Introduction

Abnormal liver function is usually found in thyrotoxicosis. Hyperthyroidism may cause an elevation of serum hepatic enzymes and bilirubin levels. Hepatotoxicity is also one major side effect of antithyroid agents, including carbimazole, methimazole and propylthiouracil. Cholestasis is an adverse effect of methimazole and carbimazole. We report an elderly male patient with thyrotoxicosis who developed cholestasis following treatment with methimazole.

Case Report

A 69-year-old male, a farmer, was admitted to our institution because of fever and chills lasting for 1 day. He had a history of thyrotoxicosis and received subtotal thyroidectomy about 30 years previously. No recurrence of thyrotoxicosis was noted after the management. In 6 months, his body weight decreased from 58 kg to 39 kg. Poor appetite, nausea and weakness were also present. He also had dyspnea on exertion and hand tremor. Poor sleep, loose stool and heat intolerance were also found. No other symptoms were noted. He had not had any recent change in his medication, and he denied chronic viral hepatitis, alcohol consumption, blood transfusion, recent travel or animal contact. He had no family history of thyroid or liver disease.

He visited our outpatient department because of shortness of breath, malaise, and body weight loss. He had a free thyroxine of 9.07 ng/dL (reference range, 0.80–2.00 ng/dL) and thyroid-stimulating hormone of 0.05 μIU/mL (reference range, 0.25–4.00 μIU/mL). Mild elevation of serum alanine aminotransferase (ALT) at 42 IU/L (reference range, 15–41 IU/L) and serum alkaline phosphatases at 135 IU/L (reference range, 38–126 IU/L) was found, but a normal concentration of serum aspartate aminotransferase (AST) at 40 IU/L (reference range, 14–40 IU/L) was noted. Abdominal ultrasound revealed liver calcification and a gallbladder polyp.

He was thin and chronically ill-looking. His body height of 163 cm and body weight of 39 kg were noted. Heart rate was 87 beats/min. Blood pressure was 124/87 mmHg. There was no exophthalmos. The thyroid was palpable. Physical examination did not reveal any icteric sclera, ascites, hepatomegaly, splenomegaly or other signs related to chronic liver disease. No other positive signs were found by physical examination.
Thyrotoxicosis due to Graves disease was diagnosed. During the outpatient department visit, methimazole 30 mg daily in divided doses was prescribed as well as β-adrenergic blockade with propranolol 10 mg three times a day.

Four days later, he presented at our emergency department with fever and fatigue. He exhibited a body temperature of 39.2°C, a pulse rate of 87/min and a respiratory rate of 20/min. The blood pressure was 132/63 mmHg. Icteric sclera accompanied by acute ill demeanor was found. Breathing sounds were clear. No tenderness, Murphy’s sign, knocking pain or other related signs were found. Laboratory data revealed leukocytosis with leukocytes at 20,300/μL and left shift in differential count. Elevated serum AST (134 IU/L) and ALT (124 IU/L) and total bilirubin (5.5 mg/dL) were found. No pyuria was present in the urinalysis. The chest X-ray showed emphysema changes but no consolidation or filtration as in pneumonia. Abdominal ultrasound found contracted gallbladder with gallbladder wall thickening without dilatation of the common bile duct. He was hospitalized with the suspicion of acute cholecystitis. Thyroid ultrasound revealed multinodular goiter and heterogeneous parenchyma, suggestive of autoimmune thyroid disorder.

After admission, empiric antibiotic therapy with flomoxef (3 g daily) in divided doses was started. Methimazole (20 mg daily) and propranolol (30 mg daily) were maintained because of his thyrotoxicosis. Blood culture isolated *Escherichia coli* with sensitivity to cephalosporin. Duodenal ulcer and esophageal ulcer with anemia were also found after admission.

With the initiation of antibiotic therapy, his fever and leukocytosis improved. No black stool or tarry stool was kept. At that time, the total bilirubin was 4.1 mg/dL, with an AST of 51 IU/L and an ALT of 61 IU/L. Antinuclear factor and anti-double-stranded DNA, and even liver biopsy, can be performed to differentiate autoimmune hepatitis from other hepatic injury conditions in hyperthyroidism8,9. Hashimoto thyroiditis is thought to be related to primary biliary cirrhosis8.

Cholestasis may occur in patients with hyperthyroidism. Bile transport is interfered with due to the increase of hepatic oxygen consumption but without an increase of hepatic blood flow thus lowering the oxygen tension in the centrilobular zone. Thyroxine also can cause cholestasis directly4. Jaundice from congestive liver may be secondary to thyrotoxic heart failure10.

Antithyroid agents, including methimazole and propylthiouracil, have an adverse effect on hepatic dysfunction. The injury is likely to be mediated by immune mechanisms. The estimated incidence of antithyroid agents associated with hepatotoxicity is about 0.5%11. The estimated frequency of immunoallergenic hepatitis is 0.1–0.2%. Immunoallergic hepatitis is seen exclusively in patients treated with propylthiouracil. A transient increase in AST and ALT levels is observed in 30% of patients taking propylthiouracil12. It happens at all ages and more often in females4.

**Discussion**

Hepatic dysfunctions, including elevated serum AST and ALT levels, hepatitis and cholestasis, are usually noted in patients with hyperthyroidism. This relationship was reported more than 100 years ago3. Hyperthyroidism causes hepatic dysfunction or cholestasis. Abnormal liver function tests occur in 15–76% of the cases4. The hepatic dysfunction can also be secondary to other complications of hyperthyroidism6,5. With medication, the antithyroid agents have an adverse effect on hepatic dysfunction.

The liver plays a major role in the metabolism of thyroxine6. Hyperthyroidism causes liver damage directly. Autopsies in patients with hyperthyroidism demonstrate hepatic inflammation, fibrosis, and centrilobular necrosis7. Organ oxygen consumption but not blood flow augments with the increase of the metabolic rate. The arteriovenous oxygen difference across the splanchnic bed increases, and hypoxia causes hepatic differences. A reduction in heart rate and cardiac output by β-adrenergic blockade may encourage the progress1,4,8.

Autoimmune liver disease is related to autoimmune thyroid disease, which causes most cases of hyperthyroidism. Tests for antinuclear factor and anti-double-stranded DNA, and even liver biopsy, can be performed to differentiate autoimmune hepatitis from other hepatic injury conditions in hyperthyroidism8,9. Hashimoto thyroiditis is thought to be related to primary biliary cirrhosis8.
The propylthiouracil-induced hepatic injury is usually subclinical and difficult to diagnose. It can, however, rarely cause submassive hepatic necrosis and hepatic failure. Cholestasis is a rare pattern of hepatotoxicity associated with the antithyroid agents and has been reported exclusively with Tapazole (methimazole)\textsuperscript{12}. Hepatotoxicity by Tapazole is thought to be related to cell-mediated immunity\textsuperscript{4}.

In the present case, serum AST and ALT levels were normal prior to medical management. Hyperbilirubinemia and elevated serum AST and ALT levels appeared after only a 4-day course of methimazole therapy. These abnormalities persisted with the remission of leukocytosis due to acute cholecystitis and subsided after the withdrawal of methimazole. The timing suggests a causal association between methimazole and hepatic dysfunction. Acute cholecystitis had not been previously reported as an adverse effect of antithyroid agents, but it can be secondary to cholestasis.

Hepatic dysfunction is usual in patients with hyperthyroidism. It may be due to the disease or the medication. Hepatic test function should be closely monitored in patients with hyperthyroidism. The possible etiologies of hepatic dysfunction in patients with hyperthyroidism should be kept in mind to adjust the management of hyperthyroidism.

References