Grave's Disease and Primary Biliary Cirrhosis—An Unusual and Challenging Association

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Jaundice in Grave's diseases is uncommon, but when it does occur, complication of thyrotoxicosis (heart failure/ infection) or intrinsic liver disease should be considered. Grave's disease can cause asymptomatic elevation of liver enzymes, jaundice and rarely acute liver failure. It is associated with other autoimmune diseases like autoimmune hepatitis, or primary biliary cirrhosis. The cause of jaundice in Grave's disease is multifactorial. (J CLIN EXP HEPATOL 2014;4:66–67)

Hepatic involvement in thyroid disorders is rarely reported; in some cases liver dysfunction can be cholestasis, liver cell failure or even non-specific.¹ Pathophysiology of liver dysfunction secondary to hyperthyroidism is not well established. Autoimmune thyroid disorders like Grave's disease may be associated with autoimmune hepatitis. Grave's diseases has been associated with various autoimmune diseases like diabetes, Addison's, Sjogren's syndrome and vitiligo, however, the association with primary biliary cirrhosis (PBC)² has been described in few cases in literature. We report a case of cholestatic jaundice in a patient with Grave's disease accompanying primary biliary cirrhosis.

CASE REPORT

A 50 years old female patient was diagnosed with Grave's disease in 2010 at another hospital. She was started on neomercazole, however she stopped the medication by herself in a year. When admitted in our hospital patient's complained of symptoms of progressive jaundice and pruritus for at least last 3 months. Past medical narration was unremarkable except hyperthyroidism and divulged no gastrointestinal bleed, swelling of legs, or any other marker of chronic liver disease

Clinical examination on admission confirmed severe jaundice, yet no evidence of chronic liver disease. She was afebrile with regular pulse rate of 110 per minute with normal blood pressure. Physical examination showed

exophthalmos. She had no goiter. There was no hepatomegaly or splenomegaly. Her ultrasound of the neck showed the thyroid gland was enlarged with increased vascularity.

Laboratory investigations on admission showed: normal hemogram; liver functions tests – total serum bilirubin 23.5 mg/dL, conjugated bilirubin 19.8 mg/dL, alanine aminotransferase 33 IU/L, aspartate aminotransferase 80 IU/L, alkaline phosphatase 166 IU/L, albumin 3.6 g/dL, and international normalized ratio 1.4; serum creatinine 1.0 mg/dL; blood and urine cultures were sterile; serology tests for hepatitis A to E, human immunodeficiency virus and cytomegalovirus, were negative; laboratory tests excluded copper, iron-related metabolic disorders and autoimmune liver disease. Anti-mitochondrial antibody was strongly positive. Thyroid function tests revealed low serum thyroid stimulating hormone of <0.001 U/L, and high serum free T4 (>7.7 ng/dl) and free T3 (>32.55 pg/ml). Thyroid peroxidase antibody was also positive.

Thyroid nuclear scan results were consistent with a diffuse homogenous high-level uptake of radioactive iodine suggestive of Grave's disease. Both magnetic resonance imaging and magnetic resonance cholangiography findings were normal and showed no biliary system obstruction. Upper gastrointestinal endoscopy showed no varices. Echocardiogram was observed to be normal. Histopathological findings from a liver biopsy specimen revealed features of primary biliary cirrhosis, as shown and described in Figure 1a and b.

She was started on ursodeoxycholic acid and anti-thyroid drug (neomercazole), beta blocker (Propranolol). On the fourth day her total bilirubin levels started rising from 23.5 mg/dl to 27 mg/dl, compelling us to discontinue her anti-thyroid drugs. Surgical option was ruled out due to thyrotoxicosis with liver dysfunction and alternately radioactive ablation therapy along with short course of oral steroids was administered. Post radioactive ablation therapy was uneventful.

Keywords: Grave's disease, jaundice, biliary cirrhosis

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Abbreviation: PBC: primary biliary cirrhosis

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Figure 1 a: Bile stasis, balloon degeneration, lymphocytic infiltration, bile duct damage and inter phase hepatitis. b: Bile duct damage, focal lobular necrosis, ductal reaction, no granuloma and mild fibrosis—consistent with primary biliary cirrhosis.

The patient was discharged 2 weeks later with clinical and biochemical improvement. Her follow up assessment after 8 weeks showed normal thyroid function with total bilirubin 6 mg/dl. A repeat liver function test after 6 months showed drop in total bilirubin level to 3 mg/dl and normal thyroid function test.

DISCUSSION

Hepatic involvement in Grave's disease is infrequent, however, abnormal liver function test are relatively common. Episodes of cholestasis and jaundice are less common which makes the diagnosis difficult. The cause of hepatic dysfunction in hyperthyroidism is multifactorial; it may occur due to hyperthyroidism per se, drug treatment, associated autoimmune liver disease.^{1,2} Drugs like carbimazole

and propylthiouracil used for treating hyperthyroidism can also cause liver dysfunction. Various theories try to explain cholestasis in hyperthyroidism in the absence of cardiac failure. Hyperthyroidism is associated with hyper metabolic state, which increases hepatic oxygen consumption without increase in hepatic blood flow lowering oxygen tension in centrilobular zones.

Jaundice may be unrelated to hyperthyroidism, and can occur owing to other factors such as viral hepatitis, alcohol abuse, sepsis and some medications (anti tubercular drugs, analgesics).³⁻⁵

Our patient had progressive jaundice with cholestasis and her initial etiological work up for jaundice was negative and liver biopsy was done in view of rising bilirubin levels, which showed features of primary biliary cirrhosis.

Hyperthyroidism associated with PBC has been reported only in few cases. Nieri et al,⁶ has reported association with Grave's disease and primary biliary cirrhosis. Thompson et al⁷ showed association between reversible jaundice in primary biliary cirrhosis and hyperthyroidism. In our case patient had strong Anti-mitochondrial antibody positivity with liver biopsy suggestive of PBC. Jaundice is uncommon but when it does occur, complications of thyrotoxicosis or intrinsic liver disease need to be excluded. It is important to evaluate jaundice in case of hyperthyroidism when no obvious cause is found. PBC is another autoimmune disease that should be considered in adult female with Grave's disease presenting with cholestatic jaundice when other causes are excluded. Early identification might help to plan the management and prognosticate the illness.

CONFLICTS OF INTEREST

All authors have none to declare.

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