Autoimmune Cholangiopathy and High-Output Heart Failure in a Patient with Graves Disease

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raves disease has a myriad of known symptoms, ranging from typical symptoms—such as anxiety, palpitations, diaphoresis, weight loss, heat intolerance, and muscle weakness—to less common symptoms such as high-output heart failure and cholestasis. A delay in the recognition of the underlying thyroid disease causing these symptoms can result in fatal consequences. We report a 36-year-old patient with Graves disease who had an atypical presentation of high-output heart failure and cholestasis secondary to autoimmune cholangiopathy (AIC); discussion of this case is followed by a review of AIC and autoimmune liver disease associated with Graves disease. To our knowledge, this case study is the first report of Graves disease associated with AIC.

Case Report

Initial Presentation and Patient History
A 36-year-old Hispanic woman presented to our hospital with a 3-month history of worsening jaundice. One month prior to admission, the patient had presented to another hospital with jaundice. Initial testing at this hospital revealed a total bilirubin level of 44 mg/dL, an indirect bilirubin level of 19.7 mg/dL, a positive antinuclear antibody (ANA) titer greater than 1:2,560, unremarkable findings from a toxicology screening, and negative serologic test results for hepatitis A, B, C, and D virus infection. Imaging did not show any biliary tract abnormalities. A liver biopsy revealed portal inflammation with lymphocytic predominance, fibrosis, and bile duct proliferation. Steroid therapy was initiated for a presumed diagnosis of autoimmune hepatitis, and the patient was discharged home with improving biochemical parameters. After this initial improvement, however, the patient's jaundice failed to resolve. In addition, she developed progressively worsening exertional dyspnea, orthopnea, and peripheral edema. These symptoms were associated with fatigue, general malaise, pruritus, nausea, and vomiting; however, she did not have a fever or chills.

The patient's medical history was otherwise unremarkable. Her only medication was prednisone 10 mg daily. Her mother was infected with hepatitis B virus and had a history of alcoholism; the patient had no other significant family history of liver, autoimmune, cardiac, or pulmonary disease. She denied having a history of alcohol or drug abuse.

Physical Examination
The patient was a thin, ill-appearing, jaundiced woman. She was afebrile, with a heart rate of 120 beats per minute, respiration rate of 20 breaths per minute on room air, and blood pressure of 170/70 mmHg; in addition, she was 160 cm tall and weighed 65 kg. The patient had thin, dry hair; scleral icterus with protuberant eyes; sublingual jaundice; a 6-cm jugular venous distension at a 45-degree head-of-bed elevation; and a diffusely enlarged, nontender thyroid gland. No lymphadenopathy was noted. A cardiac examination revealed a regular heart rhythm with a grade III/VI holosystolic murmur at the left midsternal border and an S3 gallop. The patient had inspiratory crackles at both lung bases. Significant nontense abdominal ascites was noted, but there was no appreciable hepatospleno-megaly. The patient had bilateral 4+ pitting edema to the thighs; also noted were bilateral pretibial waxy skin lesions.
with hyperpigmentation. There was no cyanosis or clubbing of the extremities. The remainder of her examination yielded unremarkable findings.

**Laboratory Evaluation**

Initial laboratory tests showed a hemoglobin level of 9.1 g/dL, hematocrit of 26%, platelet count of 109,000/μL, and a white blood cell count of 8,400 cells/μL with a normal differential. The patient’s international normalized ratio was 1.4. Other laboratory findings included a total bilirubin level of 25.7 mg/dL, direct bilirubin level of 18.1 mg/dL, aspartate aminotransferase level of 47 U/L, alanine aminotransferase (ALT) level of 22 U/L, alkaline phosphatase level of 156 U/L, total protein level of 5.6 g/dL, and albumin level of 2 g/dL. The patient’s brain natriuretic peptide level was elevated (527 pg/mL).

A chest radiograph revealed cardiomegaly, interstitial edema, and a small right pleural effusion. Cardiac echocardiography revealed a normal left ventricular ejection fraction, a mildly dilated right ventricle, and moderate pulmonary hypertension with a right ventricular systolic pressure of 49 mmHg.

Serologic test results for Epstein-Barr virus; herpes simplex virus; cytomegalovirus; HIV; and hepatitis A, B, C, and D virus infection were negative. The patient’s ANA level was strongly positive (titer of 1:2,560) and was characterized by a speckled and nucleolar pattern, but antimitochondrial antibodies (AMA), antismooth muscle antibodies (ASMA), antineutrophil cytoplasmic antibodies, and liver-kidney-microsomal antibodies were absent. Her serum immunoglobulin (Ig)G and IgM levels were normal (1,216 mg/dL and 141 mg/dL, respectively), whereas her IgA level was mildly elevated (485 mg/dL). The patient’s alpha-1-antitrypsin level was also elevated (280 mg/dL), and her ceruloplasmin level was normal.

A right upper quadrant ultrasound showed increased periportal echogenicity consistent with fibrosis, but no biliary dilation was noted. A magnetic resonance cholangiopancreatography scan was negative for intra- or extrahepatic biliary dilatation or strictures.

**Clinical Course**

The patient was initially treated with prednisone 40 mg daily, as well as aggressive diuresis with intravenous furosemide. Despite these measures, the patient continued to deteriorate from cardiopulmonary and hepatic perspectives. Due to her physical examination findings, worsening heart failure, and progressive liver disease (despite adequate steroid therapy), thyroid testing was subsequently performed. Her thyroid-stimulating hormone (TSH) level was undetectable, and her free T4 and T3 levels were elevated (6.00 ng/dL and 17.2 pg/mL, respectively). Her thyroglobulin level was also elevated (1,142 ng/mL), and her thyrotropin receptor antibodies were strongly positive (94 IU/L). An I-123 thyroid uptake scan performed on her fourth day in the hospital demonstrated homogeneous uptake bilaterally throughout the thyroid gland, which is consistent with Graves disease. No hot or cold nodules were seen.

A diagnosis of autoimmune hepatitis was considered due to the patient’s lack of response to aggressive immunosuppression. On her fifth day in the hospital, a review of her liver biopsy from the first institution revealed portal, periportal, and bridging fibrosis; cholestasis with interface hepatitis; and a mixed inflammatory portal infiltrate consisting of lymphocytes, neutrophils, eosinophils, and plasma cells. Lymphoplasmacytic inflammation of the bile ducts was present without significant bile duct loss. A rhodamine stain showed periportal copper deposition consistent with chronic cholestasis. Based on the patient’s serologic studies and histologic findings, a diagnosis of AIC was made.

The patient was started on ursodeoxycholic acid 300 mg twice daily and azathioprine 100 mg daily; in addition, she continued to take prednisone 40 mg daily, with significant improvement in her biochemical profile. Diuresis was also continued, and the patient was started on propranolol LA 120 mg daily to manage her severe symptomatic hyperthyroidism. Beta-blockade and diuresis resolved her heart failure symptoms. Due to her thyroid disease, the patient eventually received a dose of radioactive iodine on her eighth day in the hospital. Despite her liver disease, propylthiouracil (PTU) 200 mg 3 times daily was initiated due to the severity of her Graves disease–induced cardiopulmonary symptoms. Treatment of her Graves disease resulted in a modest improvement of her liver function profile, and she was discharged from the hospital with the requirement that she return for endocrinology and hepatology follow-up visits.

Three weeks later, the patient suddenly collapsed at home. Emergency Medical Services initially noted asystole, which converted to fine ventricular fibrillation after the administration of epinephrine and atropine. Despite attempts at resuscitation, the patient died shortly after arriving at the hospital. The patient’s family declined a postmortem examination. Thyrotoxicosis was suggested as the cause of death, as her TSH level remained undetectable at the time of cardiac arrest.

**Discussion**

In this case report, we describe a patient with Graves disease–induced thyrotoxicosis, whose presentation with jaundice and hepatic dysfunction led to unnecessary investigations and a delay in disease recognition and man-
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Management. Cholestasis is a well-documented consequence of Graves disease; AIC may also be present in these patients.1 Aggressive treatment of cholangiopathy and recognition of Graves disease is important.

Autoimmune Cholangiopathy

AIC is a syndrome that encompasses features of both primary biliary cirrhosis (PBC) and autoimmune hepatitis.2 Diagnosis is based on the presence of a positive ANA or ASMA titer; hypergammaglobulinemia; a negative AMA titer; histologic features of cholestatic and hepatocellular injury similar to those seen in PBC; and the exclusion of chronic viral, metabolic, or toxic liver disease.3

Clinical Features Similar to PBC, AIC is typically observed in middle-aged women with fatigue, pruritus, and jaundice.4 Laboratory evaluation of an AIC patient reveals cholestasis with abnormalities in liver function tests, with initial marked elevation in alkaline phosphatase level, moderate elevation in total and direct bilirubin levels, and minor elevations in transaminase levels. As previously mentioned, diagnosis is suggested by a positive serologic test result for ANA and a negative test result for AMA in the presence of classic PBC features.5 Abdominal ultrasound, computed tomography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography are important tools for excluding biliary obstruction. Liver biopsy typically shows evidence of interface hepatitis and bile duct inflammation with lymphocytes and plasma cells in addition to granulomatous destruction of bile ducts with less severe bile duct loss than that seen in PBC (Figure 1).6

Treatment The distinction between PBC and AIC is important for guiding appropriate therapy. Ursodeoxycholic acid is the standard-of-care therapy for PBC. However, outcomes in AIC patients are significantly improved when immunosuppressive agents such as steroids or azathioprine are added to ursodeoxycholic acid therapy. In a recent study, the progression of fibrosis was lower and biochemical response (reduction in ALT and IgG levels) was greater when immunosuppressive agents (steroids alone or steroids plus azathioprine [Imuran, Prometheus] or mycophenolate mofetil) were added to ursodeoxycholic acid therapy.7

Graves Disease and Liver Dysfunction

Graves disease has been shown to be associated with autoimmune liver disease such as autoimmune hepatitis or primary sclerosing cholangitis.8 In our patient, however, there was the unique finding of Graves disease in the setting of AIC. Although this overlap has not been previously recognized, there have been many reported cases of jaundice or cholestatic hepatitis in association with Graves disease.9 Thus, we suspect that the occurrence of AIC in patients with Graves disease is underrecognized. Notably, PTU or methimazole therapy for Graves disease can cause cholestasis or even severe hepatitis, leading us to speculate on the potential presence of underlying subclinical liver disease such as AIC in some of these patients.10

Conclusion

This case study illustrates several valuable lessons for clinicians. Patients who are diagnosed with AIC or who present with cholestatic jaundice should undergo thyroid function testing. In addition, the presence of autoimmune liver disease (including AIC)—as well as hepatic injury caused by thyroid disease or its treatments—should be considered in patients with autoimmune thyroid disease and liver dysfunction. Finally, severe pulmonary hypertension and high-output heart failure should be recognized as serious and potentially fatal sequelae of Graves disease. Recognition of the link between thyroid disease and cholangiopathies will enable appropriate and early diagnosis of potentially fatal thyroid conditions in patients presenting with jaundice of indeterminate origin.

References


Figure 1. Bile duct lymphoplasmacytic inflammation and granulomatous destruction in a patient with autoimmune cholangiopathy (hematoxylin and eosin stain, 100× magnification).
Hyperthyroidism can affect multiple organ systems, including the cardiovascular, nervous, gastrointestinal, and hepatic systems. The interaction between the thyroid and liver is critical for maintaining homeostasis in both sites. Thyroid hormones are glucuronidated and sulfated within the liver and subsequently excreted into bile; in addition, these hormones maintain the metabolism of bilirubin by playing a role in the enzymatic activity of glucuronyltransferase and by regulating the level of ligandin, a major organic anion-binding protein. Therefore, it is not surprising that hepatic dysfunction is commonly observed in patients with thyroid disease. In 1874, Habershon described a patient with exophthalmic goiter, heart disease, and jaundice who died. Many subsequent case reports and series have highlighted the prevalence of liver test abnormalities (ranging from 15% to 76%) in the setting of hyperthyroidism. There are several mechanisms of liver dysfunction in the setting of hyperthyroidism, including liver abnormalities due to hyperthyroidism alone, liver damage related to heart failure and hyperthyroidism, and concomitant liver disease in the setting of hyperthyroidism.

In our hyperthyroidism and liver dysfunction case series, patients were categorized into 3 groups: patients without heart failure, patients with heart failure, and patients without heart failure who had concomitant liver disease. In patients without heart failure, liver dysfunction ranged from mild liver test abnormalities to deep jaundice. This range of liver dysfunction is consistent with other cases reported in the literature. However, no studies have demonstrated a correlation between abnormal liver biochemical tests and thyroid hormone levels. Studies monitoring treatment of hyperthyroidism have noted that improvement in a patient’s thyroid function is accompanied by normalization of the liver panel. The mechanism of liver injury in pure hyperthyroid states is not well understood. Recently, Upadhyay and colleagues used in vivo and in vitro models to show that excess T3 induces apoptosis of hepatocytes and causes liver dysfunction through activation of the mitochondrial-dependent pathway.

In most cases of hyperthyroidism and liver dysfunction without heart failure, liver histology demonstrates some degree of fatty infiltration, cytoplasmic vacuolization, nuclear irregularity, and hyperchromatism in hepatocytes. Functional changes in mitochondria (such as enlargement) and formation of megamitochondria have been reported in the livers of hyperthyroid patients and in a rat model of hyperthyroidism.

Hyperthyroid patients with heart failure in our series were more likely to manifest more severe liver dysfunction.
with respect to deep jaundice (mean, 5.3 mg/dL; highest, 24 mg/dL), coagulopathy, hepatomegaly, and even ascites, compared to patients without heart failure.\(^3\) Heart failure resulting in hepatic congestion—even in the absence of hyperthyroidism—is often associated with protein liver test abnormalities, including acute hepatocellular injury, hyperbilirubinemia, and coagulopathy.\(^11\) In particular, right-sided heart failure can result in passive congestion of the liver usually referred to as “congestive hepatopathy.” Decreased cardiac output may also result in decreased hepatic blood flow and arterial oxygen saturation. These processes are intertwined, and clear distinctions may not be possible.\(^12\) The liver is often enlarged and pulsatile in patients with congestive hepatopathy. Ascites is common due to enlargement of sinusoidal fenestrae secondary to sinusoidal congestion and exudation of protein-rich fluid into the space of Disse, which subsequently overwhelms the lymphatic vessels.\(^13\) Myers and colleagues assessed sinusoidal congestion and exudation of protein-rich fluid in 83 patients with congestive hepatopathy; mild abnormalities in liver enzymes and bilirubin levels were noted in most patients.\(^11\) However, aminotransferase levels may be higher than 2,000 IU/L in the setting of acute cardiac dysfunction, and patients may have profound jaundice along with coagulopathy.\(^11\)

Hyperthyroidism, particularly Graves disease, can also be associated with other liver conditions. Up to 10% of patients with Graves disease have a coexisting autoimmune disorder.\(^14\) The association between Graves disease and primary biliary cirrhosis (PBC) or autoimmune hepatitis is well described in the literature. Conversely, Graves disease is a common concurrent autoimmune condition associated with various chronic liver diseases.\(^15\)

The case reported by Venkat and colleagues—which describes a patient with Graves disease, heart failure, jaundice, and positive autoimmune markers—illustrates the challenges of discerning the cause of liver dysfunction in this setting.\(^16\) The clinical presentation of this patient was very similar to that of our own patients. However, this case study is the first reported case of Graves disease coexisting with autoimmune cholangiopathy (AIC). Originally referred to as “immunocholangitis” by Brunner and Klinge, AIC is an antimitochondrial antibody (AMA)-negative and antinuclear antibody (ANA)-positive condition; otherwise, AIC shares the typical clinical and histologic features of PBC.\(^17\) Mitochondrial antigen has been shown to be expressed on the apical membranes of biliary epithelial cells from AMA-negative as well as AMA-positive PBC patients, suggesting that the pathogenesis of both conditions is very similar.\(^18\) Micheletti and associates compared 17 AIC patients with 17 PBC patients and found that both conditions had a predilection for women and an association with hypothyroidism.\(^19\) Liver tests were characterized by high alkaline phosphatase levels (mean, 500 U/L). In the patient treated by Venkat and coworkers, histopathologic findings were consistent with AIC, although the alkaline phosphatase level was not as elevated as in a typical AIC patient.\(^16\) The presence of a high ANA value and a negative AMA titer is also consistent with AIC. The interpretation of autoimmune markers in Graves disease should take into consideration the high prevalence of nonthyroid autoantibodies, particularly ANA.\(^20\)-\(^22\)

In conclusion, it is apparent that the thyroid and liver are intertwined in many ways. A vigilant effort should be undertaken to diagnose the liver condition of patients who present with hyperthyroidism and liver dysfunction—as in the case report by Venkat and associates—so that appropriate therapy can be promptly initiated.

References


**Critical Reading**

- **IL-28B as a Predictor of Sustained Virologic Response in Chronic Hepatitis C**
  S. A. Gonzalez and E. B. Keeffe

- **The Importance of Visceral Sensitivity in Clinical Gastroenterology**
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- **Targeting Mucosal Healing in Crohn’s Disease**
  A. Kakkar, S. Wasan, and F. A. Farraye

- **Prognostic Value of Liver Fibrosis Biomarkers**
  T. Poynard et al