CASE REPORT | LIVER

Cholestatic Hepatitis in Graves' Disease: A Diagnostic Challenge

Metri Haddaden, MD[1], Angy Hanna, MD[2], Fadi Odish, MD[2], Samir Husami, MBBS[3], Zaid Imam, MBBS[2], and Mamon Tahhan, MD[2]

[1]Department of Internal Medicine, MedStar Health, Baltimore, MD
[2]Department of Internal Medicine, William Beaumont Hospital, Royal Oak, MI
[3]Division of Nephrology, Department of Medicine, Washington University School of Medicine, St. Louis, MO

ABSTRACT

Cholestatic hepatitis is a rare presentation of thyrotoxicosis potentially confused as an adverse effect of antithyroid therapy. We report a 37-year-old man with cholestatic hepatitis as an initial presentation of Graves' disease. Diagnostic evaluation demonstrated (i) elevated transaminases and alkaline phosphatase (R-factor value: 2.6), and marked cholestasis (total bilirubin: 17.3 mg/dL, direct bilirubin: 9.4 mg/dL); (ii) negative hepatitis, viral, and autoimmune serologies; (iii) normal magnetic resonance cholangiopancreatography; (iv) liver biopsy with marked cholestasis and no fibrosis; (v) thyroid-stimulating hormone <0.01, fT4 (free thyroxine): 1.5, fT4 (free triiodothyronine): 4.3 and positive thyroid-stimulating immunoglobulins. Radioiodine uptake scan confirmed Graves' disease. Clinical resolution was achieved with propranolol, prednisone, methimazole, and thyroidectomy.

INTRODUCTION

Clinical signs and symptoms of thyroid overactivity, goiter, and orbitopathy represent the cardinal features of Graves' disease, the leading cause of hyperthyroidism.[1] A large cohort of patients with thyrotoxicosis reported elevated alkaline phosphatase (ALP) levels in 29% of patients, but elevated transaminases and hyperbilirubinemia were less common.[2] Direct catabolic effects of excessive thyroid hormone on bone turnover and a bone origin of ALP may explain this discrepancy.[2] Severe symptomatic cholestasis in patients with Graves' disease is rare, and etiology is often attributed to antithyroid therapy or occurring in the setting of thyroid storm.[3–5] Less common etiologies include concomitant autoimmune hepatitis or primary biliary cholangitis.[6,7] We report a case of cholestatic hepatitis in a 37-year-old man as an initial presentation of Graves' disease, highlighting the importance of a thorough diagnostic evaluation in a case that represents a diagnostic and therapeutic challenge.

CASE REPORT

A 37-year-old man complained of jaundice, pruritus, fatigue, diarrhea, and significant weight loss for 3 months. His only medication was oxycodone for chronic back pain after a car accident. He had no other medical problems and no family history of cholestatic or other chronic liver disease. He denied alcohol, supplement, or excessive acetaminophen use. Physical examination demonstrated scleral icterus and jaundice with no encephalopathy, exophthalmos, heart murmurs, hepatosplenomegaly, or stigmata of chronic liver disease. His blood pressure was 122/82 mm Hg, and heart rate was 85 beats per minute. An electrocardiogram showed atrial fibrillation. Initial laboratory test results showed a normal platelet count, international normalized ratio, albumin, and renal function. A mixed pattern of elevated transaminases and ALP (R-factor value: 2.6) was noted with an aspartate aminotransferase (AST) of 132 U/L, alanine aminotransferase (ALT) of 222 U/L, and ALP of 222 U/L. Significant cholestasis with a total bilirubin of 17.3 mg/dL and a direct fraction of 9.4 mg/dL was noted. No baseline liver chemistries were available. Hepatitis A, B, and C, human immunodeficiency virus, cytomegalovirus, and Epstein Barr virus testing was negative.

Autoimmune workup was unremarkable with a negative antinuclear antibody, antimitochondrial antibody testing, normal immunoglobulins, and antismooth muscle antibody titer of 1:20. A magnetic resonance cholangiopancreatography was normal. Serum ferritin was 2,938 ng/mL, and ceruloplasmin was normal. Hemochromatosis gene testing was heterozygous for the H63D mutation.

Given the patient's presenting symptoms, a thyroid profile as obtained demonstrating suppressed thyroid-stimulating hormone of <0.01 mcIU/mL, fT4 (free thyroxine) of 1.5 ng/mL, and fT3 (free triiodothyronine) of 4.3 pg/mL. Thyroid-stimulating immunoglobulins, thyroid-stimulating hormone receptor antibodies, and antithyroid peroxidase antibodies were positive. A radioiodine (RAI) uptake scan demonstrated 90% diffuse uptake of radiotracer consistent with Graves' disease. To evaluate for alternative etiologies, a transcutaneous liver biopsy was performed and was inconsistent with autoimmune hepatitis and showed minimal inflammation and marked cholestasis, with no fibrosis or excess iron deposition.

A diagnosis of severe thyrotoxicosis manifesting as cholestatic hepatitis was established. Treatment was started with propranolol and low-dose methimazole. Minimal improvement occurred in the first 2 days and oral prednisone (60 mg/daily) was started on day 2 of hospitalization and tapered over 2 months. Although serum bilirubin fell by 57% to 5.3 mg/dL by day 18, serum AST and ALT increased to 205 and 452 IU/L, respectively. A surgical thyroidectomy was performed on day 18 of hospitalization, yielding a 44 g thyroid gland. Liver chemistries markedly improved in 2 weeks after thyroidectomy (AST: 67 U/L, ALT: 126 U/L, total bilirubin 1.9 mg/dL) and demonstrated near-complete resolution 2 months from hospital discharge. He was lost to follow up, and hence, no further liver chemistries were obtained. Figure 1 summarizes liver chemistry trends during the patient's illness.

DISCUSSION

Cholestatic hepatitis represents a diagnostic challenge considering the broad differential diagnosis and the variability in clinical presentation and severity. In the reported case, the presence of weight loss, diarrhea, and atrial fibrillation prompted early thyroid function testing to establish the diagnosis. Nevertheless, a thorough evaluation for viral hepatitis, biliary disease, drug-induced or supplement-induced liver injury, Wilson's disease, hemochromatosis, autoimmune liver pathologies, and cardiac disease was required before confirming the diagnosis. Ferritin elevation was noted in the case as an elevated acute-phase reactant rather than a manifestation of iron overload. Severe cholestasis in hyperthyroidism could occur, regardless of the concomitant presence of thyroid storm or heart failure, as in our patient.[8]

Previous similar cases in the literature reported cholestatic liver enzyme patterns (R factor <2) and mild ALT elevation (<100 U/L).[9–14] Interestingly, our patient developed a mixed liver injury pattern with peak ALT levels >10 times the upper limit of normal. Although a rapid improvement in our patient's cholestasis occurred with methimazole and prednisone therapy, complete resolution of jaundice occurred only 2 weeks after definitive treatment with surgical thyroidectomy. The severity of liver injury could pose a management challenge, given the need to balance the risks of worsening hepatotoxicity by using antithyroid therapies to treat the underlying primary process.[10,15,16]

Both methimazole/carbimazole and propylthiouracil have risks of cholestatic liver injury but overall low liver failure risks. In the setting of existing liver dysfunction, these risks may be increased and should be carefully weighed against these therapies' benefits. Closer monitoring of liver function in patients with existing liver dysfunction receiving antithyroid therapies may be necessary. RAI ablation may present the preferred modality for treating Graves' disease patients with liver dysfunction, but further evidence is
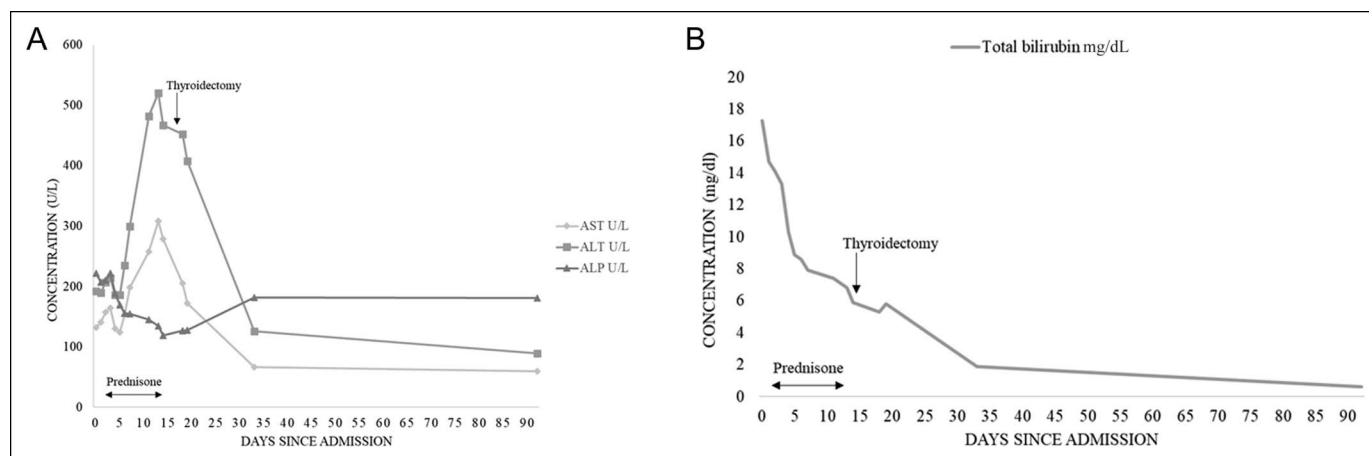

Figure 1. (A) Liver enzyme trend since hospitalization and (B) serum total bilirubin trend since hospitalization.

required.[9,10,17,18] In our case, the management strategy comprises lower dose methimazole therapy, followed by surgical thyroidectomy because of patient preference.

Suggested mechanisms for liver injury in hyperthyroidism include mitochondrial structural disruption and apoptotic activation of hepatocytes by triiodothyronine (T3).[19] Clinical correlates associated with liver dysfunction in Graves' disease include higher free T3 levels, age greater than or equal to 45, and thyrotropin receptor antibody concentration. Despite the absence of all 3 correlates in our patient, significant liver injury was present. In conclusion, Graves' disease should be entertained on the differential diagnosis for cholestatic hepatitis, even in the absence of thyroid storm. Treatment choice may prove to be challenging, and further studies are required to corroborate the safety of RAI in this setting and to identify mechanisms of liver injury secondary to hyperthyroidism.

DISCLOSURES

REFERENCES

1. Smith TJ, Hegedüs L. Graves' disease. *N Engl J Med* 2016;375(16):1552–65.
2. Lin TY, Shekar AO, Li N, et al. Incidence of abnormal liver biochemical tests in hyperthyroidism. *Clin Endocrinol (Oxf)* 2017;86(5):755–9.
3. Ozenne G, Manchon ND, Doucet J, Hémet J, Schrub JC, Bercoff E. Carbimazole-induced acute cholestatic hepatitis. *J Clin Gastroenterol* 1989;11(1):95–7.
4. Woeber KA. Methimazole-induced hepatotoxicity. *Endocr Pract* 2002;8(3):222–4.
5. Kibirige D, Kiggundu DS, Sanya R, Mutebi E. Cholestatic hepatic injury due to a thyroid storm: A case report from a resource limited setting. *Thyroid Res* 2012;5(1):6.
6. Shetty S, Rajasekaran S, Venkatakrishnan L. Grave's disease and primary biliary cirrhosis-an unusual and challenging association. *J Clin Exp Hepatol* 2014;4(1):66–7.
7. Sato I, Tsunekawa T, Shinohara Y, et al. A case of autoimmune hepatitis with Graves' disease treated by propylthiouracil. *Nagoya J Med Sci* 2011;73(3–4):205–9.
8. Khemichian S, Fong TL. Hepatic dysfunction in hyperthyroidism. *Gastroenterol Hepatol (NY)* 2011;7(5):337.
9. Barnes SC, Wicking JM, Johnston JD. Graves' disease presenting with cholestatic jaundice. *Ann Clin Biochem* 1999;36(5):677–9.
10. Majeed M, Babu A. Cholestasis secondary to hyperthyroidism made worse by methimazole. *Am J Med Sci* 2006;332(1):51–3.
11. Soylu A, Taskale M, Ciltas A, Kalayci M, Baki Kumbasar A. Intrahepatic cholestasis in subclinical and overt hyperthyroidism: Two case reports. *J Med Case Rep* 2008;2:116.
12. Wickramasinghe RDSS, Luke WANV, Sebastiampillai BS, Gunathilake MPML, Premaratna R. Thyrotoxic crisis presenting with jaundice. *BMC Res Notes* 2016;9(1):320.
13. Gargouri L, Charfi M, Maalej B, et al. Cholestasis and protein-losing enteropathy secondary to hyperthyroidism in a 6-year-old girl. *J Pediatr Endocrinol Metab* 2014;27(9–10):1017–9.
14. Khelifi D, Ben Nacef I, Rojbi I, McHirgui N, Khiari K. Anicteric cholestasis: A rare hepatic dysfunction caused by hyperthyroidism. *Pan Afr Med J* 2019;34:215.
15. Wang MT, Lee WJ, Huang TY, Chu CL, Hsieh CH. Anti-thyroid drug-related hepatotoxicity in hyperthyroidism patients: A population-based cohort study. *Br J Clin Pharmacol* 2014;78(3):619–29.
16. Kim HJ, Kim BH, Han YS, et al. The incidence and clinical characteristics of symptomatic propylthiouracil-induced hepatic injury in patients with hyperthyroidism: A single-center retrospective study. *Am J Gastroenterol* 2001;96(1):165–9.
17. Wang R, Tan J, Zhang G, Zheng W, Li C. Risk factors of hepatic dysfunction in patients with Graves' hyperthyroidism and the efficacy of 131 iodine treatment. *Medicine (Baltimore)* 2017;96(5):e6035.
18. Wang S, Liang C, Zhao L, et al. Influence of radioactive iodine therapy on liver function in patients with differentiated thyroid cancer. *Nucl Med Commun* 2018;39(12):1113–20.
19. Upadhyay G, Singh R, Kumar A, Kumar S, Kapoor A, Godbole MM. Severe hyperthyroidism induces mitochondria-mediated apoptosis in rat liver. *Hepatology* 2004;39(4):1120–30.