Letters to the Editor

Adrenal Cushing Syndrome Shortly After Adrenal Insufficiency

To the Editor:

A 57-year-old woman presented to the emergency department because of a 1-month history of abdominal pain, nausea, vomiting, fatigue, diarrhea, and weight loss. Before this episode, the patient had had an 11.3-kg weight gain during a 2-year period that resulted in truncal obesity after 3 intra-articular injections of cortisone (dose unknown) in the right hand, elbow, and shoulder, respectively. She also had harbored an adrenal mass that was incidentally identified a couple of years before but without further work-up.

Physical examination on admission revealed pronounced orthostatic hypotension, tachycardia, and central obesity. Pertinent laboratory findings included the following: morning cortisol level, 2.2 μg/dL (reference range, 6 to 19); adrenocorticotropic hormone (ACTH), 3 pg/mL (reference range, 6 to 58); and potassium, 3.5 mEq/L (reference range, 3.5 to 5.0). A cosyntropin stimulation test revealed an insufficient cortisol response (cortisol levels of 12.4 μg/dL at 30 minutes and 15.4 μg/dL at 60 minutes). Computed tomography of the abdomen showed a left adrenal mass (2.5 by 2.3 cm) with heterogeneous enhancement (Fig. 1 *A*). Urine metanephrines, plasma renin activity, and aldosterone levels were within the reference ranges. She was diagnosed as having adrenal insufficiency possibly related to exogenous corticosteroid use as well as a nonfunctioning adrenal mass; treatment with hydrocortisone resulted in rapid resolution of symptoms.

The patient discontinued hydrocortisone therapy 4 months after discharge, without symptoms of adrenal insufficiency. At 6 months after discharge, a random cortisol level (27.4 μg/dL) suggested recovery of adrenal functions, and repeated computed tomography showed that the adrenal mass had high attenuation (38 Hounsfield units) without appreciable growth (Fig. 1 *B*). At 8 months after discharge, she complained of weight gain of 4.5 kg in a month. Urine free cortisol levels were elevated up to 197 μg/24 h (reference range, 4 to 50) on multiple occasions. Dexamethasone (1 mg) did not suppress cortisol, and morning ACTH levels were 2 to 4 pg/mL. At 17 months after discharge, magnetic resonance imaging confirmed the presence of the heterogeneous left adrenal mass (Fig. 1 *C*), which was unchanged in size, and did not identify any extra-adrenal lesions. The patient was diagnosed as having ACTH-independent Cushing syndrome and underwent left adrenalectomy. On histologic examination, the mass was found to be a benign adrenocortical adenoma. She received hydrocortisone replacement therapy and did well postoperatively.

To our knowledge, we describe, for the first time, a case of overt adrenal Cushing syndrome appearing shortly after the diagnosis of adrenal insufficiency. The most likely explanation for this bizarre sequence of events is that the adrenal adenoma was initially nonfunctioning but underwent functional transformation during the 8 months after the patient's initial presentation with adrenal insufficiency. Functional transformation occurs in only 1.7% of adrenal incidentalomas and is usually associated with a substantial increase in tumor size (1). Adrenal adenoma can rarely cause cyclic Cushing syndrome, but the adrenal function is normal during the interspersing periods (2). Our case demonstrates that functional transformation can occur rapidly without tumor enlargement in an apparently benign adenoma, the mechanism of which remains to be elucidated.

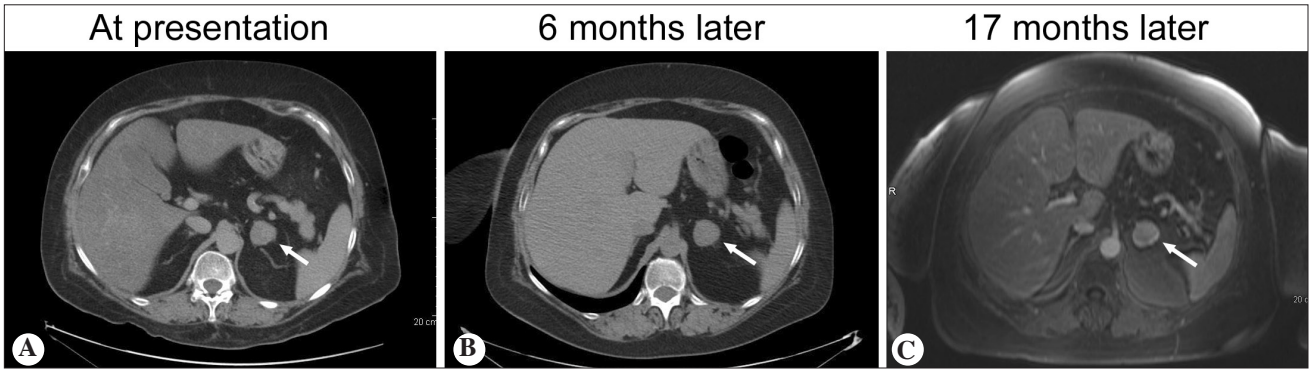

Fig. 1. Representative computed tomographic scans (*A* and *B*) and magnetic resonance image (*C*) of abdomen of study patient. Note the stable size of the left adrenal nodule (*arrow*) and the large amount of truncal fat on the magnetic resonance image done 17 months after the initial presentation.

We conclude that transformation from adrenal insufficiency to adrenal Cushing syndrome is possible in a patient with an adrenal tumor and should be actively investigated. Therefore, clinicians should be aware of this rare clinical entity.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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REFERENCES

1. **Barzon L, Sonino N, Fallo F, Palu G, Boscaro M.** Prevalence and natural history of adrenal incidentalomas. *Eur J Endocrinol*. 2003;149:273-285.
2. **Meinardi JR, Wolffenbuttel BH, Dullaart RP.** Cyclic Cushing's syndrome: a clinical challenge. *Eur J Endocrinol*. 2007;157:245-254.

Lack of Increase in the Serum Thyroid-Stimulating Hormone Level After Intramuscular Administration of Recombinant Human Thyroid-Stimulating Hormone Doses in a Morbidly Obese Patient

To the Editor:

We describe a morbidly obese patient who had insufficient elevation of the serum thyroid-stimulating hormone (TSH) level after receiving three 0.9-mg doses of recombinant human thyroid-stimulating hormone (rhTSH) and reveal our subsequent approach to obtaining the expected serum TSH levels.

Investigators have reported that body surface area (BSA) is independently associated with serum peak TSH levels after administration of rhTSH (1). Although BSA seems to be an important factor in predicting serum TSH levels achieved after rhTSH injections, there is another situation that should be considered when drugs are administered intramuscularly in obese patients, as highlighted in our current case.

A morbidly obese 62-year-old woman with a body mass index of 55 kg/m^2 and a diagnosis of papillary thyroid carcinoma was first seen in our hospital after she had undergone total thyroidectomy. Radioiodine remnant ablation was performed with 100 mCi of iodine 131 (^{131}I) after 2 consecutive injections of 0.9 mg of rhTSH (Genzyme Corporation, Cambridge, Massachusetts) into the gluteus muscle. After the injections, a whole-body scan showed faint uptake in the thyroid bed. Thyroglobulin levels were undetectable in the presence of positive titers of antithyroglobulin antibodies.

The serum TSH concentration, measured on day 3 after the first injection of rhTSH, was 27 mIU/L. This is not the usual serum TSH level achieved after 2 conventional injections of rhTSH in normal subjects (2). One year later, another radioiodine dose of 100 mCi of ^{131}I was prescribed. We then administered three 0.9-mg doses of rhTSH, according to the initially proposed pre-rhTSH protocol approved by the Food and Drug Administration (2). Serum TSH levels obtained are shown in Figure 1. The serum thyroglobulin level was again undetectable, with positive thyroglobulin antibodies. After administration, a whole-body scan again showed faint uptake in the thyroid remnant. Thyroglobulin antibodies became negative 3 years after the initial treatment.

Two new conventional 0.9-mg rhTSH injections were administered, in an effort to measure a stimulated thyroglobulin level, but this time the rhTSH was injected into the deltoid muscle instead of the buttocks to ensure the correct intramuscular administration. The serum TSH level obtained after this procedure was 176 mIU/L, measured on the third day after the first rhTSH injection. These results suggest that, in this obese woman, the initial intramuscular injections presumably into the gluteus maximus were not absorbed and that the rhTSH was likely deposited in adipose tissue. The blood levels reflecting release of rhTSH after injection into fat are not known and might, indeed,

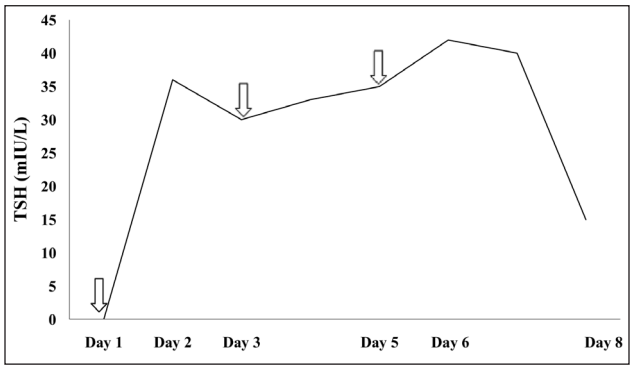

Fig. 1. Serum thyroid-stimulating hormone (*TSH*) levels measured in a morbidly obese patient after three 0.9-mg injections of recombinant human thyrotropin (*arrows*), presumably administered in the gluteus muscle.

be lower than those after injection into muscle. Recently, it was shown that the lean body mass was the only variable independently associated with the serum peak TSH level after administration of rhTSH (3). In addition to BSA and lean body mass, we think that another factor to consider in morbidly obese patients in this scenario should be the certainty of injection into the correct intramuscular site, which can be very difficult to achieve in patients with increased adipose tissue localized in the gluteus region, as observed in this case.

In conclusion, we recommend that, in morbidly obese patients, administration of rhTSH injections should be in the deltoid or perhaps the quadriceps muscle to guarantee the correct drug absorption.

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The authors have no multiplicity of interest to disclose.

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REFERENCES

1. **Vitale G, Lupoli GA, Ciccarelli A, et al.** Influence of body surface area on serum peak thyrotropin (TSH) levels after recombinant human TSH administration. *J Clin Endocrinol Metab*. 2003;88:1319-1322.
2. **Haugen BR, Pacini F, Reiners C, et al.** A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab*. 1999;84:3877-3885.
3. **Castagna MG, Pinchera A, Marsili A, et al.** Influence of human body composition on serum peak thyrotropin (TSH) after recombinant human TSH administration in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab*. 2005;90:4047-4050.

Rapid Weight Loss and Decrease in Hemoglobin A_{1c} After Treatment With Topiramate in a Patient With Status Epilepticus

To the Editor:

A 59-year-old woman with type 2 diabetes mellitus treated with metformin was admitted to the hospital because of pneumonia and chronic obstructive pulmonary disease on June 9, 2010. The patient had had a seizure disorder for the previous 10 years that had been well controlled with phenytoin. During hospitalization, however, status epilepticus developed as a result of a decrease in her phenytoin level, and she was treated in the intensive care unit. She had 2 new anticonvulsants, levetiracetam (500 mg twice daily) and topiramate (100 mg twice daily) added to her treatment regimen on June 16, 2010. On November 19, 2010, the patient had a hemoglobin A_{1c} (A1C) value of 4.9%, as determined by high-performance liquid chromatography (Tosoh G7). Review of laboratory data revealed that the patient's A1C level had been maintained between 7.1% and 7.4% from November 2008 to July 2010 (Table 1). Interestingly, the patient's fasting plasma glucose (FPG) concentration had also decreased, and she had lost 30% of her baseline body weight between June 2010 and December 2010, declining from obese class II to slightly overweight as defined by the World Health Organization classification (Table 1).

Low A1C results measured by high-performance liquid chromatography may be due to hemoglobinopathies, low hematocrit, anemia, or factors that shorten erythrocyte

Table 1
Patient's Hemoglobin A_{1c}, Fasting Plasma Glucose, and Body Mass Index Before and After Introduction of Topiramate on June 16, 2010[a]

Hemoglobin A_{1c} (%)	Fasting plasma glucose (mmol/L)[b]	Body mass index (kg/m^2)
11/24/08: 7.4	*11/24/08:* 11.1	*06/12/10:* 35.9
02/16/10: 7.2	*03/08/10:* 10.0	*08/18/10:* 33.4
07/02/10: 7.1	*07/02/10:* 6.4	*11/01/10:* 28.7
11/19/10: 4.9	*11/19/10:* 4.5	*12/17/10:* 25.3

[a] Dates are shown as month/day/year.
[b] For conversion of mmol/L to mg/dL, divide values by 0.0555.

life span (for example, hemolytic processes). We excluded all these potential causes in this patient, and the performance of our Tosoh G7 assay had been satisfactory for the past 5 years. Repeated testing in this patient on December 24, 2010, showed an A1C level of 4.6%. The patient had had no change in her diet or activity since June 2010. Her metformin dose had remained the same until November 2010, when the dosage was decreased because she had lost weight and her FPG value had declined. No new antidiabetes medications were used. Phenytoin (400 mg daily) has been continuously administered to control her seizures.

There is no published report on the effect of levetiracetam on A1C or FPG values; one study demonstrated that it does not alter body weight (1). Three recent, independent, randomized, double-blind, placebo-controlled studies indicated that, besides the labeled use as an adjunctive antiseizure medication, topiramate significantly reduced A1C, FPG, and body mass index in obese patients with type 2 diabetes (2-4). The weight loss and metabolic effects of topiramate are even more robust in drug-naïve patients with type 2 diabetes (5). Topiramate treatment (192 mg/d) for 40 weeks has been shown to decrease baseline body weight by about 9.1% and reduce A1C levels by 1.1% ± 0.9% (3,5). In our current patient, topiramate had even greater effects on A1C, FPG, and body weight. Finally, a computed tomographic scan of the chest, abdomen, and pelvis of our patient identified no evidence of underlying cancer to account for her weight loss.

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REFERENCES

1. **Gidal BE, Sheth RD, Magnus L, Herbeuval AF.** Levetiracetam does not alter body weight: analysis of randomized, controlled clinical trials. *Epilepsy Res*. 2003;56: 121-126.
2. **Toplak H, Hamann A, Moore R, et al.** Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Int J Obes (Lond)*. 2007;31:138-146.
3. **Eliasson B, Gudbjörnsdottir S, Cederholm J, Liang Y, Vercruysse F, Smith U.** Weight loss and metabolic effects of topiramate in overweight and obese type 2 diabetic patients: randomized double-blind placebo-controlled trial. *Int J Obes (Lond)*. 2007;31:1140-1147.
4. **Rosenstock J, Hollander P, Gadde KM, Sun X, Strauss R, Leung A (OBD-202 Study Group).** A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. *Diabetes Care*. 2007;30:1480-1486.
5. **Stenlöf K, Rössner S, Vercruysse F, Kumar A, Fitchet M, Sjöström L (OBDM-003 Study Group).** Topiramate in the treatment of obese subjects with drug-naïve type 2 diabetes. *Diabetes Obes Metab*. 2007;9:360-368.

Three-Dimensional Ultrasound Images and Fine-Needle Aspiration Biopsy of a Thyroid Nodule

To the Editor:

Ultrasonography is the preferred technology for visualizing the thyroid gland and detecting thyroid malignant lesions. It defines the shape, size, texture, and vascularity of the thyroid gland and any lesion within or adjacent to the gland. Commonly used ultrasound technology provides 2-dimensional (2D) images. Three-dimensional (3D) ultrasound technology offers greater detail and is now being applied extensively in fetal imaging and other medical arenas. Currently, however, it is not being used for imaging of thyroid nodules and thyroid-related pathologic conditions. The subsequent case illustrates the detail of the 3D ultrasound images of a thyroid nodule and fine-needle aspiration biopsy (FNAB) of that nodule.

A 74-year-old woman with no prior history of thyroid disease or thyroid irradiation was referred for evaluation of thyroid nodules. There were no palpable thyroid nodules. A 2D thyroid ultrasound study revealed 2 nodules in the right lobe: an isoechoic nodule measuring 5 by 3 by 4 mm and a hypoechoic nodule measuring 3 by 3 by 3 mm. In the left lobe, there was one nodule measuring 15 by 10 by 14 mm with increased peripheral vascularity. The thyroid-stimulating hormone level was 0.87 mIU/L, and free thyroxine was 1.2 ng/dL. Thyroid peroxidase and thyroglobulin antibody titers were not elevated. FNAB of the left lobe thyroid nodule was performed under 3D ultrasound guidance with use of a linear probe adjusted to 11 MHz and a General Electric LOGIQ ultrasound machine equipped with the software technology to convert multiple 2D images to 3D images. The 3D ultrasound images of the thyroid nodule and the location of the biopsy needle within the thyroid nodule are shown in Figures 1 *A*, *B*, and *C*. The cytopathology report indicated a benign lesion.

The illustrations highlight the fine detail obtained with 3D ultrasound technology when imaging thyroid nodules and FNAB of these nodules. The role of 3D ultrasound

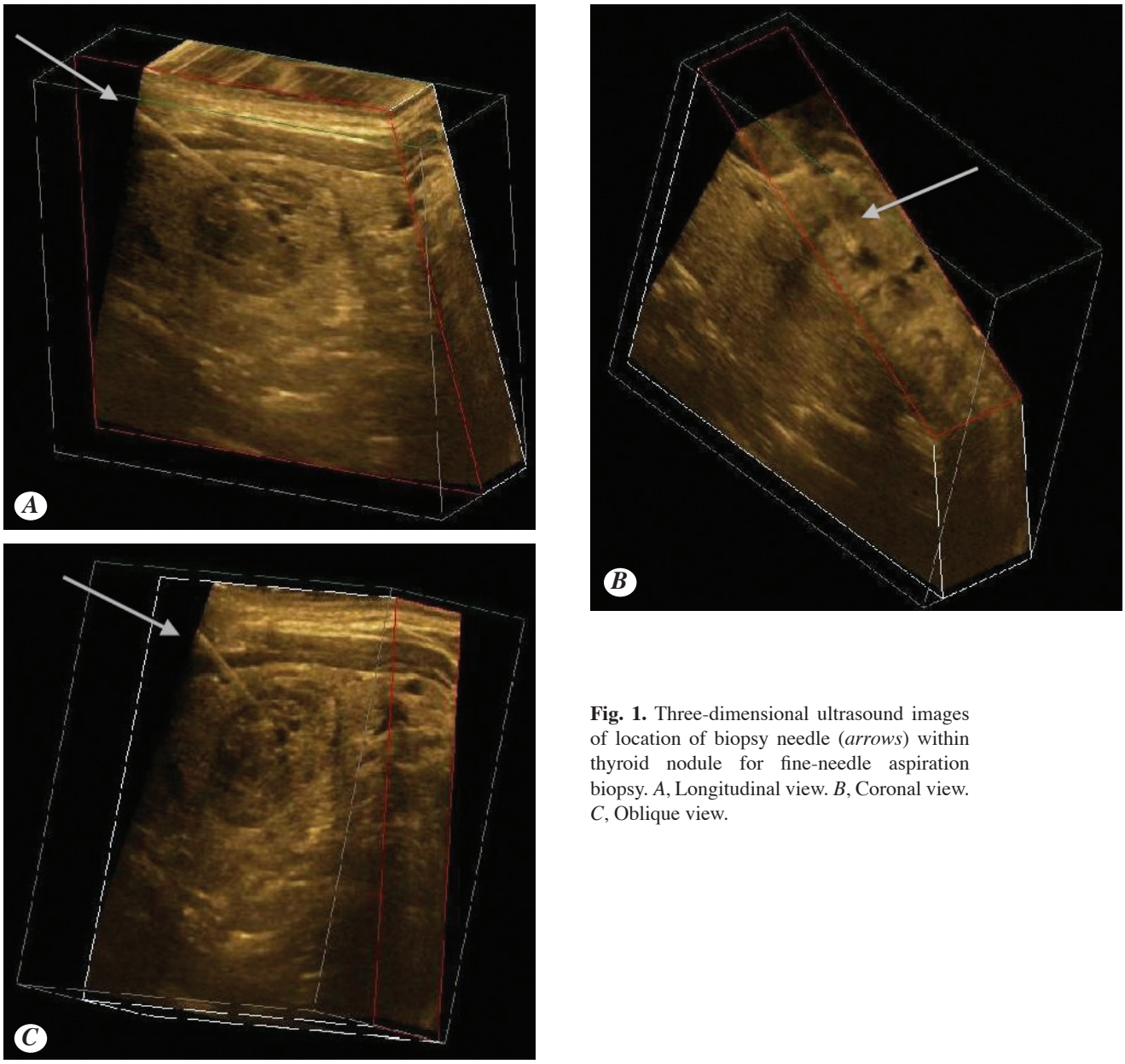

Fig. 1. Three-dimensional ultrasound images of location of biopsy needle (*arrows*) within thyroid nodule for fine-needle aspiration biopsy. *A*, Longitudinal view. *B*, Coronal view. *C*, Oblique view.

technology in the evaluation of thyroid nodules remains to be determined. Potential clinical uses include FNAB of thyroid nodules with more accurate needle placement. This application may be of particular importance in the future—for example, when obtaining samples for analysis of gene mutation and expression used to predict the malignant potential of thyroid nodules. Moreover, 3D ultrasound technology may be able to provide more accurate information about the borders of thyroid nodules and the presence of microcalcifications, fluid, and colloid, which would be useful in predicting the malignant potential of thyroid nodules. In addition, it may improve visualization of structures close to the thyroid gland, including parathyroid adenomas, benign and malignant lymph nodes, and blood vessels. Volume measurement with 3D ultrasound technology was discussed in the most recent thyroid nodule management guidelines published by the American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association (1). The latest real-time 3- or 4-dimensional equipment acquires and constructs the volumetric data set instantaneously, a feature that allows for coronal, sagittal, and lateral scanning as well as oblique planes to see anatomic relationships with rotating planes. By more carefully delineating anatomic relationships, volume measurement may aid in surgical planning.

Potential drawbacks to the use of this technology include cost, limited availability, and the necessary

physician training. Although an ultrasound machine from General Electric was used to create our current images, several ultrasound machines from other companies can create similar images.

We conclude that 3D ultrasound technology is likely to provide greater detail of thyroid nodules, FNAB needle placement, parathyroid adenomas, and other thyroid-related pathologic conditions. The utility of this information will be determined by carefully designed clinical investigations.

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REFERENCE

1. **Gharib H, Papini E, Paschke R, et al; for the AACE/AME/ETA Task Force on Thyroid Nodules.** American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract*. 2010; 16(suppl 1):e1-e43. https://www.aace.com/sites/default/files/ThyroidGuidelines.pdf. Accessed for verification May 20, 2011.