

37-Year-Old Woman With Palpitations and Fatigue

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A 37-year-old woman presented to the emergency department with palpitations, fatigue, and exertional dyspnea of 2 months' duration. The palpitations were persistent at rest and were not associated with anxiety. Review of the patient's medical history revealed that a prior pregnancy was complicated by postpartum cardiomyopathy. She was afebrile, had tachycardia (120 beats/min), and had a normal blood pressure of 118/64 mm Hg. Findings on physical examination were unremarkable, apart from trace bilateral lower extremity edema. Cardiac assessment yielded negative results, other than sinus tachycardia revealed on electrocardiography. The patient was referred to the general internal medicine clinic.

Ten days later she was seen in the medicine clinic with symptoms of semiformal bowel movements after each meal; progressive fatigue, light-headedness, and diaphoresis associated with palpitations; and a 5.5-kg weight loss over 2 months. Her menstrual cycles were normal, and she denied any fevers, chills, or rigors. She had a regular heart rate of 99 beats/min, a blood pressure of 112/70 mm Hg, and a body mass index of 26.9 kg/m². A nontender diffusely enlarged and smooth but firm thyroid gland with audible bruit was noted. A soft, midsystolic murmur was present at the left upper sternal border. There was a slight lid lag, but no significant exophthalmos, extraocular muscle weakness, or pretibial dermopathy. Her thyroid-stimulating hormone (TSH) level was suppressed to 0.05 mIU/L (reference ranges provided parenthetically) (0.3-5.0 mIU/L).

1. Which one of the following diagnoses most likely explains this patient's clinical presentation?

- Graves disease
- Subacute granulomatous thyroiditis
- Hashimoto (chronic lymphocytic) thyroiditis
- Toxic multinodular goiter
- Papillary carcinoma of the thyroid

Graves disease is the most likely diagnosis and is supported by the subacute to chronic course; the symptoms of thyrotoxicosis, including tachycardia, palpitations, diaphoresis, weight loss, and diarrhea; a suppressed TSH level; and physical examination findings of diffuse thyromegaly with thyroid bruit. As opposed to Graves disease, which causes painless thyromegaly, subacute granulomatous thyroiditis usually has a self-limiting course and causes painful and tender thyroid enlargement, often associated with transient hyperthyroidism due to thyroid hormone release

from the inflamed thyroid follicles. Hashimoto thyroiditis is a painless chronic thyroid disorder characterized by lymphocytic inflammation of the thyroid. It commonly leads to hypothyroidism, although transient hyperthyroid episodes can occasionally occur early in the disease course. Toxic multinodular goiter has discrete palpable thyroid nodules as opposed to the diffuse thyromegaly observed in this case. Papillary carcinoma usually does not cause any biochemical thyroid hormone abnormalities and can present as an incidentally noted thyroid nodule on imaging, a palpable thyroid nodule with or without fixation to surrounding tissues and ipsilateral cervical lymphadenopathy, or as new-onset hoarseness or vocal cord paralysis.^{1,2}

A complete thyroid profile yielded the following results: TSH, 0.05 mIU/L (0.3-5.0 mIU/L); free thyroxine (T₄), 5.3 ng/dL (0.8-1.8 ng/dL); and free triiodothyronine (T₃), 15.4 pg/mL (2.0-3.5 pg/mL).

2. An elevation in which one of the following is most specific for Graves disease?

- TSH receptor antibodies (TRAb)
- Thyroid-stimulating immunoglobulin (TSI)
- TSH receptor–blocking antibodies
- Antithyroid peroxidase antibodies
- Antithyroglobulin antibodies

The TRAb bind to the TSH receptor and have 2 subtypes: TSI and the TSH receptor–blocking antibodies. The TSI subtype is elevated in Graves disease and correlates with thyroid disease activity. Assays for both TRAb and the TSI subtype are elevated in Graves disease, but TSI is more specific for this diagnosis. However, TSI is a bioassay and is thus much more expensive and has a longer turnaround time than TRAb, which is an immunoassay. The TSH receptor–blocking antibody subtype, which can also be measured using a bioassay, can occasionally be present in Graves disease but may also be present in other autoimmune thyroid disorders. Antibodies to antithyroid peroxi-

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See end of article for correct answers to questions.

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dase and antithyroglobulin can be nonspecifically elevated in any thyroiditis.¹

The patient returned for follow-up 1 week later with worsening palpitations and increasing neck swelling. Her level of TSI was increased at 2.2 TSI index (≤ 1.3 TSI index). The urine pregnancy test yielded negative results. The patient was prescribed propranolol for symptomatic relief of her palpitations.

3. Which one of the following would be the most appropriate next step in the management of this patient?

- a. Endocrinology consultation to discuss treatment of Graves disease
- b. Surgical consultation to evaluate for thyroidectomy
- c. Initiation of antithyroid drug (ATD) therapy
- d. 24-Hour radioactive iodine (RAI) uptake thyroid scan
- e. Ultrasonographic evaluation of the neck and thyroid

An endocrinology consultation is recommended for the management of Graves disease but would be most appropriate after completing the evaluation. Surgical thyroidectomy and antithyroid medications are among treatment options; however, these should also be discussed after completing the work-up. The next step in management would be to obtain a 24-hour RAI uptake thyroid scan to rule out other causes of hyperthyroidism, especially silent thyroiditis. Graves disease causes diffuse radiotracer uptake by the thyroid gland as opposed to the suppressed uptake seen in thyroiditis. Ultrasonography of the neck and guided fine-needle aspiration for cytology are not helpful in diffuse thyroid enlargement unless there are discrete nodules.^{1,3}

In this case, an I¹²³ uptake thyroid scan showed diffusely increased radiotracer uptake by the thyroid gland consistent with Graves disease. Alternatively, an I¹³¹ uptake study could have been performed.

4. Which one of the following is the most appropriate treatment for this patient's hyperthyroidism?

- a. Administer saturated solution of potassium iodide
- b. Continue propranolol and recheck biochemical thyroid profile in 4 weeks before committing to any treatment
- c. Perform RAI ablation
- d. Prescribe ATDs (eg, propylthiouracil [PTU] or methimazole)
- e. Perform surgical thyroidectomy

Saturated solution of potassium iodide or potassium iodide-iodine (Lugol solution) transiently reverses the hyperthyroidism, but its use is limited to a 10-day prethyroidectomy treatment when ATDs cannot be used. Once a diagnosis of Graves disease has been established, waiting has no merit, and treatment should be initiated sooner rather than later. Radioactive iodine, ATDs, and surgical thyroidectomy are all treatment options for Graves disease. The

first-choice treatment is usually RAI, and this would be the preferred option in this case. Alternatively, ATDs could be used but have a higher risk of failure or relapse. Surgical thyroidectomy is usually reserved for patients who do not benefit from or are not candidates for RAI and ATDs.^{1,3,4}

After discussion regarding ATDs, RAI, and surgical management, the patient elected to proceed with ATD therapy. She began taking methimazole, and propranolol was continued.

5. Which one of the following recommendations regarding family planning is most appropriate after initiating methimazole treatment?

- a. There is no contraindication to pregnancy
- b. Pregnancy is contraindicated until biochemical euthyroid status is achieved
- c. Use of ATDs is a contraindication to pregnancy
- d. Use of ATDs is a contraindication to breast-feeding
- e. The fetus is at risk of complications from fetal hyperthyroidism irrespective of Graves status in the mother

Maternal hyperthyroidism is associated with risk of miscarriage, placental abruption, preterm delivery, as well as fetal malformations, and pregnancy should be deferred at least until maternal euthyroid status has been achieved. Both methimazole and PTU are classified as pregnancy category D drugs, although the risk of congenital malformations is very low, especially with PTU. Therefore, these drugs are acceptable in the pregnant patient, especially because the risks of untreated hyperthyroidism are much greater. Antithyroid drugs are secreted only in small quantities in breast milk and are considered safe during lactation. Fetal hyperthyroidism is caused by maternal TRAb that cross the placenta and is not a concern when the mother is in remission with negative findings on a serum TRAb assay.⁴⁻⁶

The patient was counseled regarding risks associated with pregnancy while receiving treatment. She continued methimazole and was scheduled for clinical follow-up of her response to therapy.

DISCUSSION

Graves disease is responsible for 50% to 80% of cases of hyperthyroidism and affects 0.5% of the population. It has a female-to-male ratio between 5:1 and 10:1, has a peak incidence between ages 40 and 60 years, and is associated with a maternal family history of Graves disease.^{1,2,7} Environmental triggers that have been identified include infection, recent childbirth, smoking, corticosteroid use and withdrawal, and iodine and iodine-containing medications.^{1,8} Graves disease results from thyroid follicular hypertrophy and hyperplasia with increased T₃ and T₄ production caused

by TSI IgG-mediated TSH receptor activation.² A higher TRAb titer is associated with more severe hyperthyroidism and is seen in young and asthenic patients.

Laboratory evaluation shows suppressed TSH levels with elevated T_4 and T_3 levels, with higher increases in T_3 than T_4 . Serum TRAb levels, specifically TSI, are elevated. Diffusely increased radiotracer uptake is revealed on the 24-hour RAI uptake scan. Any nonfunctioning nodules need ultrasonography-guided fine-needle aspiration and cytology to rule out malignancy. Doppler ultrasonography shows increased blood flow into the gland.¹

Patients should be counseled to quit smoking.^{8,9} β -Blockers are used to ameliorate anxiety, tremor, palpitations, and tachycardia and to slow ventricular response in atrial fibrillation. Propranolol has the additional advantage of inhibiting peripheral conversion of T_4 to T_3 . Surgical thyroidectomy, RAI, and ATDs are all acceptable treatments, and patient preference should be factored into the choice of first-line therapy. In the United States, RAI is preferred in most cases because of its very high long-term remission rates compared with the only 30% to 40% long-term remission rates with 18 months of ATD therapy. Surgical thyroidectomy is usually reserved for patients who have contraindications to or do not benefit from other options. The choice of treatment for Graves disease should be individualized, and patients should be encouraged to make an informed decision on the basis of their needs.^{1,3}

Antithyroid drugs (thioamides) concentrate in the thyroid gland and decrease thyroid hormone production by inhibition of thyroid peroxidase and immunosuppressive effects.⁴ Methimazole and PTU, both available in the United States, normalize free T_4 in greater than 80% and free T_3 in two-thirds of patients within 12 weeks of treatment initiation. Methimazole is usually preferred because it can be dosed once a day vs 3 times daily for PTU, achieves euthyroidism sooner, and may have a more favorable adverse effect profile.³ Factors associated with increased relapse in patients treated with ATDs are severe hyperthyroidism, large goiter, high blood flow, a high $T_3:T_4$ ratio, a high TRAb level, young age, male sex, smoking, ophthalmopathy, and delay in treatment. In addition to weight gain, minor adverse effects of ATDs include urticarial or macular reactions, arthralgias, gastrointestinal effects, and (rarely with methimazole) an abnormal sense of taste or smell. Major adverse effects occur rarely and include polyarthritis, agranulocytosis (1-2 per 1000 cases) and other hematologic adverse effects, hepatitis (particularly with PTU and potentially with more severity in children), and vasculitis.^{3,4}

With RAI¹³¹ ablation, which has been safely used since the mid-1940s, most patients have reduction in goiter and achieve a euthyroid state within 6 to 8 weeks. With appro-

priate dosing, 80% to 90% of patients become hypothyroid in 3 to 6 months and subsequently require levothyroxine replacement. Treatment with RAI is contraindicated in pregnancy, lactation, childhood, and adolescence because of concern of teratogenic and carcinogenic effects. Treatment with RAI as opposed to ATDs may be associated with worsening of Graves ophthalmopathy (permanently in up to 5% and transiently in 10% of cases). This can be prevented with concomitant glucocorticoid use.^{3,10,11}

Total or near-total thyroidectomy results in rapid correction of hyperthyroidism. β -Blockers and antithyroid therapy with ATDs, inorganic iodine (eg, saturated solution of potassium iodide or lithium carbonate), or oral cholecystographic agents (eg, sodium iopanoate or sodium ipodate) are used to optimize the preoperative metabolic state. Lifelong postoperative monitoring of thyroid and parathyroid function is needed. Surgical complications include recurrent laryngeal nerve damage and hypoparathyroidism.^{3,4}

Graves disease is associated with clinically significant symmetric ophthalmopathy or orbitopathy in 20% to 30% of patients. Medical management includes smoking cessation, corneal lubrication to prevent keratitis, corticosteroids, and external-beam radiotherapy. Staged rehabilitative eye surgery is used for inactive disease. Emergent surgery can preserve eyesight in patients with severe disease.^{12,13}

Coexisting pregnancy and Graves disease often require complex medical decision making. Most women will have remission or improvement of Graves disease during pregnancy. Thyroid function and TRAb levels need to be closely monitored; euthyroid or hypothyroid women after RAI or surgical treatment could still have high TRAb levels. Total T_3 and T_4 levels are elevated because of excess binding globulin. Maternal TRAb as well as ATDs cross the placenta and have even greater effects on the thyroid of the fetus than of the mother; however, levothyroxine has incomplete placental passage. Preferred treatment is with low-dose ATDs titrated to avoid clinically hyperthyroid status in the mother, which appropriately maintains fetal euthyroidism in most cases. During the first trimester of pregnancy, PTU is preferred over methimazole because the latter is associated with a small risk of fetal malformations such as aplasia cutis and, very rarely, choanal or esophageal atresia. Maternal hyperthyroidism increases risk of miscarriage, placental abruption, preterm delivery, and fetal malformations. Fetal hyperthyroidism causes tachycardia, growth retardation, accelerated bone maturation, goiter, pituitary-thyroid axis abnormalities, malformations, and death. In contrast, fetal hypothyroidism is associated with neural abnormalities and cerebral impairment. Propranolol reduces placental perfusion, causing fetal bradycardia, hypoglycemia, and pulmonary-cardiac complications.^{4,6}

The postpartum period is associated with relapse and new onset of Graves disease. The persistence of maternal TRAb in the fetal circulation for a couple of months after birth can cause transient hyperthyroidism, followed by transient hypothyroidism due to pituitary suppression. Methimazole and PTU are safe in lactation; however, monitoring of infant thyroid function is advised. Breast-feeding is not recommended with propranolol, which is secreted in milk.^{3,4}

Graves disease is the most common cause of endogenous hyperthyroidism and should be evaluated with blood tests, including thyroid function tests, thyroid receptor antibody assays (TRAb or TSI), and a 24-hour thyroid RAI uptake scan. In addition to symptomatic management, therapeutic options include RAI, ATDs, and surgical thyroidectomy. The clinical situation and patient preferences should guide the final choice of therapy. After the diagnosis has been established, an endocrinology consultation is recommended in most cases. Graves ophthalmopathy is a common feature and may require management by the ophthalmologist. Pregnancy poses a complex situation in which the thyroid status in both mother and fetus needs to be addressed, requiring teamwork among the obstetrician, the endocrinologist, and the internist.

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Correct answers: 1. a, 2. b, 3. d, 4. c, 5. b