CASE REPORT

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Severe cholestatic jaundice secondary to hyperthyroidism

Yousef Usta, Julia Massaad, Samir Parekh, Laura Knecht

ABSTRACT

Introduction: Hyperthyroidism is a known cause of nonspecific abnormalities in liver biochemistries; most commonly mild elevations in serum bilirubin and liver enzymes. **Case Report:** A case of severe cholestatic jaundice secondary to Grave's disease. The patient is a 28-year-old African-American male who presented to the emergency room with chronic diarrhea, weight loss and jaundice. At presentation, his liver enzymes were elevated in a cholestatic pattern and his bilirubin was 21.4 mg/dL. Upon treatment with propranolol and propylthiouracil, his diarrhea, pruritus, jaundice, and liver enzymes quickly improved. His bilirubin returned to normal over a period of two months. **Conclusion:** While severe intrahepatic cholestasis and jaundice due to hyperthyroidism is rare, the diagnosis should be considered in patients presenting with manifestations of liver disease, as appropriate treatment of hyperthyroidism results in resolution of jaundice.

Keywords: Hyperthyroidism, Cholestasis, Jaundice

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INTRODUCTION

The term thyrotoxicosis refers to the clinical syndrome resulting from serum elevations in thyroid hormone levels. The cause of hepatic dysfunction in hyperthyroidism may be multifactorial, occurring solely as a result of hyperthyroidism, drugs used to treat hyperthyroidism, hepatic congestion from thyrotoxic heart failure, autoimmune hepatitis, primary biliary cirrhosis, viral hepatitis, alcohol abuse, sepsis, and cholangitis. Medications such as oral contraceptives, propylthiouracil, acetaminophen, isoniazid and rifampicin can also be implicated as well [1–5].

Thyrotoxicosis is known to cause a variety of nonspecific abnormalities in liver biochemistries, but there has been no evidence to suggest that thyroid hormones have a direct toxic effect on the liver. The liver is the primary organ of thyroid hormone metabolism, which may explain how thyroid disorders can result in liver profile derangements. Hepatic dysfunction associated with hyperthyroidism has been documented in literature for over 100 years, but the pathophysiology is yet to be determined. Modest elevation in transaminases is the most common liver manifestation of thyroid disease. However, cholestatic jaundice may rarely occur [5]. We present an interesting case of severe cholestatic jaundice secondary to hyperthyroidism due to Grave's disease.

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CASE REPORT

A 28-year-old obese African-American male was referred to our hospital for evaluation of chronic diarrhea, jaundice, and pruritis of three months duration. His diarrhea was nonbloody, watery, and was associated with mild nonspecific abdominal pain. In addition, he reported a 100 pound unintentional weight loss over a three-month period. His past medical history included only hypertension, and he was not taking any prescribed medications.

The patient denied any history of hepatitis, blood transfusions, high risk sexual behavior, international travel, or intravenous drug use. He denied heavy alcohol or over the counter/herbal medication use. He denied family history of liver or autoimmune diseases.

General examination showed a 60-in tall male weighing 232 lbs who claimed to weigh over 300 lbs. Vital signs were notable for tachycardia with a heart rate of 110. He had significant scleral icterus. His neck was soft and symmetric with palpable prominence of the isthmus and pyramidal lobes of the thyroid. A thyroid bruit was not appreciated. There was no hepatosplenomegaly or stigmata of chronic liver disease other than jaundice.

His laboratory examination, on admission, were as follows: total bilirubin 18.1 mg/dL (0.3–1.2 mg/dL) peaking at 21.4 mg/dL, direct bilirubin was too high to measure >10 mg/dL (0–0.3 mg/dL), alkaline phosphatase 200 U/L (36–92 U/L), ALT 62 U/L (0–35 U/L), AST 89 U/L (0–35 U/L), amylase 66 U/L (0–130 U/L), lipase 19 U/L (<95 U/L), LDH 199 U/L (60–100 U/L), and albumin was 2.0 g/dL (3.5–5.5 g/dL). INR was 1.0, white blood cell count 7800/mm³ (4–10x10³/mm³), hemoglobin 8.8 g/dL (14–17 g/dL), and platelets 316x10³/μL (150–350/μL). TSH was 0.02 mU/mL (0.5–5 mU/mL), T₃ 546 ng/dL (70–195 ng/dL), and T₄ 15.5 ug/dL (5–12 ug/dL).

Abdominal ultrasound as well as magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography of the abdomen showed a normal appearing liver without biliary ductal dilatation. Endoscopic retrograde cholangiopancreatography was performed demonstrating a small sized common bile duct with intrahepatic ductopenia. No strictures or classic features of primary sclerosing cholangitis were noted. A liver biopsy showed a predominantly centrilobular cholestasis with hepatocellular feathering degeneration, as well as acute cholangitis and pericholangitis with predominant periportal and perivenular fibrosis. Other work-up including viral hepatitis serologies, autoimmune liver disease markers, HIV testing, and stool studies which were all negative. Flexible sigmoidoscopy with random biopsies was negative for a diarrhea work up.

A thyroid scan showed an enlarged thyroid gland with a homogenous increased diffuse uptake. Antimicrosomal and thyroid peroxidase antibodies were found to be positive and consistent with Grave's disease. He was started on propranolol and propylthiouracil. After completing the thorough diagnostic work-up

mentioned above, his hepatic dysfunction was attributed to hyperthyroidism due to Grave's disease by exclusion. Upon discharge, the patient's liver and thyroid profiles improved TSH 0.31 mU/mL (0.5–5 mU/mL), T₃ 486 ng/dL (70–195 ng/dL), and T₄ 4.7 ug/dL (5–12 ug/dL). At follow-up two months later, his jaundice (total bilirubin 0.7 mg/dL (0.3–1.2 mg/dL)), pruritis, and diarrhea had completely resolved.

DISCUSSION

The pathophysiologic effects of thyrotoxicosis on the liver remain unclear. The liver has an important role in metabolism of thyroid hormone, and autopsies have shown hepatic inflammation, fibrosis, and centrilobular necrosis in patients with hyperthyroidism [6].

Some theorize that thyrotoxicosis may cause a defect in bilirubin metabolism by decreasing bilirubin UDP-glucuronosyl transferase activity. With the presence of increased substrate build-up, hyperbilirubinemia ensues due to decreased conjugation [7]. Another proposed theory involves supply and demand mismatch. The physiologic effects of hyperthyroidism may create increased hepatic oxygen consumption without an equal increase in blood flow, causing focal hypoxemia and hepatic dysfunction [7, 8]. It has also been hypothesized that these abnormalities are in part related to congestive heart failure and venous congestion caused by hyperthyroidism, although features of congestive hepatopathy were not evident in our patient's liver biopsy [9].

Hyperthyroidism is a well recognized cause of abnormal liver enzymes. Acute hepatitis may increase thyroid hormone-binding globulin (TBG), causing an increase in the total T₄ level and a decrease in the thyroid hormone binding ratio. Bilirubin can also interfere with the measurement of T₄ by lowering the affinity of T₄ for thyroid hormone-binding proteins [10]. Kim et al. found up to 40% of patients with hyperthyroidism having increased alkaline phosphatase [11]. Similarly, Tibi et al. documented mild elevations in AST, ALT, and/or alkaline phosphatase in 30% of untreated hyperthyroid patients, with most of these cases normalizing following hyperthyroidism treatment [12]. Thompson et al. presented 85 patients with hyperthyroidism and abnormal liver function tests. The highest bilirubin value reported in this cohort was 3.5 mg/dL [13] comparing to our patient which presented with a more severe hyperbilirubinemia of 18.1 mg/dL (0.3–1.2 mg/dL), which is very rare. In the setting of hyperthyroidism, only three cases in literature have reported hyperbilirubinemia to this degree, with total bilirubin levels of 16.7 mg/dL, 18.9 mg/dL and 35 mg/dL [14–16].

Liver biopsy is a frequent tool used in the work up abnormal liver biochemistries. With hyperthyroidism, the histologic findings are nonspecific, and the main utility of liver biopsy in these cases is to exclude other potential etiologies. Sola et al. presented liver biopsies

of five patients with hyperthyroidism that revealed nonspecific changes including mild to moderate intrahepatic cholestasis, lobular inflammation of eosinophilic origin, and Kuppfer cell hyperplasia. There was no correlation between the severity of the histologic damage and thyroid function tests [4, 17]. Our patient's liver biopsy demonstrated a predominantly centrilobular cholestasis with hepatocellular degeneration, features in keeping with the previously reported literature.

CONCLUSION

The primary differential diagnosis for this patient's severe cholestasis included drug toxicity, infection, autoimmune liver disease, and thyrotoxicosis. History excluded the first differential. Laboratory, imaging, and histology ruled out infectious or autoimmune etiologies. By exclusion of other diagnoses and documented improvement in the liver biochemistries with treatment of his hyperthyroidism, we concluded that this patient's hepatic dysfunction was induced by thyrotoxicosis. We were unable to prove the patient's claim of a 45.35 kg weight loss, but we suspect that chronic uncontrolled Grave's disease played a critical role in his weight loss.

This case demonstrates that hyperthyroidism can result in cholestasis, and, may even cause severe hyperbilirubinemia. Hyperthyroidism should be considered in the differential diagnosis of a patient presenting with abnormal liver biochemistries. Prompt recognition and treatment of hyperthyroidism should result in clinical improvement and avoidance of unnecessary testing.

Author Contributions

Yousef Usta – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Julia Massaad – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Samir Parekh – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Laura Knecht – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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