RadioGraphics

Scintigraphic Manifestations of Thyrotoxicosis[1]

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LEARNING OBJECTIVES FOR TEST 2

After reading this article and taking the test, the reader will be able to:

- Discuss the distinction between thyrotoxicosis and hyperthyroidism.
- Identify the thyroid uptake and scintigraphic findings in both the common and uncommon causes of thyrotoxicosis.
- Describe the therapeutic approach for the patient with thyrotoxicosis.

The term *thyrotoxicosis* refers to the clinical syndrome of increased systemic metabolism that results when the serum concentrations of free thyroxine, free triiodothyronine, or both are elevated. The term *hyperthyroidism* refers to overactivity of the thyroid gland with a resultant increase in thyroid hormone synthesis and release into the systemic circulation. These terms are not interchangeable, since thyrotoxicosis can develop in thyroid conditions that are not associated with increased thyroid function, such as thyroiditis, or in so-called factitious hyperthyroidism. The clinical signs and symptoms of thyrotoxicosis are virtually identical regardless of the cause. However, in a given patient, every attempt should be made to determine the exact cause of the thyrotoxicosis, as this in turn determines the prognosis and treatment. Since thyroid scintigraphy demonstrates the functional state of the thyroid gland, it should be used, in conjunction with determination of radioactive iodine uptake, as the imaging modality of choice for diagnosis of thyrotoxicosis. Although the scintigraphic features of several of the thyroid disorders that cause thyrotoxicosis may overlap, their recognition helps narrow the differential diagnosis, thereby guiding the referring physician in the work-up and management of this disorder.

Abbreviations: RAIU = radioactive iodine uptake, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid-stimulating hormone

Index terms: Thyroid, 273.58, 273.64 • Thyroid, hyperthyroidism, 273.522 • Thyroid, radionuclide studies, 273.1217 • Thyroiditis, 273.292

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Introduction

There are numerous causes of thyrotoxicosis encountered in clinical practice, both common and uncommon. Over the years, the Thyroid Center at our institution has referred a large number of thyrotoxic patients for thyroid scintigraphy and, in some instances, radioiodine therapy.

The purpose of this article is to illustrate the thyroid uptake and scintigraphic findings in those forms of thyrotoxicosis likely to be encountered in clinical practice. These include *(a)* increased thyroid function (Graves disease, Marine-Lenhart syndrome, toxic autonomous nodule, toxic multinodular goiter), *(b)* thyroid inflammation (subacute and silent thyroiditis), and *(c)* iodine-induced hyperthyroidism. In addition, we present the less common and rare causes of thyrotoxicosis, such as factitious hyperthyroidism, ectopic thyroid hormone production (metastatic thyroid cancer, toxic struma ovarii), and thyrotropin-induced hyperthyroidism (pituitary adenoma).

The necessity for thyroid scintigraphy in all cases of thyrotoxicosis is somewhat controversial. For example, a thyrotoxic patient presenting with a diffusely enlarged thyroid suggests the diagnosis of Graves disease. With such a straightforward presentation, it can be argued that thyroid imaging is unnecessary. However, most clinicians would nevertheless request a radioactive iodine uptake (RAIU) determination and thyroid scintigraphy as a pretherapeutic measurement in anticipation of radioiodine therapy (a common treatment). In addition, thyroid scintigraphy will indicate the presence of a solitary "cold" nodule within the diffuse toxic goiter, the former of which usually requires further work-up to exclude malignancy. Furthermore, thyroid enlargement is not necessarily present in all cases of Graves disease; the gland could be normal in size, particularly in the early stages of the disease. In this instance, the RAIU and scintigraphy will allow differentiation from various stages of silent thyroiditis or from so-called factitious hyperthyroidism. Regardless of this controversy over the use of thyroid scintigraphy in the thyrotoxic patient, the fact is, these patients nonetheless are being referred to the imaging specialist for this procedure. Familiarity with the scintigraphic findings will allow a reasonable differential diagnosis to enable the clinician to care for the patient with thyrotoxicosis.

Table 1 categorizes this disorder according to cause. The normal values for thyroid function tests performed at the clinical laboratory of our institution are listed in Table 2. All images in this article are those of patients who presented to our clinic with signs and symptoms of thyrotoxicosis.

Table 1
Classification of Thyrotoxicosis

Thyrotoxicosis associated with increased thyroid function
Graves disease
Marine-Lenhart syndrome
Toxic autonomous nodule
Toxic multinodular goiter
Thyrotoxicosis associated with inflammation
Subacute thyroiditis
Silent thyroiditis
Postpartum thyroiditis
Iodine-induced hyperthyroidism
Thyrotoxicosis of extrathyroidal origin
Factitious hyperthyroidism
Metastatic thyroid cancer
Struma ovarii
Thyrotropin-induced hyperthyroidism
Pituitary adenoma

Table 2
Normal Thyroid Function Test Values*

Test	Symbol	Normal Range
Thyroxine	T4	4.5–12.0 μg/dL
Triiodothyronine	T3	90–200 ng/dL
Thyroid-stimulating hormone	TSH	0.4–4.5 μIU/mL
Free T4	FT_4	0.7–1.6 ng/dL
Free T3	FT_3	230–420 ng/L
Iodine-131 uptake	RAIU	8%–35% at 24 h

*For the laboratories of the authors' institution.

Scintigraphic Technique

Most commonly, at our institution, thyroid scintigraphy is performed with technetium-99m pertechnetate. Imaging begins 15 minutes after intravenous injection of 10 mCi (370 MBq) of Tc-99m pertechnetate. A pinhole collimator with a 3.5-mm aperture is used as well as an energy setting of 140 keV photopeak for Tc-99m. Images are acquired at 100,000 counts in the anterior and both right and left anterior oblique projections with the collimator positioned as close to the patient's extended neck as possible. A so-called distant anterior projection is then acquired with the collimator positioned 10 cm above the patient's extended neck and a 2-cm cold lead

marker placed at the sternal notch. The field of view for this image extends from the sternal notch to the salivary glands, thereby allowing one to assess the size of the thyroid or any intraglandular abnormalities by comparing these sizes with the 2-cm lead marker. With pinhole collimators, the magnification will change, depending on the distance of the thyroid from the detector. Therefore, optimal imaging technique includes placement of a marker of a known size to facilitate internal measurements. RAIU measurements are made with a thyroid uptake probe 24 hours after oral administration of a capsule consisting of 5 μCi (0.19 MBq) of I-131.

Alternatively, thyroid uptake measurement and scanning may be performed with I-123. The RAIU measurement is obtained approximately 24 hours after oral ingestion of a capsule consisting of 300 μCi (11.11 MBq) of I-123. Subsequent imaging consists of the same four scans as for Tc-99m; however, the energy setting is on the 159-keV photopeak for I-123. We prefer the use of Tc-99m over I-123 for two reasons. First, the acquisition time for obtaining 100,000-count images is much faster with Tc-99m than with I-123. This is due to the fact that the allowable dose of Tc-99m administered (5–10 mCi [185–370 MBq]) is considerably higher than that of I-123 (200–300 μCi [7.2–11.11 MBq]); therefore, a significantly greater amount of Tc-99m can be administered, resulting in significantly faster image acquisition. Consequently, Tc-99m is a more "patient-friendly" radiopharmaceutical; a shorter acquisition time translates into less time required for a patient to lie supine with the neck extended, a considerable advantage when scanning elderly patients. Second, Tc-99m has a logistical advantage over I-123. Since Tc-99m is readily available either from molybdenum generators in hospital nuclear laboratories or in bulk unit doses that are delivered daily to hospital radiopharmacies, scheduling of the study is facilitated, particularly for last-minute requests. On the other hand, I-123 capsules are cyclotron-produced and must be ordered in advance from outside vendors. For these reasons, many laboratories favor the use of Tc-99m over I-123 in most instances.

The advantage of using I-123 over Tc-99m lies in the evaluation of certain solitary cold thyroid nodules. Up to 10% of solitary cold thyroid nodules are malignant (1), and therefore these require further work-up. Occasionally, a nodule will appear "warm" on a Tc-99m scan but cold on an I-123 scan (ie, the lesion traps Tc-99m but does not organify iodine); this is termed a *discordant nodule*. Since a discordant nodule is in effect a true cold nodule, it requires further work-up (such as fine-needle aspiration biopsy), depending on the patient's risk factors for malignancy. Therefore, a solitary cold nodule that appears warm or "hot" on a Tc-99m scan without suppression of the remainder of the gland could conceivably represent a discordant nodule, and one should repeat the scan using I-123. Those in favor of using I-123 routinely claim that the need for a second examination is circumvented by using I-123 to begin with. However, since less than 5% of thyroid carcinomas manifest as discordant nodules (2), those who prefer routine use of Tc-99m argue that a discordant nodule is encountered too infrequently to warrant routine use of I-123. In this article, images obtained with both radiopharmaceuticals are illustrated.

Thyrotoxicosis Associated with Increased Thyroid Function

Graves Disease

Graves disease (also known as *diffuse toxic goiter*) is an autoimmune disorder caused by antibodies against the thyrotropin (TSH) receptors on the cell surface of the thyroid follicle (3). By mimicking TSH, the thyroid receptor antibodies excessively stimulate the thyroid cells, which in turn increase thyroid hormone production with its associated sequelae. Serum thyroid hormone levels are elevated, and the pituitary TSH level is appropriately suppressed. The RAIU is usually elevated at 24 hours. Occasionally, however, in patients with markedly increased thyroid hormone synthesis and turnover, the 24-hour uptake is normal but a 4-hour or 6-hour RAIU measurement is elevated; this is termed *rapid iodine turnover* (4).

Scintigraphy demonstrates that the thyroid is usually enlarged. Activity throughout the gland is increased relative to the background due to both increased stimulation and function of the gland (Fig 1). Such stimulation at times results in visualization of the pyramidal lobe (a remnant of the thyroglossal duct) projecting cephalad from the isthmus or occasionally from the medial aspect of the left or right lobe. Owing to its relatively small size, the pyramidal lobe is normally not seen unless the gland is overly stimulated.

For most patients, I-131 therapy is recognized as the simplest, safest, and most effective form of therapy, except for those who are pregnant or lactating or who have severe Graves ophthalmopathy (4,5). Alternatively, some endocrinologists prefer antithyroid drugs, particularly in patients with normal-sized glands or less severe disease (4). The thionamide group of drugs, methimazole (Tapazole; Eli Lilly, Indianapolis, Ind) and propylthiouracil, block thyroid hormone synthesis (6). Occasionally, thyroidectomy is recommended for patients with marked thyromegaly, particularly those with evidence of tracheal compression, or for cosmetic purposes.

Marine-Lenhart Syndrome

Marine-Lenhart syndrome is a Graves disease variant in which Graves disease coexists with TSH-dependent cold thyroid nodules (7). These nodules appear as cold areas on thyroid scans because of the TSH suppression secondary to the Graves disease itself (Fig 2). However, the eponym *Marine-Lenhart syndrome* is rarely used. Most often, this condition is simply referred to as *Graves disease coexistent with a multinodular goiter*. It is also referred to as *nodular Graves disease*. The TSH level is suppressed, whereas thyroid hormone levels and RAIU are elevated.

Scintigraphy demonstrates diffusely increased activity with a decreased background, as in Graves disease. However, one or more cold nodules are also present (Fig 2).

Radioiodine therapy is the treatment of choice.

Toxic Autonomous Nodule

Also referred to as *Plummer disease* or *toxic adenoma*, the term *toxic autonomous nodule* denotes hyperthyroidism caused by one or two hyperfunctioning nodules in the thyroid (8). Functioning independently of the normal pituitary-thyroid control mechanism (thus the designation *autonomous*), the nodule produces excessive amounts of thyroid hormone. This in turn suppresses TSH production (9). Histologically, these nodules are adenomas, although occasionally they are referred to as *adenomatous nodules*. Unlike in Graves disease, the mechanism of toxic autonomous nodule is not autoimmunity. Instead, it is presumed that the TSH receptors on the adenoma surface undergo gene mutation, resulting in their continuous activation (10). Serum thyroid hormone levels are elevated, the TSH level is suppressed, and

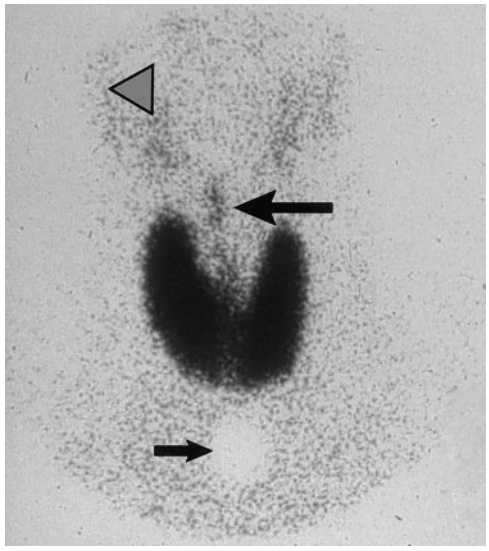


Figure 1. Graves disease in a 24-year-old woman. Laboratory values were as follows: T4 = 16.7 μg/dL, T3 = 311 ng/dL, and TSH < 0.01 μIU/mL. The 24-hour RAIU was 84%. Anterior distant image obtained with Tc-99m pertechnetate shows an enlarged thyroid. The target-to-background activity is increased to such an extent that the submandibular salivary glands (arrowhead) are barely visualized. Note the appearance of the pyramidal lobe (large arrow). The round photopenic area (small arrow) in this and subsequent figures represents the 2-cm lead marker placed at the suprasternal notch.

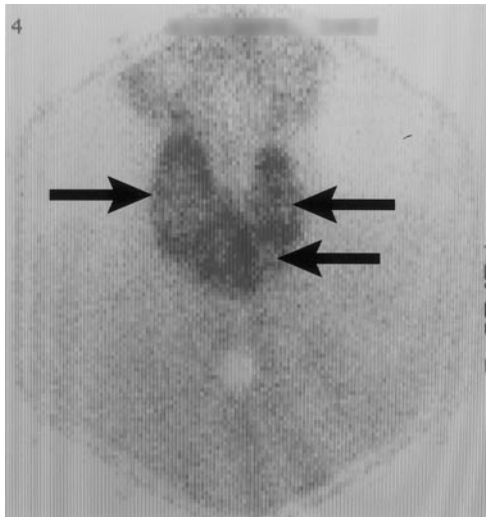


Figure 2. Marine-Lenhart syndrome in a 52-year-old woman. Laboratory values were as follows: free T4 = 2.9 ng/dL, T3 = 181 ng/dL, and TSH < 0.01 μIU/mL. Anterior Tc-99m pertechnetate image shows an enlarged thyroid with diffusely increased radiotracer trapping, as in Graves disease per se. However, within the gland are distinct cold nodules (arrows).

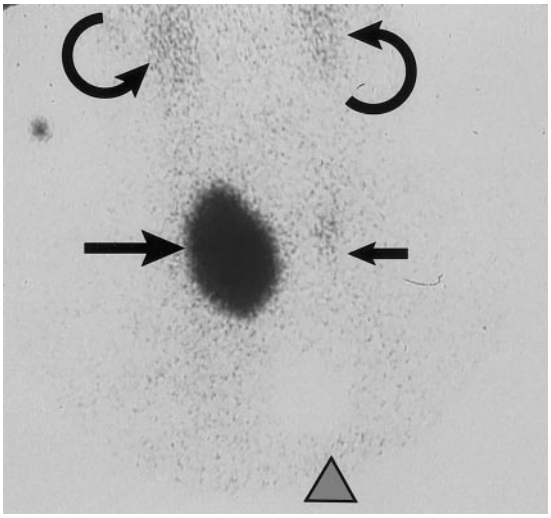


Figure 3. Toxic autonomous nodule in a 49-year-old woman. Laboratory values were as follows: T4 = 15.1 μg/dL, T3 = 304 ng/dL, and TSH < 0.01 μIU/mL. The 24-hour RAIU was elevated (46%). Anterior distant Tc-99m pertechnetate image shows a hot nodule that occupies most or all of the right thyroid lobe (large straight arrow) with near-total suppression of the left lobe (small straight arrow). The background activity is diminished to such an extent that the salivary glands (curved arrows) are barely visualized. Arrowhead = 2-cm lead marker.

the RAIU is mildly to moderately elevated or occasionally is in the upper range of normal. This is in contradistinction to Graves disease, in which the RAIU is usually significantly elevated. Not all autonomous nodules are toxic; the term *toxic* is applicable if the patient is clinically hyperthyroid. If the patient is euthyroid, the term *autonomously functioning thyroid nodule* is appropriate. All toxic autonomous nodules are autonomous; however, not all autonomous nodules are toxic.

Scintigraphy demonstrates toxic autonomous nodule as a hyperfunctioning (ie, hot) nodule, since it concentrates the radiopharmaceutical to a far greater degree than the surrounding extranodular thyroid tissue (Fig 3). The latter, because of the suppressed TSH level, demonstrates decreased tracer uptake (partial suppression) or absent tracer uptake (complete suppression). If two nodules are present, the condition is still referred to as *toxic autonomous nodule* (8).

Antithyroid drugs are not a treatment option due to the high frequency of recurrence on cessation of the drug. Instead, I-131 is the preferred therapy (11,12). Alternatively, some clinicians advocate surgical removal of the toxic nodule. Still others advise surgery only for relatively young patients and I-131 therapy for older patients and those in whom surgery is contraindicated (4).

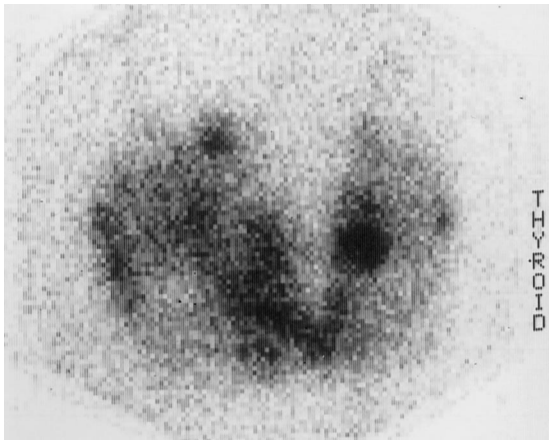


Figure 4. Toxic multinodular goiter in a 71-year-old man with anxiety and weight loss. Laboratory values were as follows: T4 = 12.1 μg/dL, T3 = 299 ng/dL, and TSH < 0.01 μIU/mL. The RAIU was 17% at 6 hours and 37% at 24 hours. Anterior close-up I-123 image shows an enlarged thyroid with overall nonuniform uptake. Areas of both increased and decreased activity are scattered throughout the gland; the increased uptake represents hot nodules, whereas the decreased uptake represents a combination of suppressed extranodular tissue and cold thyroid nodules.

Toxic Multinodular Goiter

Toxic multinodular goiter is best described as a multinodular goiter associated with hyperthyroidism. By definition, a multinodular goiter is a clinical diagnosis made on palpation (or diagnostic imaging) of multiple (ie, two or more) nodules in the thyroid. Although the mechanism is unknown, several of these nodules gradually form areas of hyperplasia that eventually grow into autonomously functioning nodules (13). Consequently, thyroid scintigraphy demonstrates functioning (hot) nodules scattered within suppressed extranodular thyroid tissue. The functioning nodules may eventually secrete enough thyroid hormone for the patient to become hyperthyroid. The thyroid hormone levels are mildly elevated and the TSH level is suppressed, but the RAIU is normal or slightly elevated. This disorder generally occurs in the elderly, unlike Graves disease, and the degree of thyrotoxicosis signs and symptoms is generally milder compared with that in Graves disease. Confusion arises when certain references in the literature use the terms *toxic multinodular goiter* and *Plummer disease* synonymously. Contemporarily, however, most agree that the latter is synonymous with *toxic autonomous nodule* (8).

Scintigraphy demonstrates multiple nodular areas, both cold and hot, resulting in an overall heterogeneous appearance (Fig 4).

Treatment with antithyroid drugs is ineffective. In general, I-131 is most frequently used (14). However, surgical removal of the gland is preferred if the patient has a very large goiter, especially if there is airway compression or substernal extension of the goiter (15). In the latter, I-131 therapy could potentially cause thyroid swelling, thereby increasing airway compromise.

Thyrotoxicosis Associated with Inflammation

Subacute Thyroiditis

Subacute thyroiditis (also known as *subacute granulomatous thyroiditis*, *giant cell thyroiditis*, or *de Quervain thyroiditis*) is a thyrotoxic condition characterized by neck pain, fever, and a tender diffuse goiter. Subacute thyroiditis is presumed to be caused by a viral infection and is usually preceded by an upper respiratory tract infection. A postviral inflammatory response leads to giant cell infiltration into the thyroid follicles, ultimately resulting in follicular swelling and disruption with release of stored thyroid hormone into the circulation (16). The swelling of the thyroid follicles results in stretching of the thyroid capsule with subsequent pain and tenderness to palpation, while the release of excess thyroid hormone results in thyrotoxic signs and symptoms. The TSH level is suppressed, and the RAIU is very low since the affected thyroid is unable to transport or organify iodine.

The disruption of the follicle membranes inhibits the transport of iodine and similar anions such as pertechnetate across the thyroid cells, resulting in no or minimal activity within the gland on scans (Fig 5).

Salicylates and other nonsteroidal anti-inflammatory drugs are usually sufficient to provide symptomatic relief. In more severe cases, steroids are the most effective therapy. Their mechanism of action is suppression of the thyroid inflammation (17).

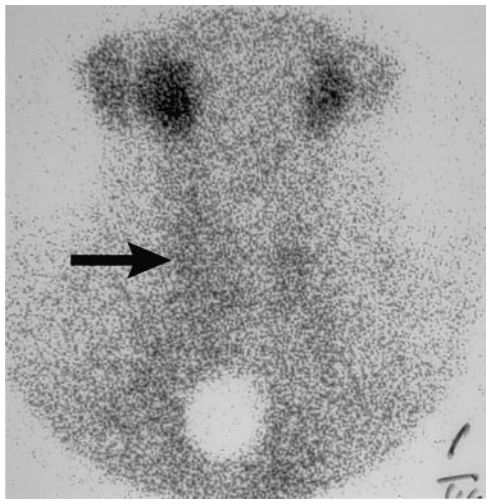


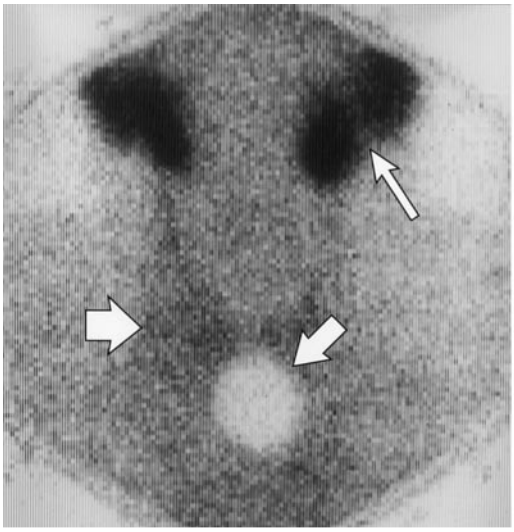
Figure 5. Subacute thyroiditis in a 32-year-old woman with relatively rapid onset of palpitations, insomnia, anxiety, neck pain, and mood swings, all of which were preceded by an upper respiratory tract infection. Physical examination demonstrated neck tenderness. Laboratory values were as follows: free T4 = 2.5 ng/dL, free T3 = 640 ng/L, and TSH < 0.01 μIU/mL. The 24-hour RAIU was 0.5%. Anterior distant Tc-99m pertechnetate image shows minimal thyroid activity (arrow) only slightly higher than background activity.

Silent Thyroiditis

Silent thyroiditis was initially described as a painless variant of subacute thyroiditis and is also known as *painless thyroiditis*, *atypical thyroiditis*, or *subacute lymphocytic thyroiditis*. It is considered a variant form of Hashimoto thyroiditis. An autoimmune response initiates an infiltration of lymphocytes into the thyroid follicles, causing their disruption, with subsequent release of excess thyroid hormone, resulting in thyrotoxicosis (18). Unlike subacute thyroiditis, there is no neck pain or tenderness, since the lymphocytic infiltration in silent thyroiditis results in less follicular swelling compared with the giant cell infiltration and edema characteristic of subacute thyroiditis.

Silent thyroiditis is self-limiting, lasting from several weeks to several months followed by a period of transient hypothyroidism, which in turn is followed by complete recovery to the euthyroid state. This disorder can recur at any time, and about 10% of patients will have recurrent episodes of thyroiditis (19). Serum T3 and T4 levels are high, whereas the TSH level is very low. RAIU measurements are also very low, as with subacute thyroiditis, secondary to cell damage. The thyroid peroxidase antibody levels are elevated, as well as the thyroglobulin antibody titer.

Silent thyroiditis during the postpartum period is called *postpartum thyroiditis* and occurs in 5% of pregnancies. The thyrotoxicosis manifests 2–6 months after delivery and lasts 2–6 weeks, followed by transient hypothyroidism, which also lasts 2–6 weeks. Occasionally the hypothyroidism is permanent.



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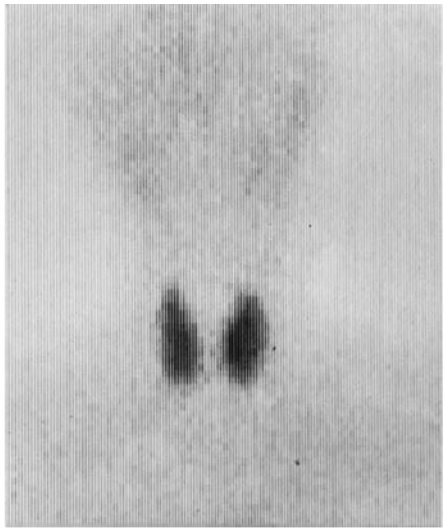

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Figures 6, 7. **(6)** Silent thyroiditis in a thyrotoxic 28-year-old woman. Laboratory values were as follows: T4 = 21 μg/dL, T3 = 289 ng/dL, and TSH < 0.02 μIU/mL. The 24-hour RAIU was 0.6%. Anterior distant Tc-99m pertechnetate image shows a barely visible thyroid (thick arrow). The dark structures (thin arrow) are the salivary glands, which are very prominent due to the low thyroid-to-background activity. The round photopenic area (medium-sized arrow) is the 2-cm lead marker placed at the suprasternal notch. Owing to slight thyromegaly and the patient's morbid fear of thyroid cancer (as diagnosed in a sibling), a large-core needle biopsy was performed, which demonstrated lymphocytic infiltrations within the thyroid parenchyma. (Reprinted, with permission, from reference 34.) **(7)** Silent thyroiditis during the recovery phase in a 55-year-old woman with intermittent episodes of anxiety, palpitations, and irritability. Laboratory values were as follows: free T4 = 1.9 ng/dL, total T3 = 265 ng/dL, and TSH = 0.1 μIU/mL. Physical examination revealed a pulse rate of 68 beats per minute (during β-blockade), and there was no hand tremor. On palpation of the neck, there was no goiter, no palpable nodules, and no tenderness. One week after thyroid function testing, the 24-hour RAIU was 37%. Tc-99m pertechnetate image obtained at this time shows a normal-sized gland with increased thyroid-to-background activity. On thorough questioning, the patient thought that her symptomatic episodes had become slightly less frequent over time (although this conclusion was not entirely reliable due to the β-blockade). The differential diagnosis was Graves disease with both a normal-sized gland and relatively rapid iodine turnover versus a healing or recovery phase of silent thyroiditis. Since the probability of the former was intuitively less likely than that of the latter, the presumptive diagnosis was silent thyroiditis in recovery. We recommended to the patient that any treatment for Graves disease be deferred pending repeated thyroid function testing 4–6 weeks later to definitely exclude the possibility of Graves disease. The results of her thyroid function tests eventually normalized.

As with subacute thyroiditis, there is minimal radiotracer concentration by the thyroid on scans because of the associated follicular cell damage (Fig 6). However, during the recovery phase (which occurs after the period of hypothyroidism), the RAIU increases and the scan demonstrates diffusely increased activity (Fig 7), representing a "rebound" phenomenon. This could potentially lead to confusion with Graves disease without thyroid enlargement, thereby posing a diagnostic dilemma. In general, however, patients recovering from silent thyroiditis either demonstrate somewhat less thyrotoxic symptoms or notice an interval decline in symptoms, whereas a patient with Graves disease without thyromegaly will be more symptomatic (unless elderly) and will not experience an interval decrease in symptoms.

Definitive differentiation between these disorders can be made simply by waiting: A patient recovering from silent thyroiditis will symptomatically improve with time, and results of thyroid function tests will normalize. On the other hand, a patient with Graves disease will not experience abatement of symptoms, nor will results of thyroid function tests normalize. This distinction is crucial to avoid inappropriate treatment with radioiodine of a patient with recovering thyroiditis.

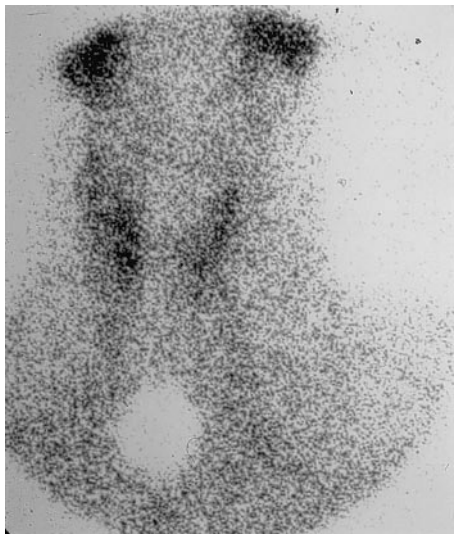


Figure 8. Iodine-induced hyperthyroidism in a 68-year-old man. His history was significant for amiodarone therapy for intractable atrial fibrillation. Laboratory values were as follows: free T4 = 1.7 ng/dL, T3 = 351 ng/dL, and TSH = 0.05 μIU/mL. The 24-hour RAIU was 2.7%. Anterior distant Tc-99m pertechnetate image shows decreased radiotracer trapping throughout the thyroid.

If the imaging specialist is not certain of the diagnosis, he or she should recommend to the clinician that any considerations for treatment be deferred and that thyroid function tests be repeated 4–6 weeks later.

Usually, the thyrotoxicosis resolves spontaneously without treatment, although symptomatic relief from an elevated pulse rate or anxiety can be accomplished with β-blockers (20).

Iodine-induced Hyperthyroidism

Iodine-induced hyperthyroidism occurs insidiously when there is an excessive exposure to iodine, such as with iodine-containing drugs or radiographic contrast agents. Ordinarily, excess iodine administration does not lead to increased thyroid hormone synthesis and release due to a protective saturation mechanism whereby further thyroidal iodine organification is inhibited, which is known as the *Wolff-Chaikoff effect*. Lack of this protective mechanism is occasionally encountered in individuals with an underlying multinodular goiter, particularly those residing in endemically iodine-deficient areas (21). It is presumed that such individuals harbor one or more autonomous areas (nodules) within the thyroid. On iodine repletion, these autonomous areas are then able to synthesize and release excess amounts of thyroid hormone, resulting in thyrotoxicosis. This escape from the protective Wolff-Chaikoff effect is known as the *Jod-Basedow phenomenon*. The prevalence of iodine-induced hyperthyroidism is lower in iodine-sufficient geographic areas such as North America (22).

The iodine-containing drug most commonly associated with iodine-induced hyperthyroidism is amiodarone, an antiarrhythmic cardiac drug used for refractory arrhythmias. Its iodine content is 75 mg per 200-mg tablet. Amiodarone causes thyrotoxicosis by two possible mechanisms: directly via iodine-induced hyperthyroidism per se (ie, loss of the Wolff-Chaikoff effect) or indirectly by inducing a destructive thyroiditis (23). However, hypothyroidism rather than hyperthyroidism is the more common amiodarone-induced thyroid disorder; approximately 20% of patients treated with amiodarone in the United States develop hypothyroidism (24).

In all cases of iodine-induced hyperthyroidism, the thyroid hormone levels are elevated, the TSH level is suppressed, and the RAIU determinations are low due to the excess stable iodine within the gland, which competes with the radioactive iodine for cellular transport and organification. (The RAIU is inversely proportional to the iodine pool within the thyroid.)

Scintigraphy demonstrates diminished tracer concentration uniformly, with both I-123 and Tc-99m pertechnetate, for the same reason that the RAIU is low, namely competitive inhibition by the excess iodine (Fig 8).

Antithyroid drugs in high doses are the treatment of choice, with or without the addition of potassium perchlorate, which blocks further iodine uptake by the gland (25). If this regimen is unsuccessful, steroids are warranted (26).

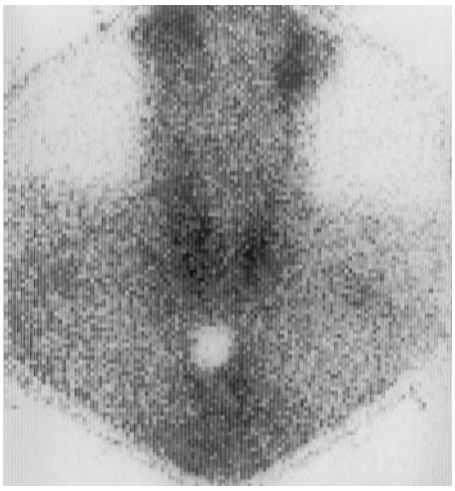


Figure 9. Factitious hyperthyroidism in a 72-year-old male physician who was admitted to the hospital with multiple premature ventricular contractions. The work-up included thyroid function testing, which demonstrated the following values: free T4 = 5.5 ng/dL, T3 = 150 ng/dL, and TSH < 0.01 μIU/mL. The I-123 RAIU at 24 hours was low (2%). Anterior distant I-123 image shows decreased activity throughout the thyroid. The possibility of iodine-induced hyperthyroidism was not considered because there was no known previous iodine administration. The initial presumptive diagnosis was silent thyroiditis. However, the consulting endocrinologist measured the serum thyroglobulin level, which was undetectable; this result essentially confirmed the diagnosis of factitious hyperthyroidism. When confronted with this information, the patient admitted he was secretly taking L-thyroxine (a T4 preparation) to "enhance sexual potency."

Thyrotoxicosis of Extrathyroidal Origin

Factitious Hyperthyroidism

The term *factitious hyperthyroidism* is a misnomer, since the thyroid itself is not overactive. Instead, this condition should be called *factitious thyrotoxicosis*. Nevertheless, the former term refers to thyrotoxicosis due to administration of excess exogenous thyroid hormone, either knowingly or inadvertently. The former is commonly seen with health care personnel, that is, those who are able to obtain thyroid hormone, often for the purpose of weight loss. Such patients become a diagnostic challenge when they present with thyrotoxicosis, since they generally deny ingestion of thyroid hormone or extracts.

Inadvertent excess thyroid hormone use can occur upon ingestion of certain health food store nutrients that contain desiccated thyroid (27). The latter was once mistakenly dispersed into ground beef in a Midwestern town in the United States, an event that subsequently became infamously known as "hamburger thyroiditis" (28). In addition, patients placed on supplementary or suppressive doses of thyroid hormone by their physician could become thyrotoxic if overdosed; this is referred to as *iatrogenic hyperthyroidism*.

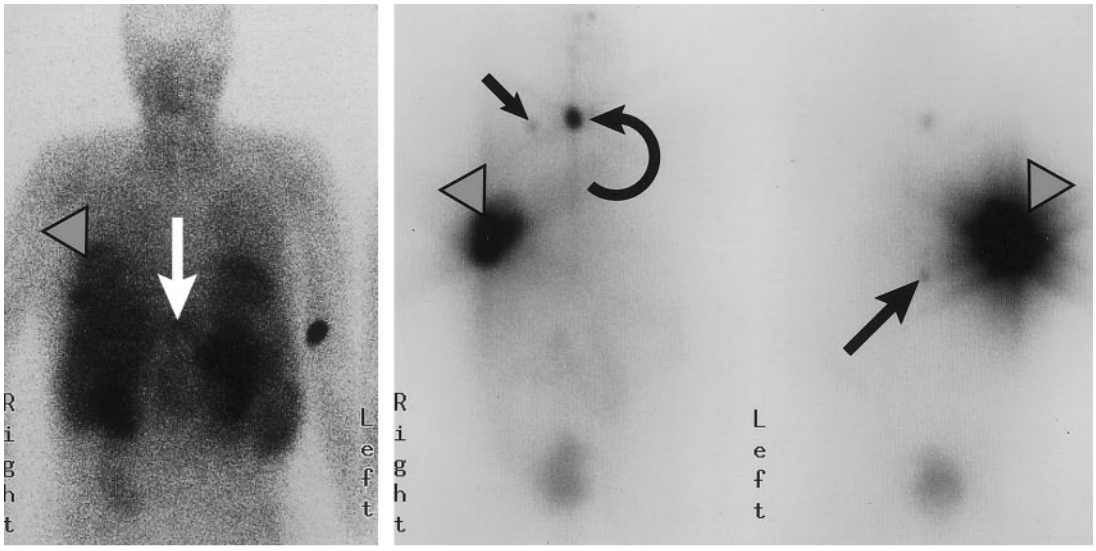
In all cases of factitious hyperthyroidism, there is elevation of the T3 and T4 levels, which in turn suppresses the TSH level via negative feedback. If the hormone ingested is a pure T4 preparation (which is usually the case), then the serum T4/T3 ratio is higher than that seen in endogenous thyrotoxicosis. A helpful diagnostic tool in factitious hyperthyroidism is the serum thyroglobulin level, which is very low or undetectable in this situation. In contrast, the serum thyroglobulin level is generally elevated in endogenous thyrotoxicosis (29).

Since the serum TSH is suppressed, both RAIU and the glandular tracer concentration are decreased (Fig 9).

Treatment is self-explanatory: The patient must discontinue ingestion of thyroid hormone.

Metastatic Thyroid Cancer

Ordinarily, thyroid hormone synthesis and secretion by well-differentiated thyroid carcinomas are much less efficient in comparison with the normal thyroid. Nevertheless, there are reported cases in the literature of patients with metastatic follicular cancer developing thyrotoxicosis. Although the pathogenesis is unknown, it is postulated that the tumors are stimulated to produce thyroid hormone by thyroid-stimulating immunoglobulins (30). It is these same antibodies that are implicated in Graves disease. In most cases, a diagnosis of thyroid malignancy has been well established, so the cause of the thyrotoxicosis is apparent.



a. **b.**

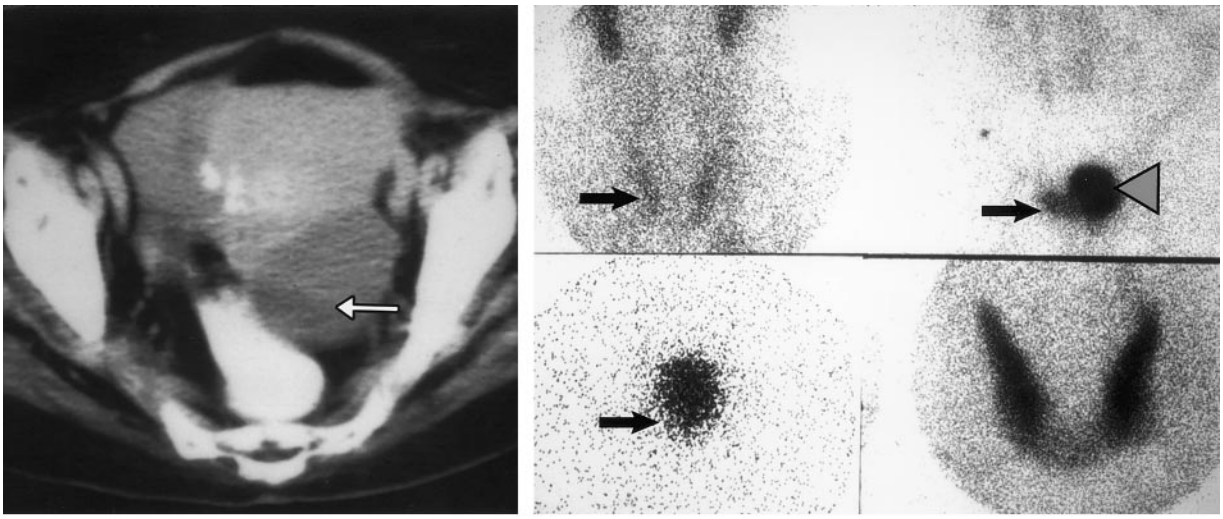
Figure 10. Thyrotoxicosis from metastatic thyroid cancer in a 53-year-old man with a mass compressing the lower thoracic spinal cord and a history of subtotal thyroidectomy for follicular thyroid cancer 5 years earlier (at another institution). Biopsy of the mass revealed metastatic follicular thyroid cancer. Iatrogenic hyperthyroidism from overzealous thyroid suppression with L-thyroxine was the presumptive diagnosis. In preparation for I-131 ablation, L-thyroxine therapy was stopped for 5 weeks. However, the thyrotoxic symptoms persisted; the free T4 level was 2.6 ng/dL, the free T3 level was 752 ng/L, and the TSH level was 0.02 μIU/mL. Computed tomography (CT) of the chest showed a destructive mass in the right chest wall. The diagnosis of thyrotoxicosis caused by metastatic follicular thyroid cancer was made. I-131 ablation was then considered. Thallium-201 whole-body scanning was performed immediately before I-131 ablation. We eliminated the diagnostic I-131 study to save time (scanning is performed 48 hours after administration of the diagnostic dose of I-131) and to avoid the possibility of stunning by the diagnostic dose. **(a)** Anterior Tl-201 whole-body image shows metastases in the right chest wall (arrowhead) and thoracic spine (arrow). **(b)** Anterior (left) and posterior (right) postablation I-131 images obtained 1 week after administration of 200 mCi (7,400 MBq) of I-131 show thyroid bed uptake (curved arrow), a right infraclavicular lymph node (small straight arrow), the chest wall metastasis (arrowheads), and the thoracic spine lesion (large straight arrow).

The diagnosis of metastatic thyroid cancer is often established by thyroid cancer whole-body imaging with 5–10 mCi (185–370 MBq) of I-131 or by postablation I-131 scanning. A scan positive for metastases, in conjunction with high thyroid hormone levels and a suppressed TSH level, would confirm a suspected diagnosis of thyrotoxicosis secondary to metastatic thyroid cancer (Fig 10).

In patients with multiple metastases, treatment with I-131 is more effective than surgery. However, if a single metastasis is causing the thyrotoxicosis, then surgical removal is warranted, provided the lesion is accessible.

Struma Ovarii

Struma ovarii is a very rare teratomatous ovarian tumor that contains functioning thyroid tissue. It is usually benign and is most commonly discovered by the pathologist when an ovarian tumor is removed. In most instances, the thyroid tissue within the tumor does not produce a significant amount of thyroid hormone (31). In a minority of cases, however, the tumor behaves autonomously and produces excess thyroid hormone. This in turn suppresses the normal (cervical) thyroid and causes thyrotoxicosis. Serum T3 and T4 levels are elevated, and the TSH level is suppressed. Most often these tumors are insidious, so a strong clinical suspicion for their diagnosis, such as signs and symptoms relating to the abdomen or pelvis, needs to be present. There are other pelvic tumors that cause thyrotoxicosis, namely the trophoblastic tumors such as hydatidiform moles and choriocarcinomas. These tumors secrete human chorionic gonadotropin, which is a thyroid stimulator (32).



a. b.

Figure 11. Struma ovarii in an 81-year-old woman with thyrotoxicosis, ascites, and a pelvic mass. Laboratory values were as follows: T4 = 13.7 μg/dL, T3 = 200 ng/dL, and TSH < 0.01 μIU/mL. The initial imaging study was pelvic CT. **(a)** CT scan shows a left ovarian mass (arrow). **(b)** Top left: Anterior distant Tc-99m pertechnetate image shows decreased tracer activity in a small thyroid (arrow). The 24-hour RAIU was 3%. Because of the known pelvic mass, imaging of the pelvis was also performed. Top right: Anterior image shows the pelvic mass (arrowhead) displacing the bladder to the right (arrow). To optimally image the pelvic mass without the background activity that appears with Tc-99m pertechnetate, scanning was repeated with I-123. Bottom left: I-123 image obtained after voiding shows the mass (arrow). At surgery, the entire left ovary was removed, revealing a large struma ovarii containing thyroid tissue, which stained positive for thyroglobulin. Thyroid function soon returned to normal. Two months later, the 24-hour RAIU was 16%; Tc-99m pertechnetate scanning was performed. Bottom right: Anterior close-up Tc-99m pertechnetate image of the thyroid shows normal tracer concentration. Ectopic thyroid tissue within the pelvis is better visualized with I-123 than with pertechnetate, since the bladder is visible with the latter. Conceivably, this visibility could result in the bladder obscuring the ectopic thyroid tissue or erroneously being interpreted as representing the thyroid tissue.

Suppression of the thyroid by the ectopic thyroid hormone lowers both the RAIU as well as the tracer uptake by the thyroid. The ovarian tumor itself is visualized in the pelvis (Fig 11).

Surgical removal is the treatment of choice.

TSH-induced Thyrotoxicosis

The term *TSH-induced thyrotoxicosis* refers to an adenoma within the anterior pituitary gland that produces an excessive amount of TSH, which in turn overly stimulates the thyroid, resulting in goiter and thyrotoxicosis (33). In addition, often noted are symptoms related to a mass effect within the suprasellar region, such as headache or diplopia. TSH-secreting pituitary tumors are extremely rare and account for less than 1% of all pituitary tumors. The high TSH levels lead to elevation of the thyroid hormone levels and RAIU. Unlike in practically all other causes of thyrotoxicosis, it is the elevated TSH level that should lead to consideration of a TSH-secreting pituitary tumor, for which a brain imaging study such as CT or magnetic resonance imaging would be the next logical step.

Scintigraphy demonstrates increased tracer concentration in the thyroid due to stimulation by TSH. Target-to-background activity is elevated, similar to that seen in Graves disease (Fig 12).

Surgical removal of the pituitary gland is the cornerstone of therapy.

Conclusions

The patient with thyrotoxicosis is a diagnostic challenge to the clinician; symptoms can be mild to severe, signs can be subtle to obvious. Regardless, the correct underlying cause must be determined for appropriate management and therapy. The history and physical examination, along with thyroid function tests, enable the clinician to make the diagnosis of thyrotoxicosis. Diagnostic imaging of the thyroid further aids the clinician in determining the underlying cause. As a functional imaging modality, thyroid scintigraphy (in conjunction with RAIU measurement) is the logical diagnostic imaging study.

It is our role as imaging specialists to correctly interpret the study results. At times this may be difficult, since there is an overlap in scintigraphic appearance among different diseases: Subacute thyroiditis, silent thyroiditis, iodine-induced hyperthyroidism, and factitious hyperthyroidism all have similar scintigraphic appearances and RAIU levels, namely very low RAIU values and poor thyroidal radiopharmaceutical concentration. However, subacute thyroiditis can be excluded on clinical grounds by the absence of neck pain or tenderness. The possibility of iodine-induced hyperthyroidism is excluded in the absence of a history of iodine administration or ingestion, and factitious hyperthyroidism is ruled out by an elevated serum thyroglobulin level. If all of these possibilities are eliminated, then silent thyroiditis is the most likely diagnosis. If any of this information is not available at the time of scan interpretation, then the differential diagnosis should be provided, at the very least. The more clinical information and pertinent facts we gather and utilize at the time of scan interpretation, the greater our ability to narrow the differential diagnosis and the more helpful we are to the referring physician. This in turn enhances our role as consultants rather than image interpreters.

One difficulty that sometimes arises when interpreting thyroid scans and reporting the results in this clinical setting is the fact that there are variations in the terminology used by clinicians in defining certain nodular thyrotoxic diseases. For example, confusion may arise in the case of *Plummer disease*, which is defined by some as a single hyperfunctioning nodule causing hyperthyroidism and by others as multiple nodules causing hyperthyroidism. The current consensus (8) is that *Plummer disease* is the eponym for a toxic autonomous nodule or toxic adenoma (either one or two hyperfunctioning nodules) that suppresses the remainder of the gland (which is normal thyroid tissue). When reporting such findings on a thyroid scan, it is preferable to use the term *toxic autonomous nodule* or *toxic adenoma* rather than *Plummer disease* to avoid such confusion. This is not to be mistaken for *toxic multinodular goiter*, which denotes a heterogeneous gland with numerous hyperfunctioning nodules on a background of suppressed extranodular tissue and hypofunctioning nodules. However, exact distinction between the two disorders is not essential, since the treatment of choice in both disorders is radioiodine therapy.

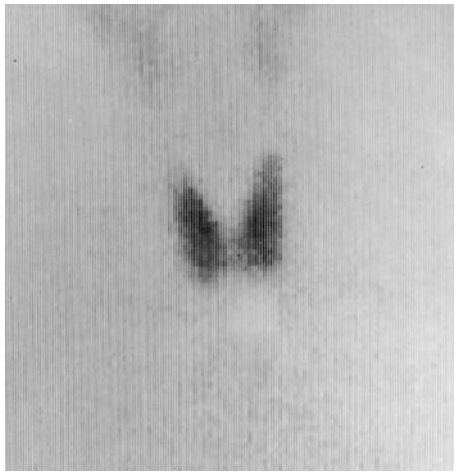


Figure 12. TSH-induced thyrotoxicosis in a 33-year-old woman. Laboratory values were as follows: free T4 = 2.0 ng/dL, T3 = 191 ng/dL, and TSH = 37.1 μIU/mL. The latter measurement was repeated, and the value was 39.0 μIU/mL. Anterior distant Tc-99m pertechnetate image shows relatively high target-to-background activity, similar to that seen in Graves disease. CT of the brain performed at an outside imaging center revealed a pituitary tumor. Upon removal of the tumor, the symptoms subsided and thyroid function returned to normal.

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