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Atypical Presentations of Hyperthyroidism

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Hyperthyroidism is one of the most readily recognized entities in clinical medicine. It is a disorder with easily recognized symptoms and signs that make the diagnosis obvious. (*See Table 1.*) Almost all of these manifestations are expressions of increased adrenergic receptor response to normal and/or raised circulating catecholamines. In many patients, however, the diagnosis of hyperthyroidism is overlooked because the onset is insidious, and the symptoms and signs are minimal, atypical, or unusual.[1] These unusual presentations are observed predominately in the elderly but are not necessarily exclusive to them. Many terms have been used in the literature to describe these unusual or atypical forms, including "masked" and "apathetic" hyperthyroidism. The latter is used for a condition initially described by Lahey in which the manifestations are closer to those frequently noted in hypothyroidism and, therefore, are the opposite of those seen in classic or hyperkinetic hyperthyroidism.[2-4] The manifestations of hyperthyroidism are protean, prompting Whishaw in 1939 to comment that it resembles syphilis in this regard.[5] Literature documenting these unusual, atypical, and apathetic manifestations is sparse. The older literature divides these masked forms into three types: the clinical manifestations are not truly atypical but are overshadowed by prominent signs or symptoms of some other coincidental disease or symptom complex; the monosymptomatic form, in which disturbances of one organ system are prominent and suggest disease of that organ system; and another variety without some or most of the classic clinical features.[3] While this classification is arbitrary, it elegantly frames the issues in atypical presentations of hyperthyroidism and will be used as a framework for this discussion. The term atypical hyperthyroidism, however, may be used to describe a presentation in which the clinical diagnosis has been difficult. This article is meant to provide clinical vignettes that will alert the clinician to the diagnosis of hyperthyroidism and help in prompt and appropriate management of the disorder.

Statement of Financial Disclosure

To reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief), Dr. Kabadi (author), and Dr. Wilke (peer reviewer) report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Congestive Heart Failure without Underlying Cardiovascular Disease

A 66-year-old Caucasian man presented to the emergency room with edema, shortness of breath, and palpitations. A quick diagnosis of congestive heart failure was made. He had no history of coronary artery disease and/or hypertension. He denied changes in eating or bowel habits and recent chest pain. His appetite was a little diminished. Heat intolerance and nervousness were not reported. On examination, an irregularly irregular pulse, bi-temporal wasting, an irregular heart beat, and bibasilar crackles up to two-thirds of the lung fields were noted. The thyroid was enlarged. It was about 40 g (normal is 20-25 g), firm, nontender, diffuse, freely mobile on swallowing, and without a bruit. Specifically, the presence of a bruit indicates increased vascularity of the thyroid gland caused by vasodilation secondary to enhanced beta adrenergic receptor activity. Therefore, surgery without resolution of the bruit (e.g., increased vascularity) by treatment with a nonselective beta adrenergic blocker (e.g., propranolol) is likely to result in excessive bleeding at the surgical site. Finally, the bruit also denotes severity of beta adrenergic hyperactivity caused by thyrotoxicity in other tissue as well. It therefore calls for appropriate preparative therapy with beta-blockers and antithyroid agents to achieve euthyroidism prior to either surgery or radioactive iodine to avoid post therapy "thyroid storm." There was no evidence of orbitopathy, proptosis, or exophthalmos, (*see Table 2*) or tremor of outstretched fingers. An ECG revealed atrial fibrillation. An echocardiogram showed left ventricular ejection fraction of 56%, suggesting high output congestive heart failure.

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Therapy with IV diuretics as well as oral digoxin and propranolol relieved some of the symptoms, but the dose of digoxin was greater than usual and the patient still had residual pulmonary crackles. Thyroid functions obtained because of the enlarged thyroid gland and presence of atrial fibrillation revealed a free thyroxine (FT4) of 2.6 ng/dL (normal is 0.5-1.5) and TSH of less than 0.01. The patient's symptoms remitted totally over the next 2 weeks after administration of methimazole (Tapazole) while continuing other drugs. A coronary angiogram was performed promptly and did not reveal a significant abnormality indicating the presence of coronary artery disease.

This patient exemplifies masked hyperthyroidism with congestive heart failure but without underlying cardiac disease. The diagnosis is often not entertained because the symptoms are attributed to a worsening of the underlying disease including the more common causes (e.g., coronary artery disease, hypertension, as well chronic obstructive pulmonary disease with hypoxia) as opposed to the occurrence of a new entity. The elderly patient often lacks ocular signs, tremor, smooth skin, nervousness, heat intolerance, and other symptoms associated with classic or hyperkinetic hyperthyroidism.[6-8] Thyroid functions are often obtained only because of an enlarged thyroid gland. However, the diagnosis must not be overlooked even in the absence of prominent thyromegaly because hyperthyroidism frequently occurs in the elderly without a goiter.[6]

Moreover, hyperthyroidism frequently is heralded in the elderly by supraventricular tachyarryhthmias, with atrial fibrillation being the most common, and with a rapid ventricular rate, refractory or new onset congestive heart failure, or angina pectoris. Although thyrotoxic heart disease does occur in patients in the absence of heart disease, as noted in this patient, it is more common in the presence of underlying heart disease and therefore explains the increased frequency of this presentation in the elderly who are more likely to have previously unknown cardiac dysfunction.[9-21] Sandler and Wilson have demonstrated that congestive heart failure occurs only in about 5% of thyrotoxic patients without underlying heart disease.[10] Therefore, unexplained cardiac decompensation, decompensation out of proportion to the underlying cardiac disease, or decompensation refractory to conventional therapy should prompt an evaluation for occult hyperthyroidism.

Atrial fibrillation in hyperthyroidism is not characterized by specific ECG abnormalities.[22-27] Many patients exhibit an unusually rapid ventricular response with a relative resistance to digoxin.[28] The reported prevalence of undetectable TSH in patients with atrial fibrillation defined as subclinical hyperthyroidism is between 4% and 17%, as opposed to 0.4% in the general population, leading to the widespread practice of obtaining thyroid function tests (e.g., serum concentrations of Free T4, T3, and TSH) in all patients presenting with atrial fibrillation.[26]

Abdominal Pain, Nausea, and Vomiting

A 60-year-old Latina woman was referred to the outpatient clinic because of persistent epigastric pain for two months. The pain was continuous, with intermittent colicky exacerbation. The

Table 1. Typical Clinical Manifestations of Hyperthyroidism

SYMPTOMS	SIGNS
• Increased hunger	• Goiter (> 25 g)
• Weight loss	• Tremor
• Heat intolerance	• Tachycardia
• Palpitations	• Warm moist palms
• Excessive sweating	• Lid lag
• Nervousness	• Brisk tendon reflexes
• Muscle weakness	• Bruit (marked increased vascularity)
• Asthenia	
• Increased number of daily bowel movements	
• Disturbed sleep	

pain was nonradiating and was not affected by food or changes in position. The pain was accompanied by nausea and vomiting. There was no diarrhea or increase in number of bowel movements. She denied any other previous medical illnesses. A review of systems revealed a 15-pound weight loss in the previous three months. On examination, she was irritable and appeared emaciated. A pulse rate of 110/min was regular. Her BP was 150/80 mmHg. The abdomen was soft and diffusely tender without organomegaly, ascites, or masses. The bowel sounds were normal, and reflexes were brisk and symmetrical. The blood chemistry revealed a serum calcium of 10.8 mg/dL with an albumin of 4.0 g/dL. Upper endoscopy, barium studies, colonoscopy, and abdominal imaging were unremarkable. Endocrinology consultation was sought for evaluation of hypercalcemia. Thyroid function tests were requested because hyperthyroidism is one of the known causes, and the tests revealed an FT4 of 3.1 and a TSH of less than 0.01. The 24-hour radioactive iodine uptake was 45%. Radioactive iodine therapy was refused by the patient. Methimazole and propranolol were started, with relief of abdominal pain within a week.

This patient is an example of a presentation of thyrotoxicosis with symptoms confined to one organ system. Gastrointestinal manifestations of hyperthyroidism, e.g., increased appetite, increase in number of daily bowel movements, and weight loss are well known. However, in the absence of hyperkinetic manifestations, a futile search for a primary pathology of the gastrointestinal tract involving considerable expenditure often is the result. Similar presentations with abdominal pain and protracted nonbloody vomiting relieved within 36 hours after administration of propylthiouracil (PTU) and propranolol have been reported.[29,30] The pain usually is generalized. However, in rare cases it may be localized. It almost always is present as one of the symptoms of thyroid storm. Infrequently, acute abdominal pain, rebound tenderness, and guarding have resulted in laparotomies, appendectomies, and cholecystectomies.[31] The exact mechanism of abdominal pain in thyrotoxicosis is unclear. It may be induced by increased GI motility. In this patient, abdominal pain may have been exacerbated further by hypercalcemia known to induce hyperacidity via enhanced secretion of gastrin as well as constipation. Therefore, the importance of recognition of hyperthyroidism with this presentation of GI manifestations is crucial. The ever looming risk of unnecessary surgery primarily inducing thyroid storm cannot be over-emphasized because of its role in worsening morbidity and mortality.

Infrequently, the disease may mimic other gastrointestinal presentations, e.g., constipation or dysphagia. Rarely, the patients may present with secretory diarrhea or nonspecific liver function abnormalities including elevated liver enzymes, especially alkaline phosphatase secondary to intra or extra hepatic cholestasis.[32-34]

Hypercalcemia

An endocrinology consultation was obtained in a 68-year-old African American woman for evaluation of hypercalcemia (11.2 mg/dL) with albumin level of 2.3 g/dL and a serum parathyroid hormone (PTH) level of 10 pg/dL (normal is 10-60). She was admitted with chest pain and shortness of breath. Her past medical history was remarkable for a 30-pound weight loss in the previous eight months. Her family members reported that she had become increasingly depressed and had been spending more of her time alone and in bed. She had little appetite and was constipated. An evaluation by a psychiatrist two months prior to admission documented serum Free T4 of 1.6 ng/dL (normal is 0.7-1.72), T3 of 90 ng/dL (normal is 80-180), and a TSH less than 0.01. The patient was told that she was euthyroid, and the suppressed TSH was attributed to depression. The patient was started on antidepressants with no significant improvement. On the day prior to admission she complained of shortness of breath of sudden onset. A provisional diagnosis of pulmonary embolism was confirmed by a high probability ventilation-perfusion scan. On physical examination, she was lethargic and emaciated; her skin was cool and dry; her pulse was 60 beats per minute, and her blood pressure was 100/60 mmHg. Extraocular movements were intact. An examination of the neck revealed jugular venous distension with a nodular firm, nontender, freely mobile, slightly enlarged thyroid gland without a bruit. (*See Table 1.*) The rest of the examination was unremarkable. Laboratory tests revealed a normal magnesium with hypercalcemia, elevated FT4 (4.6 ng/dL), a suppressed TSH (< 0.01 mIU/L), and a normal T3 (96 ng/dL). Methimazole and propranolol were initiated with improvement of symptoms. After normalization of FT4, she received an ablative therapy with radioactive iodine.

This patient represents a characteristic presentation of apathetic thyrotoxicosis.[2-4] The diagnosis is always challenging and, unfortunately, may be missed or delayed with grave consequences. Lahey's description of this condition almost 65 years ago is unparalleled to this day.[4] The symptoms often are the opposite of those in classic or hyperkinetic hyperthyroidism, more frequently in elderly women as compared to younger adults, although it does occur in all age groups. Nodular thyroid disease (as opposed to Graves' disease) is more common in these patients.[2,4] Tachycardia and ocular signs may be conspicuously absent, and blepharoptosis rather than proptosis may be present. The patient is slow both mentally as well as physically, withdrawn, with a blunted affect, and often is lethargic, listless,

Table 2. Classification and Staging of Graves' Orbitopathy

CLASS	DEFINITION	STAGE		
		I	II	III
0	No signs or symptoms	—	—	—
1	Only signs, no symptoms	Lid retraction and stare without lid lag or proptosis		
2	Soft tissue involvement	Conjunctival Injection	Conjunctival Edema	Periorbital Edema
3	Proptosis	2 mm over normal*	2-4 mm over normal*	> 4 mm over normal*
4	Extraocular muscle involvement	1 muscle	2 muscles	> 2 muscles
5	Corneal involvement	Abrasion	Ulceration Inflammation	Scarring
6	Sight loss	Secondary to optic atrophy or anterior staphyloma		

* Normal = < 20 mm in Non-African Americans, < 22 mm in African Americans

and depressed. The skin is dry, coarse, cool, wrinkled, and pigmented. Muscle wasting and proximal myopathy as well as weight loss are characteristic. The presentation is so unlike hyperthyroidism that the diagnosis often is never entertained and is established fortuitously. "Despite the apparent unobtrusiveness of the disease, its effects may be severe and even fatal."[4] A T3 level in the low normal range in the presence of hyperthyroidism in this patient may be attributed to prolonged associated disorders, e.g., depression, inadequate food intake, or even pulmonary embolism similar to low T3 noted in euthyroid sick syndrome.[35-37] Moreover, hypercalcemia may have contributed to the apathetic nature of this patient.[2] In most patients, the exact mechanism of apathetic presentation continues to remain a mystery. The "burn out" hypothesis **of** excessive chronic stimulation does not seem to explain the manifestations. Some authorities have suggested that adrenergic unresponsiveness may be the cause, but this does not seem to stand up to close scrutiny with the exception of the elderly.[2-4,7,8] There are some reports linking this presentation to hypomagnesemia, but this is not noted in most other reports.[4,7,8] T3 levels have been reported to be inappropriately low in some, as seen in this patient.[35-37] However, recurrence is frequent if not treated definitively with either antithyroid drugs or radioactive iodine, and the mortality remains high especially in the elderly with progression of apathetic hyperthyroidism into thyroid storm.[38] The high mortality seems to be related predominantly to the delay in diagnosis and, therefore, institution of therapy.[38] Hypercalcemia is reported to occur in almost 20% of patients manifesting hyperthyroidism.[39-41] A distinct pathophysiologic mechanism remains unclear. Enhanced bone resorption as a part of hyperthyroid catabolic state is implicated.[39-41] Alternatively, increased GI absorption of calcium secondary to preferential generation of 1-25 OH vitamin D3 also may contribute to hypercalcemia.[39-41]

Gynecomastia

A 23-year-old Latino man was referred to an endocrinology clinic for evaluation of gynecomastia. On inquiry, he reported that the breast swelling began 4 months prior to his presentation as an alveolar "nubbing" with irritation, pain, and increased sensitivity and then growing gradually to the present size of about 3 cm. There was no change in the left breast. On further interrogation, he also reported excessive sweating, increased appetite with weight gain of 5 pounds, disturbed sleep, jitters, as well as a decrease in libido and erectile dysfunction. He denied any change in bowel habits, heart racing, nausea, vomiting, weakness or fatigue, breast discharge, dysphagia, dysphonia, or dyspnea. He was a non-smoker and consumed alcohol socially once or twice a month. The relevant family history included a mother who was treated with radio iodine for Graves' disease. The past history was unremarkable. The physical examination showed an apparently healthy looking man with right gynecomastia; a diffuse, nontender, firm, mobile thyromegaly about 40-45 g without a bruit; hyperdynamic, regular, apical impulse with a rate of 82 beats/m and BP 140/70 mmHg; a II/VI ejection systolic murmur at the left sternal edge in second intercostal space; and brisk ankle reflexes. Laboratory tests showed serum testosterone level of 375 ng/dL (normal 300-1000 ng/dL), with normal FSH, LH, and prolactin levels as well as elevated Free T4 2.8 ng/dL (normal 0.7-1.6) and T3 195 ng/dL (normal 80-180 ng/dL), and suppressed TSH less than 0.01. The 24-hour I-131 uptake was 47% and revealed a diffuse goiter. He was promptly treated with I-131, and seven days later, oral methimazole 20 mg daily was initiated. Three months following radioiodine therapy, his thyroid

functions were normal and methimazole was discontinued. His gynecomastia started receding and his libido and erectile function improved. By six months, he remained euthyroid with a complete resolution of gynecomastia and sexual dysfunction. The serum testosterone level rose to 580 ng/dL.

Gynecomastia is described to occur in 15-25% of men with hyperthyroidism.[41-46] Other sexual dysfunction also has been reported.[47] Oligomenorrhea or amenorrhea is a frequent manifestation of hyperthyroidism in young adult women.[48] The altered sexual function is attributed to inhibition of hypothalamic pituitary gonadal axis with lowering of circulating testosterone and estrogen levels in men and women, respectively.[43,45-48] Gynecomastia is thought to be secondary to rising estrogen/testosterone ratio due to enhanced metabolism of circulatory androgens into estrogens.[43,44]

Severe Headache

A 37-year-old female physician reported having severe bilateral throbbing headache for two weeks. Initially, the headache was mild and intermittent with no other symptoms. Gradually, the headache became progressively severe and continuous accompanied by nausea and vomiting as well as photophobia, causing the physician to abstain from work. The initial physical examination and CT scan of the head were normal. However, a further detailed history revealed transient vomiting, nausea, and diarrhea approximately two weeks prior to onset of headache, and worsening pain in the front of the neck for about a week suggestive of a viral syndrome. Further physical examination revealed tender thyromegaly without a bruit and tender anterior cervical lymphadenopathy. She denied classic symptoms of hyperthyroidism as well as prior history of migraine. However, warm moist palms, bilateral lid lag without proptosis, and a fine tremor of outstretched fingers were present.

A provisional diagnosis of sub-acute viral thyroiditis with initial acute hyperthyroid phase was made and then confirmed by elevated levels of ESR of 70 mm/hr, serum C-reactive protein (10), as well as free T4 of 2.7 ng/dL, and undetectable TSH less than 0.01. The 24-hour I-131 uptake of thyroid was 2%, consistent with thyroiditis. Treatment with propranolol and ibuprofen was initiated and her symptoms resolved promptly. She became clinically and biochemically hypothyroid within four weeks and both medications were discontinued. Over the next six weeks she gradually attained euthyroid state, confirmed by normal FT4 and TSH. Disabling headache appears to be an extremely uncommon major presentation of hyperthyroidism, although its presence with other clinical features has been described. The probable pathophysiologic mechanism is vasodilation of temporal vessels induced by adrenergic stimulation promptly relieved by propranolol, a beta-blocker.[49-55]

Bilateral Total Blindness

A 43-year-old Caucasian man presented to the emergency room with bilateral total blindness of sudden onset. The patient denied history of premonitory symptoms, e.g., fever, chills, eye pain, headache, nausea, vomiting, chest pain, palpitations, dysphagia, dysphonia, choking sensation, including parasthesia and neurological problems. However, he reported an increased appetite and weight loss of 15 pounds along with disturbed sleep and excessive sweating for the previous two months. Past and family histories were noncontributory. He did not smoke, abuse alcohol, or use any illicit drugs. The physical examination revealed a complete lack of vision in both eyes, including absent pupillary reflexes without any other neurological deficit. Bilateral proptosis was present. The thyroid gland was enlarged (about 50 g), nontender, soft, and mobile on swallowing. A bruit was heard over the gland, indicating increased vascularity secondary to local vasodilation. Examination of the heart revealed hyperdynamic apical impulse with a rate of 110/min and an irregular irregular rhythm. Pretibial myxedema was present along with brisk knee and ankle reflexes bilaterally. His palms were warm and moist. An ECG showed the presence of atrial fibrillation with a rapid rate as well as left atrial and left ventricular hypertrophy. An MRI of the brain demonstrated bilateral infarcts in occipital lobes. MRA revealed occlusion of both posterior cerebral arteries without collateral circulation. An echocardiogram showed left atrial enlargement with the presence of a thrombus as well as left ventricular hypertrophy with an ejection faction of 40%. Laboratory tests showed a normal coagulation profile and elevated T4 and T3 concentrations with undetectable TSH. Thus, the diagnosis of Graves' disease with hyperthyroidism was confirmed. Bilateral blindness was attributed to emboli from left atrial thrombus secondary to atrial fibrillation.

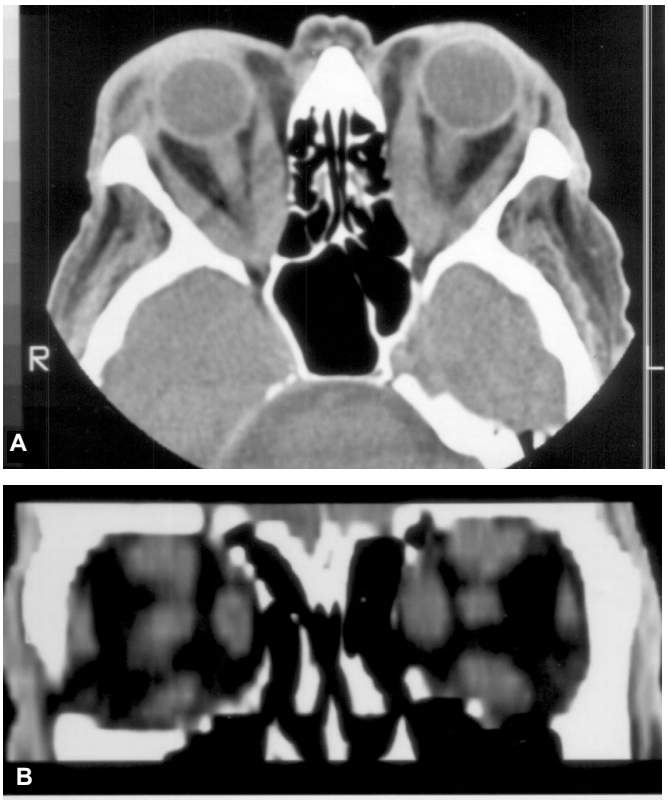
The patient was hospitalized, and treatment with IV heparin as well as oral propranolol, propylthiuracil, and warfarin was initiated. The patient was discharged 4 days later after attaining therapeutic levels of prothrombin time. Heparin was discontinued while continuing other oral medications. At the follow-up outpatient visit 6 weeks later, sinus rhythm had returned and symptoms of hyperthyroidism improved with normalizations of T4 and T3. He was treated with I-131 in the due course of time. Warfarin was discontinued after 6 months after attainment and maintenance of sinus rhythm. He never regained his sight.

Atrial fibrillation is well known to occur in hyperthyroidism.[23-28] Moreover, clinical manifestations secondary to embolism in peripheral arteries, especially if the cerebral circulation has been well documented and particularly in the presence of pre-existing cerebrovascular disease.[56] Apparently, this is the first report of the unfortunate occurrence of bilateral total blindness due to emboli from dislodgement of left atrial thrombus caused by atrial fibrillation due to hyperthyroidism.

Ocular Muscle Palsy

A 62-year-old white man was seen in the emergency room with diplopia, photophobia, blurred vision, and headache of four days duration. He denied any other symptoms including nausea, vomiting, dysphagia, dysphonia, weakness, or imbalance. His past history was unremarkable. The pertinent family history included a 36-year-old daughter with Graves' disease who had received treatment with I-131 for hyperthyroidism. He denied smoking or abusing alcohol and was receiving no medications.

Figure 1. Orbital CT Scan Demonstrating Orbitopathy



The physical examination revealed ptosis of the right eye, with a decreased upward gaze and a normal pupillary reaction to light. The rest of the neurological as well as other systemic examination was reported to be unremarkable. His blood chemistries were normal, and brain CT scan with contrast showed no distinct abnormalities. He was admitted for further assessment. The next day during the ward rounds, a detailed physical examination showed the previously described eye findings. Moreover, exophthalmus of the left eye, sinus tachycardia, moist warm palms, and brisk tendon reflexes without muscle weakness or sensory deficit were also noted. The thyroid gland was not enlarged, and the carotid arteries were well palpated without bruits. The rest of the examination remained unremarkable. A provisional diagnosis of Graves' disease with hyperthyroidism was entertained, particularly because of the eye findings, other subtle signs and symptoms of hyperthyroidism, and his daughter's history of Graves' disease. The diagnosis was confirmed by orbital CT scan. (*See Figure 1.*) Simultaneously, elevated serum Free T4 3.2 ng/dL and undetectable serum TSH less than 0.01 mIU/L confirmed the presence of hyperthyroidism. The patient was treated with a beta-blocker, methimazole, and prednisone with relief of symptoms including some improvement in diplopia and photophobia. The patient was referred to neuro-ophthalmology for further management.

The initial description by Robert Graves was "exophthalmic goiter" irrespective of functional integrity of the thyroid gland. As the disorder was characterized further, it became clear that Graves' disease is a systemic disorder involving T lymphocytes and therefore manifests involvement of multiple organs.[57] Characteristic presentations include: orbitopathy, e.g., conjunctival and corneal inflammation because of widened palpable fissure, proptosis secondary to retro-orbital infiltration, thickening and lengthening of one or more extraocular muscles leading to paresis as well as lengthening and/or compression of the optic nerve, rarely leading to optic atrophy resulting in blindness (*see Table 1*); thyroid enlargement with hyperthyroidism as the most common presentation, although infrequently both euthyroid state or hypothyroidism is present in an individual patient;[58] cutaneous involvement of the fingers (acropachy) and pretibial myxedema, secondary to infiltration of the subcutaneous tissue with mucinous material; and other systemic manifestations including generalized lymphadenopathy and hepatosplenomegaly.

This patient is a characteristic example of classic Graves' disease with progressive orbitopathy and hyperthyroidism.[58-64] The diagnosis in the absence of thyroid dysfunction is established firmly by assessment with ultrasound, CT scan, or MRI of the orbits. Severe orbitopathy also has been described as malignant exophthalmos. Treatment options consist of topical therapy with artificial tears, eye shields to prevent foreign body lodgment, and prevention of inflammation of the conjunctiva and the cornea in the earlier mild stage. With progressive disease, treatment consists of inmunosuppression with steroids or other drugs during the initial stages (*see Table 2*), whereas orbital radiation or surgical decompression and orbital muscle surgery are reserved for the more severe forms.[62,64,65] Fortunately, in most patients orbitopathy is mild and remains stable. Moreover, orbitopathy follows its own course irrespective of the functional thyroid state. Therefore, in most patients, the treatment of hyperthyroidism does not influence orbitopathy. However, precautionary steroid treatment is recommended for patients receiving I-131 ablation because of some reports in the literature describing progress of orbitopathy following I-131 therapy.[58]

Masquerading as AIDS

A 27-year-old white man presented to the emergency room with anorexia, extensive weight loss, headache, fatigue, tiredness, excessive sweating especially at night, insomnia, mild fever, and diarrhea of three months duration. He denied cough, dyspnea, dysphagia, dysphonia, visual problems, palpitations, and neurological symptoms. He reported bisexual behavior, but not blood transfusions. He smoked for more than 20 years and also had used illicit drugs, including oral and intravenous administration until two weeks ago. His family history was noncontributory. The physical examination showed a cachectic man in distress, with fever of 100°F, a pulse of 125 beats/min, BP 96/66 mmHg, dry mucus membranes, cervical discrete lymphadenopathy, firm nontender palpable liver under right costal margin, with diffuse abdominal tenderness and normal bowel sounds. His lungs were clear on auscultation, and tachycardia without a murmur was present. The neurological examination was unremarkable.

Laboratory tests in the ED revealed Hb of 10.2 g/dL and a

total WBC count of 3,500/mm^3. Chest and abdominal films were essentially unremarkable. Blood cultures were obtained. Tuberculosis testing [PPD] was conducted, and the patient was admitted with a provisional diagnosis of AIDS. During further assessment at ward rounds the next day, the patient was noted to have bitemporal wasting, diffuse, firm nontender goiter about 40-45 g, mobile on swallowing with a loud bruit, fine tremor of the outstretched fingers, along with bilateral proptosis with lid lag. At the time, a diagnosis of Graves' disease with hyperthyroidism was entertained and confirmed by positive titers of anti-thyroperoxidase antibody and elevated levels of Free T4, T3, and undetectable TSH concentrations, respectively. Therapy with propranolol and methimazole was initiated. Symptoms improved promptly, including the return of appetite and resolution of fever. Further laboratory testing revealed macrocytosis with decreased serum vitamin B12 concentration indicative of pernicious anemia. Blood cultures, HIV testing, and PPD testing were negative, eliminating the presence of infectious processes including AIDS. He was also started on intramuscular vitamin B12. Testing for antiparietal cell antibody titers was positive, confirming the presence of pernicious anemia. The patient was discharged and followed as an outpatient. He received I-131 therapy about 3 months later, achieving euthyroid state accompanied by weight gain, return of appetite, resolution of lymphadenopathy, hepatomegaly, and anemia.

This patient is an example of Graves' disease presenting primarily as a systemic disorder with involvement of T lymphocytes as described earlier including lymphadenopathy.[57] The diagnosis does not require determination of antithyroid antibodies especially in presence of a diffused thyroid gland and persistent hyperthyroidism. The test frequently is used more for corroboration of the diagnosis in the presence of nodular thyroid gland or absence of thyromegaly. A more specific test is determination of thyroid stimulating immunoglobulin (TSI). However, a clinical applicability of this expensive test in the nonpregnant population is questionable. Leukopenia is a frequent finding in the presence of Graves' disease.[57] Graves' disease frequently occurs in association with other autoimmune disorders, e.g., pernicious anemia,[66] as noted in this patient. Finally, treatment with antithyroid drugs continues to be safe even in the presence of leukopenia. However, continuous monitoring for symptoms of upper respiratory infection including fever and rash, sore throat, joint pain, and cold sores must be conducted because these manifestations may indicate onset of toxicity of antithyroid drugs and the development of agranulocytosis.

Pruritus and Rash

A 22-year-old white woman presented to a dermatology clinic for a rash with itching that was recurrent in the previous four months. On inquiry, she reported episodes of anxiety with palpitations, and heat intolerance. A diagnosis of anxiety-induced urticaria was made, and an antihistamine loratidine and an anxiolytic agent lorazepam were prescribed. The patient had some improvement over the next two weeks, but the rash and itching returned despite taking medications as prescribed. At this time, on further inquiry, she reported weight loss of 10 pounds despite an increased appetite, multiple daily bowel movements, a missed menstrual cycle, disturbed sleep, weakness, and persistent heart racing in addition to the symptoms described during the dermatology clinic visit. The itching and rash worsened on drinking alcohol, such as 4 oz. of wine or a can of beer during social gatherings. She denied dysphagia, choking sensation, or a change in voice as well as hair loss, fever, chills, nausea, and vomiting. Past and family histories were noncontributory. The physical examination revealed a pulse of 108 beats/min, BP 140/60 mmHg, bilateral lid lag without proptosis, and diffuse nontender firm thyromegaly of about 35 g without a bruit or cervical lymphadenopathy. Carotid pulses were bounding. An examination of the heart, lungs, and abdomen was unremarkable. The neurological assessment showed exaggerated ankle reflexes, and fine tremor of the outstretched fingers without a definitive focal deficit. A skin examination showed several scratch marks in areas accessible to fingers, generalized urticarial rash as well as peau d'orange type infiltration in the area of the right tibial shin. A diagnosis of Graves' disease with pretibial myxedema and hyperthyroidism was made and confirmed by skin biopsy as well as elevated serum free T4 (3.8 ng/dL) and undetectable serum TSH level, respectively. A pregnancy test was negative. She was treated with propranolol and I-131 ablation. Topical steroid cream was prescribed for her pretibial myxedema. Her generalized rash and itching remitted promptly and other symptoms resolved over the next several weeks. Beta adrenergic agonism is a hallmark of hyperthyroid state.[49-55] It is secondary to hypersensitivity of beta adrenergic receptors to circulating catecholamines induced by hyperthyroidism.[49-55] Therefore, most of the symptoms (e.g., tachycardia, hunger, heat intolerance, sweating, tremulousness) as seen in hyperthyroidism are mediated by this mechanism and nonselective beta adrenergic blockers (e.g., propranolol) have remained the hallmark of therapeutic armamentarium, especially for prompt relief of symptoms in this disorder. Pruritus and rash may be explained as secondary to warmth and sweating induced by marked peripheral cutaneous vasodilatation secondary to beta adrenergic receptor stimulation. Moreover, these symptoms are further exaggerated by concurrent use of other vasodilators, e.g., ethanol as noted in this patient.

Hypokalemic Paralysis

A 38-year-old Asian male was admitted to medical service with a history of progressive weakness in all the extremities; proximal muscles were more prominently involved. On arrival at the emergency room, he was observed to be unable to walk or to assume an upright posture and he complained of severe muscle cramps. No symptoms suggestive of cranial nerve dysfunction, sphincter involvement, or raised intracranial tension were present, nor were previous episodes of a similar nature reported. Ingestion of licorice or any kind of herbal medication was denied. The patient stated that he had been in good health until the day of admission. Weight loss (10 pounds in two months), increased sweating, heat intolerance, excessive appetite, and palpitations were reported by the patient only on repeated question-

ing. Neck swelling, nervousness, insomnia, and change in bowel habits were denied. Past and family histories were unremarkable.

The physical examination revealed an alert, stocky, afebrile Asian male. His pulse rate was 120 beats per minute and regular; his blood pressure was 137/70 mmHg. His skin appeared smooth, and the hair was fine. His palms were moist and warm. No gynecomastia was noted. The mucous membranes were pink, and nails showed no abnormality. The thyroid gland was diffusely enlarged to approximately 35 g, firm and nontender without a bruit, and it moved freely on swallowing. The neurologic examination revealed flaccid paresis of all extremities, with the lower ones more affected than the upper ones. The cranial nerves were intact, and sensory status was unimpaired. The precordium was hyperdynamic on palpation, and a grade II/VI basal ejection systolic murmur was present. The remainder of the examination findings were within normal limits. Admission laboratory data were unremarkable except for serum potassium (K+) which was 2.3 mEq per liter. The patient was treated with potassium chloride (KCl) infusion and recovered promptly from paralysis.

Blood chemistries, including enzymes and complete blood count, as well as urinalysis, skull and chest roentgenograms, radiology of gastrointestinal tract, intravenous pyelography, electromyography, and peripheral nerve conduction studies, were all within normal limits.

Thyroid function tests were performed because of the previous documentation of thyrotoxic hypokalemic periodic paralysis in the Asian population.[68-72] The patient was discharged at his request pending the results of thyroid function tests with instructions to continue the oral potassium supplement, and he was advised to attend the endocrine clinic the following week.

The patient was readmitted a day after discharge with flaccid paralysis and hypokalemia, serum K+ being 3.1 mEq per liter. The ECG (electrocardiogram) showed a prolonged P-R interval. He recovered promptly on intravenous administration of KCl. At this time, the thyroid function tests returned as follows: T3 resin uptake, 40% (normal, 25-35); thyroxine T4 by radioimmunoassay, 15.5 mcg/dL, (normal, 4.5-13); T3 by radioimmunoassay, 218 ng/dL, (normal, 60-90), and 24-hour I-131 uptake 65%, (normal, 10-30). Propranolol therapy, 40 mg per day, was begun because of its reported efficacy in preventing paralytic attacks as well as its usefulness in ameliorating manifestations of hypothyroidism prior to radioiodine therapy.[68,69] Oral K+ supplement (40 mEq per day) was continued. Within three days, the patient received I-131 and was discharged on propranolol (40 mg per day).

Three weeks later, the patient returned to the emergency room with a third episode of flaccid paralysis and was readmitted. An ECG revealed Mobitz Type 1 heart block, and serum K+ was 1.9 mEq per liter. He responded promptly to a KCl infusion. Propranolol was discontinued in view of atrioventricular block, and oral methimazole 40 mg per day was instituted. The patient was discharged four days later with instructions to continue methimazole, 30 mg per day, which was gradually reduced and finally discontinued after four months. The patient began showing manifestations of early hypothyroidism after six months, which was confirmed by thyroid function tests. He became clinically and biochemically euthyroid on levothyroxine (L-thyroxine), 0.2 mg per day, and did not experience paralytic episodes or even muscular cramps and weakness after attaining the euthyroid state. Prior to antithyroid therapy, plasma renin activity and aldosterone levels were elevated between paralytic attacks and were further raised by ingestion of a low sodium diet, but were only partially suppressible by a high sodium diet. On attainment of euthyroid status following radioiodine therapy, plasma renin activity and aldosterone declined to normal and were adequately suppressed by a high sodium diet.

Therapeutic measures such as administration of propranolol and spironolactone have been successful in preventing episodes of paralysis in thyrotoxicosis, but this is not universally true.[68,69] Therefore, it is conceivable that several mechanisms may be responsible for the onset of paralysis, but one exists in a particular patient. The migration of K+ from the extracellular compartment into cells, as demonstrated by direct measurement of intracellular and extracellular K+ contents in muscle tissue before and during paralytic attacks, may be the causative mechanism in a group of patients in whom high carbohydrate ingestion with or without insulin administration provokes hypokalemia and paralysis.[71,72] It is possible that patients having normal aldosterone excretion rates and demonstrating no significant alteration of plasma aldosterone during induction of paralysis belong to the same group. The patient in this case is distinctly different in that renin and aldosterone levels were high.[73] Marked elevation of renin may be attributed to beta adrenergic receptor stimulation. Moreover, it is likely that hyperplasia of the zona glomerulosa occurred secondary to chronic hyperreninemia (analogous to Cushing's syndrome due to pituitary adenoma), as documented by increased basal plasma renin levels during thyrotoxicosis, with normal stress or diurnal ACTH secretion leading to augmented aldosterone release and hypokalemia.[72,73]

Thus, hyperthyroidism may worsen underlying disease processes. Therefore, worsening of a previously compensated underlying disorder should prompt a search for occult thyrotoxicosis, especially when there is no obvious explanation for such a deterioration.

Alternatively, it may present with prime involvement of a single organ system. Such monosymptomatic presentations are not limited to the cardiovascular and gastrointestinal systems. Mild asymptomatic hypercalcemia may be the only manifestation, and thyrotoxicosis must be remembered as an important differential diagnosis of an elevated serum calcium. Thyrotoxic myopathy also has been well described, and this rarely may be the major reason for visiting a physician. Predominant neurologic presentations also have been reported. The most dramatic form obviously is periodic paralysis. It is more common in Asians in whom orbitopathy is not usually manifest, and in males in whom thyrotoxicosis is less common. However, more recently several well documented cases have been reported in populations belonging to other racial and ethnic backgrounds.[68-73]

Occasionally, seizures can be a presenting manifestation of thyrotoxicosis. Up to 60% of patients with thyrotoxicosis have

EEG abnormalities,[74] and in one series, three of 31 thyrotoxic patients presented with seizures.[75] Frequently, higher daily doses of anticonvulsants required for control of seizures may be the clue to the presence of hyperthyroidism. Choreoathetoid movements responsive to beta blockers have been reported as the only manifestation of hyperthyroidism.[76] Psychiatric manifestations including agoraphobia have been described as presenting features.[77] Finally, the disease also may mimic other systemic illnesses such as Lyme disease.[78]

Therefore, the caveat is to exclude thyrotoxicosis by a simple blood test in many of these situations where the underlying cause is not obvious, especially prior to conducting expensive, invasive, and risky procedures to identify the disease process.

In summary, hyperthyroidism may present in a variety of forms. The diagnosis often is dependent on a high index of suspicion for the disease, especially in the elderly since such atypical presentations are not infrequent in this population. Moreover, the prevalence of hypothyroidism rises significantly with aging,[7] and the diagnosis is difficult as well because of the presence of nonspecific symptoms and signs frequently similar to those of aging. Early recognition and intervention with definitive therapy appear to be the keys to reducing the morbidity and mortality associated with both of these disorders. Therefore, screening with determination of serum TSH concentration, especially in the elderly, is recommended by several organizations,[79-83] with a dissenting opinion by the United States Preventative Forum Task Force.[84]

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Physician CME Questions

20. Which of the following would *not* be a typical symptom of hyperthyroidism?
    A. Weight loss
    B. Palpitations
    C. Nervousness
    D. Muscle weakness
    E. Dry skin

21. Which of the following signs would *not* typically be found in hyperthyroidism?
    A. Tremor

In Future Issues:

Insomnia

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

B. Brisk tendon reflexes
C. Dry palms
D. Tachycardia
E. Lid lag

22. Treatment of the hyperthyroidism typically correlates closely with improvement of the orbitopathy.
A. True
B. False

23. The United States Preventative Forum Task Force recommends routine screening with TSH.
A. True
B. False

CME Answer Key

20. E
21. C
22. B
23. B