

Severe cholestatic jaundice associated with Graves' disease

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Key Clinical Message

We describe a rare case of Graves' disease presenting with atrial fibrillation and severe cholestasis. An extensive evaluation for hepatobiliary causes of cholestasis, including hepatic biopsy, was entirely negative. He was successfully treated with methimazole and eventual thyroidectomy. With caution, thionamides can be utilized successfully for such patients.

KEYWORDS

cholestatic jaundice, Graves' disease, hyperthyroidism, thyrotoxicosis

1 | BACKGROUND

Graves' disease is one of the most common causes of hyperthyroidism. There are several ways Graves' disease can manifest itself, related to either hyperthyroidism or as a result of underlying autoimmunity.¹ We present a case of Graves' disease associated with severe cholestatic jaundice; an uncommon but recognized presentation of Graves' disease.²

2 | CASE REPORT

A 45-year-old male with no past medical history was transferred to our tertiary care facility after presenting to a community hospital with a one-week history of generalized abdominal pain, jaundice, dark urine, and lower extremity edema. His initial evaluation revealed severe hyperbilirubinemia and elevated transaminases, prompting his transfer. He denied any alcohol consumption for the previous twenty years or intravenous drug use. He had no medical history, was taking no medications prior to presentation, except a multivitamin. He denied taking any herbal supplements and his family history was unremarkable. He was married and employed as an auto mechanic.

On examination, he was notably jaundiced and cachectic in appearance with a height of 1.7 m, weight of 82.5 kg, and

body mass index (BMI) of 28.3 kg/m². He was afebrile with a pulse of 95 beats per minute, respiratory rate of 16 breaths per minute, and pulse oxygen saturation of 95% while on room air. He had marked scleral icterus; proptosis was noted. On thyroid examination, he had a large symmetrical, non-tender goiter with audible bruit. Heartbeat was irregularly irregular. His abdomen was mildly tender diffusely without ascites or organomegaly. Mild bilateral lower extremity edema was present. Skin was warm to the touch. A fine tremor was noted; asterixis of hands was intermittently present.

Initial laboratory evaluation revealed a hemoglobin of 12.1 g/dL (13.5-16.5), platelet count of 115 k/μL (150-400), and white blood cell count of 11.8 k/μL (4.5-11). His international normalized ratio (INR) was 2.4. His serum sodium was 128 mmol/L (137-147), potassium of 4.3 mmol/L (3.5-5.1) with creatinine of 1.77 mg/dL (0.4-1.24), blood urea nitrogen (BUN) of 57 mg/dL (7-25) and serum glucose 159 mg/dL (70-100). Notably, his total bilirubin was 19.8 mg/dL (0.3-1.2), direct bilirubin 13.8 mg/dL (<0.4), alkaline phosphatase 332 U/L (25-110), aspartate aminotransferase (AST) 86 U/L (7-40), and alanine aminotransferase (ALT) 50 U/L (7-56). His gamma-glutamyltransferase was 20 U/L (9-64). Total iron was 32 mcg/dL (50-185), percent iron saturation 11% (28%-42%), total iron binding capacity (TIBC) was 283 mcg/dL (270-380), and ferritin 121 ng/mL (30-300). The patient also had negative serology for hepatitis A, B, and C.

A workup for thyroid dysfunction demonstrated a thyroid-stimulating hormone (TSH) of 0.026 mcg/mL (0.35-5.00) with a free T4 of 4.3 ng/dL (0.6-1.6), free T3 4.6 pg/mL (2.1-3.9), and total T3 125 ng/dL (87-180). TSH receptor antibody was >40 IU/L (0.00–1.75) and thyroid peroxidase (TPO) antibody was >1000 IU/mL (<5.61). An ultrasound of the patient's thyroid was notable for a mildly enlarged heterogeneous and hypervascular thyroid without nodularity. Based on these findings along with his presenting symptoms and signs, the patient was diagnosed with Graves' disease.

In light of worsening cholestatic jaundice (Figure 1), a thorough hepatology evaluation was undertaken for potential autoimmune, infectious, and primary hepatobiliary causes of cholestasis. The laboratory testing were all negative. Cardiac evaluation was notable for an ejection fraction of 55%-60% with right ventricular dilation and moderate mitral regurgitation. Moderate left atrial and severe right atrial enlargement was found with elevated central venous pressure as well as pulmonary artery pressure. Abdominal ultrasound demonstrated increase echogenicity of the liver and revealed trace abdominal and pelvic ascites. Further workup for cholestatic jaundice included a computed tomography scan of the abdomen and pelvis, which was notable for fatty liver, cardiomegaly, and diffuse irregular appearance of bones with prominent trabecula. Endoscopic retrograde cholangiopancreatography (ERCP) showed normal caliber common bile duct and common hepatic duct with normal intrahepatic ducts, without filling defects, strictures, or stenosis. Endoscopic ultrasound (EUS) was notable for normal pancreatic parenchyma as well as normal pancreatic and common bile ducts. The patient subsequently underwent transjugular liver biopsy with unremarkable hepatic vein pressures and a corrected sinusoidal pressure gradient of 5-6 mm Hg (normal). Pathology showed cholestasis and mild ductal proliferation with focal pericholangitis but no hepatic steatosis, fibrosis, hepatocellular injury, or necrosis. Periodic acid-Schiff (PAS) diastase digestion showed normal glycogen content without unusual intrahepatic inclusions; hepatic iron stores were normal.

Prior to transfer to our facility, he was initially stabilized with intravenous diltiazem drip 5 mg per hour titrated for rate control of his atrial fibrillation with rapid ventricular response, in combination with hydrocortisone 50 mg every eight hours and propylthiouracil (PTU) 150 mg every six hours for management of thyrotoxicosis. Due to concern for fulminant liver failure, urgent transfer was pursued to our facility. Upon arrival, the patient's thyrotoxicosis and resultant atrial fibrillation and diastolic heart failure were managed aggressively given his calculated Burch-Wartofsky score of 45. PTU was stopped in light of FDA black box warning, and methimazole was initiated at a dose of 20 mg every 8 hours; corticosteroids were continued for management of thyroid storm until normalization of total T3. The patient experienced gradual improvement in his free T4 (Figure 2). His

atrial fibrillation was managed with oral digoxin 125 µg after digitalizing doses and metoprolol 100 mg oral twice daily.

While the index of concern for acute liver failure prompted a swift and extensive investigation, it was entirely negative for primary hepatobiliary causes of his cholestasis including ERCP, EUS, and transjugular liver biopsy. Based on negative rheumatologic, autoimmune, and infectious causes workup, it was concluded that his cholestatic jaundice was related to Graves' disease related thyrotoxicosis. This clinical hunch was further solidified with his clinical and metabolic improvement (Table 1). Total bilirubin was 13.9 mg/dL on admission to the outside facility, peaking 17 days later at 39.1 mg/dL and improving to 14.0 mg/dL two weeks following discharge. An important point that needs to be made was his high bone-specific alkaline phosphatase, which was markedly elevated at 103 mcg/L (0-20), demonstrating a high bone turnover state related to his hyperthyroidism. The patient was discharged two weeks after his hospitalization with plans for definitive outpatient management of Graves' disease.

3 | DISCUSSION

We have described the case of a 45-year-old male presenting with new-onset Graves' disease, atrial fibrillation with concurrent high-output diastolic heart failure and severe cholestatic jaundice. The differential diagnosis for this patient was quite broad but accounted for primary liver injury secondary to an autoimmune process, iron, and copper storage diseases, alpha-1 antitrypsin deficiency, infectious etiologies including hepatitis or abscess, drug-induced liver injury, hepatic steatosis, primary biliary obstruction, intrahepatic cholestasis, and thyrotoxicosis related cholestasis. We completed an extensive investigation for potential causes of this patient's cholestatic jaundice. Although he had a mildly elevated antinuclear antibody, he had no other evidence of autoimmune hepatitis including negative anti-smooth muscle antibody. This was further confirmed with negative histopathology. In addition, tests for hemochromatosis, and alpha-1 antitrypsin deficiency or Wilson's disease were negative. Viral serologies were negative making viral hepatitis an unlikely cause. Furthermore, no granulomas or hepatic abscess were identified which essentially ruled out hepatic infections as a probable etiology. Medication use was excluded considering absent culprit medication intake except a multivitamin. Although PTU has been associated with hepatotoxicity in rare cases, this was unlikely in our patient as he had elevated transaminases and hyperbilirubinemia on initial presentation, prior to briefly receiving PTU. Pathology from his liver biopsy would also not support a diagnosis of PTU-related injury, which typically includes hepatocellular necrosis.³ His presentation was not consistent with alcohol-induced

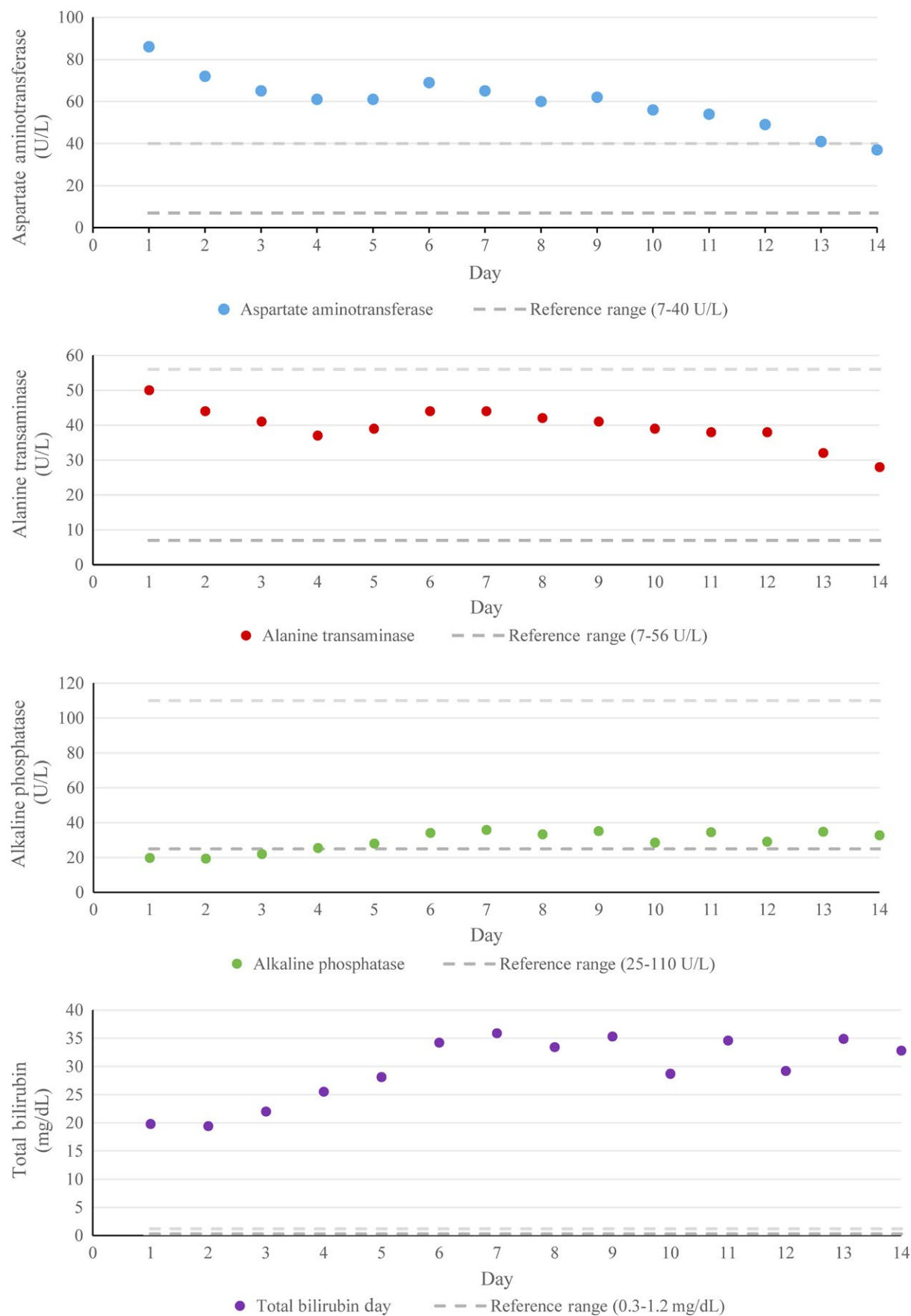


FIGURE 1 Transaminases and bilirubin changes prior to and while on treatment

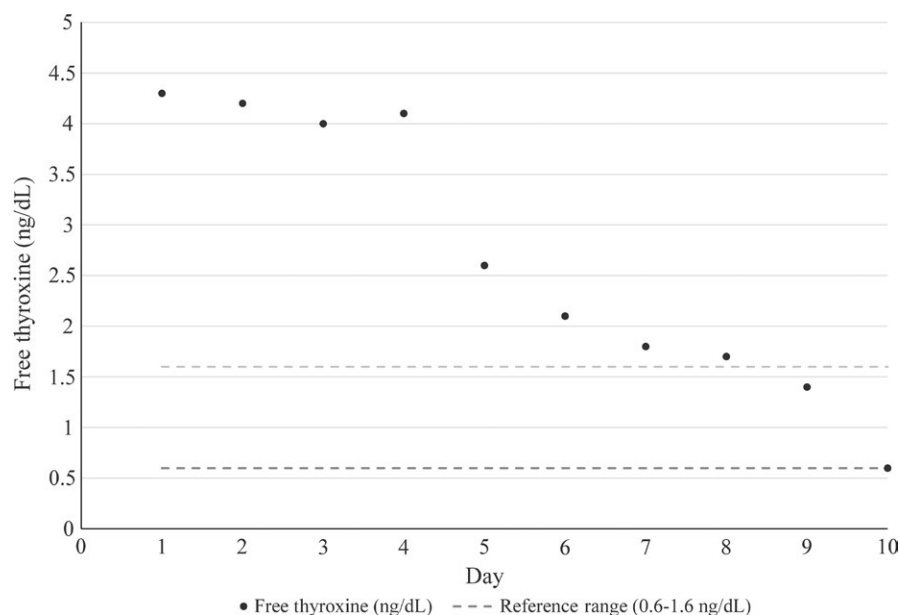


FIGURE 2 Free thyroxine changes prior to and during therapy

hepatitis based on denial of any use of alcohol, which was further confirmed with a negative ethyl glucuronide screen. Although radioiodine has been reported as a potential cause of cholestasis, our patient had not received this therapy prior to or during his hospitalization. As previously noted, potential etiologies for hepatic steatosis were excluded; we presumed that his elevated BMI was essentially from an acute volume overload, supported by findings of ascites, lower extremity edema on physical examination, echocardiographic findings of elevated central venous pressures, and absent steatosis on biopsy. EUS and ERCP failed to demonstrate choledocholithiasis, biliary stricture, and malignant obstruction as possible etiologies of cholestatic jaundice. Biopsy did not demonstrate infiltrative diseases that cause intrahepatic cholestasis, including amyloidosis, sarcoidosis, or lymphoma. As there was no evidence of primary liver disease, secondary causes were pursued. The mild elevation of ANA may raise concern for potential autoimmune cholangiopathy as an alternative etiology, but this is a very nonspecific finding and further tests did not support any autoimmune etiology including a negative antimitochondrial antibody. This theory was further strengthened as histopathology was not consistent with autoimmune cholangiopathy and marked elevation of bone component of

alkaline phosphatase level supports origin from bone turnover rather than that of hepatic origin. It is presumed that his cholestatic jaundice was due partly to hepatic congestion from acute diastolic, high-output heart failure in association with new atrial fibrillation as was discussed in the case study by Venkat et al.⁴

Thyrotoxicosis is an uncommon cause of cholestasis. Our understanding of the underlying mechanism remains incomplete. Cases have been reported to occur with and without heart failure, although cholestasis is usually more severe in cases with concurrent heart failure.⁵ There is evidence of a mechanism involving mitochondrial-induced apoptosis,⁶ another theory cites evidence that oxidative stress from a hyperthyroid state as a cause of hepatotoxicity and cholestasis.⁷ To date, there is no strong evidence to suggest that thyroid hormone is directly toxic to the liver.⁸ The workup for cholestasis in patients with autoimmune thyroid disease must include a search for possible other autoimmune etiologies as approximately 10% of patients with Graves' disease will develop liver injury via an autoimmune mechanism.⁹ Hence, patients with hyperthyroidism presenting with concurrent liver dysfunction should undergo appropriate workup for non-thyroidal autoimmune diseases.

TABLE 1 Laboratory values upon admission and at discharge

Laboratory values	Reference range	On admission	At discharge
AST (U/L)	7-40	86	37
ALT (U/L)	7-56	50	28
Alkaline phosphatase (U/L)	25-110	332	196
Total bilirubin (mg/dL)	0.3-1.2	19.8	32.8
Free T4 (ng/dL)	0.6-1.6	4.3	0.6
Free T3 (pg/mL)	2.1-3.9	4.6	3.1

Methimazole and PTU are the two thionamides used within the United States. They inhibit the production of thyroid hormone by blocking TPO iodination of tyrosine residues in thyroglobulin. PTU also prevents peripheral conversion of thyroxine to triiodothyronine.¹⁰ Multiple other immunosuppressive effects of the drugs may also contribute to remission in Graves' disease.¹⁰ Hepatotoxicity is a known, rare complication of thionamide therapy with focal hepatic necrosis seen with PTU therapy. Methimazole is more likely to be associated with cholestatic inflammation. While thionamides can be associated with hepatic injury, hepatic dysfunction is common in the presentation of thyrotoxicosis. In a recent retrospective study looking at serial changes in liver enzyme testing before and during treatment with methimazole, it was clear that in those patients with hepatic dysfunction at baseline, methimazole treatment resulted in normalization of hepatic enzymes.¹¹ We feel the use of a thionamide was justified given the severity of our patient's condition. Our patient was acutely ill with multiple organ systems impacted by his Graves' disease. He suffered from acute diastolic heart failure, atrial fibrillation, and acute kidney injury in addition to his cholestasis. Other options available for acute treatment could have included thyroidectomy versus radioactive iodine. Which, in the setting of his acute illness, would likely have carried significantly higher risk than use of a thionamide.

Prior case reports have described treatment utilizing thionamides with or without saturated solution of potassium iodide.^{2,12,13} Due to the potential for hepatotoxicity as a complication of thionamide therapy, the determination that thyrotoxicosis is the cause of hepatic dysfunction needs to be clearly elucidated prior to introducing thionamide therapy in this patient population. Because of the concern about use of thionamide therapy in the setting of hepatic dysfunction, a case report describes treatment of Graves' thyrotoxicosis with associated cholestasis without thionamide therapy; instead, managed initially with a combination of saturated solution of potassium iodide and cholestyramine.¹⁴

Prompt treatment of our patient's thyrotoxicosis with methimazole therapy along with treatment of his atrial fibrillation associated heart failure resulted in remarkable improvement of his clinical condition and metabolic parameters. While our patient's bilirubin, transaminases, and alkaline phosphatase improved after returning to a euthyroid state, this metabolic recovery lagged behind that of thyroid by several weeks. After maintaining a euthyroid state for several months, he eventually underwent total thyroidectomy for definitive treatment of his Graves' thyrotoxicosis.

This case highlights the importance of considering thyrotoxicosis as a cause of cholestasis. Due to the rarity of this presentation along with the concern for use of thionamide therapy in the setting of hepatic dysfunction, it is critical that other potential causes of acute liver injury are excluded prior

to concluding that a case is due to thyrotoxicosis. However, treatment for thyroidal disease should not be delayed. Attaining a euthyroid state quickly is critical as hepatic recovery can lag behind that of thyroid by several weeks. Our case further supports the safety and utility of using thionamide therapy in the treatment of hyperthyroidism-induced hepatic dysfunction.

4 | CONCLUSIONS

Severe cholestasis is an uncommon but potential presentation of Graves' hyperthyroidism.² This case demonstrates the need for early diagnosis and management of thyrotoxicosis and associated hepatic and cardiac conditions to mitigate worsening of hepatic status. While thionamide therapy is rarely associated with hepatic dysfunction, it is safe and effective to manage hepatic dysfunction due to thyrotoxicosis with thionamide therapy.

ACKNOWLEDGMENTS

We sincerely are grateful for the support we received from the University of Kansas Department of Internal Medicine and Dr. Cheryl Gibson for her tireless work in reviewing and help writing this manuscript. We also thank Rebecca Mount for her careful review and editorial assistance.

CONFLICT OF INTEREST

The authors have no disclosures to report.

AUTHOR CONTRIBUTIONS

MH and AA: gathered and organized information regarding the patient. MH, AA and LE: performed a literature review and drafted the manuscript. LE: critically reviewed the draft and provided expert opinion for revisions. All reviewed the final version and approve the content of the submission.

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How to cite this article: Abebe A, Eck LM, Holyoak M. Severe cholestatic jaundice associated with Graves' disease. *Clin Case Rep*. 2018;6:2240–2245. <https://doi.org/10.1002/ccr3.1859>