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Rescue of Graves Thyrotoxicosis-Induced Cholestatic Liver Disease Without Antithyroid Drugs: A Case Report

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Graves thyrotoxicosis rarely presents with painless jaundice resulting from hyperthyroidism-associated hepatotoxicity, without preexisting liver disease. Management in patients with this presentation is challenging, given that the thionamides, methimazole and propylthiouracil, have both been associated with drug-induced liver injury. Radioactive iodine ablation and thyroidectomy are well-established alternatives, but each have their associated risks and contraindications. We present an unusual case of severe hyperthyroidism-associated hepatotoxicity, in which adjuvant therapies, including glucocorticoids, saturated solution of potassium iodide, and cholestyramine, were used as a bridge to definitive therapy with thyroidectomy.

Freeform/Key Words: gastrointestinal endocrinology, liver disorders, Graves disease, hyperthyroidism

Hyperthyroidism secondary to Graves disease classically presents with palpitations, tremor, weight loss, and a diffuse goiter. Mild perturbations in liver function tests (LFTs) are common and usually of little clinical significance. Rarely, hyperthyroidism may present with painless jaundice and considerable hepatic toxicity. Treating patients with these presenting characteristics can be challenging, given that first-line therapy with thionamides may result in substantial drug-induced hepatic injury and cholestasis [1].

1. Case Report

A previously healthy, 35-year-old man with a history of remote cholecystectomy was admitted with one week of new-onset painless jaundice and pruritus.

He noted acholic stools, dark urine, and yellow sclera. He also reported two weeks of fatigue, weakness with exercise, hand tremors, and an unintended 10-lb weight loss over the past year. He denied recent illness or travel (although he did immigrate from Cuba one year prior to presentation). He described generalized pruritus, insomnia, palpitations, and nausea without fevers or abdominal pain. Other than a cholecystectomy for gallstones, he had no other medical problems. His family history was noncontributory. He reported occasional social drinking and denied smoking, intravenous drug use, and high-risk sexual behavior.

An examination revealed tachycardia, hypertension, and diffuse severe jaundice. His thyroid was symmetrically enlarged and nontender, clinically estimated to be approximately 45 g, and without audible bruit or palpable nodules. There was no evidence of Graves orbitopathy or pretibial myxedema. A cardiovascular examination was unremarkable, except

Abbreviations: CT, computed tomography; LFT, liver function test; SSKI, saturated solution of potassium iodide.

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for tachycardia, without audible murmurs or peripheral edema. There was no tenderness on abdominal examination, palpable mass, or hepatosplenomegaly. A fine tremor was noted with arm extension. Laboratory tests showed elevated aspartate aminotransferase, 135 U/L (reference range, 13 to 39 U/L), alanine aminotransferase, 270 U/L (reference range, 9 to 67 U/L), alkaline phosphatase, 379 U/L (reference range, 25 to 100 U/L), total bilirubin, 15.4 mg/dL (reference range, 0.3 to 1.2 mg/dL), direct bilirubin, 10.4 mg/dL (reference range, 0 to 0.4 mg/dL), and impaired hepatic synthetic function with an international normalized ratio of 1.79 (reference range, 0.83 to 1.20). His thyrotropin was undetectable, <0.01 μIU/mL (reference range, 0.35 to 4.9 μIU/mL), with an elevated total triiodothyronine (T3) level of 596 ng/dL (reference range, 83 to 160 ng/dL), free thyroxine index, 6.9 ng/dL (reference range, 1.0 to 4.0 ng/dL), and thyroid-stimulating immunoglobulins, 287% (reference control, <140%). Thyroid ultrasound revealed a symmetrically enlarged, hypervascular, heterogeneous thyroid gland without nodules, consistent with Graves thyroiditis. Upon admission to the emergency department, an iodinated contrast-enhanced computed tomography (CT) scan of the abdomen was obtained, which precluded diagnostic I-123 nuclear thyroid scintigraphy.

Extensive further testing excluded other causes of liver disease (Table 1). Ultrasound, abdominal CT with contrast, and magnetic resonance cholangiopancreatography showed no biliary ductal dilation, pancreatic, biliary, or intrahepatic mass, portal vein thrombosis, or findings concerning for primary sclerosing cholangitis. A chest radiograph to assess for emphysema related to α-1 antitrypsin deficiency was unremarkable. Percutaneous liver biopsy revealed acute cholestatic hepatitis with occasional single necrotic hepatocytes, without increased portal fibrosis, cirrhosis, steatosis, or iron deposits, most consistent with thyrotoxicosis-induced cholestatic liver injury.

Concurrently with this testing, atenolol was started for symptomatic palpitations. Methimazole and propylthiouracil were not initiated, given the severity of the biochemical cholestatic liver disease, because thionamides may cause both cholestatic and hepatocellular injury in up to 25% of patients [1]. Instead, dexamethasone (1 mg orally twice per day) was initiated, given that it inhibits peripheral conversion of thyroxine to T3 and has a direct

Table 1. Laboratory Workup for Cholestatic Transaminitis

Laboratory Test	Reference Range	Result
Hepatitis A Ab IgM	Negative	Negative
Heb B surface antigen	Negative	Negative
Hep B core Ab IgM	Negative	Negative
Hep C Ab	Negative	Negative
Hep E IgG	Negative	Negative
Hep E IgM	Negative	Negative
EBV IgG Ab to viral capsid antigen	≤0.90 negative; 0.91–1.09	≤0.90
EBV IgM Ab to viral capsid antigen	equivocal; ≥1.10 positive	≤0.90
EBV IgG to nuclear antigen		1.4
EBV IgG Ab to Ea-D		≤0.90
CMV IgG Ab	Negative	31
CMV IgM Ab	Negative	0.02
Actin smooth muscle IgG Ab	<20 U	<20
Antinuclear Ab screen	Negative	Negative
Ceruloplasmin	18-36 mg/dL	49
Hemochromatosis	Negative	Negative for p.C282Y, p.H63D, p.S65C
HIV antigen/Ab combined	Negative	Negative
IgG	700-1600 mg/dL	1064
Liver kidney microsomal Ab	≤20.0 U	≤20.0
Mitochondrial Ab	Negative	Negative
Mono test	Negative	Negative

Abbreviations: Ab, antibody; CMV, cytomegalovirus; Ea-D, early D antigen; EBV, Epstein-Barr virus; Hep, hepatitis; Ig, immunoglobulin; Mono, mononucleosis.

inhibitory effect on hormone secretion [2]. In addition, cholestyramine had been initiated primarily for pruritus from hyperbilirubinemia, but may have also lowered circulating thyroid hormone through decreased enterohepatic recirculation [3]. Last, the massive iodinated contrast load from the CT scan was beneficial in temporarily suppressing thyroid hormone synthesis and secretion through the acute Wolff-Chaikoff effect, but also invalidated any role for iodine-131 radioactive iodine ablation as an acute therapy. The iodine-mediated protective effect started to decline within 72 hours after the patient's CT scan, as expected, through "escape" from the acute Wolff-Chaikoff effect, with an uptick in LFTs and T3 (Fig. 1). Potassium iodine (SSKI) was initiated at this time to continue with iodine-mediated synthesis blockade and to avoid rebound hormone synthesis. Over several days, these therapies normalized the patient's T3 concentrations, with concomitant improvement in LFTs (Fig. 1). Once his LFTs approached normal, in discussion with the endocrine surgeons, methimazole was initiated (as cholestyramine, SSKI, and dexamethasone were discontinued) to maintain euthyroidism as a bridge to definitive outpatient treatment. Although initiating a thionamide may carry a risk of further liver injury, the patient's surgeons believed strongly that thyroidectomy should be postponed until resolution of his coagulopathy. Following initiation of methimazole, the patient continued to improve, with continued normalization of LFTs (Fig. 1). A few weeks later, he underwent successful thyroidectomy, with removal of a 54-g thyroid gland showing diffuse follicular hyperplasia with septal fibrosis, consistent with Graves disease.

2. Discussion

In individuals with severe hepatotoxicity as a result of hyperthyroidism, treatment can be challenging, because thionamides may worsen liver injury to the point of liver failure, although methimazole has been shown to improve preexisting mild transaminitis (<2 times the upper limit of normal) from hyperthyroidism [4]. A review of the English-language medical literature reveals only a handful of previous case reports describing thyrotoxicosis-associated jaundice in the absence of congestive heart failure, with almost all describing the use of thionamides or radioactive iodine in initial treatment [5–10]. A representative sample is detailed in Table 2. Our case suggests that alternate initial therapies can be used successfully in the setting of severe liver dysfunction, with no need to risk further liver injury with thionamides to achieve euthyroidism. The iodinated contrast received on admission

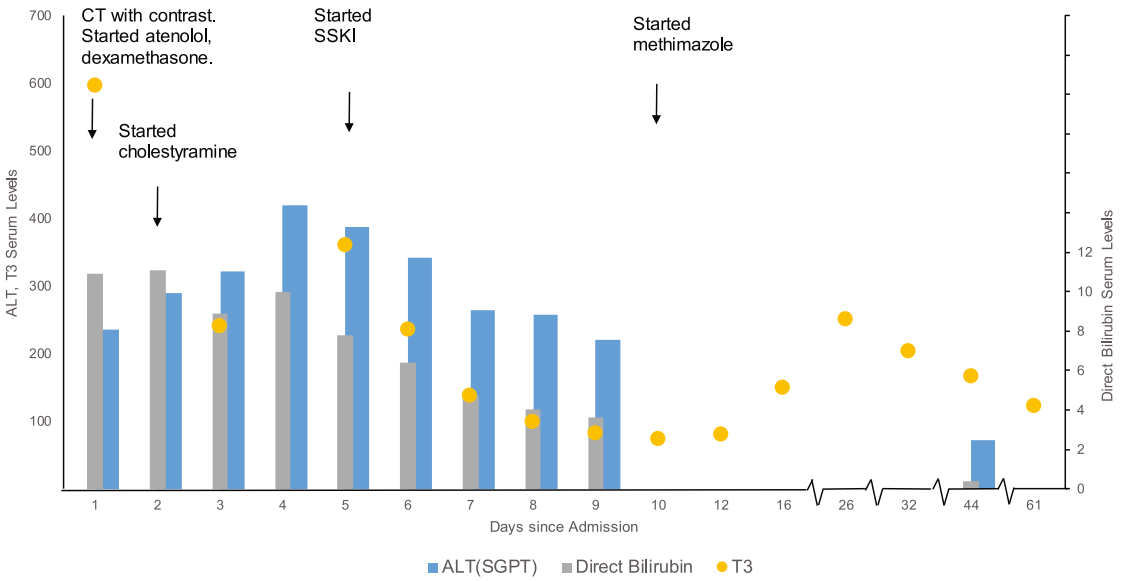

Figure 1. Correlation between T3 hormone and LFTs over time.

Table 2. Previous Case Reports of Jaundice Due to Hyperthyroidism

Authors	Patients[a]	Laboratories (Pretreatment)	Treatments	Resolution of Jaundice and Abnormal LFTs (mo)	Return to Euthyroidism (mo); Conversion to Hypothyroidism (mo)
Ding *et al.*, 2015 [7]	Jaundice in two cases (of five total) due to hyperthyroidism; case 1: woman (age 49 y) with 5-y history of hyperthyroidism	Direct bilirubin, 19.7 mg/dL T3, 402 ng/dL	Both cases received oral I-131 at dose of 3.33 to 4.44 MBq/g thyroid, lithium carbonate 0.25 g; case 2 also received six rounds of plasma exchange	4	12; 45
	Case 2: man (age 48 y) with 12-y history of hyperthyroidism	Direct bilirubin, 16.5 mg/dL T3, 555 ng/dL		3	3; 3
Klangjareonchai, 2012 [6]	Woman (age 51 y) without known hyperthyroidism	Direct bilirubin, 14 mg/dL Free T3, 5.23 pg/mL	Methimazole 10 mg/d, cholestyramine 4–5 g/d	3	3; NA
Chawla and Bal, 2008 [8]	Jaundice in one case (of four total) due to hyperthyroidism; case 1: woman (age 40 y) without known hyperthyroidism	Total bilirubin, 27.2 mg/dL T3, 260 ng/dL	I-131 at dose of 5 mCi	3	3; 6
Hull *et al.*, 2007 [5]	Case 1: woman (age 38 y) without known hyperthyroidism	Total bilirubin, 18.3 mg/dL T3, >550 ng/dL	Propylthiouracil 100 mg twice per day, propranolol hydrochloride 20 mg twice per day; after decompensation, propylthiouracil increased to 300 mg four times per day, dexamethasone 2 mg IV four times per day, and SSKI added; subsequent near-total thyroidectomy	1	1; 2
	Case 2: woman (age 35 y) without known hyperthyroidism	Total bilirubin, 30 mg/dL T3, >550 ng/dL	Propylthiouracil 300 mg every 6 hours, propranolol hydrochloride 20 mg twice per day, dexamethasone 2 mg IV four times per day, SSKI; subsequent near-total thyroidectomy	2	1; 2

Table 2. Continued

Authors	Patients[a]	Laboratories (Pretreatment)	Treatments	Resolution of Jaundice and Abnormal LFTs (mo)	Return to Euthyroidism (mo); Conversion to Hypothyroidism (mo)
Owen *et al.*, 2007 [9]	Man (age 36 y) without known hyperthyroidism	Total bilirubin, 34 mg/dL Free T3, 63.6 pg/mL	Carbimazole (dose not stated)	1	NA; NA
Arab *et al.*, 1995 [10]	Man (age 48 y) without known hyperthyroidism	Total bilirubin, 2 mg/dL Free T4, 9.2 ng/dL	Methimazole 10 mg three times per day, propylthiouracil 50 mg twice per day, I-131 at dose 15 mCi	4	3; 4

Abbreviations: I-131, iodine-131; IV, intravenously; NA, not available; T4, thyroxine.
[a]Only cases of jaundice as a result of hyperthyroidism, and not thionamide treatment, are included.

invalidated any role for I-131 radioiodine ablation, and urgent thyroidectomy is risky in a patient with marked thyrotoxicity and severe liver dysfunction and associated coagulopathy. Our case report adds to the available evidence that adjunctive combination therapies employing dexamethasone, cholestyramine, and SSKI are rapid-acting, safe alternatives to treat hyperthyroidism in individuals with contraindications to traditional treatment.

Graves hyperthyroidism can present with severe cholestasis and hepatotoxicity, without preexisting liver disease, which complicates therapeutic decision making. This case in particular was an unusually severe presentation of hepatotoxicity from Graves disease, and not simply the usual mild transaminitis that can occur with hyperthyroidism. Initiating thionamides may not be necessary in the vast majority of cases, if euthyroidism can be achieved through radioiodine ablation or thyroidectomy. Adjunctive, alternative therapies such as dexamethasone, cholestyramine, and SSKI can be successfully used as a rapid-acting bridge to definitive therapy or delayed thionamide initiation, once liver dysfunction and hyperthyroidism are under control.

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