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CASE REPORT | LIVER

Challenges in Management of Autoimmune Hepatitis With Concurrent Graves Thyrotoxicosis

Ngan Nguyen, MD[1], Yala Kirthi Reddy, MD[1], Nidhi Jain, MD[2], Vanisha Patel, BS[3], Deirdre James, MD[2], Bobbak Sistani, MD[1], and Helmut Steinberg, MD[2]

[1]*Department of Internal Medicine, University of Tennessee Health Science Center, Memphis, TN*
[2]*Department of Endocrinology, University of Tennessee Health Science Center, Memphis, TN*
[3]*University of Tennessee Health Science Center, Memphis, TN*

ABSTRACT

The management of concurrent Graves thyrotoxicosis and autoimmune hepatitis (AIH) can be challenging. We present a 37-year-old woman with a recent diagnosis of Graves disease and acute liver injury. Laboratory workup was concerning for AIH. Liver biopsy showed plasma cell infiltration and interface hepatitis consistent with AIH, and treatment with methylprednisolone was initiated. Azathioprine was started after thiopurine methyltransferase testing, and prednisone was tapered down. Thionamide use was contraindicated, so clinical euthyroidism was achieved with the use of cholestyramine and glucocorticoids. Our case highlights the complexities of management when patients are affected by 2 concurrent illnesses.

INTRODUCTION

Autoimmune hepatitis (AIH) is an inflammatory liver disease caused by a T-cell-mediated reaction to liver antigens, leading to a necroinflammatory and fibrotic process in the liver.[1] Plasma cell-rich mononuclear infiltrate mainly involving portal and periportal regions along with interface hepatitis is the characteristic feature of AIH but usually nonspecific.[2] Standard treatment includes combination steroid and azathioprine initiation unless there is some contraindication to azathioprine with the ultimate goal for maintenance to gradually withdraw steroid (Class I, Level A recommendation).[3] In the United States, thyrotoxicosis caused by Graves disease is the most common one. Thionamides are the first-line medications for Graves disease along with nonselective β-blockers for the treatment of thyrotoxicosis.[4] Guidelines recommend extreme caution regarding initiating antithyroid drug therapy when liver enzyme levels are elevated greater than 5-fold or above the upper limit of normal.[5] Few case reports exist about the association with hyperthyroidism and AIH.[6,7]

CASE REPORT

A 37-year-old African American woman with a history of recently diagnosed Graves hyperthyroidism 1-month before presented to the emergency department with complaints of fatigue, diarrhea, severe jaundice, worsening heat intolerance, and palpitations for 4 days and weight loss of 30 lbs over 6 months. The patient was not on any antithyroid medications before coming to the hospital. She had a history of increased alcohol intake (3 beers daily) but was sober for the past 2 months. Screening for drugs, alcohol, acetaminophen, and recent hepatotoxic medication use were all negative.

The patient had scleral icterus, dry mucous membranes, diffusely enlarged but nontender thyroid, and brisk reflexes. The baseline liver function is detailed in Table 1. Acute hepatic damage was suspected. The thyroid function test showed elevated free triiodothyronine (T3) at 5.86 pg/mL and free thyroxine (T4) at 5.06 pg/mL with a suppressed thyroid stimulating hormone level at less than 0.005 μU/mL and elevated thyrotropin receptor antibody (Table 1). Her international normalized ratio at admission

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Correspondence: Yala Kirthi Reddy, MD, Department of Internal Medicine Resident, PGY2, University of Tennessee Health Science and Center, 956 Court Ave, Suite H314, Memphis, TN 38163 (yreddy@uthsc.edu).

Table 1. Laboratory data on admission and discharge

	Normal values	At admission	At discharge
Thyroid function test			
Free T4	0.76–1.46 ng/dL	5.06	2.78
Free T3	2.18–3.98 pg/mL	5.86	1.95
TSH	0.358–0.374 μU/mL	<0.005	Not performed
TRAb	0–1.75 U/L	7.47	Not performed
TSI	<140	Not performed	139
Liver function test			
Alkaline phosphatase	45–117 U/L	314	231
AST	15–37 U/L	2,828	284
ALT	13–56 U/L	2,725	672
Total bilirubin	0.2–1 mg/dL	9.4	11.3
Direct bilirubin	<0.2 mg/dL	1.3	9
Hematology			
WBC	4.5–11.0 × 10^9/L	7.7	10.3
Hgb	6.6–20 g/dL	13.7	11.1
Hematocrit	34.6%–43.8%	40.9	32.5
Platelet	150–400 × 10^9/L	177	153
Immunology workup			
IgG1	382–929 mg/dL	1,910	Not performed
IgG2	241–700 mg/dL	371	Not performed
IgG3	22–178 mg/dL	120	Not performed
IgG4	4–86 mg/dL	39	Not performed
Microbiology workup			
C. Diff toxin B by PCR	N/A	Positive	Not performed
Hepatitis A IgM AB	N/A	Negative	Not performed
Hepatitis B Surf Antigen	N/A	Negative	Not performed
Hepatitis B Core IgG AB	N/A	Negative	Not performed
Hepatitis B Core IgM AB	N/A	Negative	Not performed
Hepatitis B Core antibody total	N/A	Nonreactive	Not performed
Hepatitis C antibody	N/A	Negative	Not performed
HIV 1, 2 antibody	N/A	Nonreactive	Not performed
CMV IgG antibody	0–7.9 EU/mL	145.7	Not performed
CMV DNA, quantity by PCR	N/A	Undetected	Not performed
HSV-1 IgG antibody	<0.9 index	54.3	Not performed
HSV-2 IgG antibody	<0.9 index	>23	Not performed
HSV-1 DNA, quantity by PCR	<100 copies/mL	<100	Not performed
HSV-2 DNA, quantity by PCR	<100 copies/mL	<100	Not performed

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; HCV, hepatitis C virus; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; TRAb, thyrotropin receptor antibody; TSH, thyroid stimulating hormone; TSI, thyroid stimulating immunoglobulin; WBC, white blood cell.

was 1.8; however, the patient was not encephalopathic. Ultrasound of the neck showed diffuse enlargement of both sides of the thyroid gland with hypervascularity. A full sepsis workup was negative for any infection except for *Clostridium difficile*.

Abdominal and pelvic computed tomography showed no evidence of biliary dilatation but some nonspecific periportal edema and lymphadenopathy in the porta hepatis. Her hepatitis profile was negative, and serum quantitative immunoglobulins (IgG) showed markedly elevated IgG1 level (1910 mg/dL).

Autoimmune and infectious workup for acute liver failure were obtained before initiating steroid therapy (Table 1). Considering the history of autoimmune thyroid disease and elevated serum IgG, the suspicion for AIH was heightened. Although her cytomegalovirus (CMV) and herpes simplex virus (HSV) IgG antibodies were high, the CMV and HSV 1 and 2 DNA were undetectable, suggesting previous CMV and HSV exposure. The antimitochondrial antibody, antismooth muscle antibodies, and antinuclear antibody tests were all negative. Liver biopsy performed 4 days after admission revealed plasma cell infiltration and interface hepatitis consistent with a diagnosis of AIH (Figure 1). Our patient had hypergammaglobulinemia with IgG1 level of 1910 mg/dL. Her international AIH group score was 6, which suggested the probable diagnosis of AIH.[8] On the other hand, her revised original AIH score was 21, signifying "definite AIH."[9]

High-dose intravenous methylprednisolone at 40 mg every 8 hours and cholestyramine at 4 mg twice a day was initiated, and β-blockade with propranolol at 40 mg once resumed. Owing to a contraindication to thionamide use, a trial of cholestyramine was attempted to control thyrotoxicosis. The patient responded well to intravenous steroids and oral cholestyramine. After the initiation of glucocorticoids, her transaminases and free T3 and T4 levels trended down (Figure 2). The results of the Quantiferon Gold test and hepatitis B virus core laboratory test and thiopurine methyltransferase status were negative. Azathioprine was added, and glucocorticoid was tapered.

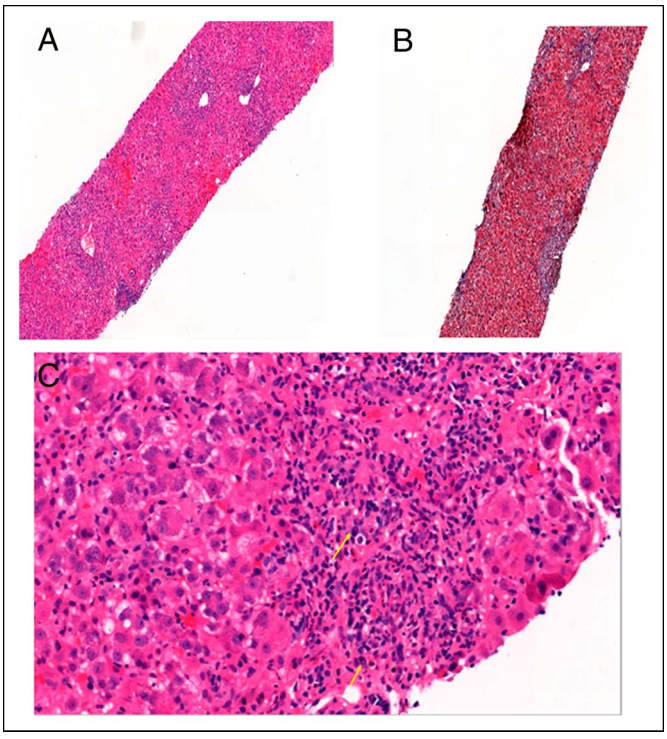

Figure 1. Liver core biopsy showing (A) expansion of portal tracts by mixed inflammation (H&E, 40×), (B) expansion of portal tracts without significant fibrosis (trichrome stain, 40×), and (C) plasma cells (yellow arrows) can be seen (H&E, 200×).

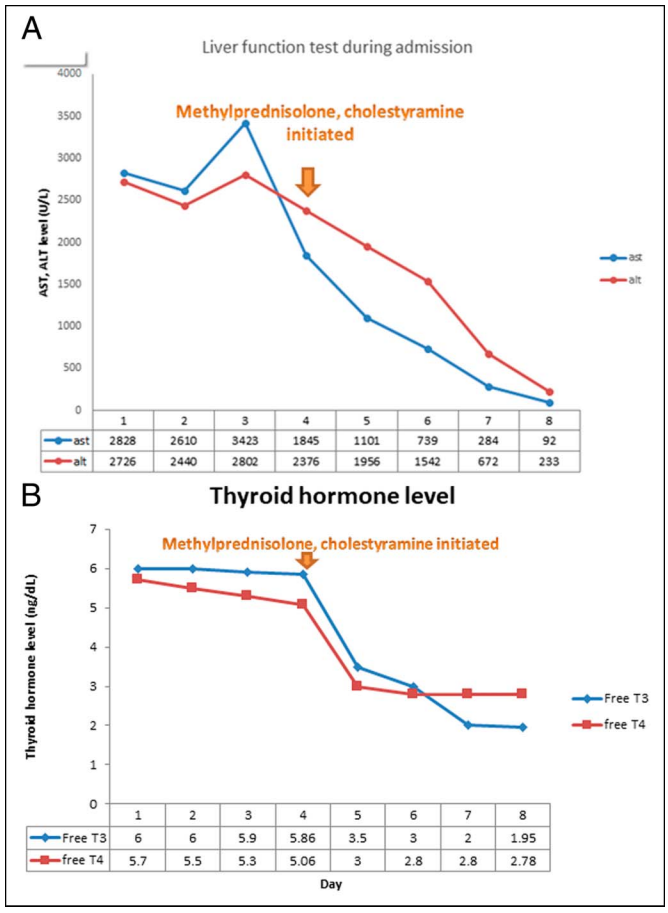

Figure 2. (A) Liver function test and (B) thyroid hormone level during admission. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The patient was discharged home with oral prednisone at 60 mg once daily with a tapering plan, azathioprine 100 mg once daily, cholestyramine 4 mg daily, and nadolol 40 mg daily. Six months after discharge, the patient remained clinically euthyroid with a low maintenance dose of oral prednisone 15 mg daily and propranolol 40 mg once daily. Her thyroid stimulating hormone level 9 months after discharge was normalized to 0.3 μU/mL. The patient opted out of Graves definitive treatment, such as thyroidectomy or radioactive iodine ablation. Her liver function test has returned to normal with the use of azathioprine.

DISCUSSION

Graves disease can be associated with other autoimmune diseases such as type 1 diabetes, pernicious anemia, rheumatoid arthritis, and systemic lupus; however, its association with AIH is rarely reported.[10] Although the actual etiologies that trigger AIH remain unclear, there has been a hypothesis that viral exposures could play a role in the induction of an autoimmune process.[1,11,12] Our patient had elevated CMV and HSV antibody with undetectable viral DNA, indicating previous exposure to both CMV and HSV. Our patient had chronic hepatitis at baseline (aspartate aminotransferase 150, alanine aminotransferase 100) 2 months before, which could be from alcohol use vs

AIH. As her Graves thyrotoxicosis began to manifest, the liver function began to worsen and eventually progressed to acute liver injury. There was rapid improvement in liver and thyroid function after initiation of steroid therapy.

In individuals with Graves hyperthyroidism concomitant with acute liver injury, treatment is challenging because thionamides can worsen liver injury.[13] The 2 definitive treatments are surgery and radioactive iodine ablation. Urgent thyroidectomy is risky in individuals who are acutely thyrotoxic with acute liver damage. Radioiodine ablation is a safer option, but the overall inhibitory effect is often temporary because of a return of high thyroid hormone concentration from escape phenomenon.[14] As a result, cholestyramine, nadolol, and glucocorticoid were used as an adjuvant therapy. Glucocorticoid suppresses the immune response process in both Graves disease and AIH and inhibits peripheral T4 to T3 conversion. Cholestyramine, a bile-salt sequestrant, binds to thyroid hormones in the intestine and increases its excretion. Cholestyramine is used as an adjunctive therapy in treating thyrotoxicosis but has no role in treating AIH. Rapid improvement of both liver and thyroid function was achieved after glucocorticoid and cholestyramine initiation. Our case highlights a rare manifestation of acute liver damage from AIH in the setting of Graves disease and outlines how a clinician can approach a similar scenario.

DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. YK Reddy is the article guarantor.

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