

# Thyrotoxic Hepatitis

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Liver abnormalities are not infrequent in thyrotoxicosis. Severe hepatitis in this clinical setting is quite rare [1]. Jaundice is hardly seen in overt hyperthyroidism and is usually attributed to congestive heart failure. We describe a young patient who presented with jaundice and fatigue. Following investigation she was diagnosed with severe hyperthyroidism compatible with Graves' disease. After excluding other etiologies for her liver injury, she was treated with antithyroid medications. In this report, we discuss the association between hyperthyroidism and hepatitis and suggest that the term "thyrotoxic hepatitis" be resumed for such rare cases.

## PATIENT DESCRIPTION

A 34 year old woman was admitted to the internal medicine ward due to fatigue and new-onset jaundice. There was no history of chronic disease, smoking, pharmaceutical or herbal medications, infections, alcohol abuse, blood transfusion or foreign travel. She had given birth 10 months previously; the delivery was normal and the child is healthy.

On initial physical examination there was significant jaundice. There was no tachycardia, and blood pressure and body temperature were normal. There was no exophthalmos or lid lag. The thyroid gland was diffusely enlarged

with audible bruit above it. There were no findings of heart failure, chronic liver disease, lymphadenopathy or hepatosplenomegaly.

Laboratory workup showed hyperthyroidism and abnormal liver function tests: Free thyroxine was > 6 ng/dl (normal 0.8–2.0), total triiodothyronine 541 ng/dl (normal 80–180), thyroid-stimulating hormone 0.01 mU/L (normal 0.23–4.0). Total bilirubin 12.9 mg/dl (normal 0.2–1.5), direct bilirubin 10 mg/dl (normal 0.0–0.5), alkaline phosphatase 196 IU/L (normal 30–120), alanine aminotransferase 1374 IU/L (normal 0–40), aspartate aminotransferase 1355 IU/L (normal 7–37), gamma glutamyltransferase 150 IU/L (normal 7–49), lactate dehydrogenase 596 IU/L (normal 230–460), calcium 9.6 mg/dl (normal 8.5–10.5), albumin/globulin 4.1/2.4 g/dl respectively, hemoglobin 14.1 g/dl, prothrombin time 14.7 seconds, PT-international normalized ratio 1.40.

Hepatic investigation included viral, immune and metabolic tests as follows: Peripheral blood was negative for hepatitis B surface antigen, antibody to HBsAg, immunoglobulin M antibody to hepatitis B core, IgM antibody to hepatitis A virus, hepatitis C virus, cytomegalovirus, Epstein-Barr virus, autoantibodies (antinuclear antibodies, antimitochondrial antibodies, antismooth muscle antibodies and antineutrophil cytoplasmic antibodies) and thyroglobulin antibodies. Serology for liver-kidney-microsomal antibodies and antiparietal cell antibodies was positive at a titer of 1/80 and 1/320 respectively. Total IgG was 1600 mg/dl (normal 700–1600), alpha-fetoprotein 15.3 ng/ml (normal 0–10) and ceruloplasmin 29 mg/dl (normal 20–60).

PT = prothrombin time

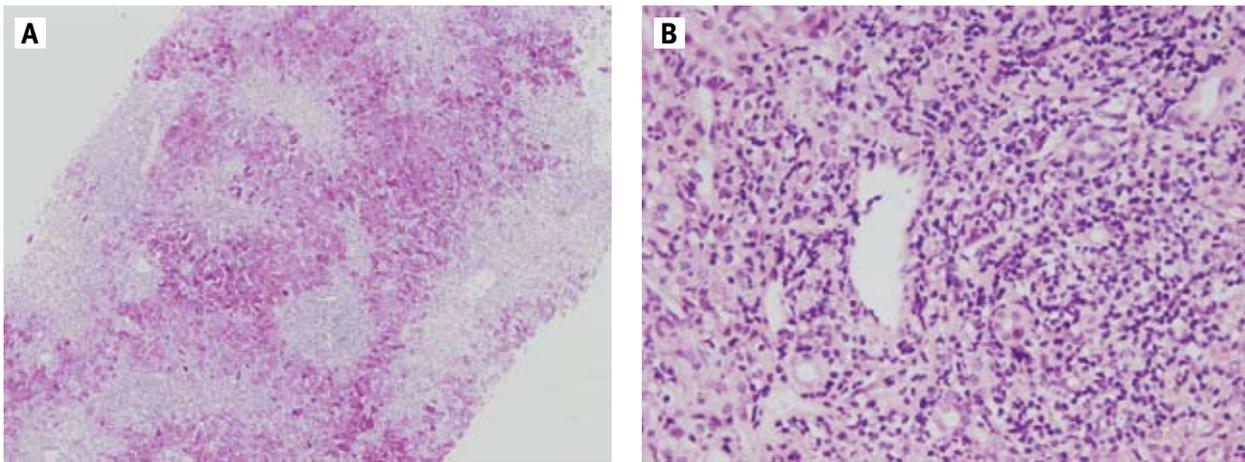
Thyroid scintigraphy demonstrated a high level of diffuse technetium uptake consistent with a diffuse hyperplastic thyroid gland compatible with the diagnosis of Graves' disease. Abdominal ultrasonography and Doppler study of the portal and hepatic veins showed normal flow. The differential diagnosis of the liver abnormality was "thyrotoxic hepatitis" versus a distinct liver disease associated with Graves' disease such as autoimmune hepatitis.

Histopathological findings at liver biopsy showed extensive centrilobular necrosis and heavy portal and lobular inflammation with a predominance of lymphocytes. Plasma cells were absent. The findings were not suggestive of autoimmune hepatitis [Figures A & B].

In view of the severe thyrotoxicosis and secondary hepatitis as presented above, treatment with propylthiouracil at a total dose of 300 mg/day was initiated. Prednisone 40 mg/day was added as additional therapy to prevent conversion of T4 to T3.

One week after starting treatment we observed a dramatic decline in total T3 to normal values, bilirubin dropped to 8.7 mg/dl and liver enzymes dropped to half of maximal values (ALT 777 IU/L, AST 369 IU/L). Four months later complete normalization of thyroid hormones, bilirubin and liver enzymes was documented. Prednisone dose was tapered down until it was completely withdrawn over a period of 4 months. Propylthiouracil was tapered down and maintained for another year. One year after the cessation of prednisone the liver enzymes were persistently normal.

T4 = thyroxine  
T3 = triiodothyronine  
ALT = alanine aminotransferase  
AST = aspartate aminotransferase



**[A]** Periodic acid Schiff stain shows extensive centrilobular necrosis

**[B]** Hematoxylin & eosin stain shows impressive portal and lobular inflammation with lymphocytes predominance

## COMMENT

We present an unusual case of postpartum Graves' disease manifested by severe hepatitis. Jaundice was the presenting symptom of this patient's thyrotoxicosis.

Graves' disease accounts for 60–80% of thyrotoxicosis cases. The prevalence varies among populations, depending mainly on iodine intake. There is a threefold increase in the occurrence of Graves' disease during the postpartum period. Associated abnormalities that may cause diagnostic confusion in thyrotoxicosis include elevation of bilirubin and liver enzymes.

The liver is the primary organ of thyroid hormone metabolism. Up to 85% of extrathyroidal deiodination of T4 to T3 and reverse T3 occurs in the liver. Moreover, plasma-binding proteins of thyroid hormone are produced by the liver. On the other hand, thyroid hormones have a major role in normal hepatic function and bilirubin metabolism. Mild liver abnormalities such as hypoalbuminemia and increased serum level of AST, ALT and ALP may be seen in 45% to 90% of patients with hyperthyroidism [1]. Clinically, patients present with self-limited hepatitis, with mild elevations in serum bilirubin in up to 5% of patients

with thyrotoxicosis [1]. Jaundice in thyrotoxic patients may be due to heart failure. Massive hepatomegaly and fulminant hepatic failure have been rarely described [2]. Cholestatic hepatitis without heart failure is rare [3].

There are a few case reports of thyrotoxicosis associated with cholestatic hepatitis with marked hyperbilirubinemia. In one case the patient presented with cholestasis secondary to autoimmune hyperthyroidism. His jaundice was aggravated by antithyroid medications and improved later when radioactive iodine (I131) treatment resulted in euthyroidism [4]. Another case showed cholestatic hepatitis caused by subclinical hyperthyroidism and was treated successfully by rifampicin [4].

Among the possible mechanisms that may be involved in liver abnormalities associated with thyrotoxicosis are venous congestion due to high output heart failure and/or relative hypoxia. Thyrotoxicosis may increase oxygen demand and utilization which cannot be totally compensated by hepatic blood flow. The pericentral areas of hepatic acini constitute the most susceptible zone to ischemia. The hyperbilirubinemia is not well understood and there are no available data supporting the direct toxic effects of thyroid hormones on the

liver. Conditions often associated with hyperthyroidism, such as congestive heart failure, infection and malnutrition, may play a role as well.

Liver biopsy findings in patients with mild hyperthyroidism-related hepatic injury are non-specific. Biopsy specimens may reveal lobular inflammation with some infiltrate consisting of polymorphonuclear leukocytes, eosinophils and lymphocytes. In addition, some patients may exhibit focal or diffuse centrilobular necrosis and perivenular fibrosis [4]. Our patient presented with severe liver injury manifested by jaundice and marked centrilobular necrosis. Autoimmune hepatitis, which is the main differential diagnosis in young women, was excluded due to the lack of hyperglobulinemia and the lack of plasma cells in the inflammatory infiltrate at liver biopsy. Although anti-LKM (liver-kidney-microsomal) antibodies were positive at a titer of 1:80, the diagnosis of autoimmune hepatitis was excluded based on the Revised Original Scoring System of the International Autoimmune Hepatitis Group [5]. The persistence of normal liver enzymes for a long period after a short course of prednisone therapy also argues against autoimmune hepatitis. The reversibility of hepatic injury by antithyroid treat-

ALP = alkaline phosphatase

ment supports our suspicion that the mechanism of liver injury involves relative hepatocellular ischemia.

Although antithyroid medication-related adverse reactions are frequently benign and transient in nearly all patients, propylthiouracil or methimazole-related hepatocellular cholestatic hepatitis may cause some concern among clinicians. Regarding this troublesome issue, we do think that after exclusion of other hepatitis etiologies, propylthiouracil or methimazole is the correct decision for such patients. The addition of corticosteroids that prevent T4 to T3 conversion remains an option in severe cases.

## CONCLUSION

Severe hepatitis may rarely occur as a presentation of thyrotoxicosis and therefore warrants the term “thyrotoxic hepatitis.” Thyroid function tests should be part of the investigation of obscure hepatitis. Although the mechanism is not completely understood, antithyroid drugs with or without corticosteroids are crucial in this life-threatening hepatitis. Further studies are needed to explore mechanisms and alternative treatments.

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