Chapter 8
Exogenous Thyrotoxicosis

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Objectives

Ingestion of excessive amounts of thyroid hormone, whether intentionally or unintentionally, results in exogenous thyrotoxicosis. Surreptitious ingestion of thyroid hormone for the purpose of feigning hyperthyroidism is more precisely termed factitious thyrotoxicosis. Less commonly, however, exogenous thyrotoxicosis may result from *inadvertent* ingestion of thyroid hormone. This can be a challenging diagnosis to establish and requires a high index of clinical suspicion. Here, we report the case of a 33-year-old woman with an 18 month history of progressive, severe hyperthyroidism who had unknowingly been consuming thyroid hormone contained in an herbal weight-loss supplement. We review the etiologies, evaluation, and treatment of exogenous thyrotoxicosis.

Case Presentation

A 33-year-old woman with no history of thyroid disease was referred for evaluation of hyperthyroidism of unclear etiology. The patient had seen two prior endocrinologists and no explanation had been found for her progressive hyperthyroidism. She had presented 18 months earlier with anxiety, diaphoresis, tremor, weight loss, and tachycardia, especially while exercising. These symptoms began 18 months after

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the birth of her second child. She had no complaints of anterior neck discomfort and had not had any recent illness. Thyroid function tests drawn at the onset of these symptoms revealed a thyroid-stimulating hormone (TSH) 0.03 mU/L (normal, 0.40–4.50), free thyroxine (T4) 1.24 ng/dL (normal, 0.8–1.8), and triiodothyronine (T3) 180 ng/dL (normal, 60–181). A technetium scan showed diminished thyroid uptake, suggestive of thyroiditis.

Over the course of the next 6 months, the patient progressed to overt hyperthyroidism, with a TSH <0.01 mU/L (normal, 0.40–4.50), free T4 2.1 ng/dL (normal, 0.8–1.8), and T3 356 ng/dL (normal, 60–181). A radioiodine uptake was 4.9 % at 24 h (normal, 18–35 %), with a heterogeneous pattern seen in both lobes. A thyroid sonogram showed a normal gland with a tiny cyst in the left lobe. To exclude the possibility that iodine contamination contributed to the low 24-h radioiodine uptake, a 24-h urine iodine level was obtained and measured 313 mcg (normal, 100–460).

Eighteen months after the onset of symptoms, the hyperthyroidism had become more severe with a free T3 > 2,000 pg/dL (normal, 230–420), free T4 6.4 ng/dL (normal, 0.8–1.8), and TSH < 0.01 mU/L (normal, 0.40–4.50). A repeat 24-h radioiodine uptake was 2.5 % (normal, 18–35 %) and scan of the patient's body including the thorax, abdomen, and pelvis showed no tracer uptake. Antithyroglobulin, antithyroperoxidase, and thyroid stimulating immunoglobulin levels were negative. The serum thyroglobulin was 1.4 ng/mL (normal, 2.0–35.0). Despite the lack of evidence of endogenous hyperthyroidism by imaging and laboratory studies, a second endocrinologist started the patient on methimazole 10 mg twice daily. This was ineffective at normalizing thyroid function, so the patient was referred to our endocrine clinic for further evaluation.

The patient had recently been diagnosed with depression in the setting of a marital separation. Her prescribed medications included methimazole 20 mg daily, fluoxetine, and an oral contraceptive pill. She denied taking any exogenous thyroid hormone preparations, but admitted to taking Redline, an herbal supplement advertised on the internet as a "multisystem rapid fat loss catalyst." It contains a number of stimulants including caffeine, synephrine, yohimbine, and other compounds. Previously, the patient had taken another weight loss supplement, Hydroxycut. Thyroid hormone is not listed as an ingredient in either of these supplements.

On physical examination, the blood pressure was 134/86, pulse was 133, weight 117 pounds. The patient was slightly hyperkinetic and anxious. There was no proptosis, lid lag, or conjunctival injection. The thyroid gland was not palpable. Lungs, heart, and abdomen were unremarkable. There was a fine tremor of the outstretched hands. Deep tendon reflexes were brisk. The skin was warm and moist.

The patient was strongly urged to discontinue Redline and any other herbal supplements she might be taking. She was also advised to stop the methimazole. Eight weeks later, the patient was euthyroid with a TSH 0.79 mU/L (normal, 0.40–4.50), free T4 0.96 ng/dL (normal, 0.8–1.8), and T3 141 ng/dL (97–219). The patient gained three pounds and her hyperthyroid symptoms resolved.

Background

Exogenous thyrotoxicosis can be intentional or inadvertent (Table 8.1). The most common and easily recognizable etiology is iatrogenic thyrotoxicosis. An excessive dose of thyroxine may intentionally be prescribed to suppress TSH secretion in the management of thyroid cancer or goiter. In some cases, patients insist on supraphysiologic doses of thyroxine to maintain energy or lose weight, frequently dismissing healthcare providers who do not accommodate their request. This condition has been termed "thyrotoxicosis insistiates" [1].

The intentional and surreptitious ingestion of thyroid hormone to feign the diagnosis of hyperthyroidism is factitious thyrotoxicosis. A form of Munchausen's syndrome, this psychiatric disorder is motivated by the patient's desire to assume the sick role for emotional gain [2]. This is most commonly observed in young or middle-aged women with a history of childhood emotional deprivation and/or current sexual or relationship problems; in some cases, the patient may carry a diagnosis of borderline personality disorder or post-traumatic stress disorder [3]. Other suggestive historical features may include a connection to the healthcare profession, lack of appropriate concern for health problems, or a past history of feigning illness [2]. On the other hand, thyroid hormone abuse may also be observed in individuals without an underlying psychiatric disorder, usually for the purpose of weight loss [4]. In these cases, the patient's motivation is not to feign a medical condition, but rather to derive perceived benefits of hyperthyroidism (weight loss, increased energy, etc.) [4].

As challenging as it may be to diagnose factitious thyrotoxicosis, it can be even more difficult to identify cases of inadvertent thyrotoxicosis. In some cases, the problem may be as simple as a pharmacy or patient medication error. For patients already prescribed thyroid hormone, it may be helpful to verify that they are taking the prescribed dose by having them bring in their medications for review and/or

Table 8.1 Examples of clinical situations resulting in exogenous thyrotoxicosis

Intentional	Inadvertent
1. Iatrogenic (a) Suppressive thyroxine dose in thyroid cancer (b) Excessive thyroxine dose to shrink goiter (c) Patient's insistence on higher thyroid hormone dose 2. Factitious (a) Surreptitious ingestion of thyroid hormone to feign hyperthyroidism 3. Thyroid hormone abuse (a) Supplements or thyroid hormone/extracts usually taken for the purpose of weight loss, without willful intention to feign hyperthyroidism	1. Medication error (i.e., patient or pharmacy) 2. Accidental ingestion of another person's or (rarely) pet's thyroxine dose in place of the patient's dose 3. Accidental overdose (i.e., children) 4. Meat contamination with thyroid hormone ("hamburger thyrotoxicosis") 5. Ingestion of herbal/weight loss supplements but unaware that thyroid hormone is an unspecified ingredient

contacting their pharmacy. One unusual cause of medication error is inadvertent ingestion of a pet's thyroxine dose in place of prescribed thyroxine [5]. Accidental thyroxine poisoning has occurred in young children with access to the medication [6, 7]. Rarely, outbreaks of thyrotoxicosis have occurred following consumption of ground beef contaminated with bovine thyroid gland (so-called hamburger thyrotoxicosis) [8].

In recent years, there have been increasing reports of accidental overdose of thyroid hormone caused by weight-reducing herbal medications containing thyroid hormone as a hidden ingredient [9, 10]. The use of herbal or natural supplements is widespread in the USA and these products are not regulated by the FDA. Surprisingly, as many as 7 % of such supplements contain undisclosed substances [9]. It has been estimated that half of patients do not disclose their use of supplements to physicians [9]. Some easily accessible nonprescription supplements taken for the purposes weight loss, energy, or "thyroid support" have been found to contain clinically significant amounts of T3 and T4 [9–11]. Therefore, the use such supplements poses a serious risk of hyperthyroidism-related cardiovascular complications. In some instances, supplements adulterated with thyroid hormone may have a beta-blocker added to mask hyperadrenergic symptoms, which could make recognition of the thyrotoxic patient even more difficult [9]. In patients with underlying thyroid disease, exogenous thyrotoxicosis can complicate the clinical picture and lead to a delay in diagnosis [10].

How the Diagnosis Was Made

The patient described in the case above presented with classic features of hyperthyroidism. Given the absence of a goiter or exophthalmos, a nontender thyroid gland, and low radioiodine uptake, the initial suspicion was that she had painless thyroiditis. The onset of symptoms 18 months after the delivery of her child made postpartum thyroiditis less probable, as this typically occurs at a shorter interval (2–12 months) after delivery.

At the outset, conservative management was recommended with the expectation that the hyperthyroid phase of thyroiditis would resolve within 3–4 months; instead, the hyperthyroidism persisted and progressed over the subsequent 18 months. Repeat radioiodine uptake was persistently low. The differential diagnosis for thyrotoxicosis associated with decreased radioiodine uptake includes various forms of thyroiditis, exogenous thyrotoxicosis, and excess iodine intake (radiographic contrast, amiodarone, iodine supplementation). Table 8.2 summarizes features that distinguish exogenous thyrotoxicosis from these other causes. Struma ovarii was another etiology considered in her case, but this was excluded by absence of ectopic uptake on whole body scan. With a normal urine iodine level, iodine contamination was ruled out as a cause of low radioiodine uptake. The patient was not taking any medications known to cause thyroiditis. The absence of thyroid autoantibodies provided further evidence against underlying thyroid disease.

Table 8.2 Distinguishing exogenous thyrotoxicosis from other causes of thyrotoxicosis associated with decreased radioiodine uptake

Factor	Exogenous thyrotoxicosis	Other causes of thyrotoxicosis associated with decreased radioiodine uptake
Thyroid function tests	Low TSH, high free T4, high T3	Low TSH, high free T4, high T3
Ratio of T3/T4	Suggested by high T3/T4 ratio (>19), but not excluded by low T3/T4 ratio (<16) [12]	T3/T4 ratio usually <16 [12]
Thyroid autoantibodies	Absent, unless underlying thyroid disease	May be positive in painless or postpartum thyroiditis
Physical examination	Normal or nonpalpable, nontender thyroid; absence of exophthalmos or other stigmata of Graves' disease	Thyroid may be enlarged or tender to palpation in some types of thyroiditis
Inflammatory markers	Normal	Elevated ESR, CRP, leukocytosis, in subacute thyroiditis
Duration of thyrotoxicosis	Variable, depending on duration of exogenous thyroid hormone intake	Usually 3–4 months in thyroiditis
24-h radioiodine uptake	Low (usually <1 %); may be higher in patients with underlying autonomy (toxic nodules)	Low (usually <1 %)
Serum thyroglobulin	Low, but not necessarily undetectable	Normal or high (may be low in presence of antithyroglobulin antibodies)
Urine iodine	Normal	Very high in cases of excess iodine (i.e., radiographic contrast, amiodarone, iodine supplementation)
Fecal thyroid hormone measurement	High	Normal

Since an 18 month phase of hyperthyroidism in the context of thyroiditis would be untenable, the differential diagnosis was narrowed down to exogenous thyrotoxicosis. This was corroborated by the patient's very low serum thyroglobulin level. Thyroglobulin can be a helpful diagnostic clue in this setting because it is typically low (though not necessarily undetectable) in exogenous thyrotoxicosis, whereas it is high in thyroiditis and endogenous hyperthyroidism [1]. It should be noted that serum thyroglobulin levels may not be suppressed to undetectable levels in all cases of exogenous thyrotoxicosis, particularly in those with adenomatous goiter or persistent thyroid cancer [10]. Regrettably, a thyroglobulin level was not obtained early in this patient's course, and this may have contributed to the long delay in diagnosis.

In addition, the markedly elevated T3 and T4 concentrations in this case suggested that the patient was either consuming thyroid extract or a combination of synthetic T4/T3. A high total T3/total T4 ratio (>19) in conjunction with low radioiodine uptake is a pattern unique to exogenous thyrotoxicosis resulting from

combination T4/T3 ingestion. By contrast, thyroiditis typically results in a lower total T3/total T4 ratio (typically <16) [12]. In clinical practice, the T3/T4 ratio is typically used to distinguish between endogenous hyperthyroidism (i.e., Graves' disease or toxic adenoma) and destructive thyroiditis, but it has a limited role in distinguishing thyroiditis from exogenous thyrotoxicosis [12]. This is because patients taking pure thyroxine have elevations in both T3 and T4 with a ratio that may overlap with that observed in thyroiditis [12]. In other words, only a high T3/T4 ratio has discriminative value in this context.

In this case, the patient explicitly denied taking exogenous thyroid hormone. With the exception of recent depression in the setting of marital problems, she had no history of a personality disorder or connection to the medical profession, and she seemed truly bothered by her symptoms. When it was discovered that she was taking an herbal weight-loss supplement, the ingredients were carefully scrutinized. Although the Redline capsules were not subjected to laboratory analysis for detection of thyroid hormones, the prompt resolution of thyrotoxicosis with discontinuation of this supplement suggests that it was indeed the culprit. Another method that could have aided in the evaluation is measurement of fecal thyroxine content, which may be markedly elevated in cases of exogenous thyrotoxicosis due to thyroxine ingestion [13].

Treatment

Typically, the only treatment required in exogenous thyrotoxicosis is discontinuation or reduction in the dose of thyroid hormone. L-thyroxine has a half-life of 7 days, so it takes approximately 5 weeks for the drug to be cleared. Liothyronine is cleared more rapidly, with a serum half-life of approximately 1 day. Patients who are very symptomatic may require beta-adrenergic blockade while awaiting resolution of thyrotoxicosis. In cases of massive overdose of thyroid hormone, management may consist of induced emesis, gastric lavage, and intragastric installation of charcoal [14]. Cholestyramine can also be given as intestinal binder of T4 and T3, thereby interrupting the normal enterohepatic circulation of the two hormones [14]. Plasmapheresis and exchange transfusion have been used to treat massive thyroid hormone overdose [14]. Fortunately, most patients, especially children, have few signs and symptoms of hyperthyroidism following accidental poisoning, and conservative management is usually satisfactory [14].

Lessons Learned

1. Exogenous thyrotoxicosis is not always intentional.
2. Thyroid hormone may be an undisclosed ingredient in many herbal supplements advertised as weight loss, energy, or "thyroid support" agents.

3. Diagnostic clues to exogenous thyrotoxicosis include the absence of a goiter or exophthalmos, a nontender thyroid gland, low radioiodine uptake (after exclusion of iodine contamination), low serum thyroglobulin, and high fecal thyroxine content.
4. The hyperthyroid phase in thyroiditis does not typically last longer than several months; therefore, in cases where thyrotoxicosis persists for a longer duration, the differential diagnosis should be expanded to include exogenous thyrotoxicosis.
5. A careful review of medications, including non-prescription over-the-counter or herbal supplements, should be undertaken when exogenous thyrotoxicosis is suspected.
6. A high T3/T4 (>19) ratio in the setting of a low radioiodine uptake favors exogenous thyrotoxicosis over thyroiditis as the etiology.

Questions

1. A 52-year-old woman with no prior history of thyroid disease is referred to you for unexplained hyperthyroidism of 1 year duration. On physical examination, there is no exophthalmos and the thyroid is small and nontender. Which of the following tests would be most helpful test in differentiating painless thyroiditis from exogenous thyrotoxicosis?

   A. Antithyroperoxidase antibody, antithyroglobulin antibody, and serum thyroglobulin
   B. Radioiodine uptake and scan
   C. T3/T4 ratio
   D. Erythrocyte sedimentation rate

2. A 28-year-old woman with a history of Hashimoto's thyroiditis returns for follow-up. She had been prescribed levothyroxine 112 mcg daily for several years and had consistently normal thyroid function tests during regular visits. She noticed that her hair was coarse and falling out in the shower, and wondered whether the levothyroxine "was working." She did some research on the internet and found an herbal supplement that claimed to provide more "natural" thyroid hormone support. She decided to stop the levothyroxine and has been taking three tablets of this herbal supplement twice daily for the last 3 months. You investigate the "thyroid support" supplement and do not see thyroid hormone listed as an ingredient. When you examine her, she appears hyperkinetic and anxious. She has lost 12 pounds since last visit and her BMI is 17 kg/m^2. Her pulse is 118, blood pressure 138/72. She has a nonpalpable, nontender thyroid gland. TSH is <0.01 mU/L (normal, 0.40–4.50), free T4 2.5 ng/dL (normal, 0.8–1.8), and T3 300 ng/dL (normal, 60–181). Which of the following is the preferred treatment strategy?

A. Refer her to a psychiatrist to evaluate for factitious disorder.
B. Advise her to reduce the dose of her supplement to three tablets once daily and recheck thyroid function tests in 6 weeks.
C. Obtain a serum thyroglobulin level and fecal thyroxine measurements.
D. Tell the patient she most likely has painless thyroiditis and arrange for an I-123 uptake and scan.
E. Advise the patient to stop the "thyroid support" supplement. Inform her that these products are not regulated by the FDA and may contain undisclosed amounts of thyroid hormone, placing her at risk of complications related to thyrotoxicosis.

3. A 68 year old woman with papillary thyroid cancer returns to see you with her husband, who is also your patient. The patient has a history of atrial fibrillation and osteoporosis. She underwent total thyroidectomy followed by radioactive iodine remnant ablation 15 years earlier and has been in remission from her thyroid cancer since. You have been aiming to maintain her serum TSH level in the normal range, and she has been well-controlled on a stable dose of L-thyroxine for years. She was recently hospitalized for an episode of atrial fibrillation with rapid ventricular response and was noted to have a TSH < 0.01 mU/L (normal, 0.40–4.50), free T4 2.9 ng/dL (0.8–1.8). The hospital team reduced her dose of levothyroxine from 150 mcg to 50 mcg daily. Thyroid function studies at the time of her visit with you show a TSH of 10.4 mU/L (normal, 0.40–4.50), free T4 0.7 ng/dL (normal, 0.8–1.8). She reports that she had been taking the medication as you prescribed. In fact, she has all of her medications organized in a pill box at home. She denies taking any herbal or over-the-counter supplements. Which of the following is the preferred treatment strategy?

A. Arrange for thyrogen-mediated thyroglobulin and whole body scan to exclude recurrent thyroid cancer.
B. Obtain a serum thyroglobulin level.
C. Contact the patient's pharmacy to verify recent medications dispensed. Ask the patient to bring in the bottles of all the medications she is taking and inquire about any over-the-counter or herbal supplements.
D. Order a 24-h urine iodine level.
E. Check a free and total T3 level.

Answers to Questions

1. A: Laboratory tests in patients with exogenous thyrotoxicosis mimic those of thyrotoxicosis caused by thyroiditis. Both conditions show low radioiodine uptake, so answer choice B is incorrect. The total T3/total T4 ratio can sometimes be helpful to distinguish between thyroiditis and exogenous thyrotoxicosis. In the former, it is usually low (<16), while in the latter it can overlap with

the pattern seen in endogenous hyperthyroidism (>19). However, in cases of exogenous T4 ingestion alone (i.e., without T3), the T3/T4 ratio may not distinguish between thyroiditis and exogenous thyrotoxicosis. In this context, the T3/T4 ratio has discriminative value only when very high, as this would be unusual for thyroiditis. Therefore, answer choice C is not correct. Thyroid autoantibodies are positive in a majority of individuals with painless or postpartum thyroiditis; these levels are typically positive early in the course of painless thyroiditis and usually remain elevated even after normalization of thyroid function. The thyroglobulin level will best distinguish between thyroiditis and exogenous thyrotoxicosis. In the former, it will be high, and in the latter it will be low. It is important to know the thyroid autoantibody status of the patient when interpreting the serum thyroglobulin level as it may be falsely low in the setting of positive antithyroglobulin antibodies. Thus, answer choice A is correct.

2. E: The patient has disclosed that she is taking thyroid hormone to you; therefore, the diagnosis is not factitious thyrotoxicosis, so answer choice A is incorrect. The "thyroid support" supplement almost certainly contains an undisclosed amount of T3 and T4. Since the amount of these compounds is uncertain, it would be difficult for the physician to safely adjust the dose of this compound to achieve euthyroidism, so answer choice B is incorrect. Answer choice C would be a possible choice to evaluate for factitious thyrotoxicosis, but the patient does not have this condition. Rather, this clinical picture is better described as unintentional thyroid hormone abuse. Painless thyroiditis is less likely than thyroid hormone abuse in this clinical scenario, so answer choice D is incorrect. The correct answer is E. The patient should be urged to stop the herbal supplement.
3. C: This is most likely a case of iatrogenic thyrotoxicosis due to a medication error. The fact that the patient's husband is also your patient raises the possibility that she may have inadvertently taken his higher thyroxine dose in place of hers. This resulted in thyrotoxicosis, which likely contributed to the episode of atrial fibrillation w/rapid ventricular response. Careful review of her medications to verify that the she was taking the correct dose is the first-step in management. It may be helpful to contact the pharmacy to verify that the correct dose was recently dispensed. Although thyrotoxicosis can be observed in some cases of metastatic thyroid cancer, this would be less likely given the patient's long duration of remission, so answer choices A and B are incorrect. The patient is status post total thyroidectomy. Urinary iodine would be used to exclude iodine contamination obscuring the interpretation of a radioiodine uptake and scan, which is not directly applicable to this case. Since the patient does not have a thyroid gland, there is no concern for T3-toxicosis, unless there is suspicion that she is taking a supplement containing T3. Given her long history of stable thyroid function on levothyroxine, this is highly unlikely, so answer choice E is incorrect.

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