregnancies and SCH in 2-4% of pregnancies (5,6,9,70,72). Numerous studies document an adverse impact on pregnancy (and fetal well-being) when thyroid dysfunction (particularly hypothyroidism) or TPO antibodies are detected (5, 6, 9, 69, 70, 131). Optimal treatment of maternal overt hypothyroidism prevents these complications (9,72, 139).

Maternal SCH is associated with increased incidence of adverse outcomes of pregnancy including preterm delivery, placental abruption, respiratory distress, early pregnancy loss, and admissions to the intensive care unit (4,5,21,81,137). Randomized, prospective study documents an increase in pregnancy complications among women with elevated serum TSH concentrations of 2.5-5.0 mIU/liter in the first trimester without TPO antibodies (138). These data are supported by other retrospective analysis (131). Correction of hypothyroidism before pregnancy restores the pregnancy outcomes to the rate seen in euthyroid TPO-Ab+ women (133,139).

Although the majority of large-scale, well-designed studies depict a consistent adverse impact from mild to moderate maternal hypothyroidism, some studies are contradictory (9,80). Noting that modest discordance exists in the published literature, the task force feels that the majority of available, high-quality data do support the finding that both subclinical and overt hypothyroidism increase the risk of adverse pregnancy outcomes.

Of separate concern, although of equal importance, is the potential for maternal hypothyroidism to also adversely affect fetal cognitive development. Several retrospective studies document danger to the developing fetal brain from both overt

and subclinical maternal hypothyroidism (6,22).

Two recent reports focus on the issue of treatment of SCH and screening. The primary endpoint of the report by Negro *et al.* (137) indicates that universal screening by 9 wk had no benefit on the overall outcome of the total screened vs. nonscreened populations. However, in their study individuals considered high risk were tested and treated in both populations. When the screened and detected “low-risk” pregnancies were compared with the low-risk hypothyroid patients diagnosed after pregnancy, there was a significant reduction in adverse outcomes. Still, it must be noted that screening was done at an early time (about 9 wk) and that the comparison groups had both SCH and positive anti-TPO-Ab.

Information on effects of screening and treatment in relation to neural development are sparse. Correction of iodine deficiency during pregnancy prevents adverse fetal neural development (see Section 6). In the “CATS” study recently published by Lazarus *et al.* (140), the overall outcomes on IQ testing at 3 yr of age between universally screened and not screened pregnancies were not significantly different. Importantly, assessment of maternal thyroid function in this study and initiation of levothyroxine when indicated occurred at 12 wk gestation or thereafter.

Two studies have assessed the efficacy of targeted screening of pregnant women for evidence of hypothyroidism. In the report of Vaidya *et al.* (133), 7.4% of “high-risk” pregnancies were found to have TSH above 4.2 mIU/liter. This represents 1.3% of the entire population studied. In this study, targeted screening failed to detect 28% of pregnancies with elevated TSH, representing 0.7% of the total population. Li *et al.* (81) found in a similar study that targeted screening missed 36% of all individuals with a TSH

above 4.0 mIU/liter.

The complexity of how to interpret and effectively translate the above prospective investigations into clinical screening recommendations has led to mixed viewpoints among members of the task force. Some believe the data support a recommendation for universal screening of newly pregnant women by the ninth week or at the time of first visit. The Vaidya *et al.* (133) and Li *et al.* (81) studies suggest that universal screening is easily done, is reliable, has been deemed cost-effective in one published analysis, is already accepted in many practices and in some countries, but also that a targeted screening approach will fail to detect 30-40% of pregnancies with thyroid dysfunction and that targeted screening imposes the burden of an extended questionnaire, and possibly unreliable or incomplete data. The majority of committee members believed that although secondary endpoints suggest benefit in selected (TPO-Ab+) populations, the primary endpoints of both studies remain negative, and therefore a universal mandate for all women can be recommended neither for nor against at this time.

Regardless, there is unanimous task force agreement that targeted screening of high-risk women is recommended (Table 1) during the prenatal and perinatal periods. With this approach, the committee acknowledges the important data confirming that such case finding will unfortunately miss 30% or more of women with overt or subclinical hypothyroidism (133,137).

Finally, women with known thyroid dysfunction and receiving levothyroxine deserve special attention prenatally. T₄ requirements increase 30-50% during gestation, beginning as early as 4-6 wk gestation (141). In women without residual thyroid function, exogenous levothyroxine must be increased at

the time of pregnancy detection or hypothyroidism will occur. These data suggest that screening women with known thyroid dysfunction (receiving levothyroxine) for abnormal TSH concentrations before pregnancy is beneficial. Furthermore, women can be simultaneously counseled to increase their levothyroxine upon their first missed menstrual cycle and biochemical confirmation of pregnancy. A prospective trial confirms that a recommendation for a two-tablet-per-week increase of their baseline levothyroxine dose (nine tablets per week instead of seven tablets) can substantially reduce the risk of maternal hypothyroidism during the first trimester (135).

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This guideline is also available with CME. Go to <http://www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm>; <http://www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm> for more details.

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11

A 23-year-old Woman with Polymenorrhea

E. Passeri, MD, and S. Corbetta, MD, PhD

A Roumanian 23-year-old girl presented with a 7-month history of polymenorrhea, fatigue, headache, slowed mentation and weight gain (body mass index: 29.9 Kg/m²). Her past medical history was otherwise unremarkable. Physical examination showed facial and peripheral edema, dry skin and fine scalp hair (Figure 11-1). She was admitted to the IRCCS Policlinico San Donato Endocrinology Unit, where bradycardia, low voltage on electrocardiography (ECG), and pericardial effusion at echocardiography were observed. Other abnormalities found included severe microcytic anemia, mild hypercholesterolemia and increased creatine phosphokinase levels.

Hormonal evaluation revealed a very high serum TSH level (1578 µU/ml) with low FT₄ (<0.3 ng/ml) and mild hyperprolactinemia (113 ng/ml). Thyroid



FIG. 11-1. Patient's clinical features at presentation.

ultrasound examination showed a small dyshomogeneous and pseudonodular gland, while thyroid autoantibodies were absent. The serum FSH level was 9.0 mUI/ml, while LH and beta-hCG levels were suppressed. Pelvic ultrasonography revealed enlarged ovaries (67 x 73 mm) with several peripheral follicles.

1. THE MOST LIKELY DIAGNOSIS IS:

- TSH- and PRL-secreting pituitary adenoma
- Severe autoimmune hypothyroidism
- Hypothalamic releasing hormone alterations
- Resistance to TSH
- Laboratory interference

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Pituitary MRI
- Radioiodine scan
- Screening for other autoimmune endocrinopathies
- Positive-emission tomography scan
- Octreoscan

Magnetic resonance imaging (MRI) detected a large sellar and suprasellar mass (23x23x10mm) that bilaterally compressed the cavernous sinus and stretched the optic chiasm (Figure 11-2). Adrenal gland function was tested performing a Synacthen 1 µg iv stimulation test, that detected a subnormal response suggestive for partial central hypoadrenalism (cortisol 9.7→14.4 µg/dl).

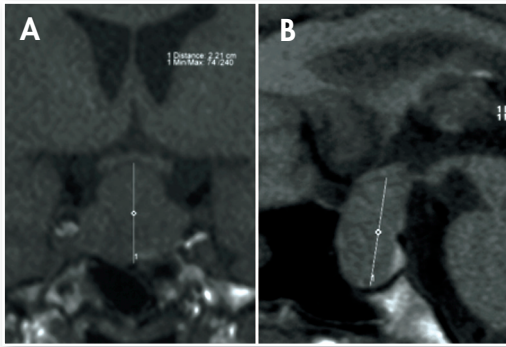


FIG. 11-2. Pituitary MRI imaging at presentation showed a large sellar and suprasellar mass (23x23x10mm) that was bilaterally compressing the cavernous sinus and stretching the optic chiasm.

3. YOUR INTERPRETATION OF THE MRI FINDINGS WOULD BE:

- Pituitary sellar and extrasellar adenoma
- Craniopharyngioma
- Pituitary hyperplasia
- Autoimmune hypophysitis
- None of the above

4. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Hormone replacement therapy with levothyroxine
- Transsphenoidal pituitary surgery
- Treatment with dopaminergic drugs
- Treatment with somatostatin analogs
- Observation

The patient was replaced with cortisone acetate (37.5 mg/die) and levothyroxine (titration up to 100 µg/day (mcg/day)) with dramatic improvement of her symptomatic complaints and modest body weight loss. Two months later, the patient was reevaluated and serum FT₄ and TSH levels were found to have normalized, and the prolactinemia had declined to 50 ng/ml. However, hypoadrenalism persisted (serum cortisol levels after stimulation with ACTH 1 µg ev: 7.3→14.2 µg/dl).

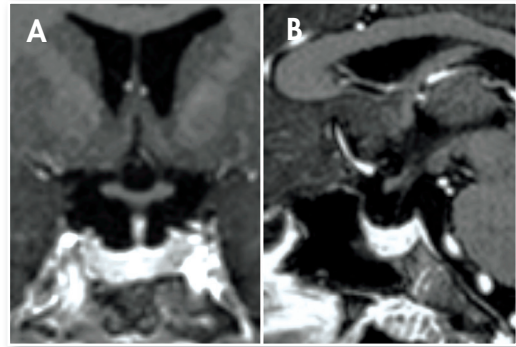


FIG. 11-3. Pituitary MRI imaging after two months of levothyroxine treatment showed complete regression of the large sellar and suprasellar mass.

Normal menses resumed, with normal estradiol and gonadotropin levels, and a GH deficit was excluded. Interestingly, follow up MRI imaging documented the complete shrinkage of the pituitary lesion (Figure 11-3). One month later cortisol secretion normalized and cortisone replacement therapy was discontinued. The patient subsequently was lost to follow up as she returned in Roumania.

Diagnosis

Extensive Pituitary Hyperplasia in Longstanding Primary Hypothyroidism.

Discussion

Thyrotroph hyperplasia and consequent pituitary enlargement in cases of longstanding primary hypothyroidism are due to the lack of thyroid hormones feedback and are generally reversible on levothyroxine replacement (1, 2). Although a rare clinical condition, it is the most frequent cause of a pituitary mass occurring in the context of untreated severe primary hypothyroidism (3) and has been reported in both adults and children (4-6). Rarely, a spontaneous ovarian hyperstimulation syndrome may occur (7), like the mild ovarian hyperstimulation observed in this patient, probably caused by the FSH-mimicking effect of elevated

TSH levels (8). Despite recent progress in imaging techniques, MRI and computed tomography scan have a low specificity in revealing pituitary hyperplasia and distinguishing it from pituitary adenomas. Moreover, thyrotroph hyperplasia may be associated with lactotroph hyperplasia and hyperprolactinemia. For these reasons, the diagnosis is often challenging and MRI confirmation of shrinkage following replacement therapy with levothyroxine may be conclusive. This patient supports the importance of early recognition of reversible pituitary hyperplasia in long standing primary hypothyroidism, in order to avoid unnecessary surgery and the neurological and visual consequences of an extrasellar mass that could occur in the absence of treatment.

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Answers:

Question 1: b

Question 2: a

Question 3: c

Question 4: a

12

A 28-year-old Woman with a Pituitary Malformation

Elena Malchiodi, MD, Marcello Filopanti, MD, PhD, and Anna Spada, MD, PhD

A 28-year-old woman with mild neurofibromatosis type 1 underwent brain magnetic resonance imaging (MRI) as part of initial evaluation. MRI showed a pituitary gland and stalk duplication (Figure 12-1) and a 6-mm diencephalic mass (Figure 12-2). The patient had normal facies and habitus, and a history of menarche at 12 years, normal menses, and no signs or symptoms of neurological dysfunction.



FIG. 12-1. Duplication of pituitary gland: coronal MRI T1-weighted sections.

1. THE MOST LIKELY DIAGNOSIS FOR THE DIENCEPHALIC LESION IS:

- Hamartoma
- Astrocytoma
- Diencephalic malformation
- Meningioma
- Metastasis

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Brain computer tomography
- 3-Tesla brain MRI
- MRI of brain after 3 months
- Antero-pituitary function testing
- Visual fields examination

To characterize the diencephalic lesion, a 3-Tesla-encephalic MRI was performed. A mild asymmetry between the two glands was found, with ectopia of right neurohypophysis and a bright spot in the left infundibulum likely due to left

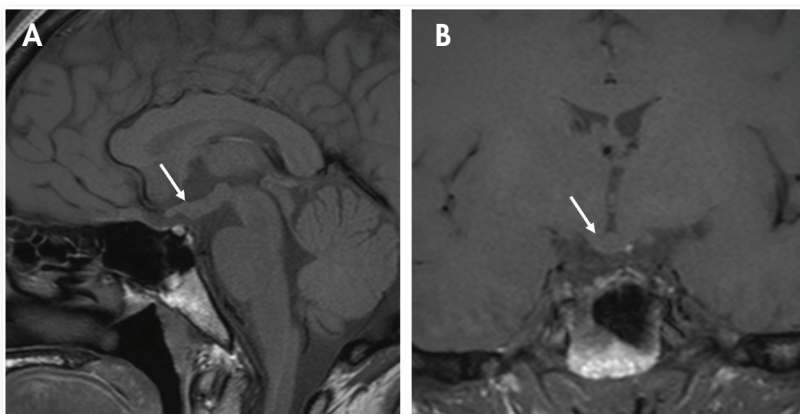


FIG. 12-2. Diencephalic mass: sagittal (A) and coronal (B) MRI T1-weighted sections.

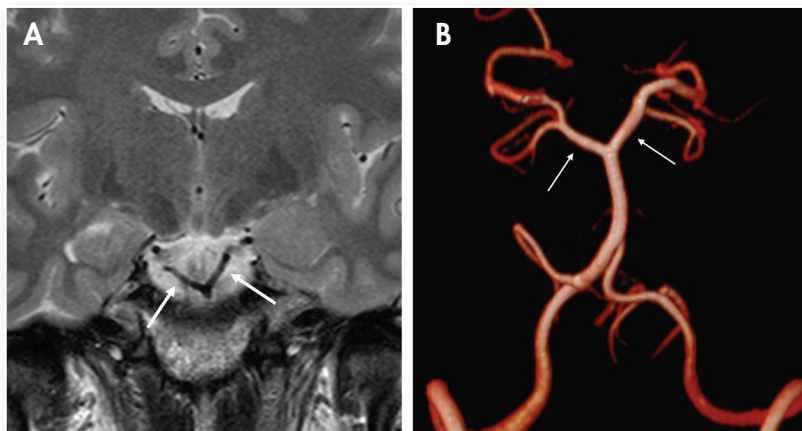


FIG. 12-3. Partial basilar artery duplication. Three-Tesla encephalic MRI: coronal T2-weighted section (A) and three-dimensional magnetic resonance angiography (B).

neurohypophysis ectopia. The diencephalic mass was attributed to incomplete hypothalamus duplication, as previously reported (1, 2). A magnetic resonance angiography, performed to assess suspected vascular abnormalities, revealed a partial basilar artery duplication (Figure 12-3), as reported in pituitary duplication (1). Visual fields were normal. Blood analysis showed normal pituitary function and electrolytes.

Six months later, the woman had a spontaneous pregnancy.

3. YOUR MANAGEMENT DURING PREGNANCY WOULD BE:

- Visual fields monthly
- Visual fields every three months
- Visual fields if a visual defect occurs
- MRI at the 18th week of gestation
- MRI if neurological symptoms occur

Visual field was normal both at 13th and 26th week of gestation. At 39th week of gestation patient developed polydipsia and polyuria (about 5 liters/day). The woman had no signs or symptoms of neurological dysfunction or visual defect. Laboratory blood testing showed: glycemia 89 mg/dl, Na 145 mEq/l, K 4.2 mg/dl, plasma

osmolality 296 mOsm/Kg. Urine specific gravity was 1008 nv: 1010-1030. Glycosuria was absent.

4. YOUR INTERPRETATION OF BIOCHEMICAL FINDINGS:

- Gestational diabetes mellitus
- Gestational diabetes insipidus
- Psychogenic polydipsia
- Dypsogenic polydipsia
- Vascular central diabetes insipidus

To correct peripartum transient gestational diabetes insipidus, the patient was treated with desmopressin.

She was delivered of a healthy newborn by cesarean section. After delivery, blood electrolytes had spontaneous normalized. Three months after discontinuation of breast feeding, pituitary imaging was unchanged and pituitary function was normal.

Diagnosis

Duplication of Pituitary Gland.

Discussion

Pituitary duplication (PD) is an extremely rare malformation that has been described in about 40 cases since 1880. Several

mechanisms have been proposed for PD: partial twinning, prenatal teratogen exposure, extreme presentation of the median cleft face syndrome or splitting of the notochord during blastogenesis (2, 3). PD is associated with additional neural, craniofacial, oropharyngeal, or vertebral malformations (2-5) that represent a continuum of defects in blastogenesis. These features include cleft palate, bifid tongue, hypertelorism, callosal agenesis, nasopharyngeal teratoma, absence of the olfactory bulb and duplication of the basilar artery (6).

This is the first patient described with association of PD, incomplete hypothalamus duplication and neurofibromatosis type 1.

In conclusion, this is an example of duplication of the pituitary gland and was reported by Filopanti *et al.* in the JCEM in 2011 (7) from which the above case was abstracted. The authors recommend regular control of pituitary function and image in these patients.

Subsequent Follow-up on the Patient:

When last seen in January 2013, the patient had normal basal pituitary function and a brain MRI was unchanged.

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Answers:

- Question 1. c
Question 2. b
Question 3. b
Question 4. b

13

A 41-year-old Woman with Sweating and Palpitations

Salvatore Maria Corsello, MD, and Rosa Maria Paragliola, MD

A 41-year-old woman came to our attention complaining of sweating, palpitations and anxiety over the past year. Her physician suggested an endocrinological evaluation because of suspicion of hyperthyroidism. During her clinical evaluation, she also reported hypertensive crises (blood pressure 190/110 mmHg) with headache, and weight loss. She also complained of oligomenorrhea.

Physical examination showed an enlarged and painless thyroid gland without ophthalmopathy. Her blood pressure was normal but tachycardia was present, confirmed by an electrocardiogram showing sinus tachycardia without any ST segment or T wave abnormalities.

1. THE MOST LIKELY DIAGNOSIS IS:

- a. Graves' disease
- b. Premature ovarian failure
- c. Pheochromocytoma
- d. Painless thyroiditis
- e. Anxiety

Clinical evaluation was strongly suggestive of pheochromocytoma. Thyroid and ovarian function were evaluated, excluding hyperthyroidism and premature ovarian failure. Twenty-four hour urinary fractionated metanephrines and catecholamines were collected, showing

very high values of normetanephrines and norepinephrines (Table 13-1).

2. YOUR NEXT STEP IN EVALUATION IS:

- a. Abdominal computer tomography (CT) scan
- b. Metaiodobenzylguanidine (MIBG) scintigraphy
- c. ¹⁸F DOPA - PET
- d. Abdominal ultrasound
- e. a + b

Abdominal CT scan was performed. The right adrenal gland was normal, and an approximately 3.5 cm mass was detected in the left adrenal gland (Figure 13-1).

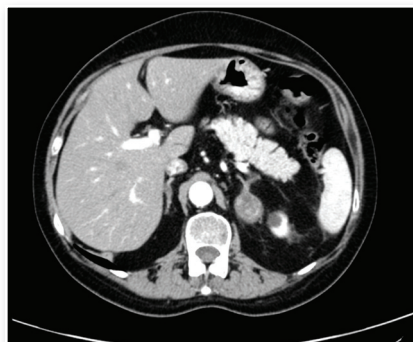


FIG. 13-1. Abdominal CT scan showed a left adrenal mass with regular margins, of 33 x 31 x 35 mm. The lesion appeared hypodense in basal conditions, with gradual enhancement after iodinated contrast medium.

TABLE 13-1:

Metanephrines 133 µg/24h	n.v. 50–340	(674 nmol/d, n.v. 253–1,720)
Normetanephrines 3,418 µg/d	n.v. 90–445	(18,662 nmol/d, n.v. 491–2,430)
Epinephrines 4.4 µg/d	n.v. 2–22	(24 nmol/d, n.v. 11–120)
Norepinephrines 828 µg/d	n.v. 12–86	(4,893 nmol/d, n.v. 71–507)

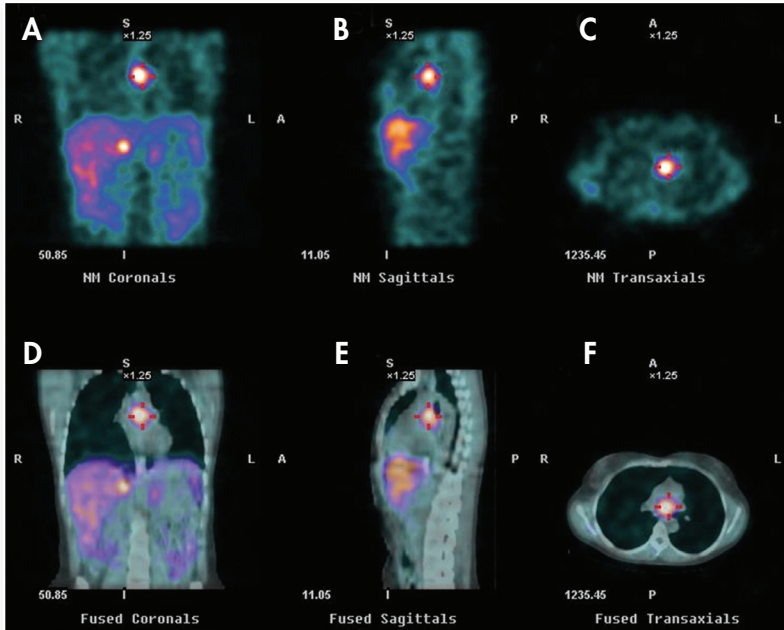


FIG. 13-2. At ^{123}I -MIBG scan, a single focal uptake in the mediastinum was revealed (**A**, coronal view; **B**, sagittal view; **C**, transaxial view). Computed tomography-fused images were suggestive for a retrocardiac paraganglioma (**D-F**).

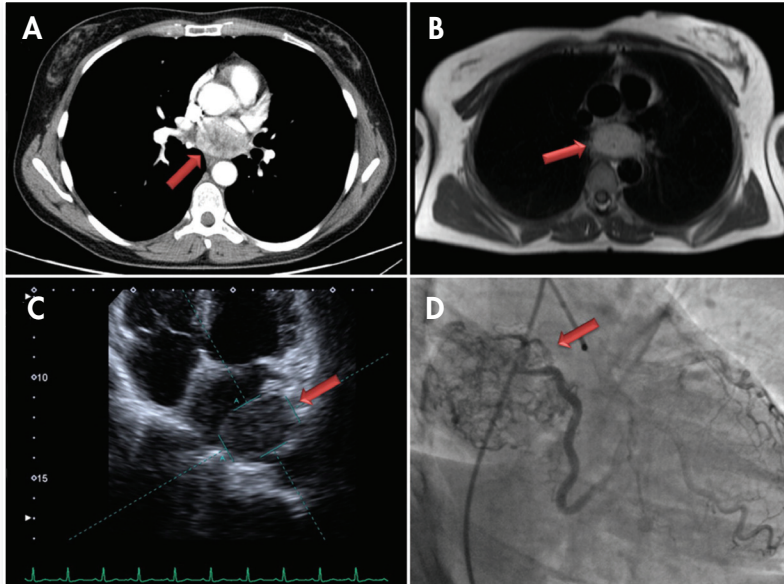


FIG. 13-3. Cardiac CT scan (**A**) showed a subcarinal retrocardiac 46 mm mass, characterized by inhomogeneous enhancement with hypodense areas, close to left superior pulmonary vein and causing compression to left atrium, corresponding with the uptake revealed by MIBG scintigraphy. The lesion was suspected for retrocardiac paraganglioma and the diagnosis was confirmed by cardiac magnetic resonance imaging (MRI) (**B**) and by transesophageal echocardiography (**C**). Coronary angiography (**D**) showed a retrocardiac lesion that was supplied by coronary circle and in particular from the circumflex artery.

To confirm the clinical suspicion of pheochromocytoma, a ^{123}I -MIBG scan was performed. However, no adrenal uptake was present, while a single focal uptake of approximately 4 cm was documented in the mediastium (Figure 13-2).

The MIBG scintigraphy was integrated with other radiological techniques which allowed diagnosing a 46 mm retrocardiac paraganglioma (Figure 13-3). Biochemical evaluation confirmed that the adrenal mass was a non-secreting incidentaloma.

Genetic test evaluation was performed, excluding succinate dehydrogenase (SDH) complex subunit (SDHB, SDHC, and SDHD) mutations. The patient was treated with doxazosin treatment (starting at 2 mg/day and progressively increased to 8 mg/day) to control hypertension and to avoid arrhythmia. One month later, the subject underwent cardiac surgery under extracorporeal circulation. The surgical approach was through a median sternotomy. The aorta and the pulmonary artery were divided to access the tumor, which was posterior to the left atrium. Macroscopically, the tumor was encapsulated, and there was a plane of cleavage with the surrounding structures, and complete resection was achieved. In spite of adequate preoperative medical treatment, a hypertensive crisis occurred during surgical manipulation.

3. IN YOUR OPINION, INTRAOPERATIVE HYPERTENSIVE CRISIS DURING PHEOCHROMOCYTOMA/ PARAGANGLIOMA SURGERY SHOULD BE TREATED WITH:

- a. Clonidine
- b. Phentolamine
- c. Labetalol
- d. Verapamil
- e. Furosemide

The intraoperative hypertensive crisis was treated with intravenous phentolamine. After surgery, the patient was treated with copious hydration aimed to expand plasma volume and to avoid hypotension. Antihypertensive therapy was withdrawn. Blood pressure was maintained on low to normal values and no hypertensive crises were documented.

Final histology confirmed a paraganglioma (chromogranin A and synaptophysin chromogranin A and synaptophysin positive at immunohistochemistry; Ki 67, 2%).

Diagnosis

Retrocardiac Paraganglioma.

Discussion

Pheochromocytomas and paragangliomas are rare tumors of the autonomic nervous system which derive from neuroectodermal tissue in the adrenal medulla or extra adrenal ganglia, respectively. These tumors, which occur in 2–8 per million people, have a peak incidence in the third to fourth decade of life (1). Even if they are often benign lesions, high morbidity and mortality are related to mass effect and high circulating catecholamines levels, which cause severe hypertension and arrhythmias leading to cardiovascular complications.

The clinical presenting hallmarks of catecholamine-secreting tumors are headaches, palpitations and diaphoresis associated with hypertension, although these symptoms are not always present (2).

Paragangliomas, also termed extra-adrenal pheochromocytomas, account for approximately 20% of catecholamine-producing tumors (3) and are mostly found in the head and neck (4), whereas the retrocardiac location represents an unusual finding (5–7). Cardiac paragangliomas can be classified, on the basis of their origin, into intra-pericardial tumors if

they arise from the ganglia associated with the aorta, pulmonary arteries or coronary arteries, and into intra-cardiac tumors if derived from the ganglia of the atrial walls (8). Population-based studies found that approximately one-third of patients with what initially appeared to be sporadic catecholamine secreting tumor, had a germline mutation in a known susceptibility gene (9). To date, 10 susceptibility genes have been identified: *VHL* for von Hippel-Lindau disease (vHL), *NF1* for Neurofibromatosis Type 1 (NF1) and *RET* for Multiple Endocrine Neoplasia Type 2 (MEN 2), which are three well known cancer susceptibility syndromes; moreover, SDH complex subunit genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*), one of the SDH complex cofactors, *SDHAF2* and two recently recognized susceptibility genes, *TMEM127* and *MAX*, are associated with the pathophysiology of catecholamine secreting tumors. In particular, paragangliomas are more frequently associated with mutations of SDH complex subunit genes.

Like pheochromocytomas, the diagnostic work-up of paragangliomas includes laboratory evaluation (plasma free metanephrines and/or urinary fractionated metanephrines and catecholamines) and radiological and nuclear medicine imaging techniques. In particular, MIBG scintigraphy represents an important evolution in the diagnosis of paragangliomas, having high sensitivity (~90%) and specificity (100%) (10). However, CT scan, echocardiography and, more importantly, MRI are crucial in delineating the extent of the tumor and its relation to the surrounding structures. The only curative treatment of these tumors is in fact complete surgical resection, which can be complicated both by the cardiovascular risk associated with the excess of catecholamines, and by the risk of severe hemorrhage due to local

invasion. In this context, the preoperative use of alpha-blockers becomes paramount to prevent catecholamine-related complications, and the use of intravenous phentolamine during surgical manipulation should also be considered.

Subsequent Follow-up on the Patient

Biochemical evaluations performed 3 months after the surgery confirmed remission of the disease: normetanephrines were 112 µg/d [n.v. 90–445 (611 nmol/d, n.v. 491-2430)], and norepinephrines were 20 µg/d [n.v. 12–86 (118 nmol/d, n.v. 71–507)]. Blood pressure was within normal limits. Patient is now performing yearly clinical and biochemical evaluation and can be considered free of disease.

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Answers:

Question 1. c

Question 2. e

Question 3. b

14

A 74-year-old Female with Weight Loss and Fatigue

Nicolaas A. Bakker, MD, PhD, and J. Marc C. Van Dijk, MD, PhD

A 74-year-old woman presented with a 1-year history of tiredness, dizziness, vomiting, reduced appetite and nine kilograms of weight loss. There was no history of headache, polydipsia or polyuria. Subsequent visual field perimetry revealed no abnormalities. Endocrine studies are shown in Table 14-1. Further laboratory studies were unremarkable.

TABLE 14-1:

TSH	1,53 mU/L (ref: 0,30-4,20)
T4	8.4 pmol/L (ref 12-24)
Cortisol	90 nmol (ref 220-750)
FSH	4,7 U/L (ref <40)
LH	1.8 U/L (ref <40)
Prolactin	2562 mUL (ref 102-496)

1. THE MOST LIKELY DIAGNOSIS IS:

- Neoplastic (pituitary adenoma, carcinoma, other)
- Prolactinoma
- Autoimmune (lymphocytic hypophysitis)
- Granulomatous disease (*e.g.*, sarcoidosis, hemochromatosis)
- Empty sella syndrome
- Infectious cause including tuberculosis
- Medication (opiates, glucocorticoid therapy)

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Dynamic laboratory investigations (insulin tolerance testing, ACTH stimulation testing)
- To start hormone replacement therapy
- MRI of the brain

Because of the anterior pituitary failure, subsequent magnetic resonance imaging (MRI) of the brain was performed to exclude a mass lesion (Figure 14-1).

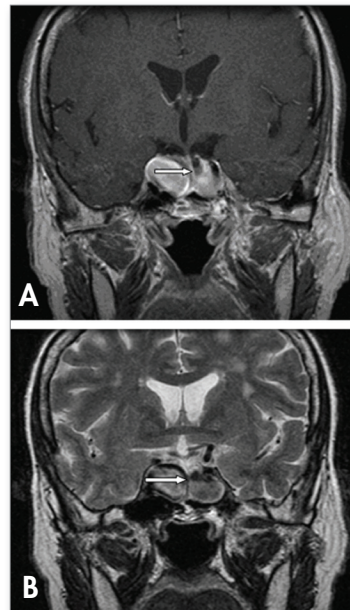


FIG. 14-1. MRI, T-1 weighted images with Gadolinium enhancement, coronal reconstruction (**A**) and T-2 weighted image, coronal reconstruction (**B**). The pituitary gland is “squeezed” between the two cavernous sinus aneurysms. The pituitary stalk is indicated by the white arrow.

3. YOUR INTERPRETATION OF THE MRI IMAGES:

- Pituitary adenoma
- Pituitary meningioma
- Carotid artery aneurysms (bilateral)

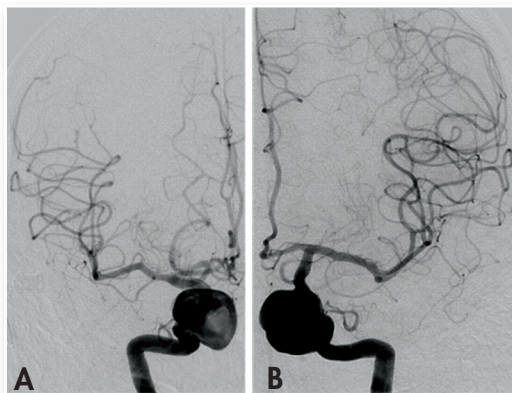


FIG. 14-2. Digital subtraction angiography of the right internal carotid artery (A) and left internal carotid artery (B) showing bilateral large cavernous sinus aneurysms.

Diagnosis

Bilateral Cavernous Sinus Aneurysms.

Discussion

To our surprise, MRI revealed two large bilateral cavernous sinus aneurysms with the pituitary gland “squeezed” in between (Figures 14-1 and 14-2). Furthermore, probably due to chronic pulsatile pressure of the aneurysms, encroachment of the sellar floor was present. As a result, the two aneurysms extended into the sphenoid sinus, thereby posing a significant risk for a potentially fatal nosebleed in case of rupture of one of the aneurysms.

Consequently, the patient was offered a bilateral stenting procedure of the internal carotid artery with additional coiling of the aneurysms to be done if deemed necessary. In the meanwhile, the patient was discharged on hydrocortisone and levothyroxine.

Although several reports have described panhypopituitarism caused by intrasellar-, or unilateral carotid aneurysms (1-4), anterior pituitary failure and hyperprolactinemia caused by “squeezing” of the pituitary gland between bilateral cavernous sinus aneurysms has never been described before to our knowledge. The mechanism causing this pituitary

failure and increased prolactin level is related to hypothalamic or pituitary stalk compression, causing interference with the delivery of releasing and inhibiting factors to the pituitary gland (1).

When there is a combination of pituitary failure and a suprasellar heterogeneously enhancing mass, an aneurysm should always be ruled out. In these cases, irradiation would be of little value and unanticipated surgery could be catastrophic (3).

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Answers:

Question 1. a

Question 2. c

Question 3. c

15

A 37-year-old Woman with a Sellar Mass

Alexander T. Faje, MD, and Nicholas A. Tritos, MD, DSc

A 37-year-old gravida 1 para 1 woman presented with increasingly frequent headache. She had noted “spots” in her peripheral visual fields. Visual field testing was normal. She had noted mild galactorrhea over the previous 4 years. She was taking an oral contraceptive and had regular withdrawal bleeding. Laboratory testing showed mild hyperprolactinemia [prolactin, 24 ng/ml (869 pmol/liter); normal, less than 20 ng/ml]. The rest of her pituitary function was normal. Magnetic resonance imaging (MRI) revealed a 2.5 by 1.6 by 1.6 cm sellar mass, displacing the pituitary superiorly. The optic chiasm was not compressed (Figure 15-1).

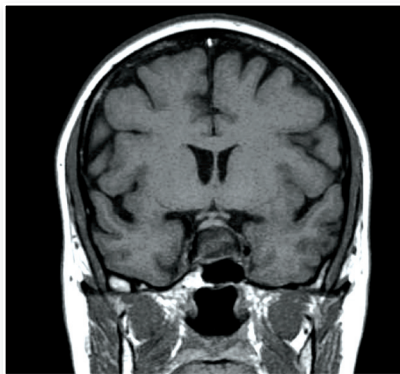


FIG. 15-1. Non-contrast enhanced T1-weighted coronal MRI image showed a heterogeneous sellar mass with peripheral flow void. The pituitary was displaced superiorly.

1. THE MOST LIKELY DIAGNOSIS IS:

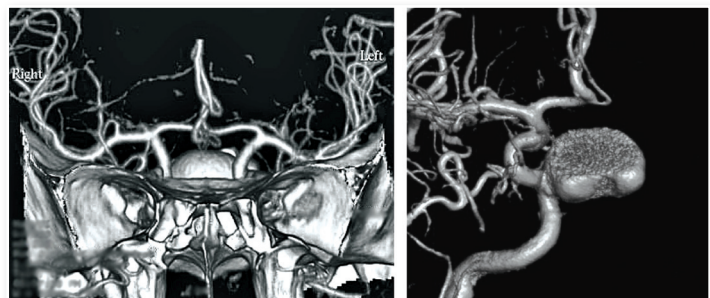
- Pituitary adenoma
- Hypophysitis
- Aneurysm
- Rathke’s cleft cyst
- Craniopharyngioma

2. THE NEXT STEP IN EVALUATION AND MANAGEMENT OF THIS PATIENT WOULD BE:

- Cabergoline therapy
- Transsphenoidal pituitary adenomectomy
- Glucocorticoid therapy in pharmacologic doses
- Computed tomography angiogram
- Observation

Computed tomography angiography (CTA) confirmed the presence of a large intrasellar aneurysm arising from the right internal carotid artery (Figure 15-2).

FIG. 15-2. Three dimensional reconstructed CTA images (left and right panel) revealing a right internal carotid artery aneurysm.



3. THE NEXT BEST STEP IN MANAGEMENT OF THIS PATIENT WOULD BE:

- a. Transsphenoidal surgery
- b. Selective coil embolization of the aneurysm
- c. Aneurysm clipping via craniotomy
- d. Observation
- e. Insertion of a flow diverting stent

Diagnosis

Right Internal Carotid Artery Aneurysm.

Discussion

Sellar aneurysms arising from the internal carotid artery represent an uncommon sellar pathology (1). A possible association between sellar aneurysms and pituitary adenomas has been proposed, but has also been disputed (2). Sellar aneurysms may uncommonly cause hypopituitarism or hyperprolactinemia (as a result of stalk compression) (3). Additional possible manifestations include headache, eye pain, visual field deficits or other cranial nerve palsies, occurring as a result of mass effect (4, 5). Rupture of an aneurysm leads to subarachnoid hemorrhage or (rarely) pituitary apoplexy (6).

The differential diagnosis of sellar aneurysms includes pituitary adenomas as well as other less common causes of

sellar masses. Preoperative diagnosis of a sellar aneurysm is essential in order to avert a potential surgical catastrophe. Imaging characteristics on MRI suggestive of an aneurysm include the presence of a flow void sign on T1-weighted images in continuity with the lumen of an adjacent blood vessel, and an onion skin appearance on T1-weighted images (indicative of intraluminal clot). These findings appear to have good diagnostic sensitivity (7). However, some cystic lesions may appear equally hypointense. Once suspected, CTA or digital subtraction angiography helps to confirm the diagnosis (8, 9).

In patients with unruptured aneurysms, selective coil embolization, performed via an endovascular approach, leads to better outcomes than aneurysm clipping and is preferred if the anatomy is suitable (10, 11). Insertion of a flow diverting stent is being investigated as a potential therapy in patients with complex intracranial aneurysms (12).

Subsequent Follow-up on the Patient

The patient underwent selective coil embolization of the aneurysm (Figure 15-3). Her headaches subsequently resolved and spontaneous menses resumed. Mild hyperprolactinemia persisted [37 ng/ml (1608 pmol/liter)], and the rest of her pituitary function remained normal. Repeat



FIG. 15-3. Carotid digital subtraction angiogram showed a right carotid artery aneurysm (left panel). Selective coil embolization of the aneurysm (right panel).

angiography was performed 6 months later and showed only a small neck residual, which remained stable on magnetic resonance angiography performed 12 months after embolization.

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Answers:

Question 1. c

Question 2. d

Question 3. b

16

Suprasellar Tumor Growing During Pregnancy: a Difficult Decision-Making Process

Matteo Zoli, MD, and Marco Faustini-Fustini, MD

A 43-year-old woman was admitted at 32 weeks into her second pregnancy with a 2-week history of progressive visual impairment (consisting of bitemporal hemianopsia and reduced visual acuity to 1/10 in the left eye and 4/10 in the right eye).

Magnetic resonance imaging (MRI) showed a suprasellar homogeneous contrast enhancing mass, overlying a normal-sized sella with a preserved pituitary gland (Figure 16-1A).

1. THE MOST LIKELY DIAGNOSIS IS:

- Pituitary adenoma
- Suprasellar craniopharyngioma
- Tuberculum sellae meningioma
- Germinoma
- Optic glioma

2. HOW WOULD YOU MANAGE THIS PATIENT?

- Observation
- Urgent surgery with fetal monitoring
- Induce delivery and then monitor visual symptoms
- Induce delivery and then plan immediate surgical resection
- Induce delivery, and then plan immediate radiosurgical treatment

She was given oral dexamethasone to accelerate fetal lung maturation. A healthy boy was born at 34 week gestation by cesarean section. After delivery, the visual disturbances did not improve, and the patient underwent an endoscopic transsphenoidal transplanum/trans-tuberculum approach, thereby achieving radical removal of the

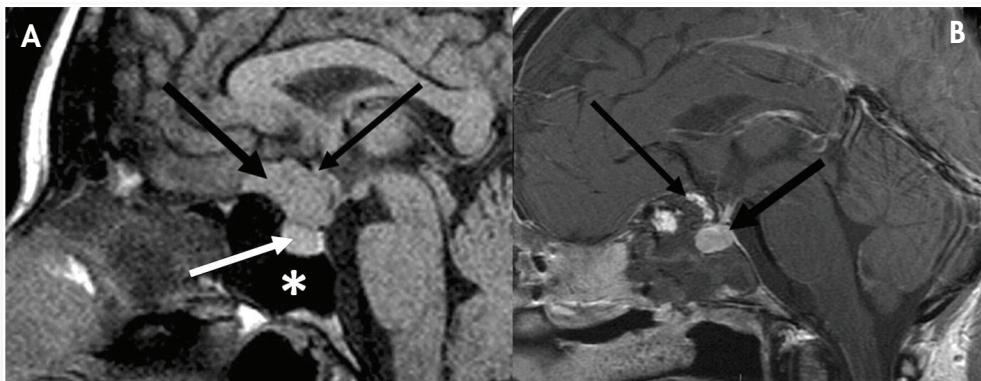
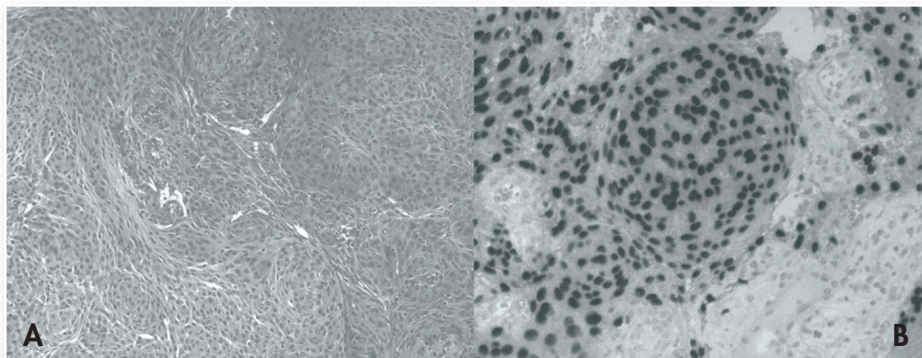


FIG. 16-1. Magnetic resonance imaging sagittal view. **A**, T1-weighted image without gadolinium. TBM, Thick black arrow; chiasm, thin black arrow; pituitary gland, white arrow; sphenoid sinus, star. **B**, T1-weighted image with gadolinium. Pituitary gland, Thick black arrow; fascia lata graft, thin black arrow.

FIG. 16-2. **A**, Hematoxylin and eosin stain showing bland cells in myxoid stroma typical for meningotheliomatous meningioma World Health Organization grade I. **B**, Expression of progesterone receptor by 80% of tumor cells.



meningioma. Histological examination showed a meningotheliomatous meningioma with marked expression of progesterone receptors (Figure 16-2). The postoperative course was uneventful, and she was discharged home on day 5 with complete recovery of her visual function. The patient did not demonstrate hypothalamic/pituitary dysfunction during or after pregnancy. Three months later, a repeat MRI confirmed the radical removal of the tumor (Figure 16-1B). When last seen 5 months after surgery, she was in good clinical condition.

Diagnosis

Tuberculum Sellae Meningioma.

Discussion

The growth of sellar tumors during pregnancy is an uncommon, but potentially dramatic event. It occurs mainly with pituitary adenomas, while tuberculum sellae meningiomas (TBM) are rarely the cause (1).

To our knowledge, 13 other cases of TBM growing during pregnancy have been reported (2-5). The growth of a meningioma during pregnancy was first reported by Hagedorn in 1937 (6). Many physiopathological hypotheses have been proposed for this phenomenon. Goldberg

pointed out that raised tissue fluid, perilesional edema, hydropic swelling and vacuolation are possible explanations for the enlargement of meningioma during pregnancy (2). However, the high expression of progesterone receptor in the specimen (Figure 16-2) strengthens the role of this hormonal factor in the rapid tumor growth, especially because it occurred in the last trimester of pregnancy when the progesterone serum levels are higher (1-4). Progesterone could be involved in the tumor growth, directly stimulating the receptors expressed by the tumor cells. In support of this hypothesis is the observation of the regression of multiple intracranial meningiomas after discontinuation of long-standing use of megestrol acetate (7).

The management of these tumors in pregnancy is particularly complex. Treatment is aimed at two purposes: on the one hand preserving the health of the mother by saving visual function, and on the other hand guaranteeing the viability of the fetus. Thus, as soon as fetal lung maturation was satisfactory, we decided to induce delivery, and then to monitor the mother's visual symptoms. Indeed, a case of spontaneous recovery of visual loss after delivery has been reported in a woman affected with a progesterone receptor-positive TBM growing during pregnancy

(3). As this event did not occur, we chose surgical intervention. In order to favor prompt return home of the mother to her child, an endoscopic endonasal transplanum transtuberculum approach was employed, which is minimally invasive and well tolerated.

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Answers:

Question 1. c

Question 2. c

17

A 26-year-old Woman with Polyuria During Pregnancy

Mitsuru Nishiyama, MD, PhD, Yasumasa Iwasaki, MD, PhD, and Shozo Yamada, MD, PhD

A 26-year-old woman with galactorrhea had an elevated serum prolactin (PRL) level (75 ng/mL). Magnetic resonance imaging (MRI) of the pituitary gland revealed a 4-mm intrasellar tumor suggestive of a PRL-producing microadenoma. Cabergoline was prescribed, which ameliorated the patient's galactorrhea. No tumor growth was observed for 1 year after the MRI (Figure 17-1), and cabergoline administration was discontinued when the patient became pregnant. At 24 weeks of gestation, she was admitted to the

obstetrics department because of intrauterine growth retardation. She developed thirst and marked polyuria (7700 mL/d) at 29 weeks of gestation.

1. THE MOST LIKELY DIAGNOSIS IS:

- Diabetes mellitus
- Diabetes insipidus
- Polydipsia
- Adrenal failure
- Renal tubular disorder

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Abdominal ultrasound
- Brain computed tomography (CT) scan
- Brain MRI
- Insulin tolerance test
- Water deprivation test

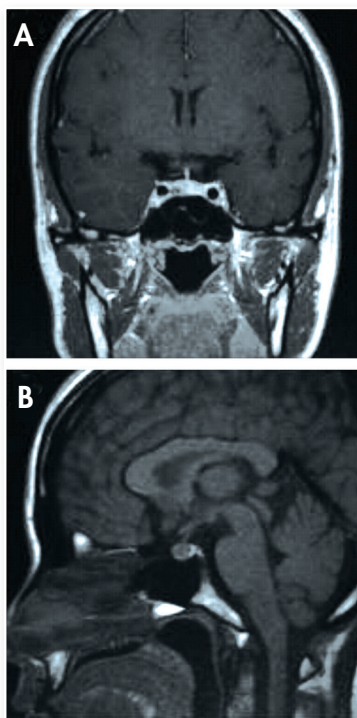


FIG. 17-1. MRI findings before pregnancy. **A**, Gadolinium-enhanced T1-weighted coronal image; **B**, T1-weighted sagittal image. A less-enhanced, 4-mm mass compatible with a pituitary microadenoma was evident.

An MRI of the pituitary gland revealed a 2-cm cystic lesion with suprasellar extension, and high-intensity signal of the posterior pituitary gland was absent (Figure 17-2). Her urine was hypo-osmotic (223 mOsm/kg), and her serum arginine vasopressin (AVP) level was low (0.5 pg/mL). Her serum PRL level robustly increased (461 ng/mL), and mild hypothyroidism was observed (TSH, 2.13 μ IU/mL; FT₄, 0.72 ng/dL). Visual field test results were normal. A pituitary cystic lesion causing central diabetes insipidus and central hypothyroidism was considered, and replacement therapy with desmopressin and levothyroxine was

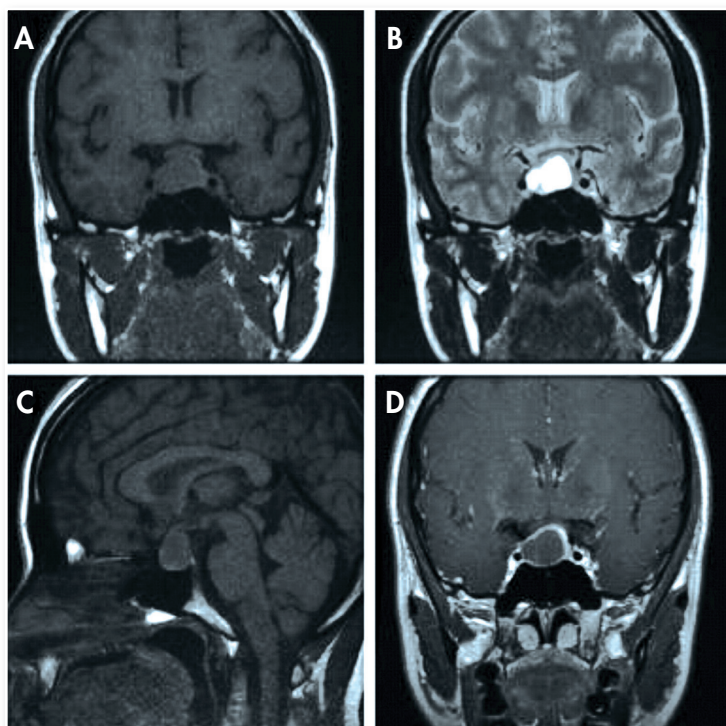


FIG. 17-2. **A–C**, MRI findings during pregnancy. **A**, T1-weighted coronal image; **B**, T2-weighted coronal image; and **C**, T1-weighted sagittal image. **D**, Gadolinium-enhanced T1-weighted coronal image obtained after delivery. A cystic lesion, 2-cm in diameter was found instead of a microadenoma, and no high-intensity signal of the posterior pituitary gland was observed.

started. A hypertonic saline infusion test conducted after a cesarean section delivery showed no AVP responses, confirming the diagnosis of central diabetes insipidus.

3. YOUR INTERPRETATION OF THE MRI FINDINGS:

- a. Rathke's cleft cyst
- b. Arachnoid cyst
- c. Craniopharyngioma
- d. Cystic prolactinoma
- e. Empty sella

Diagnosis

Cystic Prolactinoma.

Discussion

Based on the MRI findings and clinical course, cystic expansion of a prolactinoma was considered, and cabergoline was re-administered. Neurosurgical treatment using the transsphenoidal approach was performed, and histological examination confirmed a PRL-positive pituitary

adenoma. After surgery, the polyuria, hyperprolactinemia, and hypothyroidism disappeared without medication.

This is an exceptional case of microprolactinoma with remarkable growth during pregnancy. Microprolactinomas rarely expand during pregnancy (1-3), and the JCEM guideline recommends against the use of routine pituitary MRI examination during pregnancy in patients with microadenomas, unless there is clinical evidence for tumor growth such as visual field disturbances or severe headache (4). The etiology of cystic prolactinoma is unknown (5). Cyst formation due to intratumoral hemorrhage was excluded based on the intraoperative findings. There are some reports of Rathke's cleft cysts coexisting with pituitary adenomas (6); however, the MRI examination before pregnancy showed no cystic lesion in the sella (Figure 17-1).

Following successful surgical intervention, the polyuria was

ameliorated; therefore, we speculated that the marked cystic enlargement of the tumor compressed and impaired the neurohypophyseal function. Diabetes insipidus due to pituitary adenoma growth is extremely rare, although there are previous reports of pregnancy-related hemorrhage in a prolactinoma causing diabetes insipidus and visual field defects (7). In the current patient, cystic expansion towards the pituitary stalk might have caused diabetes insipidus without visual field symptoms. Furthermore, placenta-derived cystine aminopeptidase (oxytocinase, also known as vasopressinase), which is known to increase the metabolic clearance of AVP, was an additional cause of transient diabetes insipidus during pregnancy (8, 9).

In conclusion, this rare case of pregnancy-related growth of a prolactinoma causing diabetes insipidus was reported by Amano *et al.* in the JCEM in 2012 (10), from which the above case was abstracted. The authors suggest that pituitary MRI examination should be considered even in a patient with microprolactinoma during pregnancy when marked polyuria occurs.

Subsequent Follow-up of the Patient:

At the time of the last follow-up in February 2013, the patient was healthy, required no medication, and there was no evidence of a recurrence of prolactinoma. Her menstrual cycles were regular, and she hoped for a second baby.

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Answers:

Question 1. b

Question 2. c

Question 3. d

18

A 26-year-old Woman with Salty Rhinorrhea

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A 27-year-old woman presented with salty rhinorrhea, severe headaches and vomiting, 3 months after being started on cabergoline for an invasive macroprolactinoma (Figure 18-1). She was afebrile and the physical examination was unremarkable. Her prolactin level had dropped from 280,136 mIU/liter (normal range: 59–619 mIU/liter) at the time of original diagnosis to 2,353 mIU/liter at the current presentation. Computed tomography, performed to evaluate for severe headaches, showed pneumocephalus (Figure 18-2).

1. THE MOST LIKELY DIAGNOSIS IS:

- Pituitary apoplexy
- Macroprolactinoma extension
- Cabergoline-induced CSF fistula
- Meningitis
- Pneumosinus dilatans

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- To administer antibiotics
- To measure Beta-2 transferrin in nasal fluid sample
- MRI of the brain
- Hyperbaric therapy
- Lumbar puncture

A magnetic resonance image (MRI) of the brain showed more than 50% size reduction of the prolactinoma with erosions in the roof of the sphenoid sinus (Figure 18-3). A nasal endoscopy identified

3. THE MOST APPROPRIATE INTERVENTION WOULD BE:

- Start prophylactic antibiotics
- Stop cabergoline
- Skull base defect repair and tumor debulking
- Await spontaneous resolution of symptoms
- Placement of lumbar drain

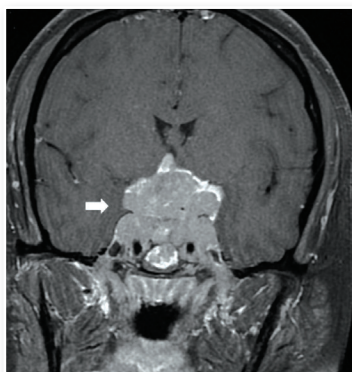


FIG. 18-1. MRI of the brain 3 months before presentation shows 5 x 4.3-cm macroprolactinoma invading the skull base, sphenoid, and cavernous sinuses.

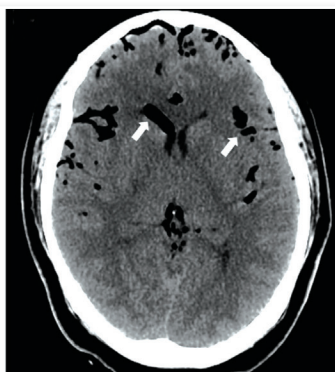


FIG. 18-2. CT scan of brain showing air filling the subarachnoid spaces and frontal horns of the ventricles.

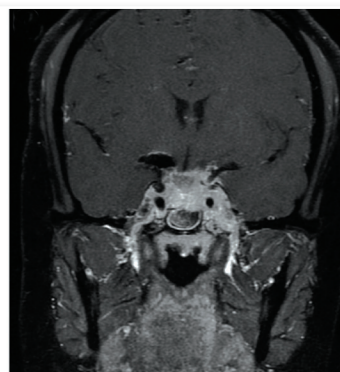


FIG. 18-3. MRI of the brain on presentation showing size reduction of prolactinoma to 1.6 x 3 cm.

a cerebrospinal fluid (CSF) leak in the central aspect of the sphenoid.

Diagnosis

Cabergoline-Induced CSF Fistula in a Medically Treated Invasive Macroprolactinoma.

Discussion

Prolactinomas are among the few pituitary tumors that may erode through bone. Tumor shrinkage with dopamine agonists (DA), such as bromocriptine or cabergoline, can unmask dural and skull base defects, resulting in fistulae and subsequent CSF leak from the subarachnoid space into the sphenoid sinus and nostrils. A few cases have been reported in the literature (1-5), as well as two small case series on medically managed macroprolactinomas (6, 7). The incidence of DA-induced CSF rhinorrhea is low and is estimated at 6-7% (6, 7). It has been reported to occur between a week and several months after the initiation of DA, and rarely after a year (6). Subjects with a sphenoid invasion are at higher risk of developing CSF rhinorrhea. Baseline prolactin level, rate of prolactin decline, and tumor volume were not predictors of CSF leakage (7). Delays in recognition and treatment can lead to life-threatening complications such as meningitis or intracranial abscess, with mortality rates as high as 50%. Pneumocephalus is a rare complication in medically treated macroprolactinomas (4-6) and develops as CSF pressure falls below atmospheric pressure (8). This may result in intracranial hypertension, potentially with ensuing downward herniation.

Management of CSF rhinorrhea is controversial. Urgent surgical fistula repair is the most accepted therapeutic intervention, with concurrent tumor debulking if possible (9). Withdrawal of DA therapy may stop the leak by tumor

re-expansion, plugging the defects in the dura and bone. However, current evidence suggests that continuation of DA is safe and should be temporally stopped only in patients unsuitable for surgical intervention. Isolated cases have reported spontaneous CSF leakage cessation with no additional therapy. Antibiotic prophylaxis for preventing meningitis in patients with CSF leakage is not supported in the current available evidence (10).

In conclusion, this is an example of cabergoline-induced CSF fistula in a woman medically treated for invasive macroprolactinoma, presenting with CSF rhinorrhea and pneumocephalus, and was reported by Machicado *et al.* in the JCEM in 2012 (11) from which the above case was abstracted. Patients started on DA therapy should be warned of the risk of this serious complication. They should be advised to present immediately after the onset of CSF rhinorrhea or sudden headaches, to allow early diagnosis and treatment.

Subsequent Follow-up on the Patient

Cabergoline was continued. An endoscopic defect repair, tumor debulking, and placement of a lumbar drain were performed, with control of CSF leak and headaches. CT of the head revealed resolution of pneumocephalus. The patient remained asymptomatic over a 6-month period of follow-up.

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Answers:

- Question 1. c
Question 2. c
Question 3. c

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Transsphenoidal surgery has an important role in the management of pituitary tumors and remains the primary treatment for most adenomas, with the exception of prolactinomas. This update will review the recent neurosurgical literature; modifications to the traditional microscopic approach, including the potential utility of endoscopy and intraoperative magnetic resonance imaging, are discussed. The value of experienced surgical judgment and expertise remains clear, over and above the possible

advantages of current technology. Preliminary data on the relative cost-effectiveness of surgery vs. medical treatment suggest that surgical approaches compare favorably. It will be important to incorporate future technological advances in surgical technique with new medical therapies in a combined multidisciplinary approach for improved treatment algorithms. (J Clin Endocrinol Metab 97:1073-1081, 2012)

Approximately 5000 transsphenoidal procedures are performed in the United States yearly, most commonly for pituitary adenomas, although the approach has been used for a variety of sellar pathologies (2, 3). The context in which these procedures are performed has dramatically changed over time. The goals of surgery and determination of acceptable risk are clearly different in cases where alternative therapies now exist, *e.g.* medical as opposed to surgical treatment of prolactinomas and acromegaly, or radiosurgical treatment of residual intracavernous tumor as opposed to attempted surgical exploration. Advances in endocrine diagnosis have led to the necessity of devising surgical techniques capable of identifying tumors that cannot be visualized even with modern imaging techniques, *e.g.* undetectable Cushing's microadenomas. The technical advances in surgery have not proceeded independently from advances in imaging, diagnosis, and alternative therapies and need to be placed in this context.

The coming of 2012 marks the 50th anniversary of Hardy's description of the first transsphenoidal resection of a pituitary microadenoma, and we are

now past the centenary of Schloffer's original description of his lateral nasal approach to the sella. Cushing modified Halstead's sublabial technique and performed over 300 transsphenoidal procedures, before abandoning it in favor of the greater exposure offered by the transcranial approach. After falling into disfavor, the transsphenoidal technique was preserved by Dott in Edinburgh and further developed by Guiot in Paris with the addition of intraoperative fluoroscopy, and again by Hardy with the introduction of the operative microscope to pituitary surgery (4). The approach was developed in response to the constraints of nasal/sinus anatomy, which provide a narrow but relatively noninvasive corridor to the skull base; these constraints remain today. Successful surgery requires the ability to navigate to the tumor, visualize the anatomy, and determine the adequacy of resection, while minimizing damage to the surrounding structures. Technological advances have improved our ability to meet each of these requirements. Navigation based upon anatomical cues alone was aided by the addition of intraoperative imaging, initially by fluoroscopy and now with

neuronavigational tools and intraoperative magnetic resonance imaging (iMRI). Anatomic visualization initially with the unaided eye was supplanted by the microscope and is now supplemented by the endoscope. Determination of the adequacy of resection initially was based on indirect visual cues, but it is now aided by intraoperative imaging and direct microscopic and endoscopic visualization. The problems have remained the same, although our response has varied as our technology has improved. Finally, it is necessary to critically examine the value of new technology, which for a variety of reasons tends to take on a life of its own and to ensure that its adoption leads to better patient outcomes.

This update will review recent advances in transsphenoidal surgical technique and discuss their role in current practice. Surgical outcome measures discussed will include biochemical and radiographic criteria, as well as incidence and relative risk of complications, and cost effectiveness.

Advances in Surgical Technique

Intraoperative visualization

It is critical to visualize the tumor as completely as possible during resection; this can be difficult during transsphenoidal resection because the access route is limited and larger tumors (often much larger than the access opening) must be removed piecemeal from within. One approach to this difficulty is to use radiographic techniques intraoperatively, whereas another has been to attempt to maximize the visualized extent of the operative field endoscopically.

Intraoperative imaging

Incorporation of iMRI into transsphenoidal surgery was initially reported by Steinmeier *et al.* (5) in Germany and Martin *et al.* (6) in the United States. Its

potential utility was suggested in these first small series by the finding that unsuspected tumor remnants were seen intraoperatively that could then be further resected in three of five and two of five patients in these first series, respectively. Its possible role in complication avoidance was shown by the imaging of a developing hematoma in the resection bed in one of the early patients (6). Widespread adoption of the technology has been hampered by the significant capital investment required both for the MRI machine itself and its related infrastructure (shielding, MRI compatible equipment, *etc.*), as well as by the changes in neurosurgical workflow necessitated by working in and around a strong magnetic field. Nonetheless, a number of series have been reported (Table 1). Most indicate that 20-30% of intraoperative images will show additional resectable tumor, with considerable variability (5-66%). It is difficult to design a study to unequivocally quantify this because the point at which the surgeon chooses to obtain the intraoperative image as the control will in part determine the amount of residual tumor seen; *i.e.* if the surgeon chooses to image relatively early in the procedure, residual tumor is likely to be found, and the value of the iMRI will tend to be overestimated. In addition, the goal is to visualize additional *resectable* tumor; it would not be unusual to visual residual tumor, *e.g.* in a case with extensive cavernous sinus involvement, but it may not be safely resectable. These factors may explain some of the variability between studies because publication bias would favor those studies that demonstrate a beneficial effect.

Studies have also shown a benefit as determined by biochemical, in addition to radiographic, criteria of successful resection. In series reporting remission rates for acromegaly, for instance, with defined biochemical criteria, rates are

TABLE 1: Improved resection after iMRI

First author, year (Ref.)	Magnet strength	No. of patients	Pathology	Resection improvement	Mean tumor size (mm)
Bohinski, 2001 (7)	0.3	30		19 of 29 (66%) had additional tumor removed after iMRI	
Fahlbusch, 2005 (8)	1.5 T	23	23 GH	5 of 23 (22%) had additional tumor removed after iMRI Remission rate increased from 33 to 44% 14 of 18 (61%) had GTR by iMRI, but only 8 of 18 (44%) achieved remission	25
Nimsky, 2006 (9)	1.5 T	106	106 NFA	37 of 106 (35%) had additional tumor removed after iMRI Rate of GTR increased from 49 of 85 (58%) before iMRI to 70 of 85 (82%) after iMRI	29.9
Gerlach, 2008 (10)	0.15 T	40		Additional resection in 7 of 40 (17.5%) cases after iMRI	6.9
Wu, 2009 (11)	0.15 T	55		Additional resection in 17 of 55 (31%) cases after iMRI GTR increased from 58.2 to 83.6%	
Bellut, 2010 (12)	0.15 T	37	37 GH, 39 procedures	Additional resection leading to remission in 5.1% Remission 73.5% after initial procedure	
Vitaz, 2011 (13)	0.5 T	100	81 Macroadenomas	76% GTR	
Berkmann, 2011 (14)		32		Additional resection in 8 of 32 (25%) after iMRI	Tumor volume mean 9.8 cc
Netuka, 2011 (15)	3.0 T	85		Additional resection in 22% after iMRI Successful radical resection increased from 34 of 49 (69%) to 45 of 49 (91%)	
Ramm-Petersen, 2011 (16)	0.5 T	20	16 NFA 3 GH 1 PRL	8 of 20 (40%) GTR before iMRI 12 of 20 (60%) GTR after iMRI	27

Data show resection improvement as determined by number (percent) of cases with additional tumor removed after iMRI and increase in remission rate for secretory tumors. T, Tesla; NFA, nonfunctioning adenomas; PRL, prolactinomas.

improved after removal of otherwise undetected tumor based on the intraoperative imaging. The discordance between radiographic and biochemical criteria for complete resection is also evident in the results reported from these studies because a number of patients without evident tumor on iMRI remain uncontrolled biochemically (8, 12). The iMRI has also been used to confirm the adequacy of chiasm decompression in those patients presenting with visual loss because it is clearly important that satisfactory decompression be achieved at the initial procedure, if at all possible. Intraoperative imaging demonstrated residual resectable tumor in eight of 15 partially resected tumors (of 32 total), which led to better decompression of the chiasm in four additional tumors (14). Overall improvement in visual fields was seen in 87% of patients at 1 month and was strongly correlated with chiasm decompression on iMRI ($P = 0.0007$). No adverse events from the iMRI itself have been reported, but anesthesia and operative times are prolonged by at least the time required to obtain the images, and it can be difficult to interpret intraoperative images in the setting of a possible subtle residual, especially with low field strength magnets (10).

Microscopic vs. endoscopic technique

The surgical technique used to approach the sella has changed over the years. A variant of the Cushing-Halstead sublabial approach was used by many neurosurgeons until relatively recently, although some adopted Hirsch's endonasal technique, where the approach is directly through the nasal passage, either via a submucosal tunnel or a direct endonasal approach. The sublabial approach requires an incision through the upper gum, with a submucosal dissection into the nasal cavity. The speculum can be opened widely with good visualization of

the sella, but the incision is painful and postoperative nasal packing is required. The endonasal technique provides a slightly smaller field of view because the opening of the intranasal speculum is now constrained by the width of the nares, but the incision can be made posteriorly along the septum, and so no postoperative packing is required, and for many tumors the width of access is not the determining factor in the adequacy of resection. Based upon the introduction and widespread adoption of the endoscope by otolaryngologists, Jankowski *et al.* (17) reported its use in pituitary surgery in 1992. The technique was described in the neurosurgical literature by Jho and Alfieri (18), and a PubMed search of "pituitary" and "endoscope" generated 206 publications as of 2011. Potential advantages include a wider field of view, as opposed to the more limited line of sight provided by the microscope; conversely, the microscope offers binocular vision and superb optics. The endoscope has been marketed as "less invasive," although the comparison group in these reports is usually the older sublabial as opposed to the endonasal approach, where the actual incision used is similar or identical and no nasal packing is needed. Because no speculum is placed to retract the turbinates, the endoscopic approach may require their resection to obtain an adequate working channel, and more of the face of the sphenoid will require removal to allow access by both the endoscope and the working instruments; in this sense, it can in fact be more invasive. One study has reported decreased operative time, shorter length of stay, and improved patient satisfaction, although the comparison group used by this study was the older, sublabial incision (19). As with the introduction of most surgical technologies, an accurate comparison of surgical results has been difficult to achieve because most comparisons are based upon historical

reports. There have been two recent meta-analyses of endoscopic series (20,21). The first included nine pooled studies and reported a 78% rate of gross total resection (GTR), 81% remission rate in Cushing's disease (CD), 84% remission in acromegaly, and 82% in prolactinomas, with a 2% incidence of cerebrospinal fluid (CSF) leak and 1% incidence of permanent diabetes insipidus. There were two deaths (0.24%), both from vascular injury (20). This meta-analysis was overweighted by a single large study that contributed 39% of the secretory cases (22). The second meta-analysis included 12 additional studies, with an overall GTR rate of 68%; with additional series added, the remission rates are lower because the effect of overweighting is less evident: 72% remission in acromegaly, 75% remission in CD, and 78% remission in prolactinomas (21). In comparison to historical microscopic series, these authors found relative improvement in remission rates for secretory macroadenomas with endoscopic resection, although no clear benefit was found overall when microadenoma results are included.

Utility in CD. There have been no large series exclusively reporting endoscopic as opposed to microscopic results in CD. Remission rates abstracted from combined endoscopic series range from 56-86% (Table 2). These results approach but do not surpass the historical series using a microscopic technique. For example, a sampling of recent microscopic series reveals remission rates of 90% for microadenomas overall (23), 94% including early reoperation after initial failure (24), and 89% in a series when a microadenoma was seen on MRI (25). Because CD tumors are generally microadenomas, intrasellar, and can be difficult to visualize, conventional microscopy may hold an advantage and is favored by some experienced pituitary

surgeons (26). A direct comparison of the endoscopic vs. the sublabial microscopic approach for CD at a single institution showed similar rates of remission (86%) and complications (19).

Utility in acromegaly. There are now a number of series describing endoscopic removal of GH-secreting adenomas (32, 33, 35, 36), as well as those cases presented as a specific subset of a larger report (Table 2). A comparison with historical series is difficult because not all stratify their results by tumor size and invasiveness, and only a few use the latest consensus criteria for remission (33, 35). Remission rates overall vary between 46 and 85%, with microadenomas 75-100% and macroadenomas 50-80%. These results are similar to those achieved in previous microsurgical series. It is conceivable that a subset of the large macroadenomas might be better served by the endoscopic approach, but it is difficult to stratify results in this fashion to demonstrate this conclusively. Comparison with historical series is also difficult because the criteria for remission in recent series have become more stringent, making surgical remission more difficult to achieve; conversely, it is also possible that the advent of primary medical treatment for tumors deemed to be surgically incurable could skew the surgical population toward a more resectable group.

Utility in prolactinomas. With the well-demonstrated long-term efficacy of dopamine agonist therapy, surgery remains a second-line treatment in the management of most prolactinomas. Given this, however, a number of the surgical series report remission rates of 85-89% (Table 2). It is likely that these were highly selected cases (encapsulated microadenomas). Recent descriptions of potential adverse effects of long-term use of cabergoline

TABLE 2. Endoscopic results for secretory adenomas

First author, year (Ref.)	Approach	Patients	Remission criteria	Remission
Jho, 2001 (27)	Endoscopic	16 CD 9 GH	CD: normal cortisol GH: normal IGF-I	11 of 16 (70%) 7 of 9 (78%)
Cappabianca, 2002 (28)	Endoscopic	13 CD 4 Macro 9 Micro 36 GH 6 Micro 30 Macro	CD: ACTH 10-90 pg/ml, normal 24-h UFC, morning cortisol <250 ng/ml GH: normal IGF-I with fasting GH <2.5 ng/ml and GH <1.0 ng/ml after OGTT	10 of 13 (77%) 3 of 4 (75%) 7 of 9 (78%) 23 of 36 (64%) 5 of 6 (83%) 18 of 30 (60%)
Kabil, 2005 (22)	Endoscopic Microscopic (historical literature)	CD GH 13 Micro 35 Macro PRL CD GH PRL	Criteria not stated	86% 85% 100% 80% 89% 81% 77% 66%
Dehdashti, 2008 (29)	Endoscopic Microsurgical (same surgeons)	27 CD 34 GH 8 Micro 26 Macro 25 PRL CD GH PRL	CD: morning cortisol <100 nmol/liter, normal 24-h UFC, and suppression to 1 mg dex GH: normal IGF-I with fasting GH <2.5 ng/ml and GH <1.0 ng/ml after OGTT PRL <20 ng/ml	22 of 27 (81%) 24 of 31 (71%) 83% 65% 22 of 25 (88%) 78% 67% 62%
D'Haens, 2009 (30)	Endoscopic Microsurgical (same surgeons)	16 CD 13 GH 13 CD 11 GH	CD: normal or suppressed ACTH, serum, and 24-h UFC GH: normal GH and IGF-I and GH <1 ng/ml after OGTT	9 of 16 (56%) 8 of 13 (62%) 6 of 13 (46%) 3 of 11 (27%)
Yano, 2009 (31)	Endoscopic	9 CD 26 GH	CD: morning cortisol <5 µg/dl, normal 24-h UFC GH: normal IGF-I with GH 1 ng/ml after OGTT	6 of 9 (67%) 20 of 26 (77%) (Knosp grade 1-2)
Campbell, 2010 (32)	Endoscopic	26 GH 4 Micro 22 Macro	Normal IGF-I with random GH <2.5 ng/ml and GH <1.0 ng/ml after OGTT	15 of 26 (57%) 3 of 4 (75%) 12 of 22 (55%)
Hofstetter, 2010 (33)	Endoscopic	24 GH 4 Micro 20 Macro	Normal IGF-I with either random GH <1 ng/ml or GH <0.4 ng/ml after OGTT	11 of 24 (46%)

Table 2 continues on next page

TABLE 2. Endoscopic results for secretory adenomas (cont.)

First author, year (Ref.)	Approach	Patients	Remission criteria	Remission
Gondim, 2010 (34)	Endoscopic	28 CD	CD: morning cortisol <100 nmol/liter, normal 24-h UFC, and suppression to 1 mg dex	71%
		58 GH	Normal IGF-I and GH <1.0 ng/ml after OGTT	71%
		41 PRL	Prl <20 ng/ml	85%
Jane, 2011 (35)	Endoscopic	60 GH	Normal IGF-I with either random GH <1 ng/ml or GH <0.4 ng/ml after OGTT	42 of 60 (70%)
		14 Micro		14 of 14 (100%)
		46 Macro		28 of 46 (61%)
Wagenmakers, 2011 (36)	Endoscopic	40 GH 40 Macro	Normal IGF-I and GH <2 mU/liter after OGTT	20 of 40 (50%)

Data show recent series describing remission rates for secretory tumors after endoscopic approaches; comparison data where shown as chosen by the author. OGTT, Oral glucose tolerance test; UFC, urinary free cortisol; PRL, prolactinoma; dex, dexamethasone.

(for review of risks. see Ref. 37) have raised the question of whether there should be some ongoing role for surgery in these patients, and a recent large retrospective review found an initial remission rate using the microscope of 91% in microprolactinomas, with 84.5% long-term remission for microadenomas, and a recurrence rate of 18.7% overall (38). Conversely, however, it is possible that the population of patients most amenable to surgical success (microadenomas) may also be the population most likely to achieve long-term remission after discontinuation of dopamine agonist

treatment because the likelihood of long-term remission off therapy appears to be a function of tumor size (39).

Utility in nonfunctioning tumors.

The absence of biochemical criteria for remission requires a radiographic estimate of degree of resection and introduces a degree of subjectivity. Given this caveat, estimates of the degree of GTR range from 66-93% (Table 3) in endoscopic series. A number of authors describe a “combined” technique, using the microscope followed by the endoscope (40, 41). It has been argued that residual tumor visualized

TABLE 3. Radiographic GTR rates

First author, year (Ref.)	No. of patients	NFA	Estimated GTR (including functional adenomas)
Kabil, 2005 (22)	300 Endoscopic	161 of 300 (54%)	149 of 161 (93%) NFA
Dehdashti, 2008 (29)	200 Endoscopic	111 of 200 (56%)	96% without cavernous sinus involvement 98% intrasellar
O'Malley, 2008 (43)	25 Endoscopic 25 Microscopic		14 of 21 (66%) 17 of 22 (77%)
Gondim, 2010 (34)	228 Endoscopic	93 of 228 (41%)	79% overall 83% NFA

NFA, Nonfunctioning adenomas.

endoscopically may obviate the need for iMRI, although iMRI found persistent residual tumor in 15% of cases predicted to represent GTR by endoscopy (42).

Extended transsphenoidal approach.

Retrochiasmatic suprasellar tumors above a normal pituitary, *e.g.* craniopharyngiomas, have been traditionally difficult to approach, especially in the setting of a “prefixed” chiasm, where the shortened intracranial optic nerves limit access, even with a craniotomy. Tumors that extend into and expand the sella can be reached transsphenoidally, traditionally with the microscope. The expanded view afforded by the endoscope has led to attempted resection of tumors of the anterior skull base and clivus with better visualization, but this has generated new technical difficulties, specifically the increased risk of CSF leak with extrasellar tumors. This approach requires drilling away an extended portion of the skull base, in addition to the face of the sella, and is considerably more “invasive” than the standard transsphenoidal approach. A number of authors have described their experience in treating suprasellar craniopharyngiomas, tuberculum meningiomas, and large invasive pituitary adenomas with reasonable results, given the difficult location of these tumors (44, 45, 46, 47, 48). The complication rate is greater, however, than in those tumors that can be reached by the conventional transsphenoidal route, and probably similar to that of a craniotomy, with the exception of an increased risk of CSF leakage. A recent large series including both approaches (extended vs. standard transsphenoidal, using the endoscope as needed, primarily for the extended approach) reported an increase in surgical mortality (1 vs. 0.1%), carotid artery injury (2 vs. 0.3%), permanent neurological

deficit (2 vs. 0.3%), CSF leak (6 vs. 2%), and postoperative meningitis (2 vs. 0.1%), in those cases where the difficult anatomy required the extended approach (41). As is evident from the above statistics, the major ongoing problem with this approach remains the increased risk of CSF leakage and difficulties with skull base repair.

Further advances. Although the endoscope may offer a wider field of view, the initial endoscopic technique was essentially one eye/one hand, although this rapidly progressed to the same bimanual technique used with microscopy with the addition of a second surgeon to manipulate the endoscope. Most endoscopes, however, remain monocular, with some estimate of depth perception obtained from endoscope movement, as opposed to the microscope’s binocular vision with better depth of field. Recently, three-dimensional endoscopy has been introduced using the stereo endoscope; this technique allows simulated depth perception (similar to that of a three-dimensional video) approaching that of the binocular microscope, and these devices remain in active development (49).

Intraoperative tumor identification

Most resources have been focused on improving surgical visualization of tumors, either by direct visualization with microscopy or endoscopy, or radiographic visualization with the iMRI. Attempts have been made to assist the intraoperative resection of adenomas by other means as well, although none has achieved widespread acceptance. Intraoperative ultrasound using a microprobe has been described to assist in the detection of Cushing’s microadenomas (50, 51), and a Doppler probe has also been used to assist in the identification of the carotid artery before an extended dural opening (52). Protoporphyrin spectroscopy has been described to assist in the intraoperative

identification of adenomas, based on differential fluorescence after administration of 5-aminolevulinic acid (53). Intraoperative biochemical testing to determine remission during resection has also been employed, with successful measurement of intraoperative GH levels as a guide to remission in acromegaly (54), although intraoperative ACTH measurements appear to provide little benefit in assessing successful resection for CD (55).

Volume-Outcome and Cost-Benefit Analyses

Volume-outcome analyses linking improved patient outcome to surgical volume and experience have been presented for a variety of surgical procedures, including carotid endarterectomy (56), coronary artery bypass surgery, and complex cancer operations, among others (57). This was first suggested in pituitary surgery by data from the United Kingdom showing improved outcomes after transsphenoidal surgery for acromegaly with a designated pituitary surgeon, presumably based upon increased experience (58, 59). The rate of surgical complications in the United States after transsphenoidal surgery as self-reported by surgeon questionnaire also showed a significant decrease with increased experience (60). This was confirmed by a study based on the Nationwide Inpatient Sample, which showed a 4-fold reduction in operative mortality in high-volume as opposed to low-volume centers (1). In an analysis of outcomes after surgery for CD, the cost of a single adverse postoperative event increased the length of stay by 3 d and the hospital charge by \$7000 (61). These issues as they affect neurosurgical training and centralization of care have been recently discussed (62); a review of the operative statistics from 94 neurosurgical

training programs nationwide found that 31% performed fewer than 20 pituitary operations per year, whereas 7.4% performed more than 100 (63). This has obvious implications for neurosurgical training as new techniques are introduced, as well as the cost-effective introduction of new, capital-intensive technologies (e.g. iMRI).

Cost-benefit analyses of surgical and nonsurgical treatment options for pituitary disease have now been published. A comparison of surgical vs. medical therapy for acromegaly suggested that the primary surgery followed by secondary medical treatment algorithm was 30% less expensive than algorithms with primary somatostatin analogs followed by secondary surgery, and algorithms including transsphenoidal surgery were 46-59% less expensive than medical therapy alone (64). The economic benefit of disease control in acromegaly has been recently reviewed (65). Two studies have analyzed the economic burden of acromegaly; in one, total health care costs were 1.6 times higher in uncontrolled vs. controlled disease in 142 patients followed for 7 yr (66). A second smaller study of 11 patients reported higher overall costs in the controlled group, although three of six uncontrolled patients were perhaps inadequately treated with relatively inexpensive dopamine agonists. The lowest overall cost was found in the surgically cured patient (67). Similarly, a recent analysis of the cost of illness in CD showed that patients not in postoperative remission had significantly higher ongoing health care costs, and that these costs decreased after successful surgery (68). The cost-effectiveness of new pharmacological treatments, when introduced, will have to be evaluated in this light.

Surgical Treatment in the Context of Overall Disease Management

It is likely that the performance of complex

neurosurgical procedures, including transsphenoidal and other skull base approaches, will become more centralized, as has been shown for supratentorial craniotomies (69). This may require changes in referral patterns, which can be made more difficult by insurance regulations that are based more on financial than medical considerations and may serve to restrict access to experienced, although not necessarily more costly, care. This may be false economy because early studies on cost effectiveness of treatment options in acromegaly, for instance, suggest that successful surgery appears to be the most cost-effective strategy over the long term, and experienced centers may have fewer costly complications and shorter lengths of stay. Outcomes analysis of both surgical and medical treatment of pituitary disease will become increasingly important. Systemwide, measures of surgical volume have become a surrogate for actual outcome data; although we can measure remission after surgery for acromegaly or CD on an individual patient level, the outcome measures available across the U.S. healthcare system are more general indices, for example, of surgical mortality or hospital readmission within 30 d. Existing administrative databases have been massaged in an attempt to yield surrogates for actual outcome, *e.g.* insurance records that do not document evidence of adjunctive treatment are used to imply remission, but it is unfortunate that there is no widely available outcomes database. All of these factors—centralization of care, inability to directly compare outcomes across centers, insurance and practice restrictions on referrals—may make it difficult for the practicing endocrinologist to determine how to obtain optimal surgical management.

Advances in surgical treatment have not occurred in isolation, and

it is important to incorporate these advances into the context of overall disease management, combined with improvements in pharmacological and radiation therapy. To this end, a number of consensus criteria have been formulated, especially for secretory tumors. Surgery remains the first-line treatment for CD (70) and in most cases of acromegaly (71). It has been replaced in the initial treatment of prolactinomas by dopamine agonist therapy for most patients (72). Numerous questions remain, however. For instance, if advances in surgical technique allow the potential removal of intracavernous tumor remnants, at some degree of increased risk, at what risk threshold does the surgical approach become preferable to radiosurgery or possible pharmacological treatment? If medical treatment of CD becomes a realistic alternative, does hypophysectomy for undetectable tumors or even surgical reexploration for recurrence remain in the treatment algorithm? If primary medical treatment for acromegaly is an option, at what risk threshold does surgical debulking of invasive tumors remain worthwhile? Surgical decision-making in these and similar circumstances will be at least as important as advances in technology, and it is here that surgical experience and specialized training will be of the most benefit. The utility of a combined interdisciplinary approach to the management of these tumors is also here most evident, as we seek to combine the advances in each individual specialty to effect overall improvement in patient care.

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Adrenal



19

A 27-year-old Woman with Hypertension

Stan Van Uum, MD, PhD, and Alyse Goldberg, MD

A 27-year-old woman, known to have a generalized anxiety disorder, presented to her family doctor with headaches and was found to be hypertensive. After confirmation of the hypertension at a subsequent visit a few days later, atenolol therapy was initiated.

Five days after initiation of therapy, the patient presented to the emergency room. The patient described 5 weeks of headache, diaphoresis and palpitations associated with pallor. On examination, her blood pressure was 226/126 mmHg, heart rate 99 beats per minute, body mass index 26.9 kg/m². Café au lait spots were present on her arms and trunk as well as axillary freckling. A diagnosis of hypertensive crisis was made.

The patient confirmed a personal history of von Recklinghausen disease (neurofibromatosis type 1), which is associated with a 2% risk of developing a catecholamine-secreting tumor that is usually solitary, benign, located in the adrenal, and occasionally bilateral.

Initial investigations included normal serum chemistries, fasting glucose and calcium. Twenty-four-hour urine analysis demonstrated elevated excretion of metanephrine [65.7 (<1.52; upper limit of reference range) mol/d] and normetanephrine [59.27 (<1.95) μ mol/d], and to a lesser extent norepinephrine [2806 (<569) nmol/d] and epinephrine [1222 (<149) nmol/d].

After biochemical confirmation of the increased catecholamine secretion (which could alternatively have been done by measuring plasma catecholamines and metanephrines), localization studies were performed. An abdominal computed tomography (CT) scan showed a large solid and cystic lesion involving the right adrenal gland (Figure 19-1A). A magnetic resonance imaging (MRI) scan confirmed that there was no direct invasion into the liver, kidney or inferior vena cava. An ¹³¹I-methyliodobenzylguanidine (¹³¹I-MIBG) scan showed a right adrenal tumor with prominent peripheral uptake and large central defect (Figure 19-1B), but no extra-adrenal metastases. Echocardiogram did not show any evidence of catecholamine-induced cardiomyopathy.

1. WHICH OF THE FOLLOWING SYNDROMES, ALL ASSOCIATED WITH THE PRESENCE OF PHEOCHROMOCYTOMA, WOULD BE MOST LIKELY TO BE PRESENT IN THIS PATIENT?:

- Von Recklinghausen disease
- MEN2B
- Von-Hippel Lindau Syndrome
- Carney complex
- Familial paraganglioma syndrome

2. YOUR NEXT DIAGNOSTIC STEP WOULD BE:

- MIBG scan
- MRI abdomen
- 24 hour urine catecholamines and metanephrines
- CT of the renal arteries
- None of the above

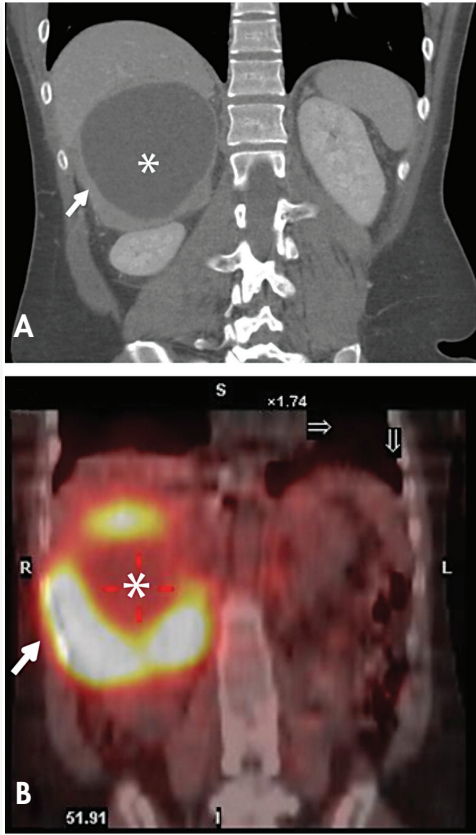


FIG. 19-1. **A**, Coronal abdominal CT image revealed a cystic/solid mass [10.5 x 10.6 cm, (arrow); cystic portion (*), 9.5 x 8.8 cm] in the region of the right adrenal gland. **B**, Single-photon emission computed tomography (SPECT)/CT with ¹³¹I methyliodobenzylguanidine confirmed right adrenal pheochromocytoma with prominent uptake at periphery (arrow) and a photopenic central defect (*) indicative of central necrosis.

Diagnosis

Cystic Pheochromocytoma.

Discussion

Pheochromocytomas are relatively rare tumors composed of chromaffin cells derived from the neural crest that occur in 0.1% to 0.6% of persons with hypertension. The tumor can secrete catecholamines (epinephrine, noriepinephrine, dopamine) and/or their metabolites. Clinical symptoms may include hypertension, headache, palpitations, diaphoresis, hyperglycemia,

pallor (due to vasoconstriction) and even cardiomyopathy. Rarely, epinephrine may cause hypotension. Most (90%) pheochromocytomas are intra-adrenal, while 5-10% are multiple, and 10% are malignant (with unclear difference in the malignant histology or biochemistry, compared to benign). In certain familial pheochromocytoma syndromes, von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2), presentation occurs at a younger age, and multiple tumors are more common. In neurofibromatosis type 1 (NF1) patients, the pheochromocytoma phenotype is similar to sporadic forms

Once a pheochromocytoma is biochemically confirmed, localization studies are performed. These could consist of CT and MRI scans, and/or MIBG scans. These scans are highly specific (99%) but less sensitive (80%) for pheochromocytoma, and are generally reserved for patients with equivocal CT results, and to look for extra-adrenal catecholamine-secreting tumors or malignancy. More recently, positron emission tomography (PET) scan imaging has also been demonstrated to be useful. Initial management of pheochromocytoma begins with stabilizing the patients hemodynamics with a focus on blood pressure control. Monotherapy with beta blockers creates the risk for hypertensive crisis due to unopposed α -adrenergic stimulation. In large pheochromocytomas, clinically adequate preoperative α -adrenergic blockade may not be sufficient to prevent hemodynamic compromise associated with anesthesia as well as tumor dissection.

Back to the Case

The patient agreed to proceed to surgery to remove the pheochromocytoma. After medical preparation with 3 weeks of phenoxybenzamine (titrating up to

90 mg/d), propranolol, and preoperative saline loading, the patient appeared clinically adequately blocked with significant orthostatic hypotension. However, anesthetic induction (fentanyl, propofol, lidocaine, and rocuronium) caused a second hypertensive crisis (280/170 mm Hg) and prevented surgery. Phenoxybenzamine dosage was increased to 60 mg three times a day, and nifedipine SR 30 mg was added. While the patient was in the intensive care, we elected to

3. WHICH OF THE FOLLOWING ARE PURE ALPHA-ADRENERGIC AGONISTS?

- a. Phenylephrine, Methoxamine, Metaraminol
- b. Phenylephrine, Norepinephrine, Ephedrine
- c. Clonidine, Norepinephrine, Epinephrine
- d. Vasopressin, Phenylephrine, Metaraminol
- e. Vasopressin, Epinephrine, Methoxamine

tests the adequacy of the alpha-blockade.

We elected to use phenylephrine, a pure alpha-agonist, just as are methoxamine and metaraminol. Phenylephrine is the most commonly available alpha-agonist in North America. Vasopressin is not an alpha agonist, but has very similar effects. Norepinephrine, ephedrine, and clonidine all have mixed effects - norepinephrine is the closest to a pure alpha-agonist, but also has beta effects.

Intravenous phenylephrine (1 mg) did not affect intra-arterial blood pressure, indicating that sufficient α -blockade had been achieved. The next day, during open adrenalectomy, brittle blood pressure was noted until completion of tumor dissection. At the end of case, after clamping all venous drainage, profound hypotension was noted requiring norepinephrine,

epinephrine and vasopressin infusions for an hour, at which point she was hemodynamically stable on no blood pressure support.

A sample of the liquefied tumor center was obtained (Figure 19-2). Compared with plasma reference values (1), the cystic fluid contained extremely high concentrations of catecholamines and metanephrines (Table 19-1). Similar findings have previously been reported

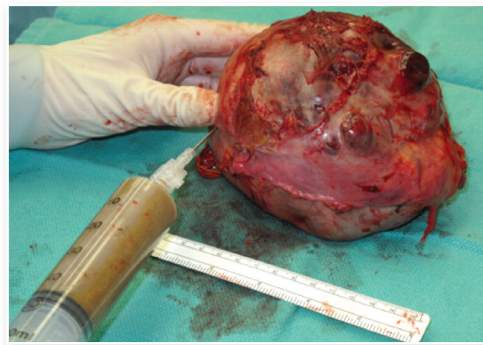


FIG. 19-2. Draining cystic components from pheochromocytoma, after resection.

TABLE 19-1. Biochemical analysis of cystic content

Cyst Fluid	Plasma Reference Values
norepinephrine 65,967	< 3.4 nmol/liter
epinephrine 51,000	< 0.8 nmol/liter
dopamine 791.5	< 0.21 nmol/liter
metanephrine 1,150	< 0.3 nmol/liter
normetanephrine 2,400	< 0.6 nmol/liter

for catecholamines.

Cystic pheochromocytoma is a special subtype of pheochromocytomas, with a specific clinical course. Laparoscopic fenestration of the cyst or attempts to embolize the tumor may result in hypertensive crisis despite appropriate preoperative management. Only complete surgical removal of the tumor can relieve the patient of the clinical symptoms. In conclusion, this patient presents as an

example of cystic pheochromocytoma that was abstracted from the case reported originally by Goldberg *et al.* in the JCEM in 2011.

Subsequent Follow-up on the Patient

The patient was discharged from the hospital in stable condition and on no blood pressure medication. Follow-up investigations demonstrated normalization of the urinary catecholamines and metanephrines. These levels remained normal during follow-up in 2012 and 2013.

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Answers:

Question 1. a

Question 2. c

Question 3. a

A 49-year-old Woman Presenting with Bilateral Adrenal Masses

Guilherme Asmar Alencar, MD, and Maria Candida Barisson Villares Fragoso, MD, PhD

A 49-year-old woman exhibiting clinical features of hypercortisolism (supraclavicular fat pads, buffalo hump, truncal obesity, easy bruising and proximal muscle weakness) was diagnosed with adrenocorticotropin (ACTH)-independent Cushing's syndrome. Hormonal evaluations revealed an abnormal overnight 1-mg dexamethasone suppression test (plasma cortisol: 32 $\mu\text{g}/\text{dL}$; normal: $<1.8 \mu\text{g}/\text{dL}$), elevated 24-hour urinary total cortisol (364 $\mu\text{g}/24 \text{ h}$; normal: 30 to 300 $\mu\text{g}/24 \text{ h}$), elevated midnight salivary cortisol (0.42 $\mu\text{g}/\text{dL}$; normal: $\leq 0.13 \mu\text{g}/\text{dL}$), suppressed dehydroepiandrosterone sulfate (DHEAS) ($<80 \text{ ng}/\text{mL}$; normal: 189 to 2050 ng/mL) and undetectable plasma ACTH ($<5.0 \text{ pg}/\text{mL}$; normal: 10 to 46 pg/mL). Unenhanced abdominal computed tomography (CT) revealed bilateral adrenal masses, with attenuation values up to 10 Hounsfield units (HU) (Figure 20-1).

The baseline endocrine evaluation was followed by an *in vivo* protocol to investigate the presence of aberrant hormone receptors in the adrenal glands (1, 2). An abnormal cortisol response (57% increase in plasma cortisol levels) was observed after provocative testing with terlipressin (0.5 mg IV), indicating vasopressin receptors aberrantly coupled to steroidogenesis in the adrenal cortex. Integrated 2-[fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F -FDG-PET/CT) revealed that ^{18}F -FDG uptake in the bilateral adrenal masses was visibly higher than that in the liver (Figure 20-2). The maximum standardized uptake value (SUVmax), which is an index used to assess metabolic disease activity in FDG-PET imaging, was increased in the adrenal masses, reaching levels usually seen in malignant tumors and metastases (SUVmax: > 3.1) (3, 4).

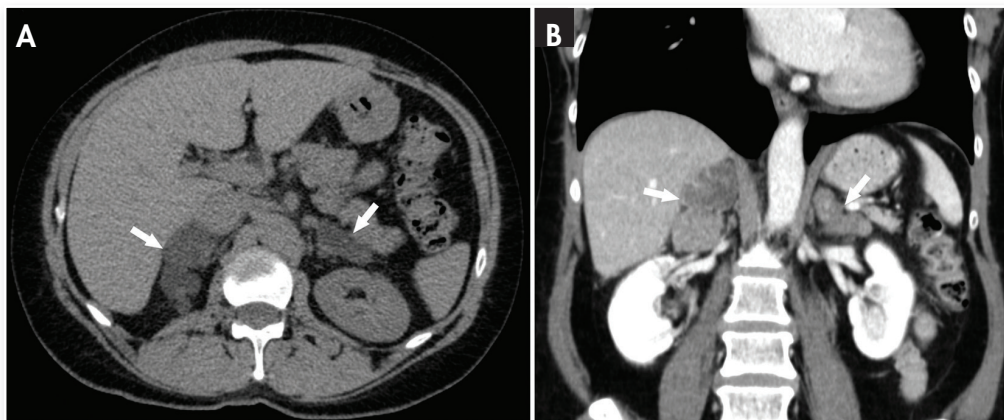


FIG. 20-1. Unenhanced CT in axial view (A) and contrast-enhanced CT in coronal view (B) showing bilateral adrenal masses (arrows).



FIG. 20-2. Transaxial images of ^{18}F -FDG-PET/CT showing bilateral adrenal masses with increased ^{18}F -FDG uptake in comparison to liver. Maximum standardized uptake value (SUVmax) was elevated in these adrenal masses (arrows).

1. BASED ON THESE FINDINGS, THE MOST LIKELY DIAGNOSIS IS:

- a. Bilateral adrenal adenoma
- b. Bilateral adrenal carcinoma
- c. Adrenal metastasis
- d. ACTH-independent macronodular adrenal hyperplasia
- e. Primary pigmented nodular adrenocortical disease

2. THE TREATMENT USUALLY RECOMMENDED FOR THIS CONDITION IS:

- a. Bilateral total adrenalectomy
- b. Unilateral adrenalectomy
- c. Medical treatment with adrenal enzyme inhibitors
- d. Specific pharmacological therapy with antagonists of aberrant hormone receptors
- e. None of the above

Bilateral total adrenalectomy is the standard treatment for this condition. However, in an attempt to control hypercortisolism and avoid lifelong glucocorticoid replacement therapy, the patient was submitted for a laparoscopic total right adrenalectomy and a subtotal left adrenalectomy (with approximately 2/3 of the left gland left intact). The extent of the surgical resection was guided by ^{18}F -FDG-PET/CT imaging with the

objective of primarily removing areas with higher ^{18}F -FDG uptake (Figure 20-3).

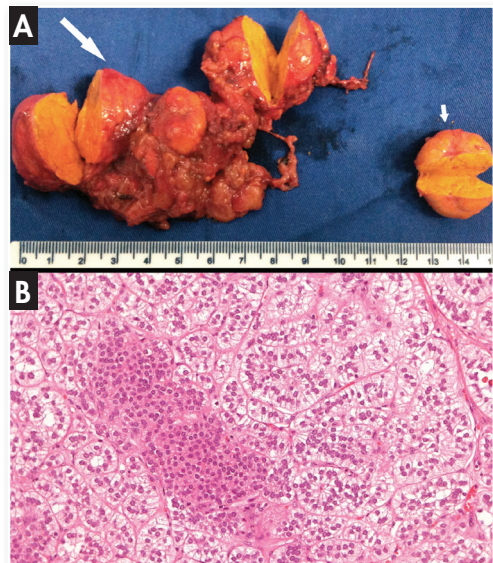


FIG. 20-3. Macroscopic view (A) of resected right adrenal gland (long arrow) and nodule resected from left adrenal gland (short arrow). 50 g of adrenal tissue was excised during surgery and several yellowish nodules of different sizes were seen on surface of right adrenal gland. Histological view (B) of resected adrenal tissue showing presence of large cortical cells with clear cytoplasm (lipid-rich), forming string-like structures and small cells with compact cytoplasm (lipid-poor), forming island-like structures. Hematoxylin and eosin staining.

3. THE MACROSCOPIC AND HISTOLOGICAL FINDINGS WERE TYPICAL OF THE FOLLOWING:

- a. Adrenal adenoma
- b. Adrenal carcinoma
- c. Adrenal metastasis
- d. ACTH-independent macronodular adrenal hyperplasia
- e. Primary pigmented nodular adrenocortical disease

Diagnosis

ACTH-Independent Macronodular Adrenal Hyperplasia.

Discussion

Endogenous Cushing’s syndrome (CS) is caused by primary adrenal over-secretion of cortisol in approximately 15 to 20% of cases (5). Bilateral lesions are involved in 10 to 15% of adrenal CS and include ACTH-independent macronodular adrenal hyperplasia (AIMAH), primary pigmented nodular adrenocortical disease (PPNAD) and, rarely, bilateral adenoma or carcinoma (5).

AIMAH is an infrequent cause of CS first described by Kirschner *et al.* in 1964 (6). Most cases of this disease become clinically manifest during the fifth and sixth decades of life, which is a later age of onset in comparison to other causes of CS. The equal gender distribution in AIMAH also contrasts with the female predominance in most causes of endogenous CS (7). Subclinical CS seems to be the most frequent presentation of AIMAH and, in some patients, adrenal lesions are found incidentally during the radiological investigation of another disease (8).

The diagnosis of AIMAH is suggested by imaging studies (CT scan or magnetic resonance imaging) in patients with the biochemical demonstration of ACTH-

independent CS. On the CT scan, numerous nodules of soft tissue density measuring up to 5 cm in diameter usually distort both adrenal glands. The adrenals sometimes seem to be diffusely enlarged without macroscopic nodules (8). In PPNAD, the adrenal glands are usually less enlarged; cross-sectional imaging frequently reveals normal to slightly hyperplastic adrenals and the nodules do not generally exceed 5 mm (9). It has recently been recognized that AIMAH, a benign adrenal disease, may exhibit intense ¹⁸F-FDG uptake on a PET/CT scan and should therefore be considered in the differential diagnosis of malignant adrenal lesions with increased ¹⁸F-FDG activity, such as carcinoma and metastasis (10).

Although AIMAH is a clinical entity known for nearly 50 years, the pathophysiology of this disease has not been fully clarified. There is evidence that steroidogenesis in AIMAH is regulated by hormones other than ACTH as a result of the aberrant expression of their respective receptors in adrenocortical tissue (1). In vivo investigative protocols have been developed to screen patients with AIMAH for aberrant receptors (1, 2). However, it is not totally clear whether aberrant hormone receptors are a primary phenomenon responsible for the pathogenesis of AIMAH or an epiphenomenon resulting from cell proliferation and dedifferentiation, although there is evidence in favor of the former hypothesis (8).

Surgical treatment is recommended for the majority of patients with AIMAH and CS, but it is questionable whether bilateral adrenalectomy should always be performed (11). In the patient described herein, the extent of surgical resection was guided by ¹⁸F-FDG-PET/CT imaging and areas with higher ¹⁸F-FDG uptake were targeted with the aim of controlling hypercortisolism and avoiding lifelong glucocorticoid replacement therapy. Longer follow up

of the patient is needed to clarify whether this surgical strategy is worthwhile.

Subsequent Follow-up on the Patient

Two years after surgery, the patient still requires low doses of glucocorticoid replacement therapy. Throughout follow-up, blood pressure control improved, body weight returned to normal (18.9 kg/m²) and the clinical features of hypercortisolism gradually disappeared. The most recent laboratory evaluation revealed unsuppressed plasma ACTH levels (19 pg/mL; normal: 10 to 46 pg/mL) and a basal cortisol of 5.7 µg/dL (normal: 8 to 25 µg/dL). Based on these results, the patient is expected to stop the glucocorticoid replacement regimen soon.

Acknowledgments

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Answers

- Question 1. d
Question 2. a
Question 3. d

21

Adrenal Masses in a Young Man with Congenital Adrenal Hyperplasia

Susan Christina McGeoch, BSc (Med Sci), MD, MRCP, and John Stuart Bevan, MD, FRCP

A 34-year-old man presented in 2010 with abdominal swelling and discomfort, tiredness, and salt-craving. Congenital adrenal hyperplasia (CAH) had been diagnosed in infancy (homozygous for gene 655A/C>G point mutation in *CYP21A2*). During adulthood, he was treated with dexamethasone 0.25 mg twice daily and fludrocortisone 0.1 mg once daily. He defaulted from adult clinic follow-up for 10 years and had not collected his dexamethasone prescriptions for one year. He suffered from epilepsy managed by a variety of anticonvulsants, including enzyme-inducing drugs. He was hyperpigmented, blood pressure was 116/78 with no postural drop and he had a 20-centimeter mass palpable in the left abdomen which extended across the midline. An ill-defined smaller mass was palpable deep in the right abdomen (Figure 21-1).

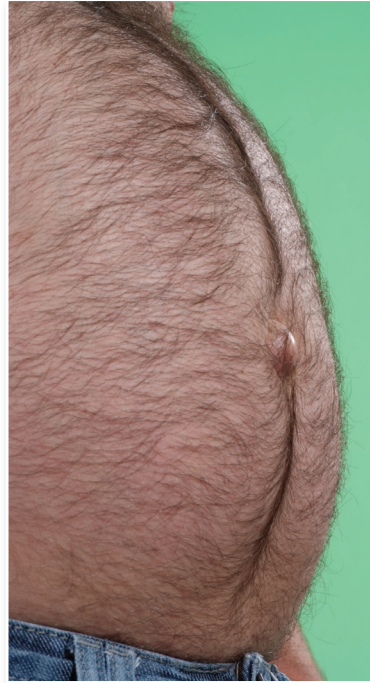


FIG. 21-1: Asymmetrical abdominal distension with umbilical hernia.

1. SELECT THE BEST OPTION FOR YOUR INTERPRETATION OF THE BIOCHEMISTRY RESULTS IN TABLE 21-1:

- Inadequate control of CAH with current steroid regime
- Elevated aldosterone level suggests an incorrect diagnosis of CAH
- Low gonadotrophins and elevated ACTH suggest a 'feedback' pituitary tumor
- Elevated testosterone level is likely to be due to exogenous testosterone abuse for 'body-building'
- Fludrocortisone replacement is adequate

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Continue present steroid regimen and perform an ultrasound of the abdomen
- Increase dexamethasone to 0.5 mg twice daily and perform a computed tomography (CT) of the abdomen
- Increase dexamethasone to 0.5 mg twice daily and perform a magnetic resonance imaging (MRI) of the abdomen
- Continue present steroid regimen and perform a CT of the abdomen
- Continue present steroid regimen and perform an MRI of the abdomen

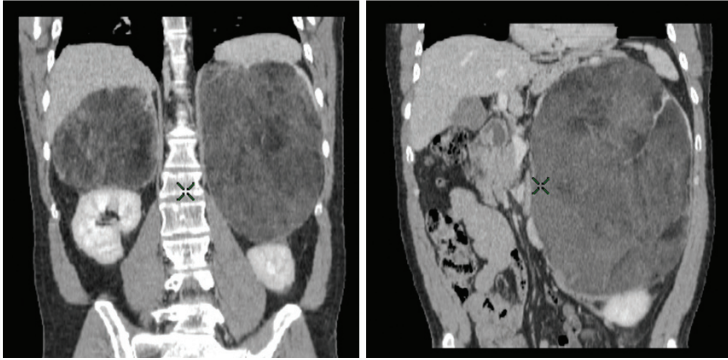


FIG. 21-2: CT scan showing large retroperitoneal swellings (left, 230 mm; right, 150 mm) producing considerable displacement of intraabdominal organs, especially the kidneys.

He proceeded to have CT imaging of the abdomen which showed large, well-defined, bilateral, retroperitoneal suprarenal masses in the expected positions of the adrenal glands. These did not contain calcification and the left mass measured 21x14 cm and the right mass 11 cm. Both were heterogeneous with high fat content and septae, but showed no contrast enhancement (Figure 21-2).

3. WHAT IS THE MOST LIKELY DIAGNOSIS?

- Bilateral adrenal incidentalomas
- Bilateral primary adrenal carcinomas
- Bilateral adrenal myelolipomas
- Bilateral adrenal metastases
- Bilateral pheochromocytomas

Diagnosis

Bilateral Giant Myelolipomas.

Discussion

In this case the diagnosis was bilateral giant myelolipomas in a patient with poorly-controlled CAH.

He underwent bilateral adrenalectomy and pathology confirmed bilateral giant myelolipomas, the left weighing 5.8 kg (230 x 110 x 190 mm) and the right 780 g (150 x 130 x 68 mm) (Figure 21-3). Post-operatively, he was managed with replacement hydrocortisone

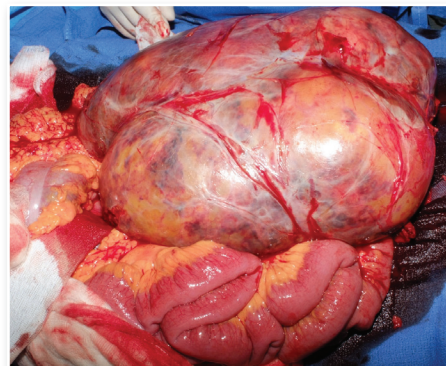


FIG 21-3: Intraoperative appearance of 5.8-kg left adrenal myelolipoma

(20 mg at 0800 h and 10 mg at 1700 h) and fludrocortisone (0.1 mg) daily. Post-operative cortisol day profile suggested adequate glucocorticoid and mineralocorticoid replacement and reactivation of the pituitary-gonadal axis, previously suppressed by high levels of adrenal derived androgens (Table 21-2).

Giant bilateral adrenal myelolipomas are rare (1-5) and are benign, non-functioning adrenal tumors comprised of mature adipose and hematopoietic tissue (6). Our patient's left-sided tumor is among the largest reported (4, 5) with about 30 such cases described in the literature (7) most of which were in patients with 21-hydroxylase deficiency. Chronic ACTH hyperstimulation present in poorly-controlled CAH is thought to be involved in the pathogenesis and in this case resulted from poor steroid compliance

Table 21-1. Hormonal profile

Time (hours)	ACTH ng/l (N<50)	Cortisol nmol/l	Testosterone nmol/l (N 10-35)	17 α OHP nmol/l (N<13)	Na+ mmol/l	Renin mIU/l (N<52)	Aldo- sterone pmol/l (N<400)
Before oral administration of dexamethasone (0.25 mg) and fludrocortisone (0.1 mg) at 0800 h	407	123	34 LH <0.1 U/l FSH <0.1 U/l	605	605	369	600
1.0	114	117	27	504			
2.0	42	129	23	560			
3.0	12	104	19	356			
4.0	61	95	12	227			

Table 21-2. Post-operative cortisol day profile on replacement steroid regimen

Time (hours)	ACTH ng/l (N<50)	Cortisol nmol/l	Testosterone nmol/l (N 10-35)	17 α OHP nmol/l (N<13)	Na+ mmol/l	Renin mIU/l (N<52)	Aldo- sterone pmol/l (N<400)
Before oral administration of hydrocortisone (20 mg) and fludrocortisone (0.1 mg) at 0800 h	83	<20	17.6 LH=14 FSH=17	6	139	60 (N<52 erect)	<70
1.0	–	858	18.8	5			
2.0	–	617	16.1	4			
3.0	11	410	16.8	4			
4.0	8	218	14.6	4			

and likely enhanced corticosteroid metabolism due to concomitant treatment with enzyme-inducing anticonvulsants.

CT scanning is usually diagnostic with myelolipomas appearing as well-delineated heterogeneous masses with low-density mature fat (less than -30 Hounsfield Units) interspersed with more dense myeloid tissue (6, 8, 9) as shown in Figure 21-2. Giant adrenal myelolipomas usually require surgical excision, as in this case, but smaller lesions can be conservatively managed due to the negligible risk of malignancy. In addition, undiagnosed CAH should be considered when such lesions are incidentally discovered.

Subsequent Follow-up on the Patient

When last reviewed in early 2013 the patient remained well on the above steroid replacement and his first child had just been born.

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McGeoch SC, Olson S, Krukowski ZH, Bevan JS 2012 Giant Bilateral Myelolipomas in a Man with Congenital Adrenal Hyperplasia. *J Clin Endocrinol Metab* 97:343–344

Answers:

- Question 1. a
Question 2. b
Question 3. c

A 77-year-old Man with Progressive Cerebellar Syndrome

Frederic Castinetti, MD, PhD, and David Taieb, MD, PhD

A 77-year-old man presented with rapidly progressive cerebellar syndrome, extrapyramidal signs, and cognitive impairment. Past medical history reported a prostate cancer treated by external radiotherapy and an essential thrombocythemia with sideroblastic anemia. Brain computed tomography (CT) scan was normal. The combination of positive antineutrophil antibodies and brain ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) uptake pattern was suggestive of paraneoplastic neurological syndrome. Whole-body ^{18}F -FDG-PET/CT imaging revealed bilateral hypermetabolic adrenal masses (right and left adrenal maximum standardized uptake value = 11.4 and 8.0). Abdominal CT scan showed a 55-mm right

adrenal lesion with two lipoid (thin arrow) and solid (large arrow) components, and an 18-mm left lipoid (thin arrow) adrenal lesion. CT densities of adrenal masses were for solid compartment—unenhanced CT, 35 Hounsfield units (HU); arterial phase, 88 HU; portal phase, 88 HU; for lipoid compartment—unenhanced CT, -61 HU; arterial phase, -62 HU; portal phase, -44 HU (Figure 22-1 A-B).

1. THE MOST LIKELY DIAGNOSIS IS:

- Bilateral adrenal metastasis
- Bilateral adrenal adenoma
- Bilateral pheochromocytoma
- Bilateral myelolipoma
- Bilateral primary adrenal carcinoma

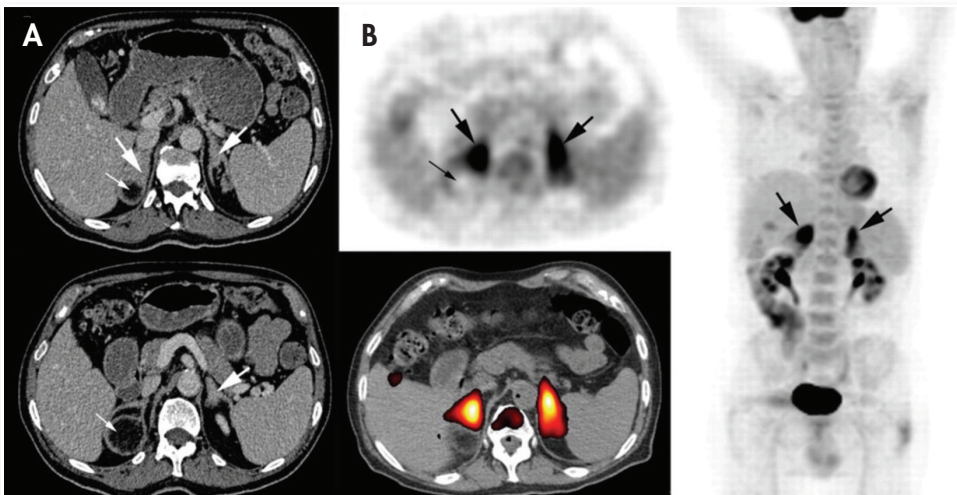


FIG. 22-1. **A**, Abdominal CT scan. **B**, Transaxial FDG-PET (left, upper) and FDG-PET/CT (left, lower) images and whole-body scan (right, Maximal Intensity Projection image) showed bilateral adrenal ^{18}F -FDG uptake (*large arrows*). Hypodense regions on CT scan were hypometabolic on FDG-PET images (*thin arrow*).

Complete endocrinological workup (24-h urinary free cortisol, low-dose dexamethasone suppression test, plasma aldosterone level, dehydroepiandrosterone sulfate, and urinary and plasma methoxyamines) was normal.

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- a. Bilateral adrenalectomy
- b. CT-scan guided biopsy
- c. ^{18}F -FDOPA PET/CT
- d. ^{123}I -MIBG Scintigraphy
- e. Follow-up with a new CT in 6-12 months

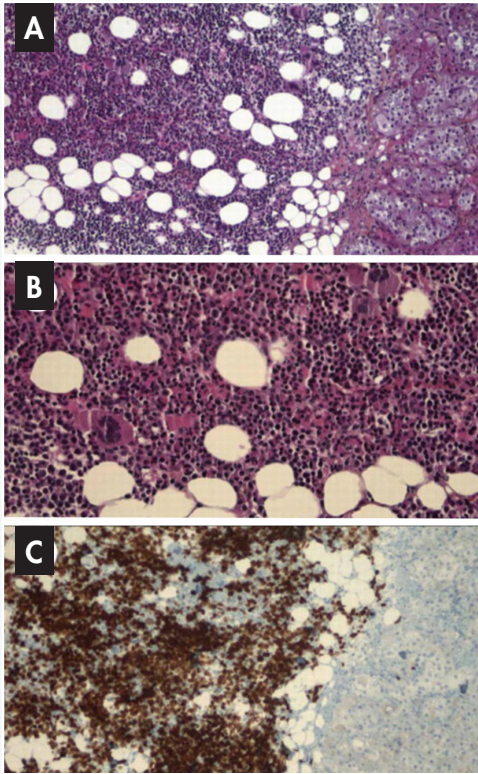


FIG. 22-2. **A** and **B**, Biopsy (hematoxylin and eosin stain; C, $\times 100$; D, $\times 200$). **C**, Proliferative index of hematopoietic cells evaluated with anti-Ki67 antibody ($\times 100$).

A CT scan-guided adrenal biopsy was performed to rule out malignancy (Figure 22-2) and showed for both adrenal masses a nonencapsulated tumor with mature adipose tissue and scattered islands of hematopoietic cells including megakaryocytes (hematoxylin and eosin stain; C, $\times 100$; D, $\times 200$). Proliferative index of hematopoietic cells evaluated with anti-Ki67 antibody was up to 80% in contrast with adrenal cortical tissue ($\times 100$).

3. CYTOLOGIC FINDINGS ARE CONSISTENT WITH THE DIAGNOSIS OF:

- a. Bilateral myelolipoma
- b. Bilateral pheochromocytoma
- c. Bilateral primary adrenal carcinoma
- d. Bilateral metastases
- e. Bilateral lymphoma

Diagnosis

Bilateral Adrenal Myelolipoma.

Discussion

Bilateral high ^{18}F -FDG PET uptake is usually due to adrenal malignancies (*i.e.*, metastases, primary adrenal lymphoma) (1). A recent study has also reported an intense glucose hypermetabolism in bilateral adrenal hyperplasia with Cushing's syndrome, which was not observed in our patient (2). We report here a very rare case of benign hypermetabolic masses secondary to adrenal myelolipomas. The few reported cases of adrenal myelolipoma have usually shown no significant ^{18}F -FDG uptake. An unusual case of giant adrenal myelolipoma with increased ^{18}F -FDG uptake has been reported (3). In another case, high tracer avidity was due to a lung cancer metastasis within a myelolipoma (4). Interestingly, in our case, increased ^{18}F -FDG avidity could be explained by

overexpression of glucose transporter-1 within the myeloid tissue component of the mass (Figure 22-3) (5). Myelolipomas should be considered as potential differential diagnoses of high ^{18}F -FDG avid adrenal lesions, which consequently do not necessarily require adrenalectomy. A definitive diagnosis of myelipoma by using CT or MRI alone may be difficult if only a small amount of fat is present. A CT-guided biopsy directed at the focal area of hypermetabolism may be needed to rule out malignancy (*i.e.*, metastasis, liposarcoma), as was reported by Castinetti *et al.* in JCEM in 2012 (6), from which the above case was abstracted.

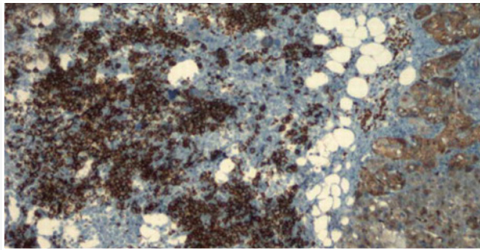


FIG. 22-3. Diffuse membrane staining with anti-GLUT1 antibody within erythroblasts (x100).

Subsequent Follow-up on the Patient

In the following weeks, the patient presented severe decline of cognitive functions. He finally died a few months later with clinical signs of encephalitis.

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Castinetti F, Verschuere A, Cassagneau P, Brue T, Sebag F, Daniel L, Taieb D 2012 Adrenal Myelolipoma: An Unusual Cause of Bilateral Highly ^{18}F -FDG-Avid Adrenal Masses. *J Clin Endocrinol Metab* 97: 2577–2578

Answers

Question 1. b

Question 2. a

Question 3. a

23

A 45-year-old Woman with Recurrent Thromboembolic Events and Increased Adrenal 2-[fluorine 18] fluoro-2-deoxy-D glucose (^{18}F -FDG) Uptake

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A 45-year-old woman living in The Netherlands was taking anticoagulation therapy (acenocoumarol) for a history of recurrent thromboembolic events. She was admitted with massive hemothorax. Recovery was complicated by cardiac arrest and hypotension requiring resuscitation. Periodic complete atrioventricular block necessitated implantation of a dual chamber/dual demand pacemaker. A few weeks later, she developed fever and abdominal distress, and was readmitted to the intensive care unit. She was treated with antibiotics because of suspected sepsis, but urinary and blood cultures proved negative. In addition, she was treated empirically with prednisolone, which was subsequently tapered and then discontinued. Since systemic inflammation markers remained elevated (C-reactive protein levels ranging from about 60 to 150 mg/liter), it was decided to perform an integrated 2-[fluorine 18] fluoro-2-deoxy-D glucose (^{18}F -FDG) positron emission tomography/low dose computed tomography (^{18}F -FDG PET/CT)

in search of an inflammatory focus. ^{18}F -FDG PET/CT was performed when the patient had been off steroids for 10 days. Besides increased ^{18}F -FDG uptake in the heart region which had been believed to be due to pericarditis rather than to an infected pacemaker lead, increased bilateral adrenal ^{18}F -FDG uptake was noted (Figure 23-1A). Because the concomitant low dose CT-scan showed adrenal enlargement, particularly on the left side, a diagnostic CT-scan was performed both with and without (Figure 23-1B) intravenous contrast. The size of the left adrenal was estimated to be 2.9 x 1.9 x 1.5 cm (unenhanced density of 36 Hounsfield units (HU)), whereas the right adrenal was also slightly enlarged (maximal diameter 1.7

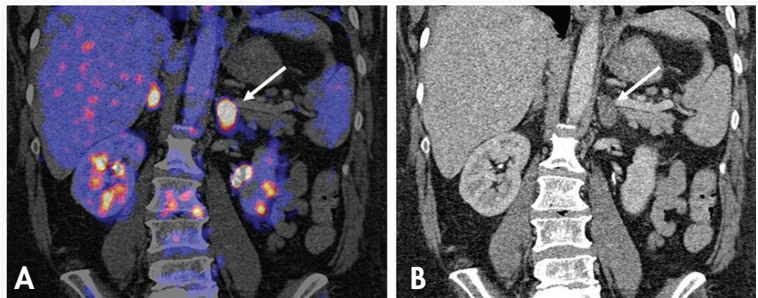


FIG. 23-1. Fusion image of ^{18}F -FDG PET/low-dose CT (A) and unenhanced CT (B). There is increased ^{18}F -FDG uptake in the left adrenal gland; uptake is somewhat increased in the right adrenal gland as well SUVmax are 4.8 in the left and 3.4 in the right adrenal, respectively; corresponding maximum SUV ratios (SUVmax adrenal gland/SUVmax liver) are 2.4 for the left and 1.7 for the right side adrenal, respectively). The unenhanced density of the left adrenal gland is 36 HU.

cm). With contrast-enhanced CT imaging, the absolute washout and the relative washout of the left adrenal amounted to 36% and 25%, respectively. At this point in her evaluation, a consultant from the Endocrinology Department was asked for advice regarding the approach to this patient with bilateral

1. AT THIS STAGE OF THE CASE PRESENTATION WHICH DIAGNOSIS WOULD YOU CONSIDER? (choose all that apply):

- a. Adrenal adenoma causing Cushing's syndrome
- b. Bilateral adrenal hemorrhage
- c. Bilateral adrenal metastases
- d. Bilateral pheochromocytoma
- e. Adrenal myelolipoma

adrenal incidentaloma.

At this time, the patient developed hyponatremia (serum sodium 128-132 mmol/liter) and hyperkalemia (serum potassium 4.7-5.9 mmol/liter). Adrenal insufficiency was suspected and a 250 microgram corticotropin test was performed. An insufficient rise in serum cortisol after synthetic ACTH (20 nmol/liter maximally) and an elevated basal ACTH (278 ng/liter), together with an undetectable aldosterone (<0.03 nmol/liter) confirmed adrenal insufficiency. Anti-adrenal antibodies were absent. Plasma metanephrine levels were within reference range of normal. Directly thereafter, treatment with glucocorticoids and fludrocortisone was started. As a consequence, the electrolyte disturbances disappeared within a few days. Variable eosinophilia had been noted earlier and was initially thought to be caused by low molecular weight heparin treatment. Eosinophilia (1.59×10^9 eosinophiles/liter; upper normal range $< 0.4 \times 10^9$ eosinophiles/liter) normalized only gradually. A tuberculin skin test was

2. WHICH OF THE FOLLOWING DIAGNOSES WOULD YOU CONSIDER VERY UNLIKELY AT THIS STAGE OF THE PATIENT'S PRESENTATION? (Choose all that apply):

- a. Bilateral adrenal hemorrhage resulting in primary adrenal insufficiency
- b. Bilateral adrenal metastases resulting in primary adrenal insufficiency
- c. Pheochromocytoma
- d. Addison's disease due to tuberculosis
- e. Secondary adrenal insufficiency consequent to glucocorticoid use

negative.

Diagnosis

Bilateral Adrenal Hemorrhage Complicating Antiphospholipid Syndrome Resulting in Permanent Adrenal Insufficiency.

Discussion

The patient described in this vignette had been diagnosed with primary antiphospholipid syndrome (APS) based on her medical history of recurrent thromboembolic events and the repeatedly documented presence of lupus anticoagulant and moderately positive anticardiolipin antibodies of the IgG isotype (1). Although recurrent arterial or venous thrombosis is a central feature of APS (1), primary adrenal insufficiency caused by bilateral adrenal hemorrhage as a consequence of APS is considered to be rare. The association of primary adrenal insufficiency with APS was first described in 1988, although this relationship was suggested by a report in 1973 of a patient with APS and systemic lupus erythematosus (2, 3). A clinical case seminar with definitive adrenal insufficiency due to bilateral hemorrhage coincident to primary APS appeared in 1997 (4). In 2003, Espinosa *et al.* described 86 patients with detectable antiphospholipid antibodies in whom

adrenal involvement was likely (2). Thirty-one of these patients (36%) were considered to present with adrenal failure. Presotto *et al.* retrieved 19 cases published between 1988 and 2005, and one additional case from their own experience in whom adrenal failure was the initial manifestation of primary APS (3). Bilateral adrenal enlargement was seen on CT or nuclear magnetic imaging (NMR) in 15 patients (3). It is estimated that autoimmune adrenalitis is currently responsible for primary adrenal insufficiency in up to 70 to 90% of patients, whereas tuberculosis, other infectious diseases, metastatic cancer, adrenal hemorrhage or the use of certain drugs are responsible for the remainder of cases (5). It is believed that primary adrenal insufficiency is due to APS in only 0.4% of cases (5). On the other hand, bilateral adrenal hemorrhages are present in roughly 1% of autopsies. In addition to hypercoagulable states like APS, sepsis, physical trauma, severe stress, the use of anticoagulant drugs, and heparin therapy are important precipitating factors for adrenal hemorrhage.

In general, congenital adrenal hyperplasia, macronodular adrenal disease, metastases, granulomas, amyloidosis, infiltrative diseases and hemorrhage may be responsible for bilateral adrenal enlargement (6). In the patient described here, imaging characteristics led us to consider that non-benign disorders could be responsible for the (bilateral) adrenal masses (6, 9). These characteristics were in respect to increased (bilateral) adrenal ¹⁸F-FDG uptake (maximum standardized uptake values (SUVmax) ratios compared to liver which were 2.4 for the left and 1.7 for the right adrenal, respectively, with a proposed cut-off value: 1.45 (7)); as well as the high density of the left adrenal at unenhanced CT (36 HU; proposed cut-off value: 10 HU (8)) and the delayed contrast

washout (absolute washout of 36 % and a relative washout of 25 % of the left adrenal; proposed cut-off values >60 % and >40%, respectively) (9).

Although adrenal hemorrhage may give rise to increased ¹⁸F-FDG uptake and high density with an unenhanced CT (10), a literature search yielded only 2 further case reports of increased bilateral adrenal ¹⁸F-FDG uptake due to hemorrhage, which in one case was attributable to heparin-associated thrombopenia (11) and in another to anticoagulation therapy (12). In the latter case, unenhanced CT density was 50-60 HU and contrast washout was delayed (12). In contrast, ¹⁸F-FDG uptake was not increased in a patient with massive idiopathic unilateral adrenal hemorrhage (13). Given these uncertainties about the etiology of the adrenal masses, it was decided to perform a laparoscopic adrenalectomy of the left adrenal gland. This procedure was uneventful. Histology showed extensive hemorrhagic changes with destruction of the adrenal gland and fat necrosis but no tumor (Figure 23-2). We propose that increased ¹⁸F-FDG uptake may have resulted from an inflammatory reaction due to fat necrosis. In this patient, the APS, the necessary anticoagulant treatment and the period of hemodynamic instability may all have contributed to adrenal infarction and secondary bleeding.

Subsequent Follow-up on the Patient

Long-term in-hospital rehabilitation was required to improve the condition of this patient. Four months after removal of the left adrenal gland, serum cortisol was undetectable shortly after withdrawal of hydrocortisone, indicating permanent adrenal insufficiency. Until now, 18 months after the initial intensive care unit admission, the patient has not experienced further thromboembolic events, while receiving coumarin anticoagulants, aspirin, as well as glucocorticoid plus

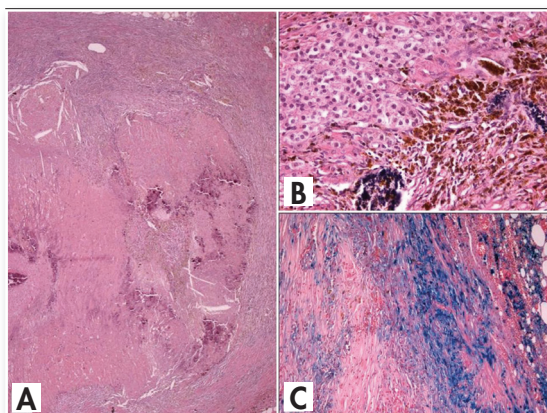


FIG. 23-2. Destruction of the adrenal gland with extensive remnants of hemorrhage, fat necrosis and degenerative changes (hematoxylin & eosin staining; original magnification 20x) (A); small area of preexistent adrenal cortex (hematoxylin & eosin staining; original magnification 400x) (B); remnants of extensive hemorrhage (Perls iron staining; original magnification 100x) (C).

mineralocorticoid replacement therapy.

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Answers:

Question 1: b, c, and d

Question 2: c, d, and e

Honglin Hu, MD, and Xiaoqing Xi, MD

A 55-year-old woman presented with a 1-year history of abdominal pain in the upper right abdomen. She complained of pain particularly in the last 2 months. Physical examination revealed mild tension in the upper right abdomen. Abdominal ultrasonography identified a well-defined 15×16 cm mass in the retroperitoneum. Abdominal computerized tomography (CT) with contrast and computed tomographic angiography (CTA) further defined the mass as of right adrenal origin and a possible adrenocortical tumor (Figure 24-1). Laboratory investigations *i.e.*, serum cortisol, renin, aldosterone and 24 hour urinary 17-ketosteroid (17-KS), 17-hydroxycorticosteroid (17-OHCS), VMA were all within normal limits. Baseline hematologic and biochemical investigations and urinalysis were normal.

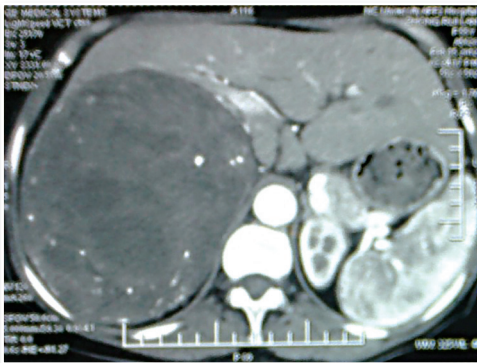


FIG. 24-1 Abdominal contrasted CT showing well-defined non-homogeneous mass of right adrenal origin.

1. THE MOST LIKELY DIAGNOSIS IS:

- Adrenal pheochromocytoma
- Adrenal nonfunctional tumor
- Adrenal primary hyperaldosteronism
- Cushing syndrome
- Other tumor

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Laparoscopic surgery
- Open surgery
- Interventional embolization before surgery

The patient was offered adrenalectomy and consented for the surgical removal of presumed adrenal gland neoplasms. With the patient under general anesthesia, a Foley catheter was inserted to drain the bladder. The patient was placed in a horizontal position and secured to the operating table. A 20 cm incision was made just below the right costal margin. The muscles were divided under direct vision, and the peritoneum was incised and the abdominal cavity entered. Dissection was carried out around the tumor. The upper end of the tumor was exposed and the liver was dissected. The medial border was separated from the inferior vena cava and the tumor was completely removed (Figure 24-2). The histopathological features confirmed the diagnosis of adrenal angiomyolipoma (Figure 24-3). The patient recovered without any complications following surgery.



FIG. 24-2 Gross specimen of removed mass.

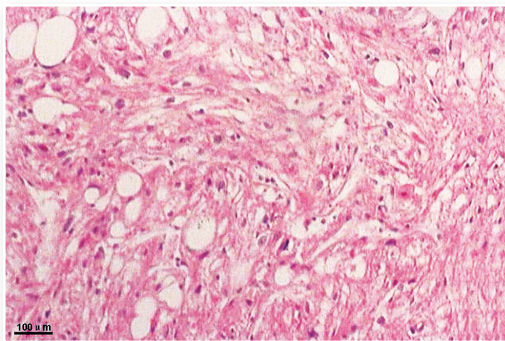


FIG. 24-3 Photomicrograph (H and E staining) revealing features of angiomyolipoma with mature fat cells, smooth muscle fibres, and thin-walled blood vessels. (original magnification $\times 200$).

3. THE PATHOLOGIC DIAGNOSIS OF ANGIOMYOLIPOMA IS BASED UPON:

- a. Adipocytes
- b. Abnormal blood vessels
- c. Smooth muscle layer
- d. All of the above

4. THE MOST COMMON SITE OF ANGIOMYOLIPOMA IS:

- a. Kidney
- b. Liver
- c. Adrenal
- d. Gastrointestinal

Diagnosis

Adrenal Angiomyolipoma.

Discussion

The increased use of abdominal ultrasonography and CT scanning has led to the frequent finding of an unexpected adrenal mass or “incidentaloma.” Fatty tumors of the adrenal gland are uncommon and their features have received little attention in the literature. The lesion has been recognized with increasing frequency because it has a characteristic appearance on CT scanning and magnetic resonance imaging (MRI) (1) that establishes the diagnosis and excludes the need for extensive metabolic evaluation or surgical exploration. Rarely, pure adrenal lipomas may occur; these should be removed to exclude the possibility of a retroperitoneal liposarcoma (2) or an adrenal leiomyosarcoma (3).

Angiomyolipoma of the adrenal gland is an extremely uncommon tumor detected incidentally at investigations for other reasons. Angiomyolipomas often arise in the kidney and are a part of a group of tumors with a diverse appearance known as tumors of perivascular epitheloid cell origin. Angiomyolipoma most commonly occurs in the kidney. The next common site is the liver. Extrarenal angiomyolipomas are extremely rare and have been reported in the liver, colon, suprasellar region, small intestine, skin, intranodal, omentum, breast and adrenal gland (4-8). Adrenal angiomyolipoma is extremely rare and only five cases have been reported, including the present case (9, 10). In our case the tumor size was (15×16 cm), the largest being reported. Angiomyolipomas predominately composed of smooth muscle cells are known diagnostic challenges to pathologists. They are often misdiagnosed as sarcomatoid carcinoma, carcinoma or sarcoma. Some of these tumors have malignant potential and recur

locally. A diligent search for adipocytes and abnormal blood vessels may help in confirming the diagnosis.

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Answers:

- Question 1. b
Question 2. b
Question 3. d
Question 4. a

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Context: Cushing's disease (CD) is associated with serious morbidity and, when suboptimally treated, an increased mortality. Although surgery is the first-line treatment modality for CD, hypercortisolism persists or recurs in an important subset of patients. Considering the deleterious effects of uncontrolled CD, there is a clear need for effective medical therapy.

Objective: In this review, we discuss molecular targets for medical therapy, efficacy, and side effects of the currently used drugs to treat hypercortisolism and focus on recent developments resulting from translational and clinical studies.

Evidence Acquisition: Selection of publications related to the study objective was performed via a PubMed search using relevant keywords and search terms.

Main Findings: Medical therapy for CD can be classified into pituitary-directed, adrenal-blocking, and glucocorticoid receptor-antagonizing drugs.

Recent studies demonstrate that somatostatin receptor subtype 5 (sst₅) and dopamine receptor subtype 2 (D₂) are frequently (co-)expressed by corticotroph adenomas. Pituitary-directed therapy with pasireotide and cabergoline, targeting sst₅ and D₂, respectively, is successful in approximately 25-30% of patients. Adrenal-blocking drugs can be effective by inhibiting steroidogenic enzyme activity. Finally, the glucocorticoid receptor antagonist mifepristone induces clinical and metabolic improvement in the majority of patients. Each drug can have important side effects that may impair long-term treatment. Generally, patients with moderate to severe hypercortisolism need combination therapy to normalize cortisol production.

Conclusion: Medical therapy for CD can be targeted at different levels and should be tailored in each individual patient. Future studies should examine the optimal dose and combination of medical treatment modalities for CD. (*J Clin Endocrinol Metab* 98:425-438, 2013)

CUSHING'S DISEASE (CD) is caused by an ACTH-producing pituitary micro- or macroadenoma that chronically stimulates cortisol production by the adrenal glands. This chronic state of hypercortisolism is associated with multiple complications resulting in significant morbidity that severely impairs quality of life and an increased mortality when the disease is not controlled or not sufficiently controlled (1, 2, 3). The clinical phenotype is characterized by features of the metabolic syndrome (central obesity, diabetes mellitus, dyslipidemia, and hypertension), hirsutism, easy bruisability, muscle weakness, cognitive dysfunction, and mood alterations including depression (1). The diagnosis of CD can be difficult and is often delayed due to the gradual development of symptoms and the overlap

in features of the metabolic syndrome.

Pituitary surgery is the first-line treatment of CD, and remission rates vary between 60 and 90% (3, 4, 5). However, the true remission rate is considerably lower because up to 25% of patients develop a recurrent adenoma (6). In addition, transsphenoidal surgery is less successful in patients with nonvisible adenomas and macroadenomas. Second surgery is an option in patients with persistent or recurrent CD, but the remission rates are lower, also with a considerable risk on hypopituitarism (6, 7). Radiotherapy can be applied in patients with persistent hypercortisolism after surgery, but it has the disadvantage of having a slow onset of action with a mean period of 2 years, after which remission is induced (8, 9). In this period,

patients remain exposed to the deleterious effects of cortisol excess. In addition, radiotherapy can induce hypopituitarism (10), and it was shown that quality of life is most impaired in those CD patients with pituitary dysfunction after treatment, despite replacement therapy (11). Bilateral adrenalectomy is an effective but rigorous treatment for CD necessitating lifelong gluco- and mineralocorticoid replacement therapy with a permanent risk on acute adrenal insufficiency in case of physical stress (12).

Considering the effects of uncontrolled hypercortisolism on morbidity and mortality and the drawbacks of radiotherapy and biadrenalectomy, there is a clear need for efficacious medical therapy for patients with CD in whom surgery is unsuccessful or not feasible. The role of medical therapy is currently limited due to moderate efficacy and/or serious toxicity of available drugs, which can hamper long-term treatment. In recent years, however, new molecular targets have been identified on corticotroph adenomas for medical treatment. In addition, based on these insights, strategies for combination treatment for CD have been developed. In this review, an overview is given on the indications for medical therapy in CD and the currently available medical treatment modalities, followed by a discussion on recent developments in the treatment of CD with (novel) somatostatin (SS) analogs (SSAs), dopamine agonists (DAs), glucocorticoid receptor (GR) antagonists, and combination therapies.

Morbidity, Mortality, and Reversibility of Complications After Treatment

Morbidity and Quality of Life

CD is associated with severe morbidity, which can be classified in several major

categories. First of all, chronic hypercortisolism induces major changes in body composition with abdominal and facial fat accumulation, muscle and skin atrophy, and osteoporosis (13). Second, cortisol excess has major effects on the brain that can result in psychopathology and neurocognitive dysfunction (14). Approximately 55-80% of CD patients have major depression or an anxiety disorder according to Depression Statistics Manual (DSM) criteria (15, 16). In addition (severe) hypercortisolism can induce psychosis (14). Neurocognitive dysfunction is characterized by impaired memory and executive functions as well as sleeping disturbances (14). Third, as mentioned before, CD is accompanied by all components of the metabolic syndrome, including overweight/obesity (up to 90% of patients), hypertension (60-80%), impaired glucose tolerance/diabetes mellitus (up to 65%), and dyslipidemia (40-70%) (13). This clustering of cardiovascular risk factors as well as possible direct cardiotoxic effects of cortisol excess predisposes patients with CD for coronary artery disease, left ventricular hypertrophy, diastolic dysfunction, and cerebrovascular disease (17, 18). Apart from an increased risk of arterial thrombosis, CD is also associated with an increased risk of venous thromboembolic disease due to both activation of the coagulation cascade and impaired fibrinolysis (19, 20). Finally, miscellaneous features of CD include hirsutism, gonadal dysfunction, nephrolithiasis, and increased susceptibility to infection (1).

Due to the broad spectrum of morbidity, it is not surprising that patients with CD have a severely impaired quality of life as assessed by questionnaires evaluating a patient's perceived health problems (Nottingham Health Profile), functional status, and general well-being

(RAND-36); physical and mental fatigue (Multidimensional Fatigue Index-20); anxiety and depression (Hospital Anxiety and Depression Scale); and a CD-specific questionnaire (CushingQoL) (13). Factors causing this impaired quality of life include tiredness, mood and sleep disturbances, impaired cognitive functions, and changes in body composition leading to an altered appearance and decreased exercise tolerance.

Mortality

With regard to mortality in CD, a distinction should be made between patients with long-term remission and patients with persistent disease. Several studies show that patients with persistent hypercortisolism have an increased mortality risk, with a standardized mortality ratio of approximately 4.0 compared to both the general population and patients with other pituitary adenomas, with cardiovascular disease as leading cause of death (2, 13, 21, 22). Conflicting data exist on patients who are biochemically cured, with some studies showing a normal life expectancy (23, 24), whereas other studies report increased standardized mortality ratio values (25, 26). Overall, it may be that sustained control of cortisol production reduces but does not completely normalize mortality in all patients with CD. Indeed, persistence of cardiovascular risk factors in cured patients (see Reversibility of complications after treatment) may translate into an increased mortality risk.

Reversibility of Complications After Treatment

The morbidity due to prolonged exposure to high cortisol levels in CD is only partially reversible in a substantial number of patients (13). With respect to cardiovascular risk factors, overweight/obesity persists in up to 40%, hypertension

in up to 60%, impaired glucose tolerance/diabetes mellitus in up to 60%, and dyslipidemia in up to 30% of patients (13,27,28,29). Colao et al (29) found that patients who were 5 years cured from CD still had a worse cardiovascular risk profile coinciding with a high prevalence of atherosclerosis as assessed by intima media thickness. Persistence of the metabolic syndrome seems to be related to disease duration before cure (28). Also, hypercoagulability is not reversible at short-term remission and may only partially be reversible at long-term remission (20,30). Bone mineral density does also not completely recover in all patients (31). Finally, psychopathology can decrease after curation in a time-dependent manner (32), although its prevalence is still increased after long-term remission (14). Similarly, cognitive function often remains impaired, suggesting irreversible effects of chronic hypercortisolism on the brain (14). Despite normalization of cortisol levels, quality of life remains impaired, in particular in those patients with hypopituitarism (11), which is in part related to ongoing morbidity (13). Overall, the duration of hypercortisolism in CD seems to be inversely related to the reversibility of complications, which in turn may increase mortality. This indicates that once the diagnosis of CD is established, cortisol production should be normalized as soon as possible, highlighting the need for effective medical therapy.

Medical Treatment of CD

Treatment Aims and Indications

There are several indications for medical therapy for CD (33,34). First of all, cortisol-lowering or -antagonizing therapy can be indicated to treat acute, potentially life-threatening complications of CD like acute psychosis, severe hypertension, and

(opportunistic) infections. These complications occur predominantly in the ectopic ACTH syndrome (EAS) but can also occur in CD in case of overwhelming cortisol excess. A retrospective analysis showed that high indices of hypercortisolism are more predictive of bacterial or opportunistic infections than body temperature and white blood cell count due to immunosuppressive effects of cortisol (35). Patients with severe hypercortisolism need therefore close monitoring, and it is recommended to initiate *Pneumocystis carinii* prophylaxis (35). Interestingly, infections can also become clinically manifest during cortisol-lowering therapy, possibly due to immune reconstitution (36).

Second, medical therapy can be applied as pretreatment before pituitary surgery to improve blood pressure and glycemic regulation and to reduce perioperative complications, eg, bleeding tendency during operation. There is, however, currently no evidence that medical pretreatment indeed has beneficial effects on perioperative morbidity and surgical outcome. Third, medical treatment is indicated in patients with persistent or recurrent CD who are not candidates for surgical retreatment, whether or not as bridging therapy to overcome the period after which radiotherapy becomes effective. As outlined in “Reversibility of complications after treatment,” the reversibility of complications of CD seems to be inversely related to disease duration. It is therefore essential to rapidly normalize cortisol production in these patients to reverse or prevent worsening of morbidity, to reverse mortality, and to improve quality of life. Primary medical therapy can be considered in patients with an unfavorable tumor localization (eg, the parasellar region), patients with macroadenomas (without optic chiasm compression), and patients with

a high operation risk due to significant comorbidity.

Molecular basis for medical therapy

Somatostatin receptors

SS has an inhibitory effect on the secretion of several anterior pituitary hormones, in particular on GH, TSH, and prolactin secretion. SS exerts its action via the activation of SS receptors (SSRs), of which 5 subtypes encoded by different genes have been documented. The normal anterior pituitary gland expresses 4 of 5 SSR subtypes (sst), eg, sst₁, sst₂, sst₃, and sst₅. Sst₄ appears not expressed at the mRNA level in the human anterior pituitary gland. Studies in rats show that corticotrope cells express all SSR subtypes. Sst₂ and sst₅ are expressed at the mRNA and protein level by only a subpopulation of rat corticotropes (37). To the best of our knowledge, however, there are no data describing the expression of SSR subtypes in the individual cell types of the human anterior pituitary gland. On the other hand, a differential expression of SSR subtypes is found in the pituitary adenomas that are derived from the different anterior pituitary cell types. Sst₂ and sst₅ are the most predominantly expressed SSR subtypes in pituitary tumors. Corticotrope pituitary tumors express in particular sst₂ (at relatively low level) and sst₅ receptors (38, 39, 40, 41, 42, 43). The relatively low expression level of sst₂ receptors in corticotrope adenomas seems due to the suppressive effects of the high levels of circulating cortisol in patients with untreated CD. Sst₅ expression is less sensitive to the suppressive effect of cortisol (44), which could be the cause for the higher expression compared to sst₂ in these adenomas. Taking these observations together, it seems that in particular, sst₅ receptors form a target for medical treatment in patients with untreated CD.

In case of lowering circulating cortisol levels in patients with CD by any kind of treatment, an up-regulation of sst_2 receptors can be hypothesized, thereby forming an additional target for treatment with SSAs to control cortisol production.

Dopamine receptors

Like SSR, dopamine receptors (DRs) are also expressed in most cell types of the anterior pituitary gland. The DR family consists of 5 receptor subtypes that, on the basis of functional and pharmacological properties, can be subdivided into D1-like (D_1 and D_4) and D2-like (D_2 , D_3 , and D_4) receptors. D1-like receptors are preferentially stimulatory, whereas D2-like receptors have mainly inhibitory properties, eg, inhibition of intracellular cAMP level (45). D_2 and, to a lesser extent, D_4 are the DR subtypes that are expressed in the anterior pituitary gland. The most well-know action of DR in the regulation of anterior pituitary hormone secretion is the inhibition of prolactin secretion. On the other hand, D_2 is expressed in more than 75% of all cells in the anterior pituitary gland, which suggests that nonlactotrope cells also express this DR subtype (46). Corticotrope adenomas express predominantly D_2 receptors, as demonstrated by in situ hybridization studies, RT-PCR, and immunohistochemistry (47, 48). The expression of D_2 in corticotrope adenomas is positively correlated to the suppressive effects of the DA cabergoline (see Dopamine agonists) on urinary free cortisol (UFC) secretion in patients with CD (47). Unlike sst_2 , but resembling sst_5 , D_2 appears not to be negatively regulated by cortisol (44). Summarizing, the expression of D_2 in a significant proportion of human corticotrope adenomas forms an important target for treatment with DAs. In one study, the coexpression of both D_2 and sst subtypes was evaluated. de Bruin *et al*

(38) showed coexpression of sst_5 and D_2 in about 60% of corticotrope adenomas. In agreement with previous studies, a low level of sst_2 expression was found at significant levels in only 30% of the adenomas.

Steroidogenic enzymes

The steroidogenic enzymes that are expressed in the cortical zones of the adrenal cortex form an important target for drugs used in the treatment of CD as well. In particular 11β -hydroxylase, an enzyme involved in the last step of conversion of 11-deoxycortisol into cortisol, is an important target enzyme that is inhibited by several adrenal-blocking drugs. In addition to 11β -hydroxylase, also 17α -hydroxylase, which is involved in the conversion of pregnenolone into 17-OH-pregnenolone and of progesterone into 17-OH-progesterone, is an important target for drugs to inhibit both cortisol and dehydroepiandrosterone synthesis. Finally, several drugs inhibit the mitochondrial side chain cleavage enzyme (CYP11A1), which is involved in the first step of steroidogenesis, eg, the conversion of cholesterol into pregnenolone.

Glucocorticoid receptor

Glucocorticoids exert their action via the GR. The GR is a member of the steroid hormone superfamily. The GR gene is located on chromosome 5 and consists of 10 exons, encoding for the transactivation domain (exon 2), the DNA binding domain (exons 3 and 4), and the hormone binding domain (exons 5-9). Two isoforms of the GR have been identified, ie, GR- α and GR- β (49). The GR is ubiquitously expressed in almost every cell in the body (50) and has pleiotropic effects on various cellular systems, including metabolism, immune response, bone and mineral metabolism, as well as tissue development. For this reason, a clinical condition of

severe glucocorticoid excess, such as in CD, results in the various, often deleterious effects on metabolism, bone integrity, and immune function. Cortisol plays a dominant role in the negative feedback regulation of pituitary ACTH secretion. Impaired glucocorticoid feedback inhibition is one of the hallmarks of CD. Several mechanisms responsible for this relative resistance of corticotrope adenoma cells to the feedback inhibitory effect of cortisol on ACTH secretion in patients with CD have been proposed. Mutations in the GR in corticotrope tumors appear to be rare (51), whereas one study suggested a frequent loss of heterozygosity at the GR gene locus (chromosome 5) as a potential mechanism causing GR resistance (52). Other studies suggested that increased expression of 11- β HSD2, an enzyme that converts active cortisol into inactive cortisone, in corticotrope tumors might form an explanation for impaired glucocorticoid feedback (53, 54). Finally, GR activation leads to inhibition of ACTH release and proopiomelanocortin transcription through protein-protein

interaction with the orphan nuclear receptors related to nerve growth factor 1B. Two intracellular proteins, Brg1 and histone deacetylase 2 (HDAC2), are critical in the process of transcriptional repression of proopiomelanocortin transcription. Brg1 and HDAC2 were frequently found to be lowered in corticotrope adenomas, and aberrant expression of these proteins is related to relative GR resistance as evidenced by an impaired dexamethasone suppression test. Therefore, lowered Brg1 and/or HDAC2 expression may also form an explanation for GR resistance in corticotrope tumors of patients with CD (55, 56).

Figure 1 summarizes the most important targets for medical treatment in patients with CD.

Pituitary-directed drugs

Somatostatin analogs

The observation that ACTH secretion can be influenced by SSA treatment, as well as the finding that SSRs (in particular sst₅) are expressed at a significant level in

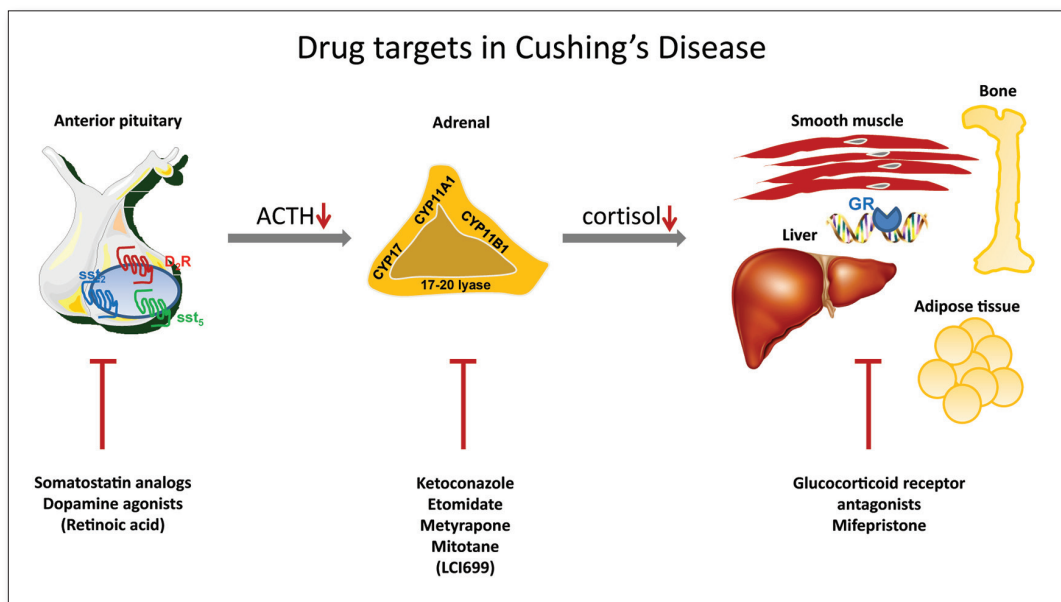


FIG. 1. Targets for medical treatment of CD.

corticotrope adenomas (see Somatostatin receptors), initiated the search for SSAs that inhibit ACTH secretion by corticotrope tumors. Octreotide, a SSA that has preferential binding affinity to sst_2 receptors, did not have a suppressive action on ACTH and UFC secretion in patients with CD (57, 58). More recently, a novel SSA named pasireotide (SOM230) was developed and evaluated for its efficacy in inhibiting ACTH and cortisol production in patients with CD, in vitro and in vivo. In vitro, pasireotide was more potent compared with octreotide in suppressing ACTH secretion by primary cultures of human corticotroph tumors (42). In 2 studies it was shown that pasireotide inhibited ACTH secretion by 30-40% (42) and by 23-56% in 3 of 5 and in 5 of 6 (40) cultures tested, respectively. On the basis of the high expression level of $sst5$ and the inhibitory effect of pasireotide on ACTH secretion by corticotrope adenomas, several clinical trials testing its efficacy in CD were initiated. In a first phase II study in 29 patients with CD, a 15-day pasireotide treatment at a dose of 600 μg twice daily resulted in normalization of UFC level in 5 patients (17%) and an overall significant reduction of UFC in 22 of 29 (76%) patients (59). In another series, pasireotide monotherapy (28 d; dose, 100-250 μg 3 times daily), normalized UFC levels in 29% of patients with de novo or recurrent CD (60). Recently, it was shown in a large double-blind multicenter phase 3 study, including 162 adult patients with CD, that treatment with a dose of 600 μg (82 patients) or 900 μg pasireotide (80 patients) twice daily resulted in UFC normalization in 15 and 26% of patients, respectively, at 6 months (61). UFC levels decreased by > 50% in 50 of the 103 patients for whom UFC data were available at 6 months. Figure 2 shows the effects of pasireotide on UFC levels in these 103 patients. An important

observation is that virtually all responders could be identified within the first 2 months of treatment. In patients with a complete response, UFC levels were rapidly controlled with sustained biochemical remission up to 1 year. In particular, at the higher pasireotide dose (900 μg twice daily), tumor shrinkage was observed after 12 months of treatment. From this trial, 58 patients who had UFC \leq upper limit of the normal range, or who were achieving clinical benefit from pasireotide, entered an extension phase. A further improvement in signs and symptoms was observed from the 12- to 24-month treatment period (eg, further decrease in systolic and diastolic blood pressure, body mass index, and total cholesterol level), which was accompanied by sustained reductions in UFC, plasma ACTH, and serum cortisol (62). Drug-induced hyperglycemia was the major adverse event reported in a majority of patients in the above-mentioned studies and may be attributed to pasireotide-mediated inhibition of incretin secretion (63). It should be noted, however, that pasireotide, due to its broad binding profile to most sst subtypes, can have other, not yet identified adverse events as well. In particular, pasireotide has a potent suppressive action on GH and IGF-I levels (64). A strong lowering of IGF-I in patients with CD, who often are already in a catabolic state, may form another unwanted adverse event of the drug. Such adverse events should be considered in the light of its potency to induce a biochemical cure in a subgroup of 20-30% of patients with CD. Pasireotide was recently approved in Europe for treatment of patients with CD after unsuccessful surgery or for whom surgery is not an option.

Dopamine agonists

Early studies already showed that short-term treatment with the DA bromocriptine

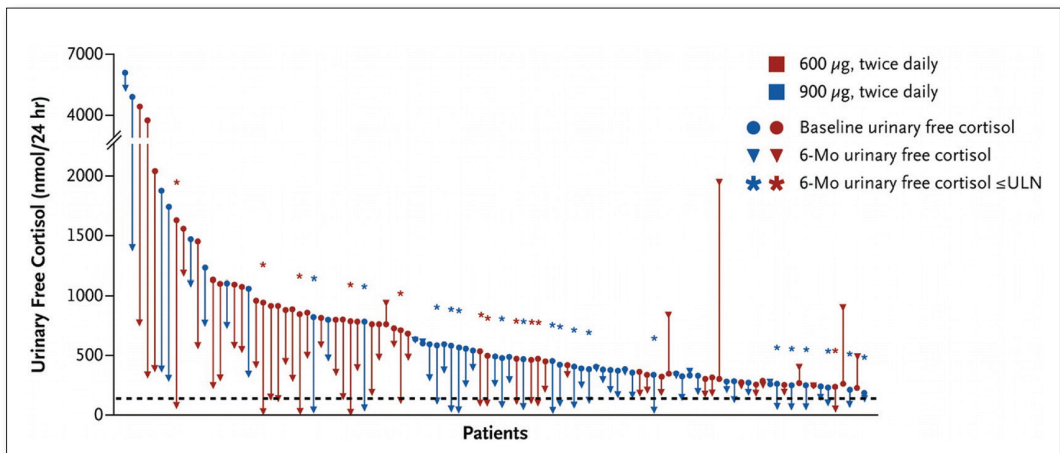


FIG.2. Absolute change in UFC levels from baseline to month 6. UFC was available at baseline and at month 6 in a total of 103 patients; 50 patients had a reduction of at least 50% in UFC levels at month 6. The black dashed line represents the upper limit of the normal range (145 nmol per 24 h [52.5 µg per 24 h]). [Reproduced from A. Colao *et al*: A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med*. 366:914-924, 2012 (61), with permission. © Massachusetts Medical Society.]

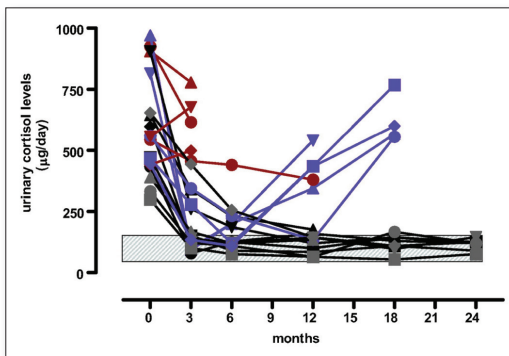


FIG.3. UFC levels during the entire period of treatment in all 20 patients treated with cabergoline. The patients' long-term response to cabergoline treatment are shown with black lines, those with early response and late escape are shown with purple lines, and nonresponders to the treatment are shown with red lines. The shaded area indicates the normal range of urinary cortisol levels (35-135 µg/d). Urinary cortisol levels represent the mean of 3 different urine collections performed on 3 different nonconsecutive days of the same week. [Reproduced from R. Pivonello *et al*: The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. *J Clin Endocrinol Metab*. 94:223-230, 2009 (68), with permission. © The Endocrine Society.]

inhibits ACTH and cortisol levels in 40% of patients with CD (65), although data on the efficacy of bromocriptine in CD appeared equivocal (66). More recently, Pivonello *et al* (47) showed that a 3-month treatment with cabergoline induced normalization of UFC in 40% of a series of 20 patients with recurrent or persistent CD (Figure 3). Vilar *et al* (67) reported reversal of hypercortisolism by 6-month monotherapy with cabergoline in 3 of 12 (25%) patients that were unsuccessfully treated by transsphenoidal surgery (Figure 4A). Similar values were reported after a more long-term, 2-year treatment period with cabergoline (median dose, 3.5 mg/wk) (68). Finally, Godbout *et al* (69) demonstrated that cabergoline normalized UFC in 11 of 20 patients (37%) after short-term and in 30% of patients with CD after long-term cabergoline treatment (at least 2 y, and in some for 5 y; mean dose, 2.1 mg/wk). In contrast to the effect of pasireotide in CD, where no long-term treatment-escapes were reported, a significant number of patients showed a treatment-escape to cabergoline treatment, even after several years of treatment

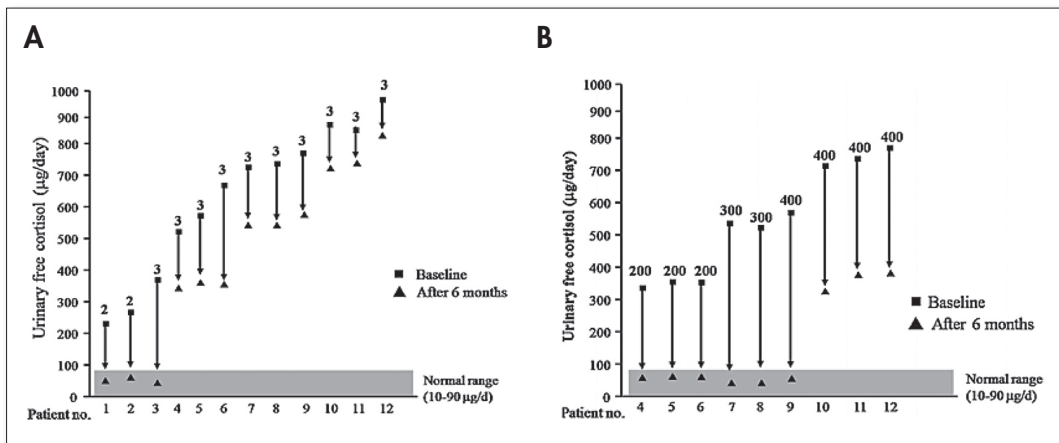


FIG. 4. **A**, Changes in 24-hour UFC levels after treatment with cabergoline. The number on each arrow indicates the maximal dose of cabergoline expressed in milligrams/week administered to each patient. **B**, Changes in 24-hour UFC levels after treatment with cabergoline and ketoconazole. The number on each arrow indicates the maximal dose of ketoconazole expressed in milligrams/day administered to each patient. [Adapted from L. Vilar *et al*: Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. *Pituitary*. 13:123-129, 2010 (67), with permission. © Springer.]

(68, 69). Figure 4 shows the effects of cabergoline treatment on individual UFC levels of 20 patients, as well as the treatment-escape in 5 of 20 patients. Summarizing, long-term treatment with the DA cabergoline is effective in a significant proportion of patients with CD. There has been a significant debate over whether or not treatment with the DA cabergoline may affect cardiac heart valve function. In patients with Parkinson's disease treated with very high doses of cabergoline, fibrosis of cardiac valves due to the activation of serotonin receptor 2B on valvular fibroblasts has been reported (70, 71). However, whereas in patients with prolactinomas treated with cabergoline at lower doses a higher prevalence of valve calcification is observed compared with a group of untreated patients, this did not result in cardiac valve dysfunction (72).

Other pituitary-directed medical treatment opportunities

Retinoic acid has been demonstrated to be an effective drug in the treatment of

CD in experimental animal models, including the dog (73, 74). Recently, in a prospective, multicenter study, 7 patients with CD were treated with 10 mg up to 80 mg retinoic acid daily for 6-12 months. Normalization of UFC was observed in 3 patients, and only mild adverse effects were reported (75). Although these data need confirmation in larger series, the results are promising.

Nuclear peroxisome proliferator-activated receptor- γ (PPAR- γ) receptors are highly expressed in corticotrope tumors (76). PPAR- γ agonist treatment was shown to inhibit ACTH and corticosterone levels, as well as tumor growth in an experimental model of CD (77). However, the clinical efficacy of PPAR- γ agonists in patients with CD seems limited (78,79,80).

Finally, the serotonin antagonist cyproheptadine, as an inhibitor of hypothalamic CRH and vasopressin secretion, as well as the γ -aminobutyric acid uptake inhibitor sodium valproate have been tested with limited success in CD to lower ACTH and cortisol levels (81).

Adrenal-blocking drugs

Mitotane

Mitotane is an adrenolytic drug that inhibits mitochondrial side chain cleavage enzyme (CYP11A1), 11 β -hydroxylation (CYP11B1), and 18-hydroxylation (CYP11B2). The drug is primarily used for the treatment of patients with adrenocortical carcinoma to reduce cortisol production and to induce tumoricidal effects (82). Mitotane stimulates CYP3A4 expression and reduces cortisol bioavailability (83). Due to the increased steroid metabolism, replacement doses of exogenous corticosteroids need to be increased to avoid adrenal crisis. Mitotane has proven efficacy in CD (84). In 46 patients with CD, treatment with mitotane induced remission in 38 patients (83%). However, a relapse was observed in 60% of these patients. Because treatment with the drug is associated with considerable adverse effects (66), its use in the treatment of CD is limited. Specific drug doses for the use of mitotane in CD have not been established, although the doses appear to be lower than those used for an antitumoral effect in patients with adrenocortical carcinoma. Recently, Baudry et al (85) showed in a series of 76 patients with CD treated with mitotane that remission, defined as normalization of UFC or hypocortisolism, was achieved in 72% of patients after a median treatment time of 6.7 months (range, 5.2-8.2). Mean plasma mitotane concentration at the time of remission was 10.5 ± 8.9 mg/L, with a mean daily dose of 2.6 ± 1.1 g. Baudry et al (85) indicated that plasma mitotane concentrations of ≥ 8.5 mg/L were associated with normal 24-hour UFC values at all time-points during the patients' follow-up. Due to the stimulatory effect of mitotane on cortisol binding globulin levels (86), total serum cortisol measurements are not very useful in patients treated with the drug (87).

Etomidate

The imidazole derivative and anesthetic drug etomidate inhibits 17-hydroxylation (CYP17) and 11- β hydroxylase. The drug is fast acting and can be used in patients with acute and/or life-threatening Cushing's syndrome (CS). Its use in the treatment of CD has been reported (33), although etomidate is generally used in patients with EAS presenting with excessive cortisol production. The dose given parenterally is between 0.03 and 0.3 mg/kg/h (3). Recently, the use of etomidate in the treatment of CS was reviewed, and protocols for a safe and effective use of etomidate in CS are warranted (88).

Metyrapone

Metyrapone primarily inhibits the last step in cortisol biosynthesis, ie, 11- β hydroxylase. The drug is used in the treatment of patients with adrenal tumors, EAS, and CD (89). Metyrapone is fast acting, eg, within 2 hours after the first dose a drop in cortisol levels is observed in patients with CD. Short-term treatment with metyrapone can be very useful, and tachyphylaxis is uncommon in CD. Clinical improvements are observed in most patients, with biochemical control in 75% (median dose, 2250 mg/d) (89). In a small series of 13 patients with CD, Jeffcoate et al (90) demonstrated a rapid clinical improvement in combination with a fall in plasma cortisol level after treatment with metyrapone in all patients. Mean duration of treatment was 21 months (range, 2-66 months) at an oral dose between .25 g twice daily and 1.0 g four times daily. However, 9 of 13 patients had received pituitary irradiation therapy, which may have resulted in overestimation of the long-term effects of metyrapone (90). Preferably, additional long-term studies with metyrapone in CD are warranted. The strong cortisol-lowering effect of metyrapone can be accompanied

by loss of feedback ACTH inhibition, resulting in overstimulation of adrenal androgen and mineralocorticoid precursor (eg, desoxycorticosterone) production. Therefore, hirsutism, acne, and mineralocorticoid effects such as hypokalemia and hypertension can limit long-term treatment with metyrapone. The dose that is used varies between 500 and 6000 mg/d (34).

Ketoconazole

Ketoconazole was originally developed as an antifungal agent. Treatment with the drug reduces adrenal steroid production due to its inhibitory effect on multiple steroidogenic enzymes as 11 β -hydroxylase, 17-hydroxylase, and 18-hydroxylase (91, 92). Ketoconazole is one of the most widely used adrenal-blocking drugs. A major side effect includes hepatotoxicity. Liver function should therefore be carefully monitored during treatment. Other adverse events of ketoconazole treatment include hypogonadism in men and gastrointestinal complaints. In a retrospective study, Castinetti *et al* (93) reported biochemical cure in 51% of patients with CD (median follow-up, 23 months), with a treatment dose starting at 200-400 mg/d and uptitration to 1200 mg/d until biochemical remission. The normalization of cortisol production was paralleled by regression of clinical features, a decrease in blood pressure, and improved glycemic regulation. Importantly, in all patients who responded, biochemical remission was achieved within 3 months, which should presumably be the time frame to evaluate efficacy of ketoconazole treatment. Ketoconazole treatment is not expensive; however, the drug is not available in every country. Because proton pump inhibitors reduce the bioavailability of ketoconazole (94), ketoconazole should not be used in combination with proton pump inhibitors.

Potential novel adrenal-blocking drugs

LCI699 is a potent inhibitor of 11 β -hydroxylase and 18-hydroxylase (95,96). The drug is currently under investigation for its efficacy in patients with CD. In a preliminary open-label study, 11 patients with mild to severe CD received oral LCI699 for 10 weeks. UFC normalization was achieved in 10 of 11 patients on day 70 at a median dose between 5 and 10 mg twice a day. The drug was generally well tolerated. Adverse events included fatigue, nausea, and headache. Five of 11 patients had elevation of ACTH of >2 times baseline. Four patients experienced drug-related hypokalemia (97).

We recently showed that pharmacological concentrations of fluconazole inhibit cortisol production by primary cultures of human adrenocortical cells in vitro. This effect is mediated via inhibition of 11- β hydroxylase and 17-hydroxylase activity (98). Although fluconazole was less potent than ketoconazole (IC₅₀ of cortisol secretion inhibition, 67 μ M vs 0.75 μ M, respectively), it might become an alternative for ketoconazole to control hypercortisolism in CS.

Glucocorticoid receptor antagonists

Pituitary-targeting drugs are effective in only a proportion of patients with CD. Higher efficacy rates have been reported for adrenal-blocking drugs, but such drugs also have a significantly higher toxicity. Therefore, other therapeutic opportunities have been evaluated, including the blocking of the GR itself. To date, the only GR antagonist available for clinical application is mifepristone. Mifepristone, due to its potent antiprogestin activity, is used as a “contragestive pill.” The efficacy of this potent GR antagonist in CS, including CD, was recently reviewed by Castinetti *et al* (99). Mifepristone treatment

has high clinical efficacy in patients with CS (99). In a recent open-label, multicenter trial (SEISMIC study), 50 patients were included, of which 43 had CD (100). Mifepristone was administered at a dose between 300 and 1200 mg/d. Treatment resulted in an improvement of diabetes mellitus in 60% of patients, diastolic blood pressure in 38% of patients, weight loss, and a decrease in waist circumference. Overall, 87% of patients had significant clinical improvement (100). Mifepristone was recently approved in the United States for treatment of patients with CS with type II diabetes mellitus or hyperglycemia that have failed surgery or are not candidates for surgery. However, treatment with the drug can induce serious adverse events, such as worsening of hypertension and hypokalemia and, in female patients, development of endometrial hyperplasia (99). In addition, no biochemical parameter is available to adjust mifepristone dose, and overtreatment can result in clinical adrenal insufficiency. Taking into account the strong clinical efficacy of the drug and considering the adverse events, mifepristone treatment should predominantly be considered in patients with acute complications of (severe) hypercortisolism (eg, acute psychosis, severe infections). Patients with adenomas with a low a priori chance of surgical cure (ie, adenomas with unfavorable localization and nonvisible adenomas) and those waiting for the maximal efficacy of radiotherapy could also be candidates for mifepristone treatment (99), provided that additional studies show long-term safety of chronic mifepristone therapy.

Targeting the GR may also indirectly influence drug target receptors in CD. Recently, in 2 patients with EAS due to an ACTH-secreting bronchial carcinoid who were treated with mifepristone, we observed an up-regulation of tumoral

sst₂ expression, as determined by uptake using octreoscan, RT-PCR, and immunohistochemistry (101). This effect is likely due to antagonizing the suppressive effect that glucocorticoids have on sst₂ expression (see Somatostatin receptors). If a similar change in tumoral expression is also present in corticotrope adenomas (see also Combination therapy), treatment with mifepristone may up-regulate sst₂ on corticotrope adenomas, which in turn may form an additional target for treatment with sst₂ preferring SSA.

Combination therapy

Medical treatment modalities for CD can be combined for several reasons. First, considering that biochemical remission should be rapidly achieved to reverse morbidity and mortality, drugs can be combined to control cortisol production within an acceptable time frame. If biochemical remission has been accomplished, drug dosage may be decreased or one of the used drugs may be withdrawn. Second, combining drugs may allow for lower doses with concomitantly less adverse events. Third, combining drugs may have potentiating effects on ACTH secretion by corticotrope tumor cells. Because most corticotrope adenomas simultaneously express sst₅ and D₂, it can be anticipated that a combination of sst₅- and D₂-targeting drugs may have additive or synergistic effects on ACTH secretion. In vitro data indeed indicate synergism between sst and D₂ that might increase therapeutic efficacy (102).

We recently reported a trial in 17 patients with CD using a stepwise approach starting with pasireotide monotherapy (300 µg/d, which could be increased to 750 µg/d) that was combined with cabergoline (1.5 mg every other day) if UFC had not normalized after 1 month of treatment (60). If after another month of combination therapy UFC was still

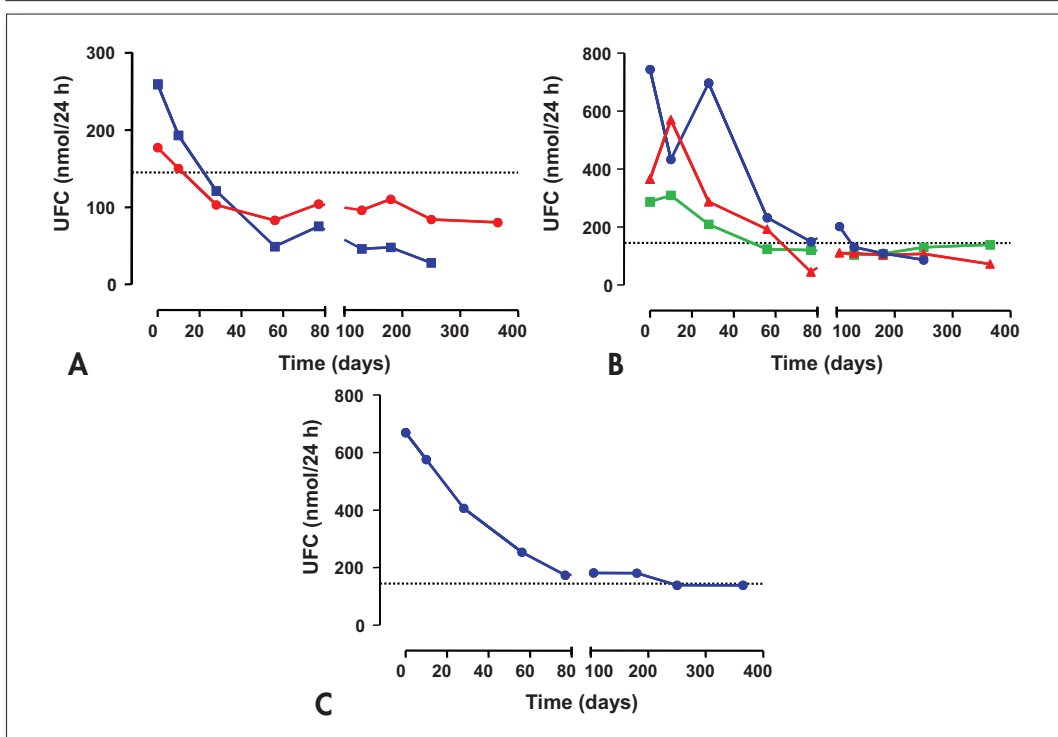


FIG.5. Individual UFC profiles in 6 patients who participated in the extension study of the pasireotide monotherapy and combination therapy trial. A, Pasireotide monotherapy (n = 2). B, Pasireotide-cabergoline combination therapy (n = 3); in the patients represented by the blue and red curve, ketoconazole was withdrawn after the regular study period of 80 days. C, Pasireotide-cabergoline-ketoconazole combination therapy (n = 1). The upper limit of the normal range is indicated by the dashed line (145 nmol per 24 h [52.5 µg per 24 h]).

elevated, ketoconazole (600 mg/d) was added to pasireotide and cabergoline. At day 80, biochemical remission was achieved in almost 90% of patients, ie, in 29% with pasireotide monotherapy, in an additional 24% by addition of cabergoline to pasireotide, and in a final 35% by triple therapy with pasireotide, cabergoline, and ketoconazole. The degree of hypercortisolism at baseline determined the amount of drugs needed to control cortisol excess. Parallel to the normalization in UFC, decreases were observed in body weight, waist circumference, and blood pressure (60). Six patients participated in an extension study (data not previously published). Two patients continued with pasireotide monotherapy, which maintained UFC levels within the normal range up to

1 year (Figure 5A). Three patients continued with pasireotide and cabergoline, and in 2 of these 3 patients ketoconazole was withdrawn after day 80, with sustained biochemical remission up to 1 year (Figure 5B), whereas 1 patient continued with triple therapy resulting in normal UFC levels at day 250 (Figure 5C). Interestingly, neither during the regular study period, nor during the extension study was any escape observed in patients on combined pasireotide-cabergoline treatment, which contrasts to previously reported escapes during long-term cabergoline monotherapy.

The question arises whether cortisol-lowering therapy can modulate $ss2$ mRNA expression. After participation in the pasireotide monotherapy and combination therapy trial, a subset of patients was

operated. We found that mean $ss2$ mRNA expression in corticotrope tumor tissue obtained from these biochemically controlled patients was almost 12-fold higher compared to $ss2$ expression levels in patients with uncontrolled CD and was comparable to $ss2$ mRNA expression in somatotroph adenomas (103). This observation indicates that the down-regulating effects of cortisol on $ss2$ expression found in vitro can indeed be translated to in vivo conditions, but it also illustrates that this is a dynamic process with recovery of $ss2$ expression once cortisol production has normalized. If this recovery of $ss2$ mRNA expression also results in increased $ss2$ protein expression, this may have important therapeutic implications. First, the effects of pasireotide could be enhanced via $ss2$ activation. Second, this may allow for sequential treatment with $ss2$ targeting compounds after induction of (partial) biochemical remission with other compounds.

Vilar *et al* (67) studied cabergoline in combination with low-dose ketoconazole in CD. In this study, 12 patients were initially treated with cabergoline, with a complete response in 3 of the 12 patients (25%) at a dose of 2 to 3 mg/wk. If UFC had not normalized after 6 months of cabergoline treatment, ketoconazole was added in 9 patients, resulting in biochemical remission after another 6 months of treatment in 6 of the 9 patients (66.7%) with ketoconazole doses ranging from 200 to 400 mg (Figure 4B). Importantly, no significant hepatotoxicity was reported during treatment with this ketoconazole dose range. The 3 patients in whom biochemical remission was not achieved had the highest UFC excretion at baseline.

A recent study showed the efficacy of combination therapy with different adrenal-blocking drugs in patients with

severe hypercortisolism due to CD or EAS complicated by pulmonary, cardiovascular, or infectious disease that needed immediate intervention (104). These patients were initially treated with mitotane (3 g/24 h), ketoconazole (800 mg/24 h), and metyrapone (2.25 g/24 h), and dosages were adjusted according to clinical signs. With this treatment regimen, UFC levels (nearly) normalized in all patients within the first 3 days with subsequent improvement of Cushingoid features and complications. This combination treatment was generally well tolerated; the main adverse events included gastrointestinal complaints, hypokalemia, and elevated cholesterol and liver enzyme concentrations. Aggressive cortisol-lowering therapy might thus be an alternative to emergency bilateral adrenalectomy in patients with severe, complicated CD.

Further study is needed on the optimal order, dosage, and combinations of available drugs in the medical treatment of CD.

Treatment of comorbidities

Apart from treating hypercortisolism, comorbidities of CD should be treated with specific medical therapy. In particular, cardiovascular risk factors that often persist despite curative treatment should be adequately treated with tight control of blood pressure, glycemic regulation, and lipid levels to prevent cardiovascular disease and mortality. In active CD, spironolactone is a rational choice to treat hypertension, considering the mineralocorticoid effects of high cortisol levels. Left ventricular hypertrophy and diastolic dysfunction are prevalent in CD (18), which may be a reason for treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Because of the high risk on venous thromboembolic events in

untreated CD, but also in the period after transsphenoidal adenectomy (19), thromboprophylaxis should be considered in every patient with active CD and in the postoperative phase (105). However, definite guidelines on dose and duration of thromboprophylaxis should be developed based on prospective, randomized trials. Data on recovery of osteoporosis are scarce, but one study shows that bone loss is only partially reversible 2 years after normalization of cortisol levels (31). Therefore, if (severe) osteoporosis is present, it seems rational to treat patients with calcium/vitamin D supplementation and bisphosphonates, although efficacy of this regimen should also be confirmed by prospective studies.

Conclusion and Future Developments

CD is associated with severe morbidity and, when uncontrolled, an increased mortality with cardiovascular disease as the leading cause of death. The inverse relationship between disease duration and reversibility of complications and the increased mortality of uncontrolled CD highlight the importance of identifying an effective medical strategy to rapidly normalize cortisol production. Sst₅ and D₂ have recently been identified as potential targets for tumor-directed medical therapy. Monotherapy with the universal SSA pasireotide and the DA cabergoline results in remission rates of 25-30%, respectively. However, in patients with moderate to severe hypercortisolism, biochemical remission can usually only be accomplished by combining medical treatment modalities. In this respect, combined treatment of CD with pasireotide and cabergoline may be a rational approach considering the frequent coexpression of sst₅ and D₂ on corticotrope adenomas, although this should be confirmed in larger studies. Suppression of adrenal steroidogenesis with ketoconazole

can be effective, also in combination with cabergoline and/or pasireotide, which may allow for lower ketoconazole doses. Finally, blockade of the GR with mifepristone can induce rapid clinical improvement of several comorbidities of CD. It should be emphasized that medical treatment should be tailored in each patient according to patient characteristics (eg, acute complications of hypercortisolism, degree of hypercortisolism, presence of diabetes mellitus, etc.) and drug properties. Future studies should further examine the optimal dose and combination of available drugs with respect to long-term efficacy and safety. Comorbidity, in particular cardiovascular risk factors, should be assessed and treated accordingly.

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A 65-year-old Woman with Pain and Fractures

William H. Chong, MD and Michael T. Collins, MD

A 65 year-old woman presents with a 2-year history of multiple low-impact trauma fractures, including left and right hip fractures, right wrist fracture, and fracture of the right lesser trochanter. She additionally reported complaints of weakness, diffuse musculoskeletal pains, and easy fatigability during this time period. She also notes that she has lost several teeth in the last 2 years. She reports no family history of similar problems. Current medications include calcium and vitamin D supplement. Physical examination was notable for obesity (body mass index 41), poor dentition, and difficulty standing from a seated position. Her evaluation revealed a normal 25-hydroxy vitamin D, a low 1,25 dihydroxyvitamin D, normal calcium and magnesium, elevated alkaline phosphatase, elevated PTH, and low phosphorus. Diagnostic imaging performed prior to referral included bone density scan showing the lowest T-score to be -2.4 in the lumbar spine, and a bone scan which showed multiple areas of tracer uptake.

1. THE MOST LIKELY DIAGNOSIS IS:

- Multiple myeloma
- Primary hyperparathyroidism
- X-linked hypophosphatemic rickets
- Tumor-induced osteomalacia
- Osteoporosis

2. YOUR NEXT STEP IN EVALUATION IS:

- Gene testing for *PHEX* mutations
- SPEP/UPEP
- Measurement of fibroblast growth factor 23 (FGF23)
- Sestamibi scan
- Bone biopsy

Suspecting a diagnosis of tumor-induced osteomalacia, the serum FGF23 levels were measured and found to be markedly elevated (2200 RU/ml, normal < 180), confirming the diagnosis of an FGF23-mediated phosphate-wasting condition. Genetic conditions were excluded on the basis of the late age of onset, and negative family history. Medical therapy with phosphorus supplementation and calcitriol was initiated concurrently with the localization attempts. The initial attempts at tumor localization were unsuccessful, and medical therapy was continued for the next 3 years. Repeated localization attempts during this time continued to be unsuccessful. She was referred to a tertiary care facility for further evaluation. It was noted that on her previous imaging studies, and on the initial imaging studies performed at the referral center, portions of her body were excluded due to body positioning to accommodate body habitus (notably the upper extremities, Figure 25-1A). Imaging of these omitted areas revealed uptake in the left elbow (Figure 25-1B-D). Anatomic imaging with magnetic resonance imaging (MRI) confirmed the presence of a tumor (Figure 25-2).

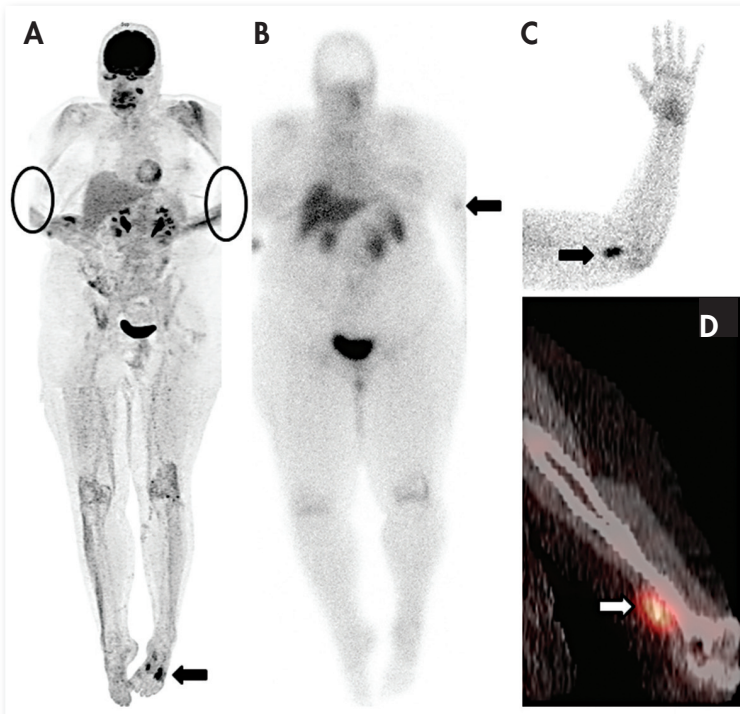


FIG. 25-1. **(A)** Functional imaging with FDG-PET/CT excluded portions of the upper extremities (*circles*). Activity in the left foot (*arrow*) was due to a fracture. **(B)** Octreo SPECT/CT suggested activity in the area of the left elbow (*arrow*). **(C, D)** Targeted octreo SPECT/CT images repeated at 24 hours confirmed the presence of activity.

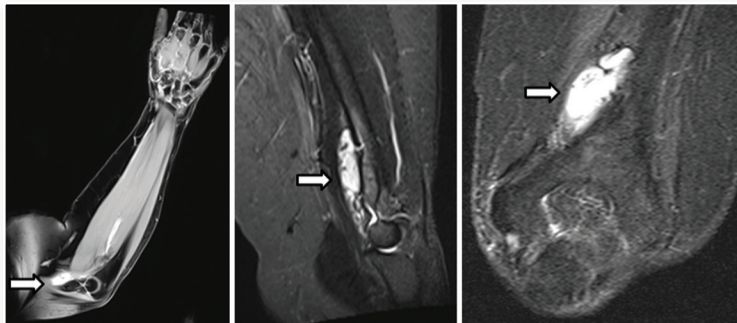


FIG. 25-2. MRI images of the left arm confirmed the tumor proximal to the left elbow (*arrows*).

3. THE NEXT BEST STEP IN MANAGEMENT IS:

- Medical therapy with phosphorus replacement
- Fine needle aspiration
- Selective venous sampling
- External beam radiation
- Surgical resection

Following surgical resection, FGF23 levels rapidly declined. Concomitantly, there was normalization of serum phosphorus levels and marked improvement in her weakness and diffuse musculoskeletal pains. In addition to the clinical evidence of successful tumor resection, immunohistochemical staining of the tumor demonstrated positive staining for FGF23 (Figure 25-3).

Diagnosis

Tumor-induced Osteomalacia.

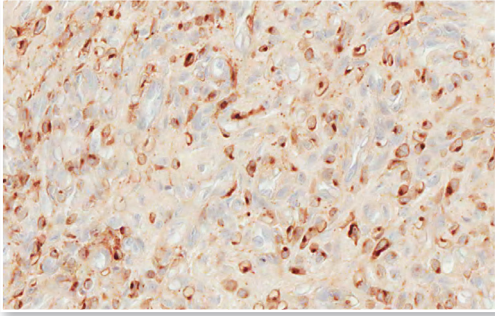


FIG. 25-3. Light microscopy of a tumor section demonstrates positive staining for FGF23 confirming tumor resection (40x magnification).

Discussion

Tumor-induced osteomalacia (TIO) is a rare endocrine disease that results from over-production of the phosphaturic hormone FGF23 by small mesenchymal tumors (1). FGF23 acts on the proximal renal tubule to induce renal phosphate wasting via the sodium-phosphate co-transporter (2). Renal phosphate wasting can be identified by calculating a low tubular reabsorption of phosphate or tubular maximum of phosphate per glomerular filtration rate. Patients present with complaints of aches and pains, fatigue, and often have multiple fractures. Frequently patients will have their hypophosphatemia unrecognized, and testing for and recognizing the need to further evaluate hypophosphatemia is the first step in making the diagnosis (1). A low 1,25 dihydroxyvitamin D is seen since FGF23 inhibits 1- α hydroxylase which converts 25 hydroxy vitamin D to 1,25 dihydroxyvitamin D (2). While elevated PTH is not classically part of the clinical picture, it can be seen in TIO (personal observation, MTC).

The differential diagnosis for hypophosphatemia due to renal phosphate wasting includes genetic disorders (X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, autosomal

recessive hypophosphatemic rickets, hereditary hypophosphatemic rickets with hypercalciuria, inherited Fanconi's), and acquired disorders (TIO, acquired Fanconi-like renal tubulopathy) (1). Measurement of FGF23 is central to making the diagnosis, as elevated versus low levels will point towards different diagnoses. The diagnosis of tumor-induced osteomalacia relies on confirmation of FGF23 excess in the setting of hypophosphatemia with exclusion of genetic disorders (by genetic testing or history) (1). After diagnosing TIO, the primary goal should be tumor localization as surgical resection is curative. While medical therapy can be useful in normalizing serum phosphate levels, the regimen can be cumbersome, difficult to tolerate, and be associated with its own adverse effects, such as gastrointestinal upset, secondary hyperparathyroidism, and nephrocalcinosis and/or nephrolithiasis.

The initial approach to tumor localization should rely on functional imaging techniques such as ¹¹¹In-octreotide single-photon emission computed tomography/computed tomography (octreo SPECT/CT) and fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) (3-6). Octreo SPECT/CT is more sensitive and specific for TIO than FDG PET/CT (3). As these tumors can occur in locations outside of the routine field of view for these studies, it is important to insure that literal whole body imaging is performed (7). As seen with this case, exclusion of small portions of the body can result in missing the tumor. Confirmation of a tumor at sites of suspicious uptake should be performed with CT and/or MRI. Selective venous catheterization with measurement of FGF23 may also be helpful in identifying causative tumors (8). Situations where this may be the case include multiple

suspicious lesions, or tumors located in areas where surgical excision may be difficult. Wide surgical excision is the treatment of choice following identification of a causative lesion, with emphasis on attaining clean surgical margins as cases of recurrent disease have been reported (3).

Subsequent Follow-up on the Patient

This patient had successful normalization of serum phosphorus levels promptly after surgical resection. She also reported significant improvement in her symptoms. Follow-up laboratory values demonstrated continued euphosphatemia at 3 months after surgery.

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Answers:

Question 1. d

Question 2. c

Question 3. e

26

An 83-year-old Man with Metabolic Syndrome, Coronary Artery Disease, and Dysphagia

Nicola Martinelli, MD, PhD, and Oliviero Olivieri, MD

An 83-year-old man with hypertension, hypertriglyceridemia, and low HDL-cholesterol levels, thus satisfying the diagnostic criteria of metabolic syndrome (Box 26-1) (1), was admitted to our Department of Internal Medicine because of unstable angina. A percutaneous intervention with angioplasty and drug-eluting stent placement in the left anterior descending coronary artery was performed.

The patient also complained about a mild persistent dysphagia of several months' duration. Any anatomical or functional disruption in the swallowing process may be defined as dysphagia. Therefore, several and various disorders affecting the oral, pharyngeal, or esophageal phases of swallowing, may lead to dysphagia. On the basis of the anatomical level of the disorder, dysphagia has been proposed to be classified as I) oropharyngeal or II) esophageal. Concomitantly, it has been classified as

I) neuromuscular or II) obstructive according to the underlying pathophysiological mechanism (Table 26-1) (2). Dysphagia is common, especially in aging persons (approximately 15% of the elderly population), and can be a serious threat because of the increased risk of aspiration pneumonia, malnutrition, and dehydration (3).

More precisely, the patient reported an abnormal sensation of food sticking in the back of the throat when he was trying to swallow. Remarkably, he did not report any other significant symptom besides dysphagia and had no odynophagia, heartburn, or regurgitation. The physical examination did not show any specific findings. In particular, no significant neurological deficits were found, and no swallowing abnormality was apparent on the basis of direct observation. A gastroscopy, performed immediately before the admission to our department, was completely normal.

BOX 26-1. Diagnostic criteria for metabolic syndrome *

- 1) Fasting glucose ≥ 100 mg/dL (or receiving drug therapy for hyperglycemia)
- 2) Blood pressure $\geq 130/85$ mm Hg (or receiving drug therapy for hypertension)
- 3) Triglycerides ≥ 150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
- 4) HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
- 5) Waist circumference ≥ 102 cm (40 in) in men or ≥ 88 cm (35 in) in women; if Asian American, ≥ 90 cm (35 in) in men or ≥ 80 cm (32 in) in women

* Metabolic syndrome is diagnosed when a patient has at least 3 of the above 5 conditions

TABLE 26-1. Causes of dysphagia according anatomical level and pathophysiological mechanism.

	Oropharyngeal Disease	Esophageal Disease
Neuromuscular Disease	<p>Diseases of Central Nervous System (e.g. cerebrovascular disease, Alzheimer's disease, Parkinson's disease, multiple sclerosis, poliomyelitis)</p> <p>Diseases of Peripheral Nervous System (e.g. peripheral neuropathy)</p> <p>Myasthenia gravis</p> <p>Myopathy (e.g. polymyositis, dermatomyositis, muscular dystrophy)</p>	<p>Primary (e.g. achalasia, esophageal spastic disorders)</p> <p>Secondary (e.g. scleroderma)</p> <p>Medication-related (e.g. drugs altering lower esophageal sphincter tone, like calcium antagonists or nitrates)</p>
Obstructive Disease	<p>Intrinsic lesions (e.g. tumors, inflammatory lesions, Zenker's diverticulum)</p> <p>Extrinsic lesions (e.g. goiter, cervical spondylosis)</p>	<p>Intrinsic lesions (e.g. esophageal tumors, esophageal strictures, Schatzki's ring)</p> <p>Extrinsic lesions (e.g. mediastinal tumors/masses, lymphadenopathy, aortic aneurysm)</p> <p>Medication-related (e.g. drugs causing direct esophageal mucosal injury, like non-steroidal anti-inflammatory drugs or bisphosphonates)</p>

1. WHAT NEXT DIAGNOSTIC TEST COULD BE PROPOSED?

- a. Computed tomographic scanning of the chest
- b. Magnetic resonance imaging of the neck
- c. Barium contrast esophagogram
- d. Esophageal manometry
- e. Ambulatory 24-hour pH monitoring

A barium contrasted esophagogram (Figure 26-1, Panels A-C) revealed a large anterior cervical osteophyte at C4-C5 level causing hypopharyngeal and esophageal compression. The presence of anterior cervical hyperostosis was confirmed by cervical spine X-rays (Figure 26-1, Panel D-F) and computed tomography (Figure 26-1, Panels G-I).

2. WHAT IS THE MOST LIKELY DIAGNOSIS?

- a. Osteoarthritis
- b. Diffuse idiopathic skeletal hyperostosis (DISH)
- c. Ankylosing spondylitis
- d. Rheumatoid spondylitis
- e. Systemic calcinosis

Diagnosis

Diffuse Idiopathic Skeletal Hyperostosis (DISH).

Discussion

Both cervical spine X-rays and computed tomography showed a flowing calcification along the C3-C7 anterolateral vertebral bodies with a relative preservation of intervertebral disc height, *i.e.* a typical feature of DISH, even if signs of osteoarthritis were also present. Subsequent X-rays of thoracic and lumbar

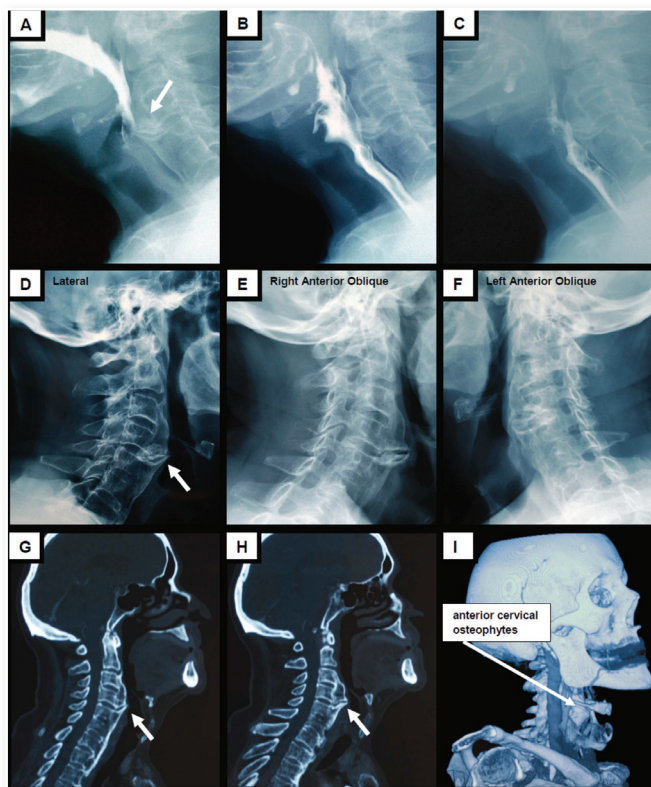


FIG. 26-1. Barium contrasted esophagogram (**Panels A-C**), cervical spine X-rays (**Panel D-F**), and computed tomography (**Panels G-I**). The white arrows in panels A, D, G, H, and I indicate the large osteophyte at C4-C5 level.

spine showed similar features, thus satisfying the classical criteria defined by Resnik and Niwayama (Box 26-2) (4).

DISH, also known as Forestier's disease, is a clinical-radiological entity characterized by calcification and ossification of enthesal sites and is usually diagnosed only on

radiographic grounds (5). Calcification and ossification of the anterolateral facet of the thoracic spine is considered the hallmark of DISH. On the other hand, DISH may not be limited to the spinal column and has also been characterized by peripheral enthesopathies (5). Accordingly it has been proposed by Utsinger to lower the threshold for spinal involvement and to require the presence of multiple peripheral enthesopathies (6). However, at present there is no agreement about the inclusion of extraspinal or other clinical manifestations in a new classification of DISH (7).

DISH is common in elderly adults, especially in men, and is usually an asymptomatic condition.

Nonetheless, symptoms

of DISH depend on the localization and involvement of adjacent structures and, noteworthy, oropharyngeal dysphagia is the most frequent symptom in patients with DISH localized to the cervical spine (5, 8, 9).

DISH is a non-inflammatory condition,

BOX 26-2. Diagnostic criteria for diffuse idiopathic skeletal hyperostosis (DISH) by Resnik and Niwayama.(4)

- 1) Presence of flowing ossification and calcification along the anterolateral facet of at least 4 contiguous thoracic vertebral segments
- 2) Preservation of the relative intervertebral disc spaces
- 3) Absence of apophyseal joint degeneration and sacroiliac joint erosion/sclerosis/fusion

3. WHAT CONDITION HAS BEEN ASSOCIATED WITH DISH?

- Obesity
- Hypertension
- Type 2 diabetes mellitus
- Hyperuricemia
- All of the above

whose etiology remains unknown. On the other hand, it is often in association with insulin resistance conditions like diabetes and metabolic syndrome, leading in turn to an increased cardiovascular risk (10, 11). DISH has been associated also with obesity, hypertension, atherogenic dyslipidemia, and hyperuricemia. On the basis of these observations it has been proposed that patients with DISH should be encouraged to reduce their cardiovascular risk (10).

In conclusion, this diagnosis of DISH localized to the cervical spine should be suspected in specific clinical settings, such as older males with metabolic disorders and with otherwise unexplained dysphagia. This clinical case was described originally by Martinelli and colleagues in the *Journal of Clinical Endocrinology and Metabolism* in 2012 (12), from which the above report was abstracted.

Subsequent Follow-up on the Patient

Considering the high operator risk of surgical osteophyctectomy and the mild degree of symptoms, no surgical approach was proposed. During the following 12 months, although mild dysphagia remained persistent, no major clinical problems due to dysphagia were reported.

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Answers:

Question 1. c

Question 2. b

Question 3. e

Ejigayehu G. Abate, MD

A 65-year-old man with a history of papillary thyroid cancer and pulmonary metastasis treated in 1978 with thyroidectomy and radioactive iodine therapy presented for his routine follow-up with neck ultrasound. He was asymptomatic. Laboratory result showed appropriately suppressed TSH of <0.01 mIU/L, Free T4 1.6 ng/dL, thyroglobulin antibody <20 IU/ml, thyroglobulin tumor marker <0.1 ng/ml and serum calcium 10.8mg/dL. Neck ultrasound showed a 3.0 x 1.3 x 0.7 cm cystic lesion in the left thyroid bed. No other abnormalities noted (Figure 28-1).

1. YOUR NEXT STEP IS:

- Fine needle aspiration of the cyst to evaluate for recurrent thyroid cancer
- Serum intact parathyroid hormone level
- Surgical referral for central neck dissection
- Whole body positron emission tomography-computed tomography scans with [18F]-fluorodeoxyglucose
- I-131 whole body scintigraphy

Serum intact parathyroid hormone level (PTH) was obtained which was 135.1pg/mL, repeat serum calcium was 10.9 mg/dL, with normal serum phosphorus, creatinine, 25-hydroxyvitamin D, and 24-hour urine calcium levels.

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- I-131 whole body scintigraphy
- Surgical referral for minimally invasive parathyroidectomy
- Parathyroid sestamibi scintigraphy
- Ultrasound guided aspiration of the cyst
- C and D

Parathyroid sestamibi scintigraphy was negative for a parathyroid lesion. Ultrasound-guided aspiration of the cyst in the thyroid bed was performed. Twenty five milliliters of clear and colorless fluid was removed.

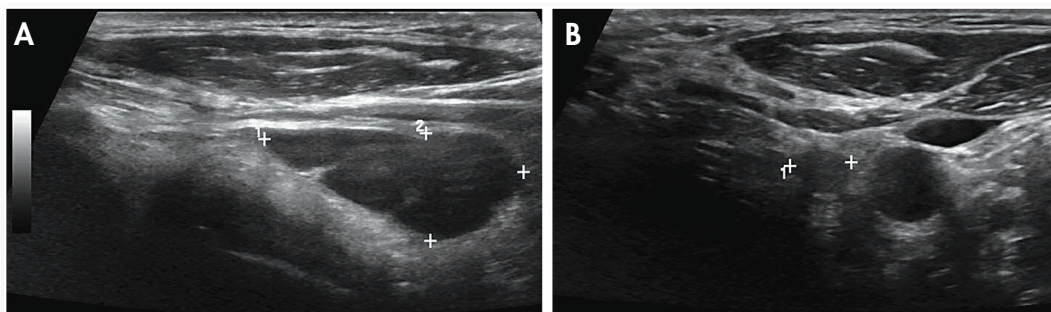


FIG. 27-1. **A**, Neck ultrasound shows a 3.0 x 1.3 x 0.7 cm cystic low thyroid bed lesion. **B**, A 30-month follow-up neck ultrasound after aspiration of cystic fluid showed a reduction in the size of the cystic mass to 0.7 x 0.6 X 0.7 cm

3. WHAT DIAGNOSTIC TEST SHOULD BE OBTAINED IN THE FLUID?

- a. Thyroglobulin level
- b. Cytology for parathyroid cells
- c. PTH level
- d. Bacterial culture
- e. None of the above

PTH in the aspirated fluid was 821 pg/ml and thyroglobulin level <0.1 ng/mL. Cytology was negative for features of papillary thyroid carcinoma. At 30 months follow-up, serum calcium and intact PTH were normal at 9.3mg/dL and 59.4 pg/ml, respectively. Neck ultrasound showed reduction of the size of the cyst at 6 months to 0.7 x 0.6 x 0.7cm and it remained unchanged at 30 months follow-up (Figure 28-1B).

4. WHAT IS THE FINAL DIAGNOSIS?

- a. Secondary hyperparathyroidism
- b. Functioning parathyroid cyst
- c. Nonfunctioning parathyroid cyst
- d. Recurrent papillary thyroid carcinoma
- e. Thyroid cyst

Diagnosis

Functioning Parathyroid Cyst.

Discussion

Parathyroid cysts are rare (1-11). They account for 0.5% of parathyroid disease and 1% of cystic neck lesions (1, 2). In most cases they are located in the neck, usually involving the lower parathyroid glands, whereas the remainder can occur between the mandible and mediastinum (3-5).

Parathyroid cysts are divided into functioning and nonfunctioning cysts. Few parathyroid cysts (10-15%) are functioning

(presenting with hypercalcemia and hyperparathyroidism). Most are nonfunctioning and asymptomatic presenting in eucalcemic patients and incidentally discovered during neck imaging or surgery (1, 2, 4). Both functioning and nonfunctioning parathyroid cysts can present as a cystic neck mass seen on imaging or otherwise found incidentally during neck surgery. Presenting symptoms may derive from tracheal narrowing or deviation resulting in dyspnea, dysphagia due to esophageal compression, hoarseness resulting from laryngeal nerve injury with vocal cord paralysis and rarely, innominate vein thrombosis (3-6). Signs and symptoms of hypercalcemia may accompany functioning parathyroid cysts (4).

Parathyroid cysts mimic thyroid cysts, thyroglossal ducts, branchial cleft cysts, thyroid adenomas and parathyroid adenomas presenting a diagnostic challenge (4). Rare cases of hypercalcemic crisis resulting from a functioning parathyroid cyst have also been reported (7-10). The presence of elevated intact PTH in aspirated fluid is the diagnostic test of choice in both functional and nonfunctional parathyroid cysts as the PTH level will be always elevated in both cases (3).

Parathyroid cysts lack uptake on radioiodine scans but a form of 'cold' uptake has been reported. They rarely are positive on sestamibi parathyroid scans. Ultrasound, computed tomography, and magnetic resonance imaging show a nonspecific cystic cervical or mediastinal mass (4, 11).

Treatment of parathyroid cysts include aspiration which can be both diagnostic and therapeutic, ablation with a sclerosing agent, ethanol injection, and surgery (6, 7). Although nonfunctioning cysts can be observed or treated with fluid aspiration if compressive symptoms are

present, surgical resection of the cyst is the treatment of choice for functioning parathyroid cysts (4). Successful treatment with aspiration has been described only in one case report (7) and here we report a functioning parathyroid cyst treated with aspiration with a 30-month remission.

Subsequent Follow-up on the Patient

The patient was last seen January 2013 for a 30-month post-parathyroid cyst aspiration. His calcium and PTH levels remain normal. A repeat neck ultrasound was stable as shown in Figure 28-1B.

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Answers:

- Question 1. b
Question 2. e
Question 3. c
Question 4. b

Akira Takeshita, MD, PhD and Toshiro Iizuka, MD

A 46-year-old woman with recurrent primary hyperparathyroidism (PHPT) subsequent to the removal of five parathyroid glands was evaluated for iron-deficient anemia. Because an obvious cause of blood loss was absent, upper gastrointestinal endoscopy was performed as part of the examination. Subsequently, a small polyp (8 x 11 mm) was incidentally found on the patient's right pyriform sinus (Figure 28-1A-B).

1. THE MOST LIKELY DIAGNOSIS IS:

- a. Lipoma
- b. Papilloma
- c. Lymphoid follicle
- d. Hypopharyngeal cancer
- e. Ectopic parathyroid gland

The biopsy specimen of the polyp showed hyperplasia of an ectopic parathyroid gland and stained immunohistochemically positive for parathyroid hormone (PTH).

At age 34, the patient was diagnosed with multiple endocrine neoplasia type 1 because she had presented with PHPT, nonfunctioning pituitary, and pancreatic neuroendocrine tumors. The patient had a family history of PHPT (brother). Serum concentrations of calcium and intact PTH at diagnosis were 12.2 (normal, 8.8–10.2) mg/dl and 206 (normal, 10–65) pg/ml, respectively. She underwent parathyroidectomy of three enlarged, eutopic, parathyroid glands (right superior, 230 mg; left superior, 117 mg; and left inferior, 316 mg) and one ectopic gland (260 mg) in the mediastinum. A right inferior parathyroid

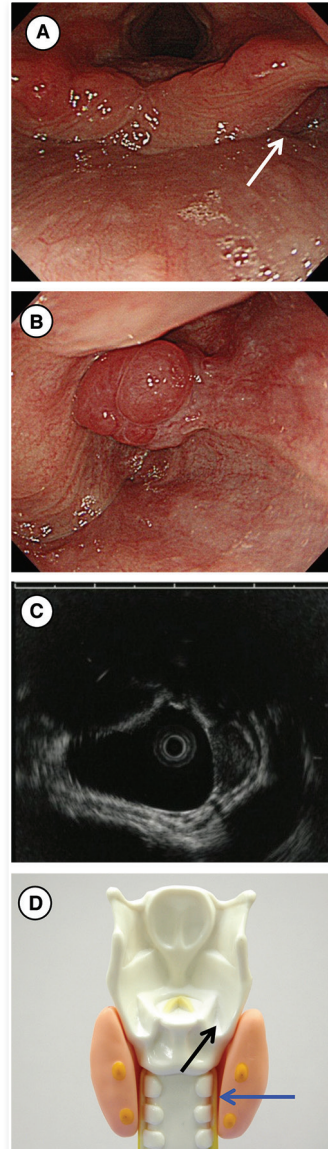


FIG. 28-1. **A**, Endoscopic image of the hypopharynx shows a partially hidden nodule (arrow). **B**, Close-up endoscopic image shows an 8- x 11-mm smooth nodule in the right pyriform sinus. **C**, Endoscopic ultrasonography with a 20-MHz probe shows a hypoechoic mass with a maximum diameter of 12 mm. **D**, Positional relationships of the pyriform sinus (black arrow), recurrent laryngeal nerve (blue arrow), and four parathyroid glands behind the thyroid.

gland, which looked normal in size, was left *in situ*. The pathology report revealed that all resected lesions were parathyroid hyperplasia. Postoperatively, the patient's serum concentrations of calcium and intact PTH were 8.0 mg/dl and 48.5 pg/ml, respectively, resulting in remission of PHPT. However, 7 years after the operation, her serum calcium and intact PTH levels gradually increased to above-normal ranges, implying PHPT recurrence. At age 42 years, the patient's serum concentrations of calcium and intact PTH were 10.8 mg/dl and 105.2 pg/ml, respectively. Parathyroidectomy of the unexcised right inferior gland (121 mg) was performed, and 40 mg parathyroid tissue was autotransplanted into the forearm. The pathology report revealed that the resected gland was parathyroid hyperplasia, but the patient's immediate postoperative serum calcium and intact PTH levels remained as high as 10.8 mg/dl and 120 pg/ml, respectively, suggesting the existence

2. WHICH OF THE FOLLOWING WOULD BE GENERALLY MOST SENSITIVE FOR DETECTING ECTOPIC GLANDS?

- Magnetic resonance imaging (MRI)
- Computed tomography (CT) scan
- Ultrasound of the neck
- Technetium-99m sestamibi scan
- None of the above

of a sixth parathyroid gland.

Because all parathyroid imaging studies were negative at that time, including a technetium-99m sestamibi (^{99m}Tc-MIBI) scan, we were unable to localize the sixth parathyroid gland until endoscopy was performed when the patient was 46 years old.

3. WHICH OF THE FOLLOWING WOULD BE MINIMALLY INVASIVE AND AN APPROPRIATE TREATMENT?

- Chemotherapy
- Surgical resection
- Endoscopic resection
- External radiation therapy
- None of the above

The parathyroidal polyp in the pyriform sinus was completely resected via endoscopic submucosal dissection (ESD) under general anesthesia (Figure 28-2). After resection, the patient's serum calcium and intact PTH levels fell to 8.9 mg/dl and 10 pg/ml, respectively. Intact PTH did not fall to undetectable levels because of PTH secretion from the transplanted parathyroid gland, as intact PTH in the basilic vein of the autotransplanted side measured 409 pg/ml. As of the most recent follow-up, 1.5 years after the resection, the patient has been euparathyroid with both normal serum calcium (9.9 mg/dl) and intact PTH (56 pg/ml) levels.

Diagnosis

Ectopic Parathyroid Hyperplasia in the Pyriform Sinus.

Discussion

The embryological migration tracts of the parathyroid glands can approximate the potential origin of the ectopic gland in the pyriform sinus. The superior and inferior parathyroid glands develop from the fourth and third pharyngeal pouches, respectively. As the inferior parathyroid glands and the thymus migrate together toward the mediastinum, they eventually separate. Identification of the ectopic gland as originating from the third pharyngeal pouch is sometimes made based on the presence of a thymic

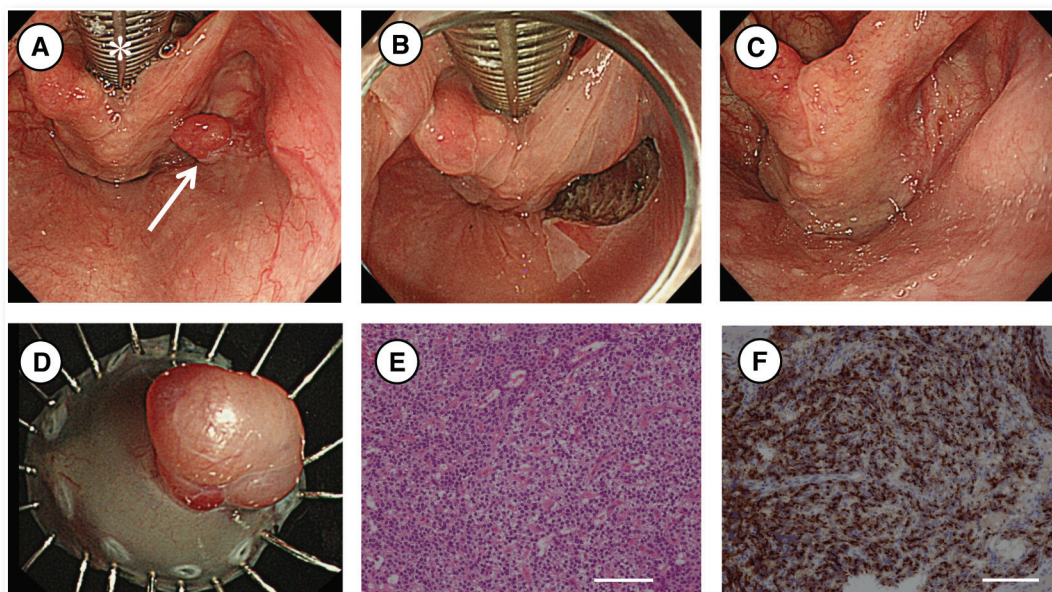


FIG. 28-2. **A**, Endoscopic image of the hypopharynx under general anesthesia shows an ectopic parathyroid gland in the right pyriform sinus (*arrow*) with a spiral endotracheal tube (*asterisk*). **B**, Endoscopic image just after resection shows an artificial ulcer. **C**, Endoscopic image 50 days after resection shows the healed wound. **D**, The specimen was resected en bloc. **E**, Hematoxylin and eosin staining shows hyperplastic parathyroid tissue consisting primarily of chief cells arranged in anastomosing cords. **F**, The tissue is immunohistochemically positive with PTH staining. Scale bars, 100 μ m.

remnant. However, thymic tissue was not found in our specimen. The sixth pharyngeal arch contains the recurrent laryngeal nerve, which lies relatively close to the fourth pharyngeal pouch, from which the superior parathyroid glands develop because the fifth pharyngeal arch is absent. The recurrent laryngeal nerve lies beneath the mucous membrane of the pyriform sinus (Figure 28-1D). It is not uncommon for ectopic parathyroid glands to be located in the path of the recurrent laryngeal nerve (1). Therefore, the ectopic gland may be derived from the fourth pharyngeal pouch.

An ectopic gland in the pyriform sinus is so uncommon that to our knowledge only nine cases have been reported (2-5). Three cases presented with hyperplasia secondary to renal failure and hemodialysis or subtotal thyroidectomy, four were parathyroid adenomata, and two were incidentally found in surgical specimens

of laryngopharyngeal cancer.

A ^{99m}Tc -MIBI scan is generally thought to be the most sensitive detection method for ectopic glands. The sensitivity of a ^{99m}Tc -MIBI scan for the detection of a parathyroid adenoma varies from 75% to 90% although the sensitivity for small adenomas, double adenomas, or hyperplasia is much lower. Image fusion coupling of ^{99m}Tc -MIBI single-photon emission CT with a conventional CT scan (^{99m}Tc -MIBI SPECT/CT) may enhance diagnostic sensitivity for detecting ectopic glands including those that lay within the pyriform sinus (5). However, all parathyroid imaging studies were negative, including the ^{99m}Tc -MIBI scan in the present patient.

Application of the endoscopic submucosal dissection (ESD) technique is widely used in the treatment of early mesopharyngeal and hypopharyngeal carcinomas as well as tumors in other

regions of the digestive system (6). ESD enables en-bloc resection of relatively large lesions. ESD is less invasive than traditional surgery and preserves swallowing and vocal functions. Incomplete resection of the parathyroid tissue may cause persistent or recurrent disease, whereas ESD is minimally invasive and an appropriate treatment for this case. Similar endoscopic therapy using a CO₂ laser has been reported (2, 5).

Because ectopic parathyroid glands in the pyriform sinus can be directly visualized and histologically confirmed by endoscopic exploration, we suggest that the pyriform sinus should be considered a potential location of ectopic parathyroid glands, especially when preoperative localization studies fail to detect abnormal glands.

Acknowledgments

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Answers:

Question 1. e

Question 2. d

Question 3. c

Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline

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Objective: *The aim was to formulate practice guidelines for management of osteoporosis in men.*

Evidence: *We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and evidence quality.*

Consensus Process: *Consensus was guided by systematic evidence reviews, one in-person meeting, and multiple conference calls and e-mails. Task Force drafts were reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee and Clinical Affairs Core Committee; representatives of ASBMR, ECTS, ESE, ISCD; and members at large. At each stage, the Task Force received written comments and incorporated needed changes. The reviewed document was approved by The Endocrine Society Council before submission for peer review.*

Conclusion: *Osteoporosis in men causes significant morbidity and mortality. We recommend testing higher risk men [aged ≥ 70 and men aged 50-69 who have risk factors (e.g. low body weight, prior fracture as an adult, smoking, etc.)] using central dual-energy x-ray absorptiometry. Laboratory testing should be done to detect contributing causes. Adequate calcium and vitamin D and weight-bearing exercise should be encouraged; smoking and excessive alcohol should be avoided. Pharmacological treatment is recommended for men aged 50 or older who have had spine or hip fractures, those with T-scores of -2.5 or below, and men at high risk of fracture based on low bone mineral density and/or clinical risk factors. Treatment should be monitored with serial dual-energy x-ray absorptiometry testing. (*J Clin Endocrinol Metab* 97:1802-1822, 2012)*

Summary of Recommendations

1.0. Evaluation

1.1. We suggest testing men at increased risk for osteoporosis by measurement of bone mineral density (BMD). Age 70 is a sufficient risk factor. Younger men (aged 50-69) should be tested if additional risk factors are present. A history of fracture after age 50 is a particularly important indication for evaluation. Other reasons for testing men aged 50-69 include diseases/conditions such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive

pulmonary disease; drugs such as glucocorticoids or GnRH agonists; life choices such as alcohol abuse or smoking; or other causes of secondary osteoporosis. FRAX, Garvan, or other fracture risk calculators can improve the assessment of fracture risk and the selection of patients for treatment. (2| $\oplus\oplus\circ\circ$)

1.2. We recommend dual-energy x-ray absorptiometry (DXA) of the spine and hip in men at risk for osteoporosis. (1| $\oplus\oplus\circ\circ$)

1.3. We suggest measuring forearm DXA (1/3 or 33% radius) when spine or hip BMD cannot be interpreted and for men with hyperparathyroidism or

receiving androgen-deprivation therapy (ADT) for prostate cancer. (2|⊕⊕○○)

1.4. We suggest a complete history and physical examination for men being evaluated for osteoporosis or considered for pharmacological treatment (e.g. those with low BMD and/or high fracture risk). Important information includes medications used, chronic diseases, alcohol or tobacco abuse, falls and/or fractures as an adult, and family history of osteoporosis. Physical examination should assess patient height in comparison with maximum height, kyphosis, balance, mobility, overall frailty, and evidence of causes of secondary osteoporosis, including testicular atrophy, signs of hyperthyroidism, and evidence of chronic obstructive pulmonary disease. Men for whom bisphosphonate therapy is considered should have an examination of the teeth. (2|⊕⊕○○)

1.4.1. We suggest measuring serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25-hydroxyvitamin D [25(OH)D], total testosterone, complete blood count, and 24-h urinary calcium (creatinine and sodium) excretion in men being evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents. (2|⊕⊕○○)

1.4.2. If history or physical examination suggest a specific cause of osteoporosis, further testing should be done. Depending on the findings of the history and physical examination, such testing may include (but is not limited to) calculated free or bioavailable testosterone (using measurements of SHBG), serum protein electrophoresis with free κ and λ light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (for celiac disease), thyroid function tests, and PTH levels. (2|⊕⊕○○)

1.4.3. In men with low bone mass

(osteopenia) or osteoporosis who might have previously undiagnosed vertebral fractures, we recommend vertebral fracture assessment (VFA) using DXA equipment. If VFA is not available or is technically limited, lateral spine radiographs should be considered. (1|⊕⊕○○)

2.0. Lifestyle

2.1. We recommend that men with or at risk for osteoporosis consume 1000-1200 mg calcium daily, ideally from dietary sources, with calcium supplements added if dietary calcium is insufficient. (1|⊕⊕⊕○)

2.2. We suggest that men with low vitamin D levels [<30 ng/ml (75 nmol/liter)] receive vitamin D supplementation to achieve blood 25(OH)D levels of at least 30 ng/ml (75 nmol/liter). (2|⊕⊕○○)

2.3. We suggest that men at risk of osteoporosis participate in weight-bearing activities for 30-40 min per session, three to four sessions per week. (2|⊕○○○)

2.4. We suggest that men at risk of osteoporosis who consume three or more units of alcohol per day reduce their alcohol intake. (2|⊕○○○)

2.5. We recommend that men at risk of osteoporosis who smoke cease smoking. (1|⊕⊕○○)

3.0. Treatment

3.1. Selection of men for treatment

All men

3.1. We recommend pharmacological therapy for men at high risk for fracture including, but not limited to:

- Men who have had a hip or vertebral fracture without major trauma. (1|⊕○○○)
- Men who have not experienced a spine or hip fracture but whose BMD of the spine, femoral neck, and/or total hip is 2.5 SD or more below the mean of normal young white males. (1|⊕⊕○○)

- In the United States, men who have a T-score between -1.0 and -2.5 in the spine, femoral neck, or total hip plus a 10-yr risk of experiencing any fracture $\geq 20\%$ or 10-yr risk of hip fracture $\geq 3\%$ using FRAX; further studies will be needed to determine appropriate intervention levels using other fracture risk assessment algorithms. For men outside the US, region-specific guidelines should be consulted. (1|⊕⊕○○)
- Men who are receiving long-term glucocorticoid therapy in pharmacological doses (*e.g.* prednisone or equivalent >7.5 mg/d), according to the 2010 guidelines of the American Society of Rheumatology. (1|⊕⊕○○).

3.2. Selection of therapeutic agent

3.2. We recommend that men at high risk of fracture be treated with medication approved by regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Union (EU) European Medicines Agency (EMA) (at the time of this writing, alendronate, risedronate, zoledronic acid, and teriparatide; also denosumab for men receiving ADT for prostate cancer) and that the selection of therapeutic agent be individualized based on factors including fracture history, severity of osteoporosis (T-scores), the risk for hip fracture, patterns of BMD [*i.e.* whether BMD is worse at sites where cortical bone (*e.g.* 1/3 radius) or trabecular bone (*e.g.* spine predominate)], comorbid conditions (*e.g.* peptic ulcer disease, gastroesophageal reflux, malabsorption syndromes, malignancy, *etc.*), cost, and other factors. In men with a recent hip fracture, we suggest treatment with zoledronic acid. When teriparatide is administered, we suggest that it not be given with concomitant antiresorptive therapy. Agents that have not been approved by

regulatory agencies for treatment of osteoporosis in men (calcitonin, ibandronate, strontium ranelate, *etc.*) should be used only if the approved agents for male osteoporosis cannot be administered. (1|⊕⊕○○)

Management of hypogonadal men at high risk of fracture

3.3. For men at high risk of fracture who are receiving testosterone therapy, we suggest adding an agent with proven antifracture efficacy (*e.g.* a bisphosphonate or teriparatide). (2|⊕○○○)

3.4. We suggest testosterone therapy in lieu of a “bone drug” for men at borderline high risk for fracture who have serum testosterone levels below 200 ng/dl (6.9 nmol/liter) on more than one determination, if accompanied by signs or symptoms of androgen deficiency (*e.g.* low libido, unexplained chronic fatigue, loss of body hair, hot flushes, *etc.*) or “organic” hypogonadism (*e.g.* due to hypothalamic, pituitary, or specific testicular disorder). If testosterone treatment does not alleviate symptoms of androgen deficiency after 3-6 months, it should be discontinued and other therapy considered. (2|⊕⊕○○)

3.5. We suggest testosterone therapy for men at high risk for fracture with testosterone levels below 200 ng/dl (6.9 nmol/liter) who lack standard indications for testosterone therapy but who have contraindications to approved pharmacological agents for osteoporosis. (2|⊕⊕○○)

Men with prostate cancer receiving ADT

3.6. We recommend pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture (see Section 3.1). (1|⊕⊕⊕○)

4.0. Monitoring therapy

4.1. We suggest that clinicians monitor BMD by DXA at the spine and hip every 1-2 yr to assess the response to treatment. If BMD appears to reach a plateau, the frequency of BMD measurements may be reduced. (2|⊕⊕⊕○)

4.2. We suggest that clinicians consider measuring a bone turnover marker (BTM) at 3-6 months after initiation of treatment using a bone resorption marker [such as serum C-telopeptide of type I collagen (CTX) or serum or urine N-telopeptide of type I collagen (NTX)] for antiresorptive therapy and a bone formation marker [such as serum procollagen I N-propeptide (PINP)] for anabolic therapy. (2|⊕⊕⊕○)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the subject of osteoporosis in men a priority and appointed this Task Force to formulate evidence-based recommendations. Consensus was guided by systematic reviews of evidence and discussions through a series of conference calls, e-mails, and one in-person meeting. An initial draft was prepared by the chair of the Task Force and was reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee and Clinical Affairs Core Committee; representatives of the American Society for Bone and Mineral Research (ASBMR), European Calcified Tissue Society (ECTS), European Society of Endocrinology (ESE), and International Society for Clinical Densitometry (ISCD); and members at large. At each stage, the Task Force received written comments and incorporated needed changes. The reviewed document was approved by The Endocrine Society Council before submission for peer review.

Evidence was rated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. The GRADE group has expertise in development and implementation of evidence-based guidelines (1); a detailed description has been published elsewhere (2). The Task Force used the best available evidence and two commissioned systematic reviews and meta-analyses (3, 4). The Task Force also used consistent language and graphical descriptions of the strength of a recommendation and the quality of evidence. Strong recommendations use the phrase “we recommend” and the number 1; weak recommendations use the phrase “we suggest” and the number 2. *Cross-filled circles* indicate the quality of the evidence: ⊕○○○ denotes very low quality; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered; in some instances, there are *remarks*, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These comments reflect the best available evidence applied to most men being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

The Endocrine Society maintains a rigorous conflict of interest review process for the development of clinical practice guidelines. All Task Force members

must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict of interest forms are vetted by the Clinical Guidelines Subcommittee (CGS) before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline but they have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (*e.g.*, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through The Endocrine Society office.

Funding for this guideline was derived solely from The Endocrine Society and thus the Task Force received no funding or remuneration from commercial or other entities.

Epidemiology and pathophysiology

Osteoporosis is a silent disorder characterized by reduced bone strength predisposing to increased fracture risk (5). Although osteoporosis affects women more often than men, approximately 20% of the 44 million Americans who have osteoporosis or low BMD are men (6). Between 30 and 40% of fractures due to

osteoporosis occur in men; the lifetime risk of fracture for men aged 50 or older is between 13 and 30% (7).

Men with hip fractures have a mortality rate two to three times higher than women (8, 9, 202). Fractures in childhood and teenage years are more common in males, probably due to differences in lifestyle and trauma; most are at peripheral sites (10, 11, 12, 13, 14, 15). Past middle age, fractures due to osteoporosis are more common in women. In later years, fracture risk rises exponentially in both sexes, but the increase occurs about a decade later in men than in women. Of the 3.5 million fractures in men worldwide in 2000, 14% were at the hip, 10% at the forearm, 16% at the vertebrae, 5% at the humerus, and 55% elsewhere (16).

The incidence of fractures due to osteoporosis varies with race/ethnicity and geography. The highest rates in men are in Northern Europe and North America (17, 18). Lowest rates are in blacks and Asians (17, 18) as well as in some parts of South America (19, 20). The ratio of hip fractures between women and men also varies by geography. Although the female-to-male ratio among Caucasians is about 3-4:1, the ratio is much closer to 1:1 or even higher in Asia (18, 21, 22).

Before puberty, BMD measured with DXA is similar in boys and girls and increases slowly but progressively. At puberty, bone turnover increases dramatically, followed by a rapid increase in BMD (23). Androgens increase periosteal bone apposition, increasing the cross-sectional diameter of bone (24). Because BMD measured by DXA is directly related to bone size, part of the apparent pubertal BMD increase is due to a projection artifact from increasing bone size. Peak spine BMD as measured by DXA is generally reached by age 18 in males. Peak trabecular volumetric BMD

as measured by quantitative computed tomography, and peak BMD of the hip, as measured by DXA, are reached several years later (25). As men and women age, bone resorption exceeds formation, leading to bone loss (26, 27, 28, 29, 30). BMD may begin to decline in men as early as age 30 to 40, decreasing slowly (about 0.5-1.0% annually), without the acceleration that is seen in women at menopause. In elderly men, however, degenerative change often increases DXA-measured BMD in the spine.

Bone quality

Microarchitectural deterioration with advancing age is an important feature of osteoporosis (31). Because of differences in bone remodeling with age, trabeculae become thinner in men, whereas in women, trabeculae lose their connectivity (32).

Sex steroids

There are many studies on the roles of gonadal steroids in bone development and adult bone homeostasis, but there are also many unanswered questions. Fully androgenized men are believed to benefit from anabolic properties of endogenous androgens with regard to bone mass and bone geometry (33). However, it is clear that estrogen is at least as important in men, particularly for skeletal accrual (34). Men with inactivating mutations of the aromatase or estrogen receptor genes (35) have markedly reduced bone mass despite normal or increased levels of testosterone (34, 35, 36, 37). Whereas testosterone administration had no effect on bone turnover in a man with an inactivating mutation in the estrogen receptor α gene, estrogen increased BMD in a man with a null mutation of his aromatase gene (38). In older men, stronger associations have been reported between blood levels of estradiol and BMD than between levels

of testosterone and BMD, although the differences are small and the associations weak (27, 39-43). Controlled physiological studies in which androgens, estrogens, or both are selectively suppressed have demonstrated that both androgens and estrogens are important regulators of bone turnover in adult men (41, 44).

Hormonal abnormalities

25(OH)D levels are higher in men than in women at all ages but decline with age in both sexes (45, 46) due to decreased sun exposure, skin production, and dietary intake (47, 48, 49, 50, 51).

PTH levels increase with age (52, 53, 54), to a large extent due to declining kidney function and reduced synthesis of 25(OH)D.

Many factors may contribute to differences in the incidence and prevalence of osteoporosis and fractures between men and women (24, 55, 56). Men's larger bones contribute to greater bone strength (57). Risk factors that may be more common in men include delayed puberty (58) and hypercalciuria. Men fall less often than women (59, 60); higher androgen levels have been associated with reduced fall risk (39). Finally, men have a shorter life expectancy.

1.0. Evaluation

Recommendation

1.1. We suggest testing men at increased risk for osteoporosis by measurement of BMD. Age 70 is a sufficient risk factor. Younger men (aged 50-69 yr) should be tested if additional risk factors are present. A history of fracture after age 50 is a particularly important indication for evaluation. Other reasons for testing men ages 50-69 include diseases/conditions such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive pulmonary disease;

drugs such as glucocorticoids or GnRH agonists; life choices such as alcohol abuse or smoking; or other causes of secondary osteoporosis. FRAX, Garvan, or other fracture risk calculators can improve the assessment of fracture risk and the selection of patients for treatment. (2|⊕⊕○○)

1.1. Evidence

In addition to low BMD, age is an independent risk factor for osteoporosis and for fracture (61, 62, 63, 64, 65). Table 1 lists other risk factors for low BMD or fractures in men (27, 42, 66, 67, 68, 69, 70, 71, 72, 73, 74). These were assessed in a systematic review and meta-analysis (4). Most of the associations were weak (*i.e.* adjusted odds ratios were in general < 2), and the level of evidence was low; therefore, the strength of this recommendation is low.

1.1. Remarks

The FRAX calculator (www.shef.ac.uk/FRAX/) and the Garvan nomogram (www.fractureriskcalculator.com) are commonly-used algorithms for predicting fracture risk. Both use age, weight, history of fracture, and femoral neck BMD, although other variables differ (75, 76). In a validation study from Australia, FRAX underestimated fracture risk in men (77). A simple score using BMD, prior fracture, and corticosteroid use developed for Canadian women (78) has been applied to men (79). Simple risk calculators such as the Osteoporosis Self-Assessment Tool (OST) and Male Osteoporosis Screening Tool (MOST) (80,81) may be useful to identify men likely to have osteoporosis by DXA. Age has been shown to be an important predictor of fracture risk (63, 71, 74).

Recommendation

1.2. We recommend DXA of the spine and hip in men at risk for osteoporosis. (1|⊕⊕○○)

1.2. Evidence

In men as in women, BMD correlates strongly with fracture risk (64). In a large study of men and women over age 65, BMD (total hip and femoral neck) was strongly associated with hip fracture risk, with a stronger association in men (82). Spine BMD was also significantly associated with hip fracture risk, although less strongly than hip DXA. Spine and hip BMD predict nonvertebral fracture risk similarly (82). Femoral neck BMD identifies fewer men than women who suffered a hip fracture (83). Using only hip BMD would identify a small proportion of the men who will experience a fracture. Although spine BMD is useful in younger men, a high frequency of artifacts and degenerative change reduce its utility in older men.

DXA is helpful in choosing men for therapy because men with DXA-proven osteoporosis or “osteopenia” plus a previous fracture respond to currently available therapy (84, 85, 86, 87, 88).

1.2. Remarks

Third-party payers, including Medicare, vary in their coverage of DXA testing in men. For example, Medicare covers initial DXA only in men who have vertebral fractures, radiographic osteopenia, hyperparathyroidism or are on oral glucocorticoid therapy (89).

Recommendation

1.3 We suggest measuring forearm DXA (1/3 or 33% radius) when spine or hip BMD cannot be interpreted and for men with hyperparathyroidism or receiving ADT for prostate cancer. (2|⊕⊕○○)

TABLE 1. Summary of risk factors for fractures in males (4)

Risk factor	No. of studies	OR	95% CI		P value	I ² ^a
			LL	UL		
Age						
Age (continuous variable) ^b	11	1.12	1.07	1.18	0.00	87
Age (every 5-10 yr) ^c	6	1.29	1.17	1.43	0.00	52
Age >70 ^d	5	1.52	1.11	2.08	0.01	69
Race (vs. White)						
Black	3	0.69	0.57	0.85	0.00	87
Hispanic	2	1.05	0.62	1.78	0.84	87
BMI						
BMI (all studies)	23	0.89	0.83	0.96	0.00	71
BMI (quintile or 1 SD increase)	18	0.77	0.68	0.87	0.00	62
BMI (1 kg/m ²)	5	1.01	0.95	1.08	0.76	66
Alcohol (daily or >10 drinks/week)	22	1.28	1.08	1.53	0.01	81
Smoking (current)	27	1.49	1.29	1.72	0.00	54
Chronic corticosteroid use (various definitions)	8	1.29	1.03	1.61	0.03	38
Prior fracture	9	2.08	1.57	2.77	0.00	75
Parental fractures						
Fracture, father	2	1.18	0.70	1.98	0.54	NA
Fracture, mother	2	1.32	0.97	1.81	0.08	NA
Fracture, parents	1	1.30	1.00	1.69	0.05	NA
History of falls within the last year	7	2.11	1.44	3.10	0.00	83
Hypogonadism (all studies)						
Hypogonadism (nonpharmacological)	4	2.77	1.30	5.87	0.01	51
Hypogonadism (drug-induced)	4	1.53	1.19	1.96	0.00	91
Kidney stones	2	0.53	0.35	0.80	0.00	NA
History of stroke	4	3.73	1.75	7.92	0.00	73
DM	8	1.57	1.14	2.15	0.01	77
Asthma	2	1.01	0.56	1.84	0.96	56
Cardiovascular disease (CHF/MI)	6	1.07	0.86	1.33	0.55	86
Dementia	2	2.84	0.93	8.64	0.07	97
Osteoarthritis	4	1.03	0.57	1.88	0.91	87
Rheumatoid arthritis	5	1.46	0.97	2.19	0.07	60

NA, Not applicable (I² is not meaningful if the number of studies is less than three); CHF, congestive heart failure; DM, diabetes mellitus; LL, lower limit; MI, myocardial infarction; OR, odds ratio; UL, upper limit.

^a I² statistic is defined as the proportion of heterogeneity not attributable to chance or random error.

^b Age as a continuous variable reflects that the OR represents increases in odds per year of age.

^c OR (95% CI) for studies: 5 yr = 1.41 (1.12-1.78); 7.7 yr = 1.16 (1.03-1.31); 10 yr = 1.39 (1.15-1.67).

^d Age > 70 is compared vs. age ≤ 70 in studies with mean age of 40-80.

1.3. Evidence

Radius BMD predicts fractures in men (90,91). BMD measurement at skeletal sites where osteoarthritis is uncommon, such as the 1/3 (33%) radius, may be more sensitive for detecting bone loss in elderly men (91, 92). A large study found osteoporosis (T-scores of -2.5 or below) at the 1/3 radius in about 15% of men aged 70 or older who had T-scores better than -2.5 in the spine and hip (92). In the Geelong Study, mean spine BMD was about the same in men aged 20-85 yr; however, after age 47, there was a considerable, progressive decrease in the midforearm BMD (93).

Radius BMD declines to a greater extent than hip or spine BMD in men with prostate cancer receiving ADT (94, 95, 96). Moreover, radius BMD measurements performed as well as spine or hip BMD for distinguishing between effects of denosumab and placebo (97).

Because artifacts and localized degenerative change in the spine and hip are common in men, particularly those older than 60 (98), radius BMD may provide a more realistic measure of skeletal status. In some subjects, such as patients with hyperthyroidism or hyperparathyroidism, T-scores for radius BMD are often lower than T-scores for the spine or hip (99). The ISCD recommends only considering the T-score from the 1/3 (33%) radius site (100).

1.3. Remarks

Medicare and other payers may not cover forearm BMD testing (89). Although radius BMD predicts fractures in men (91) and appears to be particularly important in men on ADT (94), there are no studies showing that men with osteoporosis in the radius and not at other sites respond to current treatments.

Recommendations

1.4. We suggest a complete history and physical examination for men being evaluated for osteoporosis or considered for pharmacological treatment (*e.g.* those with low BMD and/or high fracture risk). Important information includes medications used, chronic diseases, alcohol or tobacco abuse, falls and/or fractures as an adult, and family history of osteoporosis. Physical examination should assess patient height in comparison with maximum height, kyphosis, balance, mobility, overall frailty, and evidence of causes of secondary osteoporosis, including testicular atrophy, signs of hyperthyroidism, and evidence of chronic obstructive pulmonary disease. Men for whom bisphosphonate therapy is considered should have an examination of the teeth. (2|⊕⊕○○)

1.4.1. We suggest measuring serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25(OH)D, total testosterone, complete blood count, and 24-h urinary calcium (creatinine and sodium) excretion in men being evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents. (2|⊕⊕○○)

1.4.2. If history or physical examination suggest a specific cause of osteoporosis, further testing should be done. Depending on the findings of the history and physical examination, such testing may include (but is not limited to) calculated free or bioavailable testosterone (using measurements of SHBG), serum protein electrophoresis with free κ and λ light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (for celiac disease), thyroid function tests, and PTH levels. (2|⊕⊕○○)

1.4.3. In men with low bone mass (osteopenia) or osteoporosis who might have previously undiagnosed vertebral

fractures, we recommend VFA using DXA equipment. If VFA is not available or is technically limited, lateral spine radiographs should be considered.

(1|⊕⊕○○)

1.4. Evidence

Potentially important information can come from the history and physical examination. An oral exam is important; clinicians should assess whether additional dental evaluation or care may be needed before starting bisphosphonate therapy. The yield and cost-effectiveness of laboratory studies in men with low BMD are not well established. Nevertheless, in men at increased risk of fracture, laboratory tests may be useful to determine factors that contribute to low BMD or fracture risk and to design appropriate therapy. History and physical examination may provide important information. Osteomalacia, usually due to severe vitamin D deficiency, is common in men with hip fractures. Other causes of bone loss, such as hyperparathyroidism, kidney and liver disease, hypogonadism, and hypercalciuria, are sufficiently common in high-risk men to warrant evaluation (101). A 24-h urine calcium measurement is useful to identify idiopathic hypercalciuria or calcium malabsorption. Hypercalciuria can be managed with thiazide diuretics (102). Moderate vitamin D deficiency is common in men and is associated with low bone mass and increased fracture risk. Other laboratory tests may be appropriate, depending on the clinical context.

VFA is a low-cost, low-risk method for detecting vertebral fractures using standard DXA devices. The ISCD recommends VFA for men over age 80 with osteopenia or younger men with historical height loss greater than 6 cm (103). Additionally, younger men (aged 70-79) are candidates for VFA if they have a chronic disease such as rheumatoid arthritis, Crohn's disease,

or chronic obstructive pulmonary disease. Although VFA detects many vertebral fractures, imaging quality may be limited, particularly in the midthoracic spine and higher, where radiographs may be needed. Still, VFA can provide useful clinical information, particularly if there is clinical suspicion of occult vertebral fractures.

2.0. Lifestyle

Recommendation

2.1. We recommend that men with or at risk for osteoporosis consume 1000-1200 mg calcium daily, ideally from dietary sources, with calcium supplements added if dietary calcium is insufficient.

(1|⊕⊕⊕○)

2.1. Evidence

Several studies have addressed the effects of calcium on BMD and fracture risk in men, with inconsistent findings. No benefit for BMD was observed from calcium/vitamin D supplementation in well-nourished men (mean dietary calcium intake >1000 mg/d) (104). However, an increase in BMD was seen in healthy older men given calcium and vitamin D supplements (105). Calcium- and vitamin D-fortified milk increased BMD (106) and improved femoral bone structure in older men (107). Dietary calcium was not related to fractures in men in the Health Professionals Follow-Up Study (108), but low dietary calcium intake was associated with higher fracture risk in a cohort of Australian men (109). Calcium supplementation alone has not been demonstrated to reduce fracture risk in men with prior fractures (110). In clinical trials of alendronate (84), risedronate (86), and teriparatide (87) for osteoporosis in men, calcium (500-1000 mg/d) and vitamin D [400-1200 IU/d (10-30 µg/d)] supplementation was provided for all subjects.

In women, calcium supplementation is more beneficial in those with low calcium intake (111) and, together with vitamin D, reduces hip fracture risk in compliant subjects (112). There are no similar studies in men.

The Institute of Medicine (IOM) recommends a calcium intake of 1000 mg/d for men aged 51-70 and 1200 mg/d for men (and women) older than 70 (113).

A meta-analysis showed that calcium supplements may be associated with an increased risk of myocardial infarction but no other cardiovascular end points or death in women (114). This finding has not been confirmed in men (115).

In older women, calcium supplementation increases the risk of kidney stones (112). The prevalence of kidney stones is higher in men than in women, but no increase in kidney stones has been demonstrated in men at the level of calcium intake recommended for optimal bone health. An observational study suggested that the risk of metastatic prostate cancer was higher in men who received high doses of supplemental calcium (1500-2000 mg/d) (116), but this has not been substantiated in clinical trials (117).

Recommendation

2.2. We suggest that men with low vitamin D levels [<30 ng/ml (75 nmol/liter)] receive vitamin D supplementation to achieve blood 25(OH)D levels of at least 30 ng/ml (75 nmol/liter). (2|⊕⊕⊕○)

2.2. Evidence

Vitamin D deficiency is common in older men (118) and has been associated with an increased risk of hip and nonvertebral fractures (119).

Severe vitamin D deficiency [25(OH)D levels <10 ng/ml (25 nmol/liter)] may lead to osteomalacia, which should be treated with calcium and vitamin D; treatment

results in symptomatic and biochemical improvement and sometimes large increases in BMD. This degree of vitamin D deficiency should be at least partially corrected before considering treatment for osteoporosis.

Vitamin D status can be assessed by measuring serum 25(OH)D. Because vitamin D is a threshold nutrient, the usual approach to defining normality in a “healthy” population is inappropriate. Insufficiency needs to be defined with reference to changes in calcium homeostasis, BMD, or fracture risk.

Serum 25(OH)D measurement is recommended in men at high risk for vitamin D deficiency (120). This includes men with osteomalacia, osteoporosis, malabsorption (e.g. celiac disease, bariatric surgery, etc.), and liver disease, as well as older men with a history of falls and those taking medications that alter vitamin D status, such as some anticonvulsants (121).

International consensus is lacking on a reference range for 25(OH)D levels, partly due to assay variability. Many experts support a minimum desirable 25(OH)D level of 30 ng/ml (75 nmol/liter) for bone health (122), although a committee of the IOM concluded that 20 ng/ml (50 nmol/liter) was adequate for bone health (113); it should be noted that the IOM recommendations are for healthy individuals and may not be appropriate for patients with osteoporosis. For men at high risk of fracture, we are recommending a target 25(OH)D level of 30 ng/ml, consistent with The Endocrine Society 2011 Clinical Practice Guidelines on Evaluation, Treatment, and Prevention of Vitamin D Deficiency (123).

For most people, optimal vitamin D levels can be achieved with 1000-2000 IU (25-50 μ g) of vitamin D daily. Larger doses [e.g. 50,000 IU (1.25 mg) orally weekly for 8 wk or 300,000 IU (7.5 mg)

by im injection every 3 months] may be required for patients with more severe vitamin D deficiency.

Vitamin D at high doses may result in toxicity (hypercalcemia or hypercalciuria), but this is rarely seen unless 25(OH)D levels exceed 150 ng/ml (375 nmol/liter) (121), and such levels are unlikely with the doses of vitamin D recommended here. In a recent report of high-dose vitamin D [500,000 IU (12.5 mg) orally once a year] given to women older than 70 yr, there was an increased risk of fracture and falling, especially in the first 3 months after administration, when 25(OH)D levels were on average 50 ng/ml (125 nmol/liter) (124). This finding needs to be confirmed in women and has not been documented in men, but it raises caution about giving high doses of vitamin D intermittently.

2.2. Remarks

Measurement of serum 25(OH)D is challenging because assay variability is high and between-assay calibration is poor. Not unexpectedly, the intra- and interassay variability is much greater at lower 25(OH)D levels (125). Although mean serum 25(OH)D differs depending on the assay method (RIA, chemiluminescence, or liquid chromatography-tandem mass spectrometry), the relative ranking is similar between assays (125). The International Vitamin D External Quality Assessment Scheme is an effort to harmonize 25(OH)D assays (126). Still, the latitude between “reference” and “toxic” levels is quite wide.

Recommendation

2.3. We suggest that men at risk of osteoporosis participate in weight-bearing activities for 30-40 min per session, three to four sessions per week. (2|⊕○○○)

2.3. Evidence

Low physical activity in older men is associated with poor health (127). Studies of exercise interventions in men and in postmenopausal women at risk for osteoporosis have generally been of poor quality (128). However, weight-bearing activities, such as walking 30-40 min for three to four sessions per week, is a logical recommendation (129), supported by small studies showing improvement in BMD (130) and decreased fall risk (131).

Recommendation

2.4. We suggest that men at risk of osteoporosis who consume three or more units of alcohol per day reduce their alcohol intake. (2|⊕○○○)

2.4. Evidence

High alcohol intake is associated with increased bone loss, falling, and fractures in older men (132), although the mechanism is unclear. There may be a threshold effect (133, 134, 135), with no excess risk 2 U/d of alcohol [one unit of alcohol is defined as 10 ml in the United Kingdom and as 10 g (12.7 ml) in Australia—approximately half a pint of beer, one small glass of wine, or a single measure of spirits]. The relative hazard for alcohol consumption of at least 3 U/d was 1.33 for all fractures [95% confidence interval (CI), 1.10 to 1.60] and 1.92 for hip fractures (95% CI, 1.28 to 2.88), with no contribution from BMD, body mass index (BMI), or age. If the association with alcohol intake is causal, then it accounts for approximately 7% of hip fractures in men (133). The risk of fractures remains elevated even when alcohol consumption is reduced (134).

Self-reported alcohol intake may be underestimated, and the intakes in populations studied (Dutch, Canadian, Australian) appeared lower than reported for the United Kingdom (133). This may

indicate that the threshold observed in U.S. and Danish studies may be more accurate (≥ 4 U/d).

2.4. Remarks

A strategy should be in place to support men who wish to reduce their alcohol intake.

Recommendation

2.5. We recommend that men at risk of osteoporosis who smoke cease smoking. (1|⊕⊕○○)

2.5. Evidence

A meta-analysis of more than 15,000 men suggested that the association of smoking with fracture risk was higher in men than in women (136). The relative hazard for a current male smoker was 1.5 for all fractures (95% CI, 1.3 to 1.8), 1.5 for osteoporosis-related fractures (95% CI, 1.3 to 1.8), and 1.8 for hip fractures (95% CI, 1.3 to 2.5); the increase in risk was independent of age. The contribution of low BMD to increased fracture risk was 40%. BMD contributed more than BMI to the effect of smoking on fracture risk. As with alcohol, the mechanisms by which smoking may increase fracture risk have not been determined. The offset of effects in men is not known, but in women, the benefits of stopping smoking on hip fracture risk were not apparent until after 10 yr (137). This observation is in keeping with the Framingham Study; men who were current smokers had greater bone loss from the proximal femur (but not spine or forearm) than former smokers or men who never smoked (138).

2.5. Values and preferences

Smoking is harmful to health, and smoking cessation reduces risk not only of fractures but also of other diseases. Smoking cessation should be recommended as a

general health measure for current smokers. Panel members placed higher value on preventing other smoking-related complications because data showing that smoking cessation reduces fracture risk are limited.

2.5. Remarks

Medical support may be required to assist with smoking cessation (139).

3.0. Treatment

3.1. Selection of men for treatment

Recommendation

All men

3.1. We recommend pharmacological therapy for men at high risk for fracture including, but not limited to:

- Men who have had a hip or vertebral fracture without major trauma. (1|⊕⊕⊕○)
- Men who have not experienced a spine or hip fracture but whose BMD of the spine, femoral neck, and/or total hip is 2.5 sd or more below the mean of normal young white males. (1|⊕⊕○○)
- In the United States, men who have a T-score between -1.0 and -2.5 in the spine, femoral neck, or total hip plus a 10-yr risk of experiencing any fracture $\geq 20\%$ or 10-yr risk of hip fracture $\geq 3\%$ using FRAX; further studies will be needed to determine appropriate intervention levels using other fracture risk assessment algorithms. For men outside the US, region-specific guidelines should be consulted. (1|⊕⊕○○)
- Men who are receiving long-term glucocorticoid therapy in pharmacological doses (e.g. prednisone or equivalent >7.5 mg/d) according to the 2010 guidelines of the American Society of Rheumatology. (1|⊕⊕○○)

3.1. Evidence

In contrast to the large fracture-end point trials of osteoporosis therapies in women, studies in men have generally been small, with change in BMD as the primary end point. Thus, recommendations regarding treatment efficacy in men are provided with lesser confidence. Nevertheless, treatment trials in men have yielded effects on BMD, biochemical markers of bone remodeling, and trends in fracture reduction that closely mirror those seen in larger trials in postmenopausal women with osteoporosis. A systematic review and meta-analysis came to this conclusion (3). Therefore, we conclude that available therapies are likely to be effective in men and that it is appropriate to recommend pharmacological therapy in men with increased fracture risk. Alendronate increased BMD and reduced the incidence of radiographic vertebral fractures (by quantitative morphometry but not by semiquantitative assessment) in men with low femoral neck or spine T-scores or whose femoral neck BMD T-score was at least -1 with at least one vertebral deformity or a history of nonvertebral fracture (84). Risedronate increased BMD and reduced the incidence of vertebral fractures in men with T-scores in the spine of -2.0 or below and femoral neck -1.0 or below (85, 86). Teriparatide increased BMD in men with osteoporosis (87) and appeared to reduce the risk of vertebral fractures in men whose T-score for spine, femoral neck, and/or total hip was -2.0 or below (87). Similarly, zoledronic acid has been shown to have positive effects in men with low BMD (140). Based on a cost-effectiveness analysis specific to the United States, the National Osteoporosis Foundation (NOF) concluded that a 10-yr risk of hip fracture of at least 3% or 10-yr risk of major fracture of at least 20% was sufficient to justify treatment of women (141). Cost-effectiveness has not been

studied adequately in men. Because FRAX may underestimate fracture in men (77) and because the NOF study assumed a treatment cost higher than present costs, we believe that it is conservative to use the NOF treatment thresholds in men.

The evidence available to provide guidance about who is at sufficient risk to warrant pharmacological therapy is inadequate and controversial. Criteria based only on BMD T-scores (T-score -2.5 or below in the spine or hip) are too restrictive because they identify too few men for therapy (<10%), whereas approximately 25% of men experience a fracture after age 60 (142), and a majority of men who fracture have T-scores that are better than -2.5 (83). T-score-only criteria ignore important, independent contributions to fracture risk from factors other than BMD, such as age, previous fractures, and comorbidities. This along with other factors can now more accurately predict risk fractures. The use of FRAX identifies a larger proportion of older men in whom therapy appears to be cost-effective (141) than use of T-scores alone. However, these algorithms may not be sufficiently sensitive because they do not incorporate risk factors that also are likely to affect fracture risk (*e.g.* malabsorption, renal insufficiency, fall risk, some medications) and because they consider only hip BMD.

Acknowledging the shortcomings of the available data, we recognize the need to be sufficiently inclusive to identify both an adequate number of the men at risk and to incorporate multivariable risk models. Therefore, we recommend that several criteria be considered in making treatment choices.

Men who have suffered fragility hip or clinical vertebral fractures are at high risk of additional fractures and should be considered for pharmacological treatment. A T-score of -2.5 or below in the spine,

femoral neck, or total hip (using the young male reference range) should also be a factor in the decision to treat. Finally, we recommend the use of FRAX or Garvan or another risk assessment tool in men who have not sustained a fragility fracture and in whom the T-score is between -1.0 and -2.5 , and, at least in the United States, to recommend pharmacological therapy for men who have a 10-yr risk of greater than 3% for hip fracture or at least 20% for major osteoporosis-related fracture using FRAX.

We endorse the 2010 guidelines of the American College of Rheumatology (143) for selecting men who require long-term systemic glucocorticoid therapy for pharmacological treatment with bone-active agents.

Recommendation

3.2. Selection of therapeutic agent

We recommend that men at high risk of fracture be treated with medication approved by regulatory agencies such as the U.S. FDA or EU EMA (at the time of this writing, alendronate, risedronate, zoledronic acid, and teriparatide; also denosumab for men receiving ADT for prostate cancer) and that the selection of therapeutic agent be individualized based on factors including fracture history, severity of osteoporosis (T-scores), the risk for hip fracture, patterns of BMD [*i.e.* whether BMD is worse at sites where cortical bone (*e.g.* 1/3 radius) or trabecular bone (*e.g.* spine) predominates], comorbid conditions (*e.g.* peptic ulcer disease, gastroesophageal reflux, malabsorption syndromes, malignancy, etc.), cost, and other factors. In men with a recent hip fracture, we suggest treatment with zoledronic acid. When teriparatide is administered, we suggest that it not be given with concomitant antiresorptive therapy. Agents that have not been

approved by regulatory agencies for treatment of osteoporosis in men (calcitonin, ibandronate, strontium ranelate, *etc.*) should be used only if the approved agents for male osteoporosis cannot be administered. (1|⊕⊕○○)

3.2. Evidence

The effects of bisphosphonates and teriparatide on BMD and BTM appear to be similar in men and women (144). Of the FDA-approved agents used to treat osteoporosis in men, alendronate, risedronate, and zoledronic acid have been shown to reduce the risk of hip fractures in women with postmenopausal osteoporosis (145, 146, 147). Denosumab has been shown to increase BMD and reduce the incidence of vertebral fractures in men receiving ADT for non-metastatic prostate cancer. Once-yearly treatment with iv zoledronic acid reduced risk of recurrent fractures in more than 2100 subjects (~25% were men) who had undergone repair of a hip fracture within 90 d of treatment initiation (148). Teriparatide increases spine BMD more than alendronate; combining teriparatide with alendronate seems to attenuate the anabolic effect of teriparatide on BMD in both the spine and the hip (149, 150). The effects of combining teriparatide with an antiresorptive agent on fracture risk have not been examined.

3.2. Remarks

For most men who are candidates for pharmacological therapy, generic alendronate will often be preferred because of: 1) extensive experience with its use; 2) lack of evidence that other agents are more effective or better tolerated; and 3) low cost. For men with upper or lower gastrointestinal problems, a nonoral therapy (*e.g.* zoledronic acid or teriparatide) may be preferred. In postmenopausal women, risedronate

has been shown to reduce hip fracture risk and is a reasonable alternative for men at risk for hip fractures. For men at high risk of vertebral fracture, teriparatide may be preferred because it increases spine BMD more than alendronate, although it is more expensive (149). Teriparatide could also be considered for men who fail to tolerate or respond adequately to other agents. Because concomitant antiresorptive therapy seems to reduce the efficacy of teriparatide, increase costs, and expose patients to additional potential side effects, it should be discontinued when teriparatide is administered. Clinical and social context should be considered in selecting therapeutic agents, as well as side effects and safety concerns. Bisphosphonate therapy should not be used in men with impaired kidney function (estimated glomerular filtration rate \leq 30-35 ml/min). Potential safety concerns with bisphosphonates include osteonecrosis of the jaw (151) and atypical femur fractures (152). The optimal duration of bisphosphonate therapy has not been determined (153). Teriparatide should not be used in men with prior irradiation. Full prescribing information should be consulted.

Recommendations

Management of hypogonadal men at high risk of fracture

3.3. For men at high risk of fracture who are receiving testosterone therapy, we suggest adding an agent with proven antifracture efficacy (*e.g.* a bisphosphonate or teriparatide). (2| \oplus ○○○)

3.4. We suggest testosterone therapy in lieu of a “bone drug” for men at borderline high risk for fracture who have serum testosterone levels below 200 ng/dl (6.9 nmol/liter) on more than one determination, if accompanied by signs or symptoms of androgen deficiency (*e.g.* low libido, unexplained chronic fatigue, loss of body hair, hot flushes,

etc.) or “organic” hypogonadism (*e.g.* due to hypothalamic, pituitary, or specific testicular disorder). If testosterone treatment does not alleviate symptoms of androgen deficiency after 3-6 months, it should be discontinued and other therapy considered. (2| \oplus ○○)

3.5. We suggest testosterone therapy for men at high risk for fracture with testosterone levels below 200 ng/dl (6.9 nmol/liter) who lack standard indications for testosterone therapy but who have contraindications to approved pharmacological agents for osteoporosis. (2| \oplus ○○)

3.3.-3.5. Evidence

In men with congenital hypogonadal disorders, such as Kallmann’s or Klinefelter syndromes, BMD is thought to be reduced because of inadequate pubertal bone accretion leading to a lower peak bone mass (154, 155). In men with acquired disorders that reduce testosterone levels, such as primary gonadal failure, pituitary or hypothalamic tumors, or hemochromatosis, BMD declines because of accelerated bone resorption (156, 157, 158, 159, 160).

Normalization of testosterone levels increases BMD in men with hypogonadism due to GnRH deficiency, particularly in subjects who have not yet reached skeletal maturity (161). Even with prolonged androgen replacement, however, BMD fails to normalize in these men (161). Normalization of testosterone increases BMD in men with acquired hypogonadism due to prolactin-secreting adenomas (162), other pituitary-hypothalamic disorders, or primary testicular disorders (159,160). In men with acquired hypogonadism, testosterone therapy reduces BTM, suggesting that the testosterone-induced increases in BMD are due to antiresorptive effects (159,163) possibly mediated through conversion

of testosterone to estradiol.

Our recommendation to treat men with testosterone if they have hypogonadism due to organic disease or symptoms of androgen deficiency is consistent with the current standard of care in these men (164). Our suggestion to add a pharmacological agent to treat osteoporosis if fracture risk is high reflects the convincing fracture-prevention data in women treated with bisphosphonates or teriparatide and the lack of fracture-prevention data in men treated with testosterone. Our suggestion that testosterone alone be considered if such men have a modest or borderline risk of fracture reflects our desire to manage both the hypogonadism and the low BMD with a single agent, thus reducing costs and the risk of medication side effects, as well as our belief that it is likely that the beneficial effects of testosterone on BMD in hypogonadal men indicate that it will also reduce fracture risk.

Because testosterone and estradiol levels decline as men age, it has been suggested that this decline may be responsible, at least in part, for the decrease in BMD that occurs in aging men. The effects of testosterone therapy on BMD in aging men with low or borderline low testosterone levels and no known disorders of the hypothalamic-pituitary-gonadal axis have been examined in several small ($n = 13-108$) placebo-controlled studies of varying durations (6-36 months). The effect of testosterone on BMD appears to be related to baseline levels; testosterone therapy fails to increase BMD in men whose testosterone levels are within the reference range, whereas it increases BMD in men whose levels are below the reference range. For example, in men aged 65 yr or older with serum testosterone levels below 470 ng/dl (16.3 nmol/liter) [mean \pm se baseline level of 399 ± 10 ng/dl (13.8 ± 0.3 nmol/liter)], testosterone for

6 months had no significant effect on BMD (165). Similarly, in 108 men more than 65 yr of age with serum testosterone levels below 475 ng/dl (16.5 nmol/liter), spine BMD increased to the same extent in men treated with testosterone compared with those receiving with placebo for 3 yr (166). A post hoc analysis, however, suggested that testosterone therapy increased BMD more than placebo in men with baseline testosterone levels below 200 ng/dl (6.9 nmol/liter). Three placebo-controlled trials have examined the effect of testosterone administration on BMD in older men with low baseline testosterone levels. Spine, trochanter, and total hip BMD increased with testosterone compared to placebo over 36 months in men more than 65 yr of age with baseline testosterone levels below 350 ng/dl (12.1 nmol/liter) (163). In men age 60 or older with baseline testosterone levels below 320 ng/dl, 12 months of testosterone increased spine and total hip BMD, but there was no significant change at the femoral neck (167). Twelve months of testosterone prevented a decline in femoral neck BMD in men age 65 or older with baseline bioavailable testosterone levels below normal (168).

Measurements of serum testosterone levels are useful to identify men who have androgen deficiency and who may be candidates for testosterone replacement. Low levels of both testosterone and estradiol are associated with bone loss and fractures in men, although the associations are weak (43, 169, 170). Low estradiol levels are more strongly associated with increased fracture risk and accelerated bone loss in older men (27, 171, 172). Measurement of estradiol levels in clinical situations in men is not recommended because of the lack of easily available, accurate assay methods (mass spectrometry) and the absence of validated clinical algorithms that incorporate estradiol measurements into

treatment decisions. High SHBG levels are associated with increased fracture incidence and bone loss in older men.

Skeletal health may be compromised when serum testosterone levels fall below 200-250 ng/dl (6.9-8.7 nmol/liter). As noted above, testosterone administration increased BMD in elderly men whose baseline testosterone levels were 200-300 ng/dl (6.9-10.4 nmol/liter) but not in men with higher baseline levels (166). Second, in the Osteoporotic Fractures in Men study, the odds of having osteoporosis at the hip tripled, as did the odds of experiencing rapid hip bone loss in men with baseline testosterone levels below 200 ng/dl (6.9 nmol/liter) vs. men with testosterone levels above 200 ng/dl (6.9 nmol/liter) (42). Additionally, in the Dubbo Osteoporosis Epidemiology Study, the risk of low-trauma fracture was higher in men with baseline testosterone levels in the lowest quartile [median level of 227 ng/dl (7.9 nmol/liter)] (142). Finally, in healthy men given a GnRH agonist with testosterone gel for 16 wk, bone resorption increased when serum testosterone levels fell below 200 ng/dl (6.9 nmol/liter), although there did not appear to be a distinct threshold (173). Thus, men whose serum testosterone level is 200-300 ng/dl (6.9-10.4 nmol/liter) or below appear to be at higher risk for bone loss and fracture and are more likely to have a favorable response to testosterone therapy. Because the benefits of testosterone therapy are not well established and the risks of therapy are not clear, we feel that a more conservative level [i.e. 200 ng/dl (6.9 nmol/liter)] should be used for intervention until further data are available.

No studies have assessed the effects of combining testosterone with bisphosphonates or other osteoporosis drugs in hypogonadal men. The available data from both controlled and uncontrolled

trials, together with data from animal studies, suggest that testosterone is an effective therapy for hypogonadal men with osteoporosis. For men with hypogonadism due to organic disease and/or symptomatic hypogonadism who have a marginal increase in fracture risk, testosterone therapy may be adequate. However, in men who need testosterone therapy for hypogonadism and who have a high fracture risk, we recommend adding an approved pharmacological agent.

Recommendation

Men with prostate cancer receiving ADT

3.6. We recommend pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture (see Section 3.1). (1|⊕⊕⊕○)

3.6. Evidence

Orchiectomy or administration of long-acting GnRH agonists to men with prostate cancer lowers serum testosterone and estradiol levels to the prepubertal range, increasing bone resorption and inducing rapid bone loss. Several small studies have examined rates of bone loss during the first year of GnRH agonist therapy in men with prostate cancer. In general, spine BMD declines by 3-4% in the first year (95, 174-178). Decreases in hip BMD are more modest (95, 174-178). Interestingly, BMD declined more rapidly in the radius than in the spine or hip (95, 97). Fracture risk is increased in men receiving ADT (179-181).

Randomized controlled trials have been performed to determine whether antiresorptive agents prevent bone loss in men receiving ADT for prostate cancer. Intravenous pamidronate every 12 wk prevented bone loss in men with locally advanced or recurrent prostate cancer initiating GnRH agonist therapy (175, 177). Similar results have been reported

with other bisphosphonates, including iv zoledronic acid (177,182) and oral alendronate (183,184). Two randomized controlled trials have examined the effects of selective estrogen receptor modulators on bone health in men with prostate cancer receiving chronic GnRH agonist therapy. Administration of raloxifene for 12 months increased BMD of the hip and tended to increase BMD of the spine compared with placebo (183). In a study of men with prostate cancer and low BMD of the spine and/or hip receiving GnRH agonist therapy for at least 6 months, toremifene reduced the risk of new or worsening morphometric vertebral fractures, clinical fragility fractures, or significant bone loss after 24 months (184).

A placebo-controlled trial showed the benefits of denosumab in men with early prostate cancer receiving ADT; after 36 months of treatment, denosumab increased spine, hip, and distal radius BMD and decreased the incidence of vertebral fractures by 62% (97, 185); denosumab is now approved by the FDA and EU EMA for treatment of men with non-metastatic prostate cancer receiving ADT. Denosumab in higher doses than used to treat osteoporosis has been shown to improve the outcome of men with advance prostate cancer metastatic to bone (denosumab 60 mg SQ every 6 months is the dose for treatment of osteoporosis; 120 SQ monthly is the dose for treatment of bone metastases) (203).

Clinical trials of zoledronic acid on BMD have shown benefits in men with prostate cancer receiving ADT and men with prostate cancer metastatic to bone (186). If treatment with zoledronic acid is not feasible due to prior side effects, cost, or other logistical issues, oral alendronate therapy is a reasonable alternative, based on a single randomized controlled trial in men with prostate cancer receiving ADT and on the more extensive data in men

with primary osteoporosis and women with postmenopausal osteoporosis.

4.0. Monitoring therapy

Recommendation

4.1. We suggest that clinicians monitor BMD by DXA at the spine and hip every 1 to 2 yr to assess the response to treatment. If BMD appears to reach a plateau, the frequency of BMD measurements may be reduced. (2|⊕⊕⊕○)

4.1. Evidence

Treatments for osteoporosis increase BMD but only modestly. Alendronate increased BMD of the spine and femoral neck by about 7 and 2.5%, respectively, after 2 yr (84). Similarly, risedronate increased BMD of the spine and femoral neck by about 6 and 1.5%, respectively, after 2 yr (86). Teriparatide (20 µg/d) increased BMD of the spine and femoral neck by about 6 and 1.5%, respectively, after 9 months (87). In hypogonadal men, testosterone enanthate therapy (200 mg every 2 wk) increased spine, trochanter, and total hip BMD by about 8, 5, and 3.5%, respectively, after 2 yr (163). Evidence to support the use BMD for monitoring treatment response is weak but suggests that it can be used for this purpose (187).

It has been suggested that serial BMD measurements in treated subjects may identify patients who are not adhering to treatment or patients who have an overlooked cause for bone loss. Although there is evidence that total hip BMD changes reflect medication compliance (185), use of serial BMD to identify subjects with secondary osteoporosis is anecdotal. It has also been suggested that serial BMD measurements may identify subjects who fail therapy. A retrospective study in men showed that BMD monitoring was associated with good compliance (188).

4.1. Remarks

There is uncertainty over what constitutes an adequate BMD response to treatment. Stable or increasing BMD appears to indicate a good response (187). One approach is to consider whether any BMD change exceeds that expected due to normal variation (the least significant change approach); this requires information about normal BMD variability. There are no formal reports of variability in men. In women with osteopenia, estimates of least significant change at the spine and hip made in research settings are between 3 and 5% in the short term (189). In all of the studies above, changes in spine BMD were greater than least significant change in most men treated for 2 yr, whereas changes in hip BMD were generally within the expected reproducibility error.

Whether change in BMD is a suitable surrogate for fracture risk reduction in men is unclear. In women, it has been estimated that BMD response to treatment accounts for 4-41% of the fracture risk reduction with treatments for osteoporosis (190, 191). The least significant change approach can also be used to identify significant bone loss in men who are untreated or to identify offset of effect after stopping treatment for osteoporosis. Because the expected rate of bone loss is slower in these situations than the rate of gain during treatment, it may be better to wait longer between measurements (*e.g.* 2-3 yr) in untreated men.

Assessing change in BMD on serial measurements requires careful attention to detail. Using the same machine and a trained technologist aware of the pitfalls of bone densitometry can mitigate these problems. The provider responsible for reporting the results also needs to be aware of these limitations. Degenerative change in the spine is particularly common in older men and may falsely give the impression of a gain in BMD.

Recommendation

4.2. We suggest that clinicians consider measuring a BTM at 3-6 months after initiation of treatment using a bone resorption marker (such as serum CTX or serum or urine NTX) for antiresorptive therapy and a bone formation marker (such as serum PINP) for anabolic therapy. (2|⊕⊕⊕○)

4.2. Evidence

Treatments for osteoporosis in men produce significant changes in BTMs. As in women, alendronate reduces BTMs by about 40-50% (84). Reductions in BTMs become maximal within several months and remain stable throughout therapy. Bone formation and resorption markers increase dramatically during the first 6-12 months of teriparatide therapy in men, after which they gradually decline toward baseline levels (150). BTM decline consistently when hypogonadal men receive physiological doses of testosterone, indicating that testosterone in physiological doses acts as an antiresorptive agent (159), perhaps through conversion to estradiol.

There is uncertainty over what constitutes an optimal BTM response to treatment. Decreasing bone resorption markers (for antiresorptive agents) or increasing bone formation markers (for anabolic agents) indicates a good response to treatment. Clinical experience suggests that inadequate response may be due to secondary osteoporosis or noncompliance with treatment. Extrapolating data from women to men, we assume that change in BTM relates to fracture risk reduction with treatments.

4.2. Remarks

Monitoring treatment with BTMs requires attention to detail. Because of diurnal variation (higher turnover in the morning) and effect of food (bone resorption

markers decrease after eating), samples for bone resorption markers (urinary NTX, and serum CTX) should be collected with the patient in the fasting state, in the morning. Because manual and automated assays give different results for the same analysis, changes can be compared only if the lab continues to use the same assay.

As with changes in BMD, changes in BTMs can be compared with the least significant change to determine whether observed changes exceed those likely to occur as a result of normal variation. This requires information about normal variability in BTMs, but for men, little is known. Variability appears similar for bone resorption markers (such as urinary deoxypyridinoline, NTX, and CTX) for men and women (192). In women with osteopenia, estimates of least significant change for bone alkaline phosphatase (b-ALP) activity and urinary NTX made in research settings are between 14% (for b-ALP) and 37% (for urinary NTX) in the short term (192). Thus, in all of the studies above, in more than half of men receiving standard treatments for 1-2 yr, changes in BTMs would appear to exceed the least significant change, and patients would be considered to be “responders” using these markers. The response of BTMs could be identified as early as within 3 months of starting treatment. Newer markers have been developed and evaluated for treatment response in women, including serum PINP and CTX (193). They have performed well in studies of drugs such as alendronate (194) and teriparatide (195).

Evidence that change in BTM is a suitable surrogate for fracture risk reduction in men is lacking. In women, it has been estimated that BTM response to treatment may account for 30-75% of the fracture risk reduction with standard treatments for osteoporosis (196, 197, 198, 199, 200). Also, the magnitude of the BTM response has been shown to be associated

with the level of compliance (201).

Some experts recommend measuring a BTM before and 3-6 months after starting treatment. Because there have only been publications on the association of BTMs and fracture risk reduction in women (and not in men), there is some disagreement among experts regarding this issue. Urine NTX or serum CTX can be used to monitor antiresorptive treatment; PINP or b-ALP can be used to monitor anabolic treatment. If the change in markers exceeds the least significant change (~40%; see 4.2. Remarks), then one goal has been met. With women, a low risk of fractures on treatment is associated with BTMs that are below the median of the reference interval for young women (196); this could be a target for men, but it has not yet been studied. If markers do not change, there are several options, including questioning the patient about compliance with medication, considering causes of secondary osteoporosis, or changing the medication or its route of administration.

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General



29

A 46-year-old Diabetic Man with Acute-Onset Right Thigh Pain

Armin Rashidi, MD, and Otarod Bahrani, MD

A 46-year-old man with a history of long-standing type 2 diabetes, hypertension, chronic atrial fibrillation, hemodialysis-requiring end-stage renal disease, and left below-the-knee amputation due to severe peripheral arterial disease presented with a 2-day history of atraumatic, acute-onset and then progressively worsening right anteromedial thigh pain, which was constant, aching, and aggravated with motion. He was an ex-smoker and a social drinker, and he denied use of illicit drugs. Medications included sitagliptin, amlodipine, metoprolol, lisinopril, aspirin, simvastatin, erythropoietin, and warfarin. Physical examination was remarkable for weak distal pulses and severe tenderness, erythema, and edema of the affected thigh without paresthesia or focal weakness. He had a normocytic normochromic anemia without leukocytosis, serum creatinine of 12.4 mg/dl, normal alanine and aspartate aminotransferases, normal thyroid function, creatine kinase of 228 U/liter (normal range, 30-200), and aldolase of 13.9 U/liter (normal range, 1.2-7.6). Blood cultures and tests for autoimmune myositis were negative. Magnetic resonance imaging (MRI) showed extensive edema through the entire extent of the vastus medialis (Figure 29-1).

1. THE MOST LIKELY DIAGNOSIS IS:

- Autoimmune dermatomyositis/polymyositis
- Soft tissue sarcoma
- Primary muscle lymphoma
- Diabetic myonecrosis
- Necrotizing fasciitis

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- High-dose systemic corticosteroids
- Surgical debridement
- Pain control with analgesics
- Muscle biopsy
- c or d

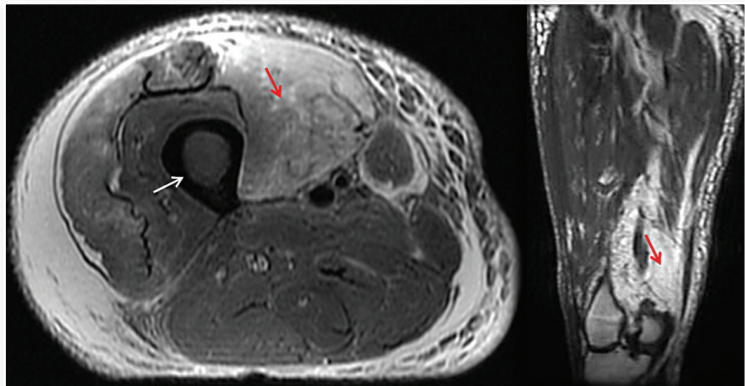


FIG 29-1: T2-weighted magnetic resonance image showing extensive edema in the vastus medialis muscle belly (red arrows). The femur is indicated by the white arrow.

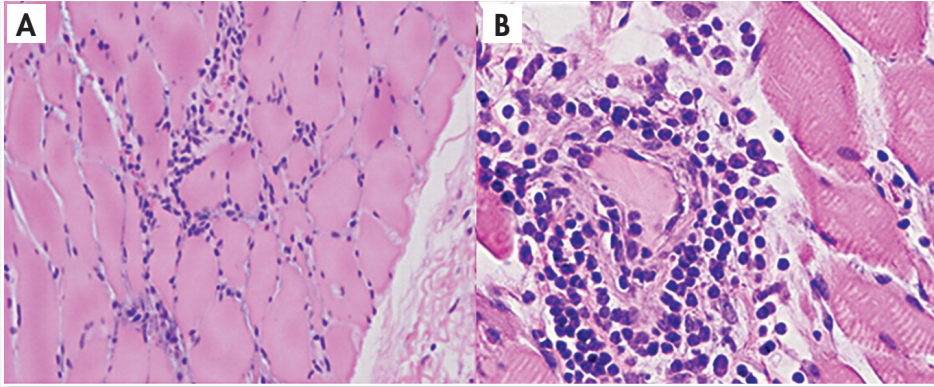


FIG 29-2: **A**, Histopathological examination shows perivascular and endomysial mononuclear infiltrate (hematoxylin and eosin; x200). **B**, Lymphohistiocytic inflammatory infiltrate surrounding a necrotic myofiber (hematoxylin and eosin; x400)

A muscle biopsy was performed, which showed muscle fibers undergoing active necrosis with extensive perivascular and endomysial lymphohistiocytic infiltrate (Figure 29-2).

3. YOUR INTERPRETATION OF THE HISTOPATHOLOGIC FINDINGS:

- a. Diabetic myonecrosis
- b. Primary muscle lymphoma
- c. Soft tissue sarcoma
- d. Pyomyositis/soft tissue abscess
- e. Autoimmune polymyositis

Diagnosis

Diabetic Myonecrosis.

Discussion

Diabetic myonecrosis, first described by Angervall and Stener in 1965 (1), is a rare complication of long-standing, poorly controlled diabetes with advanced microvasculopathy and presents most commonly with acute pain and swelling of the thigh (2). Other reported risk factors are antiphospholipid antibodies (3) and cirrhosis (4), and upper extremity involvement is extremely rare (2). Differential diagnosis includes pyomyositis, primary muscle lymphoma/sarcoma, necrotizing fasciitis, soft tissue

abscesses, deep vein thrombosis, dermatomyositis, focal/proliferative/nodular myositis, and cellulitis (2). Pathogenesis involves muscle infarction due to arteriosclerosis or diabetic microangiopathy (5). The diagnosis is often challenging due to the broad list of differential diagnoses and limited utility of routine laboratory tests. MRI is the diagnostic modality of choice. The characteristic findings on MRI are hyperintense areas in T2- and isointense or hypointense areas on T1-weighted images (6). Ultrasound and computed tomography scan findings are less specific (2, 7). Because of potential complications (*e.g.* delayed recovery), muscle biopsy is not routinely recommended except in the most challenging cases (2), and surgery only prolongs recovery (8). Diabetic myonecrosis is self-limited and usually resolves within a few weeks with conservative measures. However, it recurs in about half of patients (2) and predicts a poor long-term prognosis. Most patients with diabetic myonecrosis die within 5 years of diagnosis (9).

Once the diagnosis was established, our patient was discharged on analgesics. His symptoms resolved in a few weeks, and on a follow up visit about a year later, he was being evaluated for renal transplantation.

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Answers:

Question 1. d

Question 2. e

Question 3. a

A 60-year-old Man with a 12-year History of Soft, Progressively Swelling Masses in the Neck and Upper Back

Nai-Cheng Yeh, MD, and Kai-Jen Tien, MD

A 60-year-old Han Chinese man with a body mass index of 19.3 kg/m² presented with a 12-year history of soft, progressively swelling masses in the neck and upper back. He had abstained from alcohol for the previous 5 years. Nine years prior, the patient was diagnosed with diabetes mellitus (DM) and dyslipidemia. His family history was unremarkable. Concurrent with many years of poorly controlled DM, the patient's limbs and abdomen were relatively thin and atrophied. The patient showed no signs of moon facies, paper skin, hirsutism, or purple striae.

Laboratory results revealed a total cholesterol level of 319 mg/dL, low-density lipoprotein cholesterol level of 218 mg/dL, high-density lipoprotein cholesterol level of 43 mg/dL, triglyceride level of 286 mg/dL, and an HbA1c of 11.0%. Thyroid function and cortisol were within normal limits. Magnetic resonance imaging (MRI) revealed

diffuse, nonencapsulated fatty deposits in the subcutaneous and deeper fascial compartments of the neck, upper trunk, and upper back (Figure 30-1, panels A and B).

1. THE MOST LIKELY DIAGNOSIS IS:

- Cushing syndrome
- Congenital generalized lipodystrophy
- Multiple symmetric lipomatosis
- SHORT syndrome
- Familial partial lipodystrophy

2. YOUR NEXT STEP IN MANAGEMENT WOULD BE:

- Insulin to control DM
- Control hyperlipidemia with HMG-CoA reductase inhibitor
- Screening polyneuropathy
- Consider surgical intervention if obstructive sleep apnea is noted
- All of the above

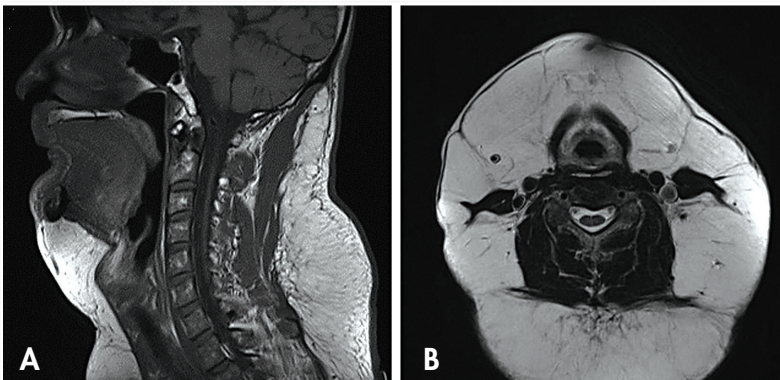


FIG. 30-1. T1-weighted MRI scan of patient showing massive fatty deposits in sagittal (A) and axial view (B).

Diagnosis

Madelung's Disease.

Discussion

Madelung's disease is a rare condition characterized by a symmetrical pattern of massive fatty deposits. The condition is also known as benign or multiple symmetric lipomatosis, or the Launois–Bensaude syndrome. Two types of Madelung's disease have been described. In type 1, fat accumulates around the neck and the nape of the neck, shoulders, upper arms, and upper back. In type 2, lipomas are distributed over much of the body, including the hips and thighs. Fatty deposits rarely extend to the lower limbs, mediastinum, and larynx in either type. Although the pathophysiology remains elusive, Madelung's disease may be caused by a local defect in catecholamine-induced lipolysis. Most patients have a history of chronic alcoholism. Mediterranean men appear to be at highest risk of acquiring the condition, while the disease is remarkably rare in Asian populations. The diagnosis of Madelung's disease is primarily based on physical examination, clinical history, and imaging studies. DM, lipid disorders, liver disease, and hypo-thyroidism are frequent comorbidities. Neuropathy, including sensory, motor, and autonomic polyneuropathy, is observed in about 85% of patients and the latter is associated with sudden cardiac death.

Subsequent Follow-up on the Patient:

The patient had expired in March of 2012 due to cardiac arrest.

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Answers:

Question 1. c

Question 2. e

Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline

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Objective: *The aim was to formulate practice guidelines on the management of hyperglycemia in hospitalized patients in the non-critical care setting.*

Participants: *The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, six additional experts, and a methodologist.*

Evidence: *This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.*

Consensus Process: *One group meeting, several conference calls, and e-mail communications enabled consensus. Endocrine Society members, American Diabetes Association, American Heart Association, American Association of Diabetes Educators, European Society of Endocrinology,*

and the Society of Hospital Medicine reviewed and commented on preliminary drafts of this guideline.

Conclusion: *Hyperglycemia is a common, serious, and costly health care problem in hospitalized patients. Observational and randomized controlled studies indicate that improvement in glycemic control results in lower rates of hospital complications in general medicine and surgery patients. Implementing a standardized sc insulin order set promoting the use of scheduled basal and nutritional insulin therapy is a key intervention in the inpatient management of diabetes. We provide recommendations for practical, achievable, and safe glycemic targets and describe protocols, procedures, and system improvements required to facilitate the achievement of glycemic goals in patients with hyperglycemia and diabetes admitted in non-critical care settings. (*J Clin Endocrinol Metab* 97:16-38, 2012)*

Summary of Recommendations

1.0 Diagnosis and recognition of hyperglycemia and diabetes in the hospital setting

1.1 We recommend that clinicians assess all patients admitted to the hospital for a history of diabetes. When present, this diagnosis should be clearly identified in

the medical record. (1|⊕○○○)

1.2 We suggest that all patients, independent of a prior diagnosis of diabetes, have laboratory blood glucose (BG) testing table. (2|⊕○○○)

1.3 We recommend that patients without a history of diabetes with BG greater than 7.8 mmol/liter (140 mg/dl) be monitored with bedside point of care (POC) testing

for at least 24 to 48 h. Those with BG greater than 7.8 mmol/liter require ongoing POC testing with appropriate therapeutic intervention. (1|⊕○○○)

1.4 We recommend that in previously normoglycemic patients receiving therapies associated with hyperglycemia, such as corticosteroids or octreotide, enteral nutrition (EN) and parenteral nutrition (PN) be monitored with bedside POC testing for at least 24 to 48 h after initiation of these therapies. Those with BG measures greater than 7.8 mmol/liter (140 mg/dl) require ongoing POC testing with appropriate therapeutic intervention. (1|⊕○○○)

1.5 We recommend that all inpatients with known diabetes or with hyperglycemia (>7.8 mmol/liter) be assessed with a hemoglobin A1C (HbA1C) level if this has not been performed in the preceding 2-3 months. (1|⊕○○○)

2.0 Monitoring glycemia in the non-critical care setting

2.1 We recommend bedside capillary POC testing as the preferred method for guiding ongoing glycemic management of individual patients. (1|⊕⊕○○)

2.2 We recommend the use of BG monitoring devices that have demonstrated accuracy of use in acutely ill patients. (1|⊕○○○)

2.3 We recommend that timing of glucose measures match the patient's nutritional intake and medication regimen. (1|⊕○○○)

2.4 We suggest the following schedules for POC testing: before meals and at bedtime in patients who are eating, or every 4-6 h in patients who are NPO [receiving nothing by mouth (nil per os)] or receiving continuous enteral feeding. (2|⊕○○○)

3.0 Glycemic targets in the non-critical care setting

3.1 We recommend a premeal glucose target of less than 140 mg/dl (7.8 mmol/liter) and a random BG of less than 180 mg/dl (10.0 mmol/liter) for the majority of hospitalized patients with non-critical illness. (1|⊕⊕○○)

3.2 We suggest that glycemic targets be modified according to clinical status. For patients who are able to achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable. For patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia, a higher target range (BG < 11.1 mmol/liter or 200 mg/dl) –^omay be reasonable. (2|⊕○○○)

3.3 For avoidance of hypoglycemia, we suggest that antidiabetic therapy be reassessed when BG values fall below 5.6 mmol/liter (100 mg/dl). Modification of glucose-lowering treatment is usually necessary when BG values are below 3.9 mmol/liter (70 mg/dl). (2|⊕○○○)

4.0 Management of hyperglycemia in the non-critical care setting

4.1 Medical nutrition therapy (MNT)

4.1.1 We recommend that MNT be included as a component of the glycemic management program for all hospitalized patients with diabetes and hyperglycemia. (1|⊕○○○)

4.1.2 We suggest that providing meals with a consistent amount of carbohydrate at each meal can be useful in coordinating doses of rapid-acting insulin to carbohydrate ingestion. (2|⊕○○○)

4.2 Transition from home to hospital

4.2.1 We recommend insulin therapy as the preferred method for achieving glycemic control in hospitalized patients with hyperglycemia. (1|⊕⊕○○)

4.2.2 We suggest the discontinuation of oral hypoglycemic agents and initiation of insulin therapy for the majority of patients with type 2 diabetes at the time of hospital admission for an acute illness. (2|⊕○○○)

4.2.3 We suggest that patients treated with insulin before admission have their insulin dose modified according to clinical status as a way of reducing the risk for hypoglycemia and hyperglycemia. (2|⊕○○○)

4.3 Pharmacological therapy

4.3.1 We recommend that all patients with diabetes treated with insulin at home be treated with a scheduled sc insulin regimen in the hospital. (1|⊕⊕⊕⊕)

4.3.2 We suggest that prolonged use of sliding scale insulin (SSI) therapy be avoided as the sole method for glycemic control in hyperglycemic patients with history of diabetes during hospitalization. (2|⊕○○○)

4.3.3 We recommend that scheduled sc insulin therapy consist of basal or intermediate-acting insulin given once or twice a day in combination with rapid- or short-acting insulin administered before meals in patients who are eating. (1|⊕⊕⊕○)

4.3.4 We suggest that correction insulin be included as a component of a scheduled insulin regimen for treatment of BG values above the desired target. (2|⊕○○○)

4.4 Transition from hospital to home

4.4.1 We suggest reinstatement of preadmission insulin regimen or oral and non-insulin injectable antidiabetic drugs at discharge for patients with acceptable preadmission glycemic control and without a contraindication to their continued use. (2|⊕○○○)

4.4.2 We suggest that initiation of insulin administration be instituted at least one day before discharge to allow assessment of the efficacy and safety of

this transition. (2|⊕○○○)

4.4.3 We recommend that patients and their family or caregivers receive both written and oral instructions regarding their glycemic management regimen at the time of hospital discharge. These instructions need to be clearly written in a manner that is understandable to the person who will administer these medications. (1|⊕⊕○○)

5.0 Special Situations

5.1 Transition from iv continuous insulin infusion (CII) to sc insulin therapy

5.1.1 We recommend that all patients with type 1 and type 2 diabetes be transitioned to scheduled sc insulin therapy at least 1-2 h before discontinuation of CII. (1|⊕⊕⊕⊕)

5.1.2 We recommend that sc insulin be administered before discontinuation of CII for patients without a history of diabetes who have hyperglycemia requiring more than 2 U/h. (1|⊕⊕⊕⊕)

5.1.3 We recommend POC testing with daily adjustment of the insulin regimen after discontinuation of CII. (1|⊕⊕⊕○)

5.2 Patients receiving EN or PN

5.2.1 We recommend that POC testing be initiated for patients with or without a history of diabetes receiving EN and PN. (1|⊕⊕⊕⊕)

5.2.2 We suggest that POC testing can be discontinued in patients without a prior history of diabetes if BG values are less than 7.8 mmol/liter (140 mg/dl) without insulin therapy for 24-48 h after achievement of desired caloric intake. (2|⊕○○○)

5.2.3 We suggest that scheduled insulin therapy be initiated in patients with and without known diabetes who have hyperglycemia, defined as BG greater than 7.8 mmol/liter (140 mg/dl), and who demonstrate a persistent requirement

(i.e. >12 to 24 h) for correction insulin. (2|⊕○○○)

5.3 Perioperative BG control

5.3.1 We recommend that all patients with type 1 diabetes who undergo minor or major surgical procedures receive either CII or sc basal insulin with bolus insulin as required to prevent hyperglycemia during the perioperative period. (1|⊕⊕⊕⊕)

5.3.2 We recommend discontinuation of oral and non-insulin injectable antidiabetic agents before surgery with initiation of insulin therapy in those who develop hyperglycemia during the perioperative period for patients with diabetes. (1|⊕○○○)

5.3.3 When instituting sc insulin therapy in the postsurgical setting, we recommend that basal (for patients who are NPO) or basal bolus (for patients who are eating) insulin therapy be instituted as the preferred approach. (1|⊕⊕⊕○)

5.4 Glucocorticoid-induced diabetes

5.4.1 We recommend that bedside POC testing be initiated for patients with or without a history of diabetes receiving glucocorticoid therapy. (1|⊕⊕⊕○)

5.4.2 We suggest that POC testing can be discontinued in nondiabetic patients if all BG results are below 7.8 mmol/liter (140 mg/dl) without insulin therapy for a period of at least 24-48 h. (2|⊕○○○)

5.4.3 We recommend that insulin therapy be initiated for patients with persistent hyperglycemia while receiving glucocorticoid therapy. (1|⊕⊕○○)

5.4.4 We suggest CII as an alternative to sc insulin therapy for patients with severe and persistent elevations in BG despite use of scheduled basal bolus sc insulin. (2|⊕○○○)

6.0 Recognition and management of hypoglycemia in the hospital setting

6.1 We recommend that glucose management protocols with specific directions for hypoglycemia avoidance and hypoglycemia management be implemented in the hospital. (1|⊕○○○)

6.2 We recommend implementation of a standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol to prompt immediate therapy of any recognized hypoglycemia, defined as a BG below 3.9 mmol/liter (70 mg/dl). (1|⊕⊕○○)

6.3 We recommend implementation of a system for tracking frequency of hypoglycemic events with root cause analysis of events associated with potential for patient harm. (1|⊕⊕○○)

7.0 Implementation of a glycemic control program in the hospital

7.1 We recommend that hospitals provide administrative support for an interdisciplinary steering committee targeting a systems approach to improve care of inpatients with hyperglycemia and diabetes. (1|⊕⊕⊕○)

7.2 We recommend that each institution establish a uniform method of collecting and evaluating POC testing data and insulin use information as a way of monitoring the safety and efficacy of the glycemic control program. (1|⊕○○○)

7.3 We recommend that institutions provide accurate devices for glucose measurement at the bedside with ongoing staff competency assessments. (1|⊕○○○)

8.0 Patient and professional education

8.1 We recommend diabetes self-management education targeting short-term goals that focus on survival skills: basic meal planning, medication administration, BG monitoring, and hypoglycemia and hyperglycemia detection, treatment, and prevention. (1|⊕○○○)

8.2 We recommend identifying resources in the community to which patients can be referred for continuing diabetes self-management education after discharge. (1|⊕○○○)

8.3 We recommend ongoing staff education to update diabetes knowledge, as well as targeted staff education whenever an adverse event related to diabetes management occurs. (1|⊕○○○)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the management of hyperglycemia in hospitalized patients in a non-critical care setting a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop some of the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. *Cross-filled circles* indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations

will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that panelists considered in making the recommendation; in some instances, there are remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

The prevalence of diabetes has reached epidemic proportions in the United States. The Centers for Disease Control and Prevention recently reported that 25.8 million people, or 8.3% of the population, have diabetes (3). Diabetes represents the seventh leading cause of death (4) and is the fourth leading comorbid condition among hospital discharges in the United States (5). Approximately one in four patients admitted to the hospital has a known diagnosis of diabetes (6, 7), and about 30% of patients with diabetes require two or more hospitalizations in any given year (7). The prevalence of diabetes is higher in elderly patients and residents of long-term-care facilities, in whom diabetes is reported in up to one third of adults aged 65-75 yr and in 40% of those older than 80 yr (8, 9).

The association between hyperglycemia in hospitalized patients (with or without diabetes) and increased risk for complications and mortality is well established (6, 10, 11, 12, 13, 14). This association is observed for both admission glucose and mean BG level during the hospital stay. Although most randomized controlled trials investigating

the impact of treating hyperglycemia on clinical outcomes have been performed in critically ill patients, there are extensive observational data supporting the importance of hyperglycemia management among non-critically ill patients admitted to general medicine and surgery services. In such patients, hyperglycemia is associated with prolonged hospital stay, increased incidence of infections, and more disability after hospital discharge and death (6, 15, 16, 17, 18, 19). This manuscript contains the consensus recommendations for the management of hyperglycemia in hospitalized patients in non-critical care settings by The Endocrine Society and other organizations of health care professionals involved in inpatient diabetes care, including the American Diabetes Association (ADA), American Heart Association, American Association of Diabetes Educators (AADE), European Society of Endocrinology, and the Society of Hospital Medicine. The central goal was to provide practical, achievable, and safe glycemic goals and to describe protocols, procedures, and system improvements needed to facilitate their implementation. This document is addressed to health care professionals, supporting staff, hospital administrators, and other stakeholders focused on improved management of hyperglycemia in inpatient settings.

1.0 Diagnosis and recognition of hyperglycemia and diabetes in the hospital setting

Recommendations

1.1 We recommend that clinicians assess all patients admitted to the hospital for a history of diabetes. When present, this diagnosis should be clearly identified in the medical record. (1|⊕⊕○○)

1.2 We suggest that all patients, independent of a prior diagnosis of

diabetes, have laboratory BG testing on admission. (2|⊕○○○)

1.3 We recommend that patients without a history of diabetes with BG greater than 7.8 mmol/liter (140 mg/dl) be monitored with bedside POC testing for at least 24 to 48 h. Those with BG greater than 7.8 mmol/liter require ongoing POC testing with appropriate therapeutic intervention. (1|⊕○○○)

1.4 We recommend that in previously normoglycemic patients receiving therapies associated with hyperglycemia, such as corticosteroids or octreotide, EN and PN be monitored with bedside POC testing for at least 24 to 48 h after initiation of these therapies. Those with BG measures greater than 7.8 mmol/liter (140 mg/dl) require ongoing POC testing with appropriate therapeutic intervention. (1|⊕○○○)

1.1-1.4 Evidence

In-hospital hyperglycemia is defined as any glucose value greater than 7.8 mmol/liter (140 mg/dl) (20, 21). Hyperglycemia occurs not only in patients with known diabetes but also in those with previously undiagnosed diabetes and others with “stress hyperglycemia” that may occur during an acute illness and that resolves by the time of discharge (20, 22, 23). Observational studies report that hyperglycemia is present in 32 to 38% of patients in community hospitals (6, 24), 41% of critically ill patients with acute coronary syndromes (13), 44% of patients with heart failure (13), and 80% of patients after cardiac surgery (25, 26). In these reports, approximately one third of non-intensive care unit (ICU) patients and approximately 80% of ICU patients had no history of diabetes before admission (6, 13, 27-30).

The ADA Clinical Practice Recommendations endorse the initiation of glucose monitoring for both those

with diabetes and those without a known history of diabetes who are receiving therapies associated with hyperglycemia (31). We agree with these recommendations but also suggest that initial glucose measurement on admission by the hospital laboratory is appropriate for all hospitalized patients, irrespective of the presence of preexisting diabetes history or exposure to obvious hyperglycemia inducers. The high prevalence of inpatient hyperglycemia with associated poor outcomes and the opportunity to diagnose new diabetes warrants this approach (6, 24, 32, 33). Because the duration of care is frequently brief in the inpatient setting, the assessment of glycemic control needs to be performed early in the hospital course. Bedside POC testing has advantages over laboratory venous glucose testing. POC testing at the “point of care” allows identification of patients who require initiation or modification of a glycemic management regimen (20, 21). POC monitoring has been demonstrated to be essential in guiding insulin administration toward achieving and maintaining desired glycemic goals as well as for recognizing hypoglycemic events (16, 21, 34, 35). Most currently used bedside glucose meters, although designed for capillary whole-blood testing, are calibrated to report results compatible to plasma, which allows for reliable comparison to the laboratory glucose test (16, 22, 36, 37).

1.1-1.4 Values and preferences

Our recommendations reflect consideration of the face validity of soliciting and communicating the diagnosis of diabetes or hyperglycemia to members of the care team. The risk-to-benefit of glucose testing and documenting a history of diabetes favors this approach despite the lack of randomized controlled trials.

Recommendation

1.5 We recommend that all inpatients with known diabetes or with hyperglycemia (>7.8 mmol/liter) be assessed with an HbA1C level if this has not been performed in the preceding 2-3 months. (1|⊕○○○)

1.5 Evidence

We support the ADA recommendation of using a laboratory measure of HbA1C both for the diagnosis of diabetes and for the identification of patients at risk for diabetes (31). The ADA recommendations indicate that patients with an HbA1C of 6.5% or higher can be identified as having diabetes, and patients with an HbA1C between 5.7 and 6.4% can be considered as being at risk for the development of diabetes (31).

Measurement of an HbA1C during periods of hospitalization provides the opportunity to identify patients with known diabetes who would benefit from intensification of their glycemic management regimen. In patients with newly recognized hyperglycemia, an HbA1C may help differentiate patients with previously undiagnosed diabetes from those with stress-induced hyperglycemia (32,38). It is important to note that there are no randomized trials demonstrating improved outcomes using HbA1C levels to assist in the diagnosis of diabetes in inpatients with new hyperglycemia or to assist in tailoring the glycemic management of inpatients with known diabetes. Our recommendations reflect consensus opinion and the practical utility of this strategy.

Clinicians must keep in mind that an HbA1C cutoff of 6.5% identifies fewer cases of undiagnosed diabetes than does a high fasting glucose (38). Several epidemiological studies have reported a low sensitivity (44 to 66%) but a high specificity (76 to 99%) for HbA1C greater

than 6.5% in an outpatient population (39, 40). Among hospitalized hyperglycemic patients, an HbA1C level above 6.0% was reported to be 100% specific and 57% sensitive for the diagnosis of diabetes, whereas an HbA1C below 5.2% effectively excluded a diagnosis of diabetes (41).

Glucose and HbA1C values, together with the medical history, can be used to tailor therapy and assist in discharge planning (42, 43). Discharge planning, education, and care transitions are discussed in more detail in Section 4.4. Briefly, the discharge plan optimally includes the diagnosis of diabetes (if present), recommendations for short- and long-term glucose control, follow-up care, a list of educational needs, and consideration of appropriate screening and treatment of diabetes comorbidities (30, 42, 44).

There are limitations to the use of an HbA1C for diagnosis of diabetes in an inpatient population. These include the relatively low diagnostic sensitivity and potential altered values in the presence of hemoglobinopathies (hemoglobin C or SC disease), high-dose salicylates, hemodialysis, blood transfusions, and iron deficiency anemia (45). When HbA1C is used for establishing a diagnosis of diabetes, analysis should be performed using a method certified by the National Glycohemoglobin Standardization Program (31), because POC HbA1C testing is not sufficiently accurate at this time to be diagnostic.

2.0 Monitoring glycemia in the non-critical care setting

Recommendations

2.1 We recommend bedside capillary POC testing as the preferred method for guiding ongoing glycemic management of individual patients. (1|⊕⊕○○)

2.2 We recommend the use of BG

monitoring devices that have demonstrated accuracy of use in acutely ill patients. (1|⊕○○○)

2.3 We recommend that timing of glucose measures match the patient's nutritional intake and medication regimen. (1|⊕○○○)

2.4 We suggest the following schedules for POC testing: before meals and at bedtime in patients who are eating, or every 4-6 h in patients who are NPO or receiving continuous enteral feeding. (2|⊕○○○)

2.1-2.4 Evidence

Matching the timing of POC testing with nutritional intake and the diabetes medication regimen in the hospital setting is consistent with recommendations for the outpatient setting. POC testing is usually performed four times daily: before meals and at bedtime for patients who are eating (16, 21). Premeal POC testing should be obtained as close to the time of the meal tray delivery as possible and no longer than 1 h before meals (46, 47, 48). For patients who are NPO or receiving continuous EN, POC testing is recommended every 4-6 h. More frequent glucose monitoring is indicated in patients treated with continuous iv insulin infusion (49, 50) or after a medication change that could alter glycemic control, *e.g.* corticosteroid use or abrupt discontinuation of EN or PN (48, 51, 52), or in patients with frequent episodes of hypoglycemia (16, 28).

Capillary BG data facilitate the ability to adjust insulin therapy based in part on calculation of total correction insulin doses over the preceding 24 h. Consistent sampling sites and methods of measurement should be used because glucose results can vary significantly when alternating between finger-stick and alternative sites, or between samples run in the laboratory vs. a POC testing device (53). As in the outpatient setting, erroneous

results can be obtained from finger-stick samples whenever the BG is rapidly rising or falling (53).

Quality control programs are essential to meet Food and Drug Administration (FDA) requirements and to maintain the safety, accuracy, and reliability of BG testing (21). The FDA requires that the accuracy of glucose analyzers in the central lab be within 10% of the real value, whereas POC meters are considered acceptable within 20% (21,37); however, recent reports have advocated improvement or tightening of POC meter accuracy standards (37). Using meters with bar coding capability has been shown to reduce data entry errors in medical records (37). Capillary BG values can vary between POC meters, especially at high or low hemoglobin levels, low tissue perfusion, and with some extraneous substances (36, 53). Although patients can bring their own glucose meter device to the hospital, personal meters should not be used for documentation or for treatment of hyperglycemia. Hospital meters should follow regulatory and licensing quality control procedures to ensure accuracy and reliability of results. Hospital systems with data management programs can transfer results into electronic records to allow evaluation of hospital-wide patterns of glycemic control (54).

Health care workers should keep in mind that the accuracy of most hand-held glucose meters is far from optimal (53). There are potential inaccuracies of POC testing including intrinsic issues with the technology and variability between different lots of test strips, inadequate sampling site, varying hemoglobin concentrations, and other interfering hematological factors in acutely ill patients (37, 55, 56). One study from the Centers for Disease Control (CDC) of five commonly used glucose meters showed mean differences from a central laboratory

method to be as high as 32% and a coefficient of variation of 6 to 11% with a single trained medical technologist (37).

Recent studies suggest that continuous BG monitoring devices may be helpful in reducing incidences of severe hypoglycemia in acute care (57, 58). More studies, however, are needed to determine the accuracy and reliability of continuous BG monitoring devices in hospitalized patients. Although promising, continuous BG monitoring has not been adequately tested in acute care and therefore cannot be recommended for hospitalized patients at this time.

3.0 Glycemic targets in the non-critical care setting

Recommendations

3.1 We recommend a premeal glucose target of less than 140 mg/dl (7.8 mmol/liter) and a random BG of less than 180 mg/dl (10.0 mmol/liter) for the majority of hospitalized patients with non-critical illness. (1|⊕⊕○○)

3.2 We suggest that glycemic targets be modified according to clinical status. For patients who are able to achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable. For patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia, a higher target range (BG < 11.1 mmol/liter or 200 mg/dl) may be reasonable. (2|⊕○○○)

3.3 For avoidance of hypoglycemia, we suggest that antidiabetic therapy be reassessed when BG values fall below 5.6 mmol/liter (100 mg/dl). Modification of glucose-lowering treatment is usually necessary when BG values are below 3.9 mmol/liter (70 mg/dl). (2|⊕○○○)

3.1-3.3 Evidence

The Task Force commissioned systematic reviews and meta-analyses of observational

and randomized trials to evaluate the effect of intensive glycemic control on morbidity and mortality in patients hospitalized in non-critical care settings. Data were available for analysis from nine randomized controlled trials and 10 observational studies (59). Intensive glycemic control was associated with reduction in the risk of infection (relative risk, 0.41; 95% confidence interval, 0.21-0.77). There was a trend for increased risk of hypoglycemia (relative risk, 1.58; 95% confidence interval, 0.97-2.57) that was most common in surgical studies. There was no significant effect on death, myocardial infarction, or stroke. The definition of “intensive control” varied across studies but was generally consistent with BG targets in the ADA/ American Association of Clinical Endocrinologists Practice Guideline (20, 21). That guideline recommended a premeal glucose of less than 140 mg/dl (7.8 mmol/liter) and a random BG of less than 10.0 mmol/liter (180 mg/dl) for the majority of non-critically ill patients treated with insulin (21). To avoid hypoglycemia (<3.9 mmol/liter), the total basal and prandial insulin dose should be reduced if glucose levels are between 3.9 mmol/liter and 5.6 mmol/liter (70-100 mg/dl). In contrast, higher glucose ranges may be acceptable in terminally ill patients or in patients with severe comorbidities, as well as in those in patient-care settings where frequent glucose monitoring or close nursing supervision is not feasible (20,21, 31). In such patients, however, it is prudent to maintain a reasonable degree of glycemic control (BG < 11.1 mmol/liter or 200 mg/dl) as a way of avoiding symptomatic hyperglycemia.

4.0 Management of hyperglycemia in the non-critical care setting

Recommendations

4.1 Medical nutrition therapy

4.1.1 We recommend that MNT be

included as a component of the glycemic management program for all hospitalized patients with diabetes and hyperglycemia. (1|⊕○○○)

4.1.2 We suggest that providing meals with a consistent amount of carbohydrate at each meal can be useful in coordinating doses of rapid-acting insulin to carbohydrate ingestion. (2|⊕○○○)

4.1.1-4.1.2 Evidence

MNT is an essential component of inpatient glycemic management programs. MNT is defined as a process of nutritional assessment and individualized meal planning in consultation with a nutrition professional (31, 60). The goals of inpatient MNT are to optimize glycemic control, to provide adequate calories to meet metabolic demands, and to create a discharge plan for follow-up care (16, 60, 61, 62, 63, 64). Although the majority of non-critically ill hospitalized patients receive nutrition support as three discrete meals with or without scheduled snacks each day, some require EN or PN support (see Section 5).

Lack of attention to MNT in the hospital contributes to unfavorable changes in BG (28, 46, 65). Nutrition requirements often differ in the home vs. the hospital setting. The types of food may change or the route of administration may differ, *e.g.* enteral or parenteral feedings may be used instead of solid foods. Nutritional management in the hospital is further complicated by hospital routines characterized by abrupt discontinuation of meals in preparation for diagnostic studies or procedures, variability in appetite due to the underlying illness, limitations in food selections, and poor coordination between insulin administration and meal delivery that creates difficulties in predicting the efficacy of glycemic management strategies (46).

A consistent carbohydrate meal-

planning system may help to facilitate glycemic control in the hospital setting (16,46). The system is based on the total amount of carbohydrate offered rather than on specific calorie content at each meal. Most patients receive a total of 1500-2000 calories per day, with a range of 12-15 carbohydrate servings. The majority of carbohydrate foods should be whole grains, fruits, vegetables, and low-fat milk, with restricted amounts of sucrose-containing foods (66, 67). An advantage to the use of consistent carbohydrate meal plans is that they facilitate matching the prandial insulin dose to the amount of carbohydrate consumed (16). Another advantage of a consistent carbohydrate diet is the ability to reinforce education regarding meal planning for many persons with diabetes. Although there are no randomized controlled studies comparing different inpatient nutritional strategies, one study conducted during a transition from consistent carbohydrate to patient-controlled meal plans found similar glycemic measures, with a trend toward less hypoglycemia with a consistent carbohydrate plan (16, 61, 68).

4.2 Transition from home to hospital

Recommendations

4.2.1 We recommend insulin therapy as the preferred method for achieving glycemic control in hospitalized patients with hyperglycemia. (1|⊕⊕○○)

4.2.2 We suggest the discontinuation of oral hypoglycemic agents and initiation of insulin therapy for the majority of patients with type 2 diabetes at the time of hospital admission for an acute illness. (2|⊕○○○)

4.2.3 We suggest that patients treated with insulin before admission have their insulin dose modified according to clinical status as a way of reducing the risk for hypoglycemia and hyperglycemia. (2|⊕○○○)

4.2.1-4.2.3 Evidence

Patients with type 1 diabetes have an absolute requirement for insulin therapy and require treatment with basal bolus insulin regimens to avoid severe hyperglycemia and diabetic ketoacidosis. Many patients with type 2 diabetes receiving insulin therapy as basal bolus or multiple daily injections before admission are at risk for severe hyperglycemia in the hospital if insulin therapy is discontinued. Assessment of the need for modification of the home insulin regimen is important because requirements vary according to clinical stressors, reason for admission, altered caloric intake or physical activity, and changes in medical regimens that can affect glycemic levels. There are patients who require reductions in insulin doses to avoid hypoglycemia, whereas others require higher insulin doses to avoid or treat uncontrolled hyperglycemia (69).

Preadmission diabetes therapy in patients with type 2 diabetes can include diet, oral agents, non-insulin injectable medications, insulin, or combinations of these therapies. Careful assessment of the appropriateness of preadmission diabetes medications is required at the time of hospital admission. The use of oral and other non-insulin therapies presents unique challenges in the hospital setting because there are frequent contraindications to their use in many inpatient situations (sepsis, NPO status, iv contrast dye, pancreatic disorders, renal failure, *etc.*) (21). Selected patients may be candidates for continuation of previously prescribed oral hypoglycemic therapy in the hospital. Patient criteria guiding the continued use of these agents include those who are clinically stable and eating regular meals and who have no contraindications to the use of these agents. Each of the available classes of oral antidiabetic agents possesses characteristics that limit their desirability for inpatient use. Sulfonylureas

are long-acting insulin secretagogues that can cause severe and prolonged hypoglycemia, particularly in the elderly, in patients with impaired renal function, and in those with poor nutritional intake (70). There are no data on hospital use of the short-acting insulin secretagogues repaglinide and nateglinide; however, the risk of hypoglycemia is similar to that with sulfonylureas, suggesting the need for caution in the inpatient setting. Metformin must be discontinued in patients with decompensated congestive heart failure, renal insufficiency, hypoperfusion, or chronic pulmonary disease (71, 72) and in patients who are at risk of developing renal failure and lactic acidosis, such as may occur with the administration of iv contrast dye or surgery (73). Thiazolidinediones (TZD) can take several weeks for the full hypoglycemic effect, thus limiting the usefulness of these agents for achieving glycemic control in the hospital. These agents are contraindicated in patients with congestive heart failure, hemodynamic instability, or evidence of hepatic dysfunction. Dipeptidyl peptidase IV inhibitors delay the enzymatic inactivation of endogenously secreted glucagon-like peptide-1, acting primarily to reduce postprandial glycemic excursions. These agents are less useful in patients who are not eating or have reduced oral intake.

Conversion to basal bolus insulin therapy based on POC BG results is both safe and efficacious in the management of hyperglycemic patients with type 2 diabetes (33, 35, 69, 74). Patients with BG levels above 140 mg/dl (7.8 mmol/liter) who are eating usual meals can have basal bolus insulin therapy initiated at a total daily dose based on body weight (33, 35, 75). Patients who are NPO can receive basal insulin alone with correction doses with a rapid-acting analog every 4 h or with regular insulin every 6 h (16, 33, 76, 77). An example of basal bolus protocol

and correctional dose protocol is provided in Table 1 (33, 35); however, many successful insulin regimens have been reported in the literature (16, 28, 78,79).

The practice of discontinuing diabetes medications and writing orders for SSI at the time of hospital admission results in undesirable levels of hypoglycemia and hyperglycemia (80, 81, 82). In one study (81), the risk for hyperglycemia (BG > 11.1 mmol/liter or 200 mg/dl) increased 3-fold in patients placed on aggressive sliding-scale regimens.

4.2.1-4.2.3 Values and preferences

The recommendation to discontinue agents other than insulin at the time of hospitalization is based in part on the fact that contraindications to the use of these agents are present in a high percentage of patients on admission or during hospitalization (71, 73). In addition, the use of oral agents to treat newly recognized hyperglycemia can result in delays in achieving desired glycemic targets, with the potential to adversely affect patient outcomes.

4.2.1-4.2.3 Remarks

Hospitals are encouraged to:

- Provide prompts to alert care providers that a patient is receiving an oral antidiabetic agent that may be contraindicated for use in the inpatient setting (*e.g.* sulfonylureas or metformin in patients with renal insufficiency or TZD in patients with heart failure).
- Implement educational order sets that guide appropriate use of scheduled insulin therapy in the hospital (16, 46, 77, 78, 83).

4.3 Pharmacological therapy

Recommendations

4.3.1 We recommend that all patients with diabetes treated with insulin at home be

treated with a scheduled sc insulin regimen in the hospital. (1|⊕⊕⊕⊕)

4.3.2 We suggest that prolonged use of SSI therapy be avoided as the sole method for glycemic control in hyperglycemic patients with history of diabetes during hospitalization. (2|⊕○○○)

4.3.3 We recommend that scheduled sc insulin therapy consist of basal or intermediate-acting insulin given once or twice a day in combination with rapid- or short-acting insulin administered before meals in patients who are eating. (1|⊕⊕⊕○)

4.3.4 We suggest that correction insulin be included as a component of a scheduled insulin regimen for treatment of BG values above the desired target. (2|⊕○○○)

4.3.1-4.3.4 Evidence

The preferred sc insulin regimen for inpatient glycemic management includes two different insulin preparations administered as basal bolus insulin therapy, frequently in combination with a correction insulin scale. The basal component requires administration of an intermediate- or long-acting insulin preparation once or twice a day. The bolus or prandial component requires the administration of short- or rapid-acting insulin administered in coordination with meals or nutrient delivery (Table 1). Correction insulin refers to the administration of supplemental doses of short- or rapid-acting insulin together with the usual dose of bolus insulin for BG above the target range. For patients who are not eating, basal insulin is continued once daily (glargine or detemir) or twice daily [detemir/neutral protamine Hagedorn (NPH)] plus correction doses of a rapid insulin analog (aspart, lispro, glulisine) or regular insulin every 4- to 6-h interval as needed. Correction-dose insulin should not be confused with “sliding scale insulin,” which usually refers to a set amount of

insulin administered for hyperglycemia without regard to the timing of the food, the presence or absence of preexisting insulin administration, or even individualization of the patient’s sensitivity to insulin. Correction insulin is customized to match the insulin sensitivity for each patient. Most standardized order sets for sc insulin provide several different correction-dose scales to choose from, depending on the patient’s weight or total daily insulin requirement.

The safety of scheduled basal bolus insulin in patients with either newly recognized hyperglycemia or type 2 diabetes has been demonstrated in several studies of non-critically ill hospitalized patients (33,35,69,74). In one study (35), 130 insulin-naive patients with type 2 diabetes who had glucose levels above 10 mmol/liter (180 mg/dl) were randomized to receive basal bolus insulin with glargine and glulisine insulin or SSI alone. Those in the basal bolus group achieved mean glucose levels of less than 10 mmol/liter (180 mg/dl) by day 2 and of less than 8.8 mmol/liter (160 mg/dl) by day 4 with no increase in hypoglycemia (35). Among patients randomized to SSI alone, 14% required rescue therapy with basal bolus insulin due to persistent BG above 13.3 mmol/liter (240 mg/dl). A second multicenter study compared two different basal bolus insulin regimens (detemir plus aspart vs. NPH plus regular) in 130 nonsurgical patients with type 2 diabetes, of whom 56% were receiving insulin therapy before hospitalization (69). There were no group differences in the levels of glycemic control achieved or in the frequency of hypoglycemia, which occurred in approximately 30% of patients in each group. The majority of the hypoglycemic events occurred in patients treated with insulin before admission who were continued on the same insulin dose at the time of randomization, a

TABLE 1. Example of a basal bolus insulin regimen for the management of non-critically ill patients with type 2 diabetes

A. Basal insulin orders

- Discontinue oral diabetes drugs and non-insulin injectable diabetes medications upon hospital admission.
- Starting insulin: calculate the total daily dose as follows:
 - 0.2 to 0.3 U/kg of body weight in patients: aged >70 yr and/or glomerular filtration rate less than 60 ml/min.
 - 0.4 U/kg of body weight per day for patients not meeting the criteria above who have BG concentrations of 7.8-11.1 mmol/liter (140-200 mg/dl).
 - 0.5 U/kg of body weight per day for patients not meeting the criteria above when BG concentration is 11.2-22.2 mmol/liter (201-400 mg/dl).
- Distribute total calculated dose as approximately 50% basal insulin and 50% nutritional insulin.
- Give basal insulin once (glargine/detemir) or twice (detemir/NPH) daily, at the same time each day.
- Give rapid-acting (prandial) insulin in three equally divided doses before each meal. Hold prandial insulin if patient is not able to eat.
- Adjust insulin dose(s) according to the results of bedside BG measurements.

B. Supplemental (correction) rapid-acting insulin analog or regular insulin

- Supplemental insulin orders.
 - If a patient is able and expected to eat all or most of his/her meals, give regular or rapid-acting insulin before each meal and at bedtime following the “usual” column (Section C below).
 - If a patient is not able to eat, give regular insulin every 6 h (6-12-6-12) or rapid-acting insulin every 4 to 6 h following the “sensitive” column (Section C below).
- Supplemental insulin adjustment.
 - If fasting and premeal plasma glucose are persistently above 7.8 mmol/liter (140 mg/dl) in the absence of hypoglycemia, increase insulin scale of insulin from the insulin-sensitive to the usual or from the usual to the insulin-resistant column.
 - If a patient develops hypoglycemia [BG < 3.8 mmol/liter (70 mg/dl)], decrease regular or rapid-acting insulin from the insulin-resistant to the usual column or from the usual to the insulin-sensitive column.

C. Supplemental insulin scale

BG (mg/dl)	Insulin-sensitive	Usual	Insulin-resistant
>141-180	2	4	6
181-220	4	6	8
221-260	6	8	10
261-300	8	10	12
301-350	10	12	14
351-400	12	14	16
>400	14	16	18

The numbers in each column of Section C indicate the number of units of regular or rapid-acting insulin analogs per dose. “Supplemental” dose is to be added to the scheduled insulin dose. Give half of supplemental insulin dose at bedtime. If a patient is able and expected to eat all or most of his/her meals, supplemental insulin will be administered before each meal following the “usual” column dose. Start at insulin-sensitive column in patients who are not eating, elderly patients, and those with impaired renal function. Start at insulin-resistant column in patients receiving corticosteroids and those treated with more than 80 U/d before admission. To convert mg/dl to mmol/liter, divide by 18. Adapted from Refs. 16,35, and 69.

finding that emphasizes the importance of the recommendation to evaluate the home insulin regimen at the time of hospitalization.

4.3.1-4.3.4 Remarks

A scheduled regimen of sc basal bolus insulin is recommended for most patients with diabetes in non-ICU hospital settings. A suggested method for determining starting doses of scheduled insulin therapy in insulin-naïve patients in the hospital can be based on a patient's body weight and administered as a range of 0.2 to 0.5 U/kg as the total daily dose (Table 1). The total daily dose can be divided into a basal insulin component given once (glargine, detemir) or twice (NPH, detemir) daily and a nutritional or bolus component given before meals in patients who are eating or every 4 to 6 h in patients on continuous EN or PN. In patients who are NPO or unable to eat, bolus insulin must be held until nutrition is resumed; however, doses of correction insulin can be continued to treat BG above the desired range. Adjustments of scheduled basal and bolus insulin can be based on total doses of correction insulin administered in the previous 24 h (35, 74). When correction insulin is required before most meals, it is often the basal insulin that can be titrated upward. When BG remains consistently elevated at one time point, the dose of bolus insulin preceding that measurement can be adjusted (78, 79). Many patients require daily insulin adjustment to achieve glycemic control and to avoid hypoglycemia. The home total basal and prandial insulin dose should be reduced on admission in patients with poor nutrition intake, impaired kidney function, or with admission BG levels less than 5.6 mmol/liter (100 mg/dl).

These recommendations apply for patients with type 1 and type 2 diabetes; however, type 1 diabetes patients completely lack endogenous insulin

production. Type 1 diabetes patients need to be provided continuous, exogenous basal insulin, even when fasting, to suppress gluconeogenesis and ketone production. Failure to provide basal insulin to a type 1 diabetes patient can lead to the rapid development of severe hyperglycemia and diabetic ketoacidosis (84, 85). In general, type 1 diabetes patients typically exhibit less insulin resistance and require lower daily insulin dosage than type 2 diabetes patients, especially if they are not obese.

With increasing utilization of insulin pump therapy, many institutions allow patients on insulin pumps to continue using these devices in the hospital; others express concern regarding use of a device unfamiliar to staff, particularly in patients who are not able to manage their own pump therapy (86). Patients who use continuous sc insulin infusion pump therapy in the outpatient setting can be candidates for diabetes self-management in the hospital, provided that they have the mental and physical capacity to do so (20, 86, 87). The availability of hospital personnel with expertise in continuous sc insulin infusion therapy is essential (16, 86, 87). It is important that nursing personnel document basal rates and bolus doses on a regular basis (at least daily). Clear policies and procedures should be established at the institutional level to guide continued use of the technology in the acute care setting.

4.4 Transition from hospital to home

Recommendations

4.4.1 We suggest reinstatement of preadmission insulin regimen or oral and non-insulin injectable antidiabetic drugs at discharge for patients with acceptable preadmission glycemic control and without a contraindication to their continued use. (2|⊕○○○)

4.4.2 We suggest that initiation of insulin administration be instituted at least one day before discharge to allow assessment of the efficacy and safety of this transition. (2|⊕○○○)

4.4.3 We recommend that patients and their family or caregivers receive both written and oral instructions regarding their glycemic management regimen at the time of hospital discharge. These instructions need to be clearly written in a manner that is understandable to the person who will administer these medications. (1|⊕○○○)

4.4.1-4.4.3 Evidence

Hospital discharge represents a critical time for ensuring a safe transition to the outpatient setting and reducing the need for emergency department visits and rehospitalization. Poor coordination of patient care at the time of patient transfer between services, transfer to rehabilitation facilities, or discharge to home is associated with medical errors and readmission (88).

For patients discharged home on insulin therapy as a new medication, it is important that patient education and written information be provided for the method and timing of administration of prescribed doses and recognition and treatment of hypoglycemia (44). In general, initiation of insulin therapy should be instituted at least one day before discharge to allow assessment of the efficacy and safety of therapy. Insulin regimens are often complex, usually entailing the administration of two different insulin preparations that may require adjustments according to home glucose readings. Because hospital discharge can be stressful to patients and their family, orally communicated instructions alone are often inadequate. To address this problem, several institutions have established formalized discharge

instructions for patients with diabetes as a way of improving the clarity of instructions for insulin therapy and glucose monitoring (44, 79, 89). In addition, patients as well as the provider administering posthospital care should be aware of the need for potential adjustments in insulin therapy that may accompany adjustments of other medications prescribed at the time of hospital discharge (*e.g.* corticosteroid therapy, octreotide) (51).

Measurement of HbA1C concentration during the hospital stay can assist in tailoring the glycemic management of diabetic patients at discharge. Patients with HbA1C below 7% can usually be discharged on their same outpatient regimen (oral agents and/or insulin therapy) if there are no contraindications to therapy (*i.e.* TZD and heart failure; metformin and renal failure). Patients with elevated HbA1C require intensification of the outpatient antidiabetic regimen (oral agents, insulin, or combination therapy). Patients with severe and symptomatic hyperglycemia may benefit from ongoing insulin therapy (basal or basal bolus regimen).

4.4.1-4.4.3 Remarks

We suggest that the following components of glycemic management be included as part of the transition and hospital discharge record:

- A principal diagnosis or problem list
- The reconciled medication list, including insulin therapy
- Recommendations for timing and frequency of home glucose monitoring
- Information regarding signs and symptoms of hypoglycemia and hyperglycemia with instructions about what to do in each of these cases
- A form or log book for recording POC measures and laboratory BG results
- A list of pending laboratory results upon discharge, and

- Identification of the health care provider who is responsible for the ongoing diabetes care and glycemic management.

Hospitals are encouraged to standardize discharge instruction sheets that provide information on principal diagnosis, key test results from the hospital stay, timing and adjusting of insulin doses, home glucose monitoring, and signs and symptoms of hypoglycemia and hyperglycemia.

5.0 Special situations

Recommendations

5.1 Transition from iv CII to sc insulin therapy

5.1.1 We recommend that all patients with type 1 and type 2 diabetes be transitioned to scheduled sc insulin therapy at least 1-2 h before discontinuation of CII.

(1|⊕⊕⊕⊕)

5.1.2 We recommend that sc insulin be administered before discontinuation of CII for patients without a history of diabetes who have hyperglycemia requiring more than 2 U/h. (1|⊕⊕⊕⊕)

5.1.3 We recommend POC testing with daily adjustment of the insulin regimen after discontinuation of CII. (1|⊕⊕⊕○)

5.1.1-5.1.3 Evidence

As patients recovering from critical illness begin to eat regular meals or are transferred to general nursing units, they require transition from iv to sc insulin to maintain reasonable levels of glycemic control (25, 51, 90, 91). Programs that include transition protocols as part of their glycemic management strategy in patients undergoing surgical procedures have demonstrated significant reductions in morbidity and mortality, with lower costs and less need for nursing time (25, 90).

Several different protocols have been proposed to guide the transition from CII

to sc insulin (43, 88). The majority of patients without a prior history of diabetes receiving CII at a rate of 1 U/h or less at the time of transition may not require a scheduled sc insulin regimen (78, 83, 92, 93). Many of these patients can be treated with correction insulin to determine whether they will require scheduled sc insulin. In contrast, all patients with type 1 diabetes and most patients with type 2 diabetes treated with oral antidiabetic agents or with insulin therapy before admission require transition to sc long- and short-acting insulin with discontinuation of CII.

To prevent recurrence of hyperglycemia during the transition period to sc insulin, it is important to allow an overlap of 1-2 h between discontinuation of iv insulin and the administration of sc insulin.

Basal insulin is given before transition and continued once (glargine/detemir) or twice (detemir/NPH) daily. Rapid-acting insulin analog or regular insulin is given before meals or as correction doses in the presence of hyperglycemia.

5.1.1-5.1.3 Remarks

In general, the initial dose and distribution of sc insulin at the time of transition can be determined by extrapolating the iv insulin requirement over the preceding 6 to 8 h to a 24-h period. Administering 60 to 80% of the total daily calculated dose as basal insulin has been demonstrated to be both safe and efficacious in surgical patients (16, 90). Dividing the total daily dose as a combination of basal and bolus insulin has been demonstrated to be safe in medically ill patients (90, 92, 94).

It is important that consideration be given to a patient's nutritional status and medications, with continuation of glucose monitoring to guide ongoing adjustments in the insulin dose because changes in insulin sensitivity can occur during acute illness. Correction doses of rapid-

acting analogs or regular insulin can be administered for BG values outside the desired range. Hospitals are encouraged to include protocols that guide the transition from CII to sc insulin as a way of avoiding glycemc excursions outside the target range. The use of protocols helps reduce random practices that result in hyperglycemia or unwarranted hypoglycemia.

5.2 Patients receiving EN or PN

Recommendations

5.2.1 We recommend that POC testing be initiated for patients with or without a history of diabetes receiving EN and PN. (1|⊕⊕⊕⊕)

5.2.2 We suggest that POC testing can be discontinued in patients without a prior history of diabetes if BG values are less than 7.8 mmol/liter (140 mg/dl) without insulin therapy for 24-48 h after achievement of desired caloric intake. (2|⊕○○○)

5.2.3 We suggest that scheduled insulin therapy be initiated in patients with and without known diabetes who have hyperglycemia, defined as BG greater than 7.8 mmol/liter (140 mg/dl), and who demonstrate a persistent requirement (*i.e.* >12 to 24 h) for correction insulin. (2|⊕○○○)

5.2.1-5.2.3 Evidence

Malnutrition is reported in up to 40% of critically ill patients (65) and is associated with increased risk of hospital complications, higher mortality rate, longer hospital stay, and higher hospitalization costs (95). Improving the nutritional state may restore immunological competence and reduce the frequency and severity of infectious complications in hospitalized patients (96, 97, 98, 99).

There are several retrospective and prospective studies demonstrating that

the use of EN and PN is an independent risk factor for the onset or aggravation of hyperglycemia independent of a prior history of diabetes (65, 100, 101). Hyperglycemia in this group of patients is associated with higher risk of cardiac complications, infections, sepsis, acute renal failure, and death (102, 103, 104). In one study, a strong correlation was reported between PN-induced hyperglycemia and poor clinical outcome. BG measures of more than 150 mg/dl before and within 24 h of initiation of PN were predictors of both inpatient complications and hospital mortality (105). Together, these results suggest that early intervention to prevent and correct hyperglycemia may improve clinical outcomes in patients receiving EN and PN.

To address this question, several clinical trials have investigated the use of diabetes-specific formulas as a way of ameliorating the risk for hyperglycemia with EN. These diabetes-specific formulas differ from standard formulations by supplying a lower percentage of total calories as carbohydrate and substituting monounsaturated fatty acids for a major component of administered fat calories (106). In a meta-analysis of studies comparing these with standard formulations, the postprandial rise in BG was reduced by 1.03-1.59 mmol/liter (18-29 mg/dl) (106). These results suggest that the majority of hyperglycemic patients will still require insulin therapy for control of hyperglycemia while receiving this type of nutritional support.

Achieving desired glycemc goals in patients receiving EN poses unique challenges (65,74). Unanticipated dislodgement of feeding tubes, temporary discontinuation of nutrition due to nausea, for medication administration (*e.g.* T4, phenytoin), or for diagnostic testing, and cycling of EN with oral intake in patients

with an inconsistent appetite all pose clinical challenges to the prescribing of scheduled insulin therapy. In one study, patients with persistent elevation in BG above 7.2 mmol/liter (above 130 mg/dl) during EN therapy were randomized to receive glargine once daily at a starting dose of 10 U, in combination with SSI with regular insulin administered every 6 h, or SSI alone. Approximately 50% of patients randomized to SSI required rescue therapy with NPH to achieve a mean BG below 10 mmol/liter (180 mg/dl) (74). The dose of glargine insulin was adjusted on a daily basis according to results of POC testing. If more than one BG was above 10 mmol/liter in the prior 24 h, the dose of glargine was increased by a percentage of the total dose of correction insulin administered on the preceding day. With use of this approach, a mean glucose of approximately 8.8 mmol/liter (160 mg/dl) was achieved with low risk for hypoglycemia.

Suggested approaches using sc insulin therapy in patients receiving continuous, cycled, or intermittent EN therapy appear in Table 2. Many members of this writing task force prefer frequent

injections of short-acting regular insulin or intermediate-acting insulin over the rapid-acting analogs in this group of patients because of the longer duration of action, requiring fewer injections (Table 2).

For patients receiving PN, regular insulin administered as part of the PN formulation can be both safe and effective. Subcutaneous correction-dose insulin is often used, in addition to the insulin that is mixed with the nutrition. When starting PN, the initial use of a separate insulin infusion can help in estimating the total daily dose of insulin that will be required. Separate iv insulin infusions may be needed to treat marked hyperglycemia during PN.

5.3 Perioperative BG control

Recommendations

5.3.1 We recommend that all patients with type 1 diabetes who undergo minor or major surgical procedures receive either CII or sc basal insulin with bolus insulin as required to prevent hyperglycemia during the perioperative period. (1|⊕⊕⊕⊕)

5.3.2 We recommend discontinuation of oral and non-insulin injectable antidiabetic

TABLE 2. Approaches to insulin therapy during EN

Continuous EN

- Administer basal insulin once (glargine, detemir) or twice (detemir/NPH) a day in combination with a short- or rapid-acting insulin analog in divided doses every 4 h (lispro, aspart, glulisine) to 6 h (regular insulin).

Cycled Feeding

- Administer basal insulin (glargine, detemir, or NPH) in combination with short- or rapid-acting insulin analog at the time of initiation of EN.
- Repeat the dose of rapid-acting insulin (lispro, aspart, glulisine) at 4-h intervals or short-acting (regular) insulin at 6-h intervals for the duration of the EN. It is preferable to give the last dose of rapid-acting insulin approximately 4 h before and regular insulin 6 h before discontinuation of the EN.

Bolus feeding

- Administer short-acting regular or rapid-acting insulin analog (lispro, aspart, glulisine) before each bolus administration of EN.

Adapted from Refs. 16, 74, and 101

agents before surgery with initiation of insulin therapy in those who develop hyperglycemia during the perioperative period for patients with diabetes.

(1|⊕○○○)

5.3.3 When instituting sc insulin therapy in the postsurgical setting, we recommend that basal (for patients who are NPO) or basal bolus (for patients who are eating) insulin therapy be instituted as the preferred approach. (1|⊕⊕⊕○)

5.3.1-5.3.3 Evidence

There are several case-control studies that demonstrate an increased risk for adverse outcomes in patients undergoing elective noncardiac surgery who have either preoperative or postoperative hyperglycemia (19, 107, 108, 109, 110). Postoperative BG values greater than 11.1 mmol/liter (200 mg/dl) are associated with prolonged hospital length of stay and an increased risk of postoperative complications, including wound infections and cardiac arrhythmias (107, 108, 109, 110). In one study, the incidence of postoperative infections in patients with glucose levels above 12.2 mmol/liter (220 mg/dl) was 2.7 times higher than in those with glucose levels below 12.2 mmol/liter (109). In a recent report of 3184 noncardiac general surgery patients, a perioperative glucose value above 8.3 mmol/liter (150 mg/dl) was associated with increased length of stay, hospital complications, and postoperative mortality (107).

Perioperative treatment recommendations are generally based on the type of diabetes, nature and extent of the surgical procedure, antecedent pharmacological therapy, and state of metabolic control before surgery (110, 111). A key factor for the success of any regimen is frequent glucose monitoring to allow early detection of any alterations in metabolic control.

All patients receiving insulin before

admission require insulin during the perioperative period (112, 113). For most patients, this requirement includes administration of a percentage of the usual basal insulin (NPH, detemir, glargine) in combination with correction doses of regular insulin or rapid-acting insulin analogs for glucose levels from 8.3 to 11.1 mmol/liter (150 to 200 mg/dl). The safety of administering 50% of the basal insulin dose preoperatively was demonstrated in one nonrandomized quality improvement initiative (114). Admission BG levels in 584 patients with diabetes treated according to these recommendations ranged between 3.9 and 11.1 mmol/liter (70-200 mg/dl) in 77% of patients. Hypoglycemia, defined as a BG of less than 3.9 mmol/liter, occurred in only 1.7% of patients.

Patients with type 2 diabetes well-controlled by a regimen of diet and physical activity may require no special preoperative intervention for diabetes (111, 115). Glucose levels in this group of patients can often be controlled with small doses of supplemental short-acting insulin. Insulin-treated patients or those with poor metabolic control while on oral antidiabetic agents will require iv insulin infusions or a basal bolus sc insulin regimen to achieve the desired level of glycemic control.

Patients with type 1 diabetes undergoing minor or major surgical procedures require CII or sc basal bolus insulin administration adjusted according to the results of BG testing to prevent the development of diabetic ketoacidosis (85, 116, 117, 118). In one study, BG values in a group of subjects with type 1 diabetes who received their full dose of glargine insulin on a fasting day were compared with those obtained on a control day when the participants were eating their usual meals (119). There were no significant differences in mean BG levels between

TABLE 3. Pharmacokinetics of sc insulin preparations

Insulin	Onset	Peak	Duration
Rapid-acting analogs	5-15 min	1-2 h	4-6 h
Regular	30-60 min	2-3 h	6-10 h
NPH	2-4 h	4-10 h	12-18 h
Glargine	2 h	No peak	20-24 h
Detemir	2 h	No peak	12-24 h

Renal failure leads to prolonged insulin action and altered pharmacokinetics (162).

these two days, suggesting that it is safe to administer the full dose of basal insulin when a patient is made NPO. For patients with type 1 diabetes whose BG is well controlled, mild reductions (between 10 and 20%) in the dosing of basal insulin are suggested. For those whose BG is uncontrolled [*i.e.* BG > 10 mmol/liter (200 mg/dl)], full doses of basal insulin can be administered.

Because the pharmacokinetic properties of NPH insulin differ from those of glargine and detemir, dose reductions of 25-50% are suggested, together with the administration of short- or rapid-acting insulin for BG > 8.3 mmol/liter (150 mg/dl) (Table 3).

Prolonged use of SSI regimen is not recommended for glycemic control during the postoperative period in hyperglycemic patients with diabetes. In one study of 211 general surgery patients with type 2 diabetes randomly assigned to receive basal bolus insulin or SSI, glycemic control and patient outcomes were significantly better with the former (33). Patients who were treated with SSI had higher mean POC glucose values and more postoperative complications including wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia. The results of that study indicate that treatment with glargine once daily plus rapid-acting insulin before meals improves glycemic control and

reduces hospital complications in general surgery patients with type 2 diabetes (33).

5.3.1-5.3.3 Values and preferences

We place a high value on maintaining glycemic control even for brief periods of time, as occurs during periods of fasting for surgical or other procedures. Although avoidance of hypoglycemia is desired, administering a percentage of the usual dose of long- or intermediate-acting insulin appears to be safe and well tolerated, even for patients who arrive on the morning of the procedure.

5.3.1-5.3.3 Remarks

Hospitals are encouraged to:

- Implement protocols that guide safe glycemic management of patients with hyperglycemia during and after surgical procedures, and
- Abandon practices that allow for random and inconsistent glycemic management in surgical patients.

5.4 Glucocorticoid-induced diabetes

Recommendations

5.4.1 We recommend that bedside POC testing be initiated for patients with or without a history of diabetes receiving glucocorticoid therapy. (1|⊕⊕⊕⊕)

5.4.2 We suggest that POC testing can be discontinued in nondiabetic patients if all BG results are below 7.8 mmol/liter (140 mg/dl) without insulin therapy for a period of at least 24-48 h. (2|⊕○○○)

5.4.3 We recommend that insulin therapy be initiated for patients with persistent hyperglycemia while receiving glucocorticoid therapy. (1|⊕⊕○○)

5.4.4 We suggest CII as an alternative to sc insulin therapy for patients with

severe and persistent elevations in BG despite use of scheduled basal bolus sc insulin. (2|⊕○○○)

5.4.1–5.4.4 Evidence

Hyperglycemia is a common complication of glucocorticoid therapy with a prevalence between 20 and 50% among patients without a previous history of diabetes (51, 120, 121). Corticosteroid therapy increases hepatic glucose production, impairs glucose uptake in peripheral tissues, and stimulates protein catabolism with resulting increased concentrations of circulating amino acids, thus providing precursors for gluconeogenesis (122, 123, 124). The observed decrease in glucose uptake with glucocorticoid therapy seems to be a major early defect, contributing to increases in postprandial hyperglycemia. Despite its frequency, the impact of corticosteroid-induced hyperglycemia on clinical outcomes such as morbidity and mortality is not known. Few studies have examined how best to treat glucocorticoid-induced hyperglycemia. In general, discontinuation of oral antidiabetic agents with initiation of sc basal bolus insulin therapy is recommended for patients with glucocorticoid-induced hyperglycemia. The starting insulin dose and timing of insulin administration should be individualized depending on severity of hyperglycemia and duration and dosage of steroid therapy. For patients receiving high-dose glucocorticoids and in those with severe hyperglycemia that is difficult to control, the use of CII is appropriate (16, 50, 125). The use of CII on general wards and in patients receiving high glucocorticoid doses has been shown to result in rapid and sustained glycemic control and a rate of hypoglycemic events similar to that reported in recent ICU trials (50). The majority of patients with steroid-induced hyperglycemia can be treated with

a sc basal bolus insulin regimen to achieve glycemic control, with dosing based on a starting dosage of 0.3 to 0.5 U/kg · d.

Adjustment of insulin doses is required when the glucocorticoid dose is changed. Discontinuation or tapering of corticosteroid therapy in patients with diabetes has been associated with risk of developing hypoglycemia (126).

6.0. Recognition and management of hypoglycemia in the hospital setting

Recommendations

6.1 We recommend that glucose management protocols with specific directions for hypoglycemia avoidance and hypoglycemia management be implemented in the hospital. (1|⊕⊕○○)

6.2 We recommend implementation of a standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol to prompt immediate therapy of any recognized hypoglycemia, defined as a BG below 3.9 mmol/liter (70 mg/dl). (1|⊕⊕○○)

6.3 We recommend implementation of a system for tracking frequency of hypoglycemic events with root cause analysis of events associated with potential for patient harm. (1|⊕⊕○○)

6.1–6.3 Evidence

Hypoglycemia is defined as any glucose level below 3.9 mmol/liter (70 mg/dl) (127, 128). This is the standard definition in outpatients and correlates with the initial threshold for the release of counter-regulatory hormones (128, 129). Severe hypoglycemia has been defined by many as less than 2.2 mmol/liter (40 mg/dl) (128), although this is lower than the approximately 2.8 mmol/liter (50 mg/dl) level at which cognitive impairment begins in normal individuals (129).

The fear of hypoglycemia is a key barrier to the implementation of targeted

glucose control. Although not as common as hyperglycemia, hypoglycemia is a well-recognized and feared complication in hospitalized patients with or without established diabetes (130). The risk for hypoglycemia is higher during periods of hospitalization due to variability in insulin sensitivity related to the underlying illness, changes in counter-regulatory hormonal responses to procedures or illness, and interruptions in usual nutritional intake (131, 132).

The prevalence of hypoglycemic events varies across studies depending on the definition of hypoglycemia and the specific patient population evaluated. In a 3-month prospective review of consecutive medical records in 2174 hospitalized patients receiving antidiabetic agents, 206 patients (9.5%) experienced a total of 484 hypoglycemic episodes (133). A large glycemetic survey examining results of POC bedside glucose tests from 126 hospitals reported a prevalence of hypoglycemia (<3.9 mmol/liter or <70 mg/dl) as 3.5% in non-ICU patients (24). In randomized controlled studies, the prevalence of hypoglycemia has ranged from 3 to 30% of medical and surgical patients with type 2 diabetes treated with sc insulin (33, 35, 69).

The key predictors of hypoglycemic events in hospitalized patients include older age, greater illness severity (presence of septic shock, mechanical ventilation, renal failure, malignancy, and malnutrition), diabetes, and the use of oral glucose lowering medications and insulin (134, 135). In-hospital processes of care that contribute to risk for hypoglycemia include unexpected changes in nutritional intake that are not accompanied by associated changes in the glycemetic management regimen (e.g. cessation of nutrition for procedures, adjustment in the amount of nutritional support), interruption of the established routine for glucose monitoring (such as transportation off the

ward), deviations from the established glucose control protocols, and failure to adjust therapy when glucose is trending down or steroid therapy is being tapered (78, 131).

Hypoglycemia is associated with an increased risk of mortality in various hospitalized patient populations (136, 137). A J-shaped curve for mortality has been observed in patients admitted with acute myocardial infarction and in other patient groups (138). Hypoglycemia is also associated with a prolonged hospital length of stay as compared with that of similar patients who did not experience hypoglycemia (137). Serious adverse events were reported in 4% of patients with hypoglycemic events (133).

Despite these observations, it remains unclear whether episodic in-hospital hypoglycemia is a direct mediator of adverse events or is a marker of greater illness severity. A recent study of nearly 8000 patients hospitalized with acute myocardial infarction evaluated the prognostic impact of incident hypoglycemia separately in patients who developed it spontaneously and those who experienced hypoglycemia after administration of insulin (13, 76). Although patients with spontaneous hypoglycemia had markedly higher rates of in-hospital death (18.4 vs. 9.2% in those without hypoglycemia; $P < 0.001$), mortality was not increased in insulin-treated patients with iatrogenic hypoglycemia (10.4 vs. 10.2% in those without hypoglycemia; $P = 0.92$). These data have been corroborated by other studies of patients hospitalized with acute myocardial infarction (139, 140, 141), on geriatric nursing units (135), and in the ICU (139, 141, 142). These results suggest that inpatient hypoglycemia may be more of a marker for severe illness rather than a direct cause of adverse events.

Although these findings offer some

reassurance to clinicians in their efforts to control glucose levels, hypoglycemic events are associated with potential for harm and should be avoided (137). Although well-designed studies evaluating interventions aimed specifically at reducing hypoglycemia are lacking, several strategies appear reasonable. These include use of evidence-based glucose control protocols with a demonstrated safety record, establishment of hospital-wide policies that provide guidance on identification of high-risk patients, and standardization of procedures for detection and treatment of hypoglycemia across nursing units (74, 143, 144). Many patients require daily insulin adjustment to avoid hypoglycemia (BG < 3.9 mmol/liter). The total basal and prandial insulin dose should be reduced if BG levels fall between 3.9 and 5.6 mmol/liter (70-100 mg/dl).

Another method for minimizing risk for hypoglycemia is to avoid medications that are associated with a high risk for hypoglycemia such as sulfonylureas, particularly among elderly patients and those with renal impairment or poor oral intake. Modification of insulin regimens in patients with BG levels below 5.6 mmol/liter (100 mg/dl) helps to reduce risk for a hypoglycemic event. Reductions in the total daily dose of insulin by approximately 20% are recommended when BG falls below 3.9 mmol/liter (70 mg/dl), unless the event is easily explained by other factors (such as a missed meal, *etc.*).

Frequent monitoring of BG levels allows for timely detection and treatment of hypoglycemia. A system for tracking the frequency and severity of all hypoglycemic events allows for ongoing analysis of the safety of a glycemetic management program (88, 145). Hypoglycemia treatment protocols that facilitate prompt treatment of any hypoglycemic event can be useful in preventing deterioration to a more

TABLE 4. Key components of hypoglycemia prevention and management protocol

Hospital-wide definitions for hypoglycemia and severe hypoglycemia.
Guidance on discontinuation of sulfonylurea therapy and other oral hypoglycemic medications at the time of hospital admission.
Directions for adjustments in insulin dose and/or administration of dextrose-containing iv fluids for both planned and sudden changes in nutritional intake.
Specific instructions for recognition of hypoglycemia symptoms, treatment, and timing for retesting depending on glucose levels and degree of the patient's neurological impairment and for retesting of glucose levels.
Standardized form for documentation and reporting of hypoglycemic events, including severity, potential cause(s), treatment provided, physician notification, and patient outcome.

prolonged or severe episode that may be associated with adverse outcomes (68, 146). Implementation of such standardized hypoglycemia treatment protocols has been successful at reducing the frequency of severe hypoglycemic events in some institutions (144, 147, 148). The key aspects of hypoglycemia prevention and management are summarized in Table 4; a representative nurse-driven hypoglycemia management protocol is depicted in Table 5.

The success of any hypoglycemia treatment protocol depends on the ability of bedside nurses to recognize signs and symptoms of hypoglycemia, initiate appropriate treatment without delay, and retest BG at prescribed time intervals after treatment (148). For these reasons, educational initiatives at the time of protocol implementation with periodic reinforcement are essential (149).

7.0 Implementation of a glycemetic control program in the hospital

Recommendations

7.1 We recommend that hospitals provide administrative support for an inter-

TABLE 5. Suggested nurse-initiated strategies for treating hypoglycemia

For treatment of BG below 3.9 mmol/liter (70 mg/dl) in a patient who is alert and able to eat and drink, administer 15-20 g of rapid-acting carbohydrate such as:^a

- one-15-30 g tube glucose gel or 4 (4 g) glucose tabs (preferred for patients with end stage renal disease).
- 4-6 ounces orange or apple juice.
- 6 ounces "regular" sugar sweetened soda.
- 8 ounces skim milk.

For treatment of BG below 3.9 mmol/liter (70 mg/dl) in an alert and awake patient who is NPO or unable to swallow, administer 20 ml dextrose 50% solution iv and start iv dextrose 5% in water at 100 ml/h.

For treatment of BG below 3.9 mmol/liter in a patient with an altered level of consciousness, administer 25 ml dextrose 50% (1/2 amp) and start iv dextrose 5% in water at 100 ml/h.

In a patient with an altered level of consciousness and no available iv access, give glucagon 1 mg im. Limit, two times.

Recheck BG and repeat treatment every 15 min until glucose level is at least 4.4 mmol/liter (80 mg/dl)

^aDose depends on severity of the hypoglycemic event.

disciplinary steering committee targeting a systems approach to improve care of inpatients with hyperglycemia and diabetes. (1|⊕⊕⊕⊕)

7.2 We recommend that each institution establish a uniform method of collecting and evaluating POC testing data and insulin use information as a way of monitoring the safety and efficacy of the glycemic control program. (1|⊕○○○)

7.3 We recommend that institutions provide accurate devices for glucose measurement at the bedside with ongoing staff competency assessments. (1|⊕○○○)

7.1-7.3 Evidence

It is important for medical centers to target improved care of inpatients with hyperglycemia and/or diabetes by creating and supporting an interdisciplinary steering committee with representation from key groups involved in the care of these patients (51). The steering committee ideally would include representatives from physician groups, nurses, pharmacists, case managers, nutrition, information support, and quality improvement personnel empowered to:

- Assess safety and efficacy of processes for glycemic management with a focus on improving care at the identified areas of deficiency, within a framework of quality improvement.
- Implement strategies that guide staff and physician education with written policies, protocols, and order sets with integrated decision support using computer order entry.
- Consider use of checklists, algorithms, and standardized communication for patient transfers and hand off.
- Monitor the use of order sets and protocols, intervening to reinforce protocol use, and revising protocols as needed to improve integration, clarity, and ease of use.
- Institute continuing education programs for medical, nursing, and dietary staff to enhance adherence to protocols.

The inpatient care of individuals with diabetes and hyperglycemia is complex, involving multiple providers with varying degrees of expertise who are dispersed across many different areas of the hospital. A multidisciplinary systems approach can

help guide meaningful progress away from clinical inertia and toward safe glycemic control, hypoglycemia prevention, and patient preparation for care transitions (20, 54, 143, 144, 147).

The transfer of patients between nursing units of clinical care teams is a major cause of error in the care of patients with hyperglycemia in the hospital. Poor coordination of glucose monitoring, meal delivery, and insulin administration is a common barrier to optimal care (43, 150, 151).

Evidence for the advantages of using a systems approach comes from several sources: industry and high reliability organizations; endorsement by major professional organizations, based on consensus opinion and experience (21, 152); extrapolation of experience applied to other disease entities (152); and successful institutional glycemic control efforts via this approach (78, 153, 154, 155).

Resources outlining the multidisciplinary approach, protocol, and order set design, implementation strategies, and methods for monitoring and continuously improving the process are available in print and internet media (88).

8.0 Patient and professional education

Recommendations

8.1 We recommend diabetes self-management education targeting short-term goals that focus on survival skills: basic meal planning, medication administration, BG monitoring, and hypoglycemia and hyperglycemia detection, treatment, and prevention. (1|⊕○○○)

8.2. We recommend identifying resources in the community to which patients can be referred for continuing diabetes self-management education after discharge. (1|⊕○○○)

8.3. We recommend ongoing staff education to update diabetes knowledge, as well as targeted staff education whenever an adverse event related to diabetes management occurs. (1|⊕○○○)

8.1-8.3 Evidence

Diabetes self-management education has the ability to reduce length of hospital stay and improve outcomes after discharge (16). In a meta-analysis of 47 studies on the effects of diabetes education on knowledge, self-care, and metabolic control, educational interventions were shown to increase patients' knowledge and ability to perform self-care (156). The AADE inpatient position statement recommends initiation of diabetes self-management education early during the hospitalization to allow time to address potential deficits in patient knowledge (48). With early intervention, the patient will have more opportunities to practice and master survival skills. Family members should be included whenever possible to support and reinforce self-management education (157, 158).

Inpatient diabetes educational goals should focus on the following survival skills: basic meal planning, medication administration, POC testing, and hypoglycemia detection, treatment, and prevention (21, 48). Diabetes education is more complex in the hospital setting because patients are acutely ill, may be experiencing pain, and are under stress. Keeping sessions short and focused with minimal distractions and interruptions contributes to a more productive learning environment (48).

Documentation of teaching sessions by health care professionals promotes communication of progress to the next health care provider and assists in discharge planning. In situations where failure to perform diabetes self-care practices contributed to the need for the

hospitalization, education can be focused on the area of deficiency as a way of preventing readmissions (e.g. diabetic ketoacidosis) (16,48,88). Written discharge instructions on diabetes self-care, offered in the patient's primary language whenever possible, should be reviewed and provided at the time of discharge (44,159). Efforts should be made to coordinate education with those also caring for the patient and those who will be seeing the patient in transition to maximize the value of education. It would be optimal to provide recommendations, based on observations during the education of the patient, to those in the transition of care.

Staff education together with competency testing can facilitate the ability of nursing personnel to provide both inpatient diabetes management and patient education. Assessment of patients' cognitive and emotional status and medical status should be used to determine the optimal timing and strategy for in-hospital education. Diabetes educators and endocrinologists can assist with curriculum development and teaching, and diabetes resource nurses can serve as role models and sources of information for staff nurses. Topics for staff education should include recognition of types of diabetes, treatment and prevention of hypoglycemia and hyperglycemia symptoms, glycemic targets in critical care and non-critical care settings, and acute complications such as diabetic ketoacidosis (48). The Joint Commission in partnership with the American Diabetes Association has developed an advanced level of certification in inpatient diabetes care (160). Minimum requirements for certification include diabetes staff education, formal BG monitoring protocols, hypoglycemia and hyperglycemia protocols, tracking of hypoglycemia frequency and severity, providing diabetes self-management

education, and identification of a program champion or team to spearhead glycemic control initiatives (160).

The principles of diabetes education and management in the hospital apply for patients with type 1 and type 2 diabetes. Due to the lack endogenous insulin production, patients with type 1 diabetes require exogenous insulin to be provided at all times to avoid severe hyperglycemia and diabetic ketoacidosis (84, 85). In addition, patients with type 1 diabetes are less insulin resistant and are more vulnerable to hypoglycemic events than those with type 2 diabetes. Attention to type of diabetes, as well as to family dynamics and psychological and emotional maturity, is essential in developing and implementing an optimal diabetes regimen.

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