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CASE REPORT

Cholestatic jaundice caused by sequential carbimazole and propylthiouracil treatment for thyrotoxicosis

A 36-year-old Chinese man presented to the Queen Mary Hospital in August 1999 with a 2-week history of jaundice due to propylthiouracil treatment for thyrotoxicosis. He had previously received carbimazole but had developed an urticarial skin rash after 2 weeks of treatment. The patient developed liver failure and fulminant pneumonitis shortly after hospital admission. Despite receiving treatment with broad-spectrum antibiotics and intravenous immunoglobulin, he died 11 days after the onset of the respiratory symptoms. Postmortem examination using electron microscopy showed typical glycogen bodies within the cytoplasm of the hepatocytes, which corresponded to eosinophilic cytoplasmic inclusion bodies visible under light microscopy. Immunohistochemical studies of the inclusion bodies were positive for carcinoembryonic antigen and albumin, and negative for fibrinogen, complement protein C3, immunoglobulins G, M, and A, α-fetoprotein, and α-1-antitrypsin. This is the first report of a patient who received two sequential antithyroid drugs and developed predominate cholestasis with unique histological features. Extreme caution should be taken when a patient develops allergy to one type of antithyroid drug, because cross-reactivity may develop to the other type.

Introduction

Cholestatic jaundice is a rare but potentially fatal complication arising from the use of the antithyroid drugs carbimazole and propylthiouracil. The underlying mechanism of pathogenesis is still unclear, and no known effective medical therapy has been found. We report on a man who developed cholestatic jaundice shortly after receiving sequential carbimazole and propylthiouracil treatment for thyrotoxicosis.

Case report

A 36-year-old Chinese man who had neglected symptoms of thyrotoxicosis for 1 year was treated by his family physician with carbimazole 10 mg three times
daily. An urticarial skin rash developed after 2 weeks of treatment, which was thus switched to propylthiouracil 100 mg three times daily. The patient developed jaundice 2 weeks later and was referred to the Queen Mary Hospital in August 1999.

The patient gave no history of hepatitis, alcohol, or drug abuse. Physical examination detected jaundice and multiple shotty cervical lymphadenopathy. The liver was enlarged to 3 cm below the costal margin, but it was soft and smooth. There was no skin rash or any sign of chronic liver disease.

The liver biochemistry tests showed an elevated serum concentrations of bilirubin 214 µmol/L (reference range, 5-21 µmol/L), alkaline phosphatase 529 U/L (50-120 U/L), γ-glutamyltransferase 321 U/L (0-30 U/L), alanine aminotransferase 124 U/L (10-40 U/L), and aspartate aminotransferase 85 U/L (20-48 U/L). A low white blood cell count of 2.9 x 10^9/L (reference range, 4.5-11.0 x 10^9/L) was noted on admission but the count quickly returned to normal 10 days later. There was no eosinophilia, and the clotting profile was normal. The level of free thyroxine was 51 pmol/L (reference range, 12-30 pmol/L) and the level of thyrotropin (thyroid-stimulating hormone) was less than 0.03 mIU/L (0.5-5.0 mIU/L). The tests for antibodies against hepatitis A, B, and C viruses all gave negative results. Furthermore, antibodies against cytomegalovirus, herpes simplex virus, and Epstein-Barr virus were also absent. The anti-mitochondrial antibody and anti-smooth muscle antibody test results were negative as well.

An ultrasonography scan of the liver showed no stone in the gall bladder and common bile duct, although the intrahepatic ducts were prominent at the left lobe. Because cholangitis could not be excluded, an endoscopic retrograde cholangiopancreatography was performed, but the biliary tree was found to be normal. A percutaneous liver biopsy was thus performed.

The patient’s liver biochemistry test results progressively worsened after admission. A course of oral prednisolone at 0.5 mg/kg was started with the presumptive diagnosis of drug-induced cholestasis. Subsequently, the serum alkaline phosphatase concentration decreased from 657 U/L to 194 U/L, but the bilirubin concentration continued to rise and peaked at 862 µmol/L 12 days after starting therapy (Fig 1). The prothrombin time remained unchanged. Prednisolone administration was continued for 10 days and then gradually tapered off.

The patient developed a swinging fever 10 days after stopping steroid treatment and was asymptomatic, with no chest symptoms and no sputum production. Chest X-rays, ultrasonography of the liver, and echocardiography did not reveal an infective focus. However, the patient developed shortness of breath with greenish sputum 6 days later. The

![Fig 1. Time course of the change in liver biochemistry during steroid treatment](image-url)
chest X-ray showed bilateral diffused haziness with ill-defined air-space shadows in both lungs, suggesting fulminant pneumonitis. Yet, repeated sputum, blood, and broncho-alveolar lavage were all negative for known organisms.

Results from an open lung biopsy revealed no granulomatous inflammation, and staining for acid-fast bacilli and fungi was negative. Immunostaining for herpes simplex virus and cytomegalovirus was also negative. The overall picture was compatible with acute lung injury, with diffused alveolar injury, acute interstitial pneumonia, or pneumonitis. Despite treatment with broad-spectrum antibiotics and intravenous immunoglobulin, the patient died 11 days after the onset of the respiratory symptoms.

The liver tissue showed preserved acinar architecture. There was prominent intracanulicular cholestasis in acinar zones 2 and 3. Inflammation was minimal and apoptotic bodies were not visible. Fatty change was absent. In addition, microscopy revealed numerous cytoplasmic, weakly eosinophilic inclusion bodies, which were variable in size, positive for periodic acid-Schiff, and sensitive to diastase digestion.

Immunohistochemical studies showed that the inclusion bodies were positive for carcinoembryonic antigen and albumin, and negative for fibrinogen, complement protein C3, immunoglobulins G, M, and A, α-fetoprotein, and α-1-antitrypsin. Immunostaining for herpes virus antigens HBsAg and HBCAg were negative. The portal tracts were mildly expanded by moderate lymphocytic infiltration with a small number of neutrophils but no eosinophils.

Electron microscopic examination of liver tissue revealed typical glycogen bodies within the cytoplasm of the hepatocytes, which corresponded to the eosinophilic cytoplasmic inclusion bodies that were visible under light microscopy (Fig 2a). The glycogen bodies had concentric arrays of smooth membranes associated with glycogen rosettes (Fig 2b).

Discussion

The patient in this case fulfilled the diagnostic criteria of drug-induced hepatotoxicity as proposed by Hanson in 1984: the absence of serological evidence of viral hepatitis infection, absence of chronic liver disease, and absence of drug or alcohol misuse with a temporal relation to drug therapy. The persistent ultrasound findings could be attributed to the marked cholestasis.

Antithyroid drugs have been reported to induce liver toxicity but usually in the form of acute hepatitis with elevation of parenchymal enzymes. The occurrence of acute cholestasis is rare, although it is associated more commonly with carbimazole than with propylthiouracil. Hepatotoxicity, mainly in the form of cholestasis, has been reported in six cases of carbimazole use and in one of propylthiouracil use. Only one study reported that cross-reactivity of the two drugs caused hepatotoxicity.

Either carbimazole or propylthiouracil may have been the cause of the hepatotoxicity in the patient in this case. Cholestasis usually develops around several weeks after carbimazole use, but it may take only 1 day after propylthiouracil use. However, the possibility of crossover reactivity between the two drugs cannot be excluded. Cross-sensitivity has been reported to occur in about 50% of patients in one study. The levels of bilirubin and alkaline phosphatase in the patient in our case were twice as high as those reported. We thus suspect cross-reactivity of the two drugs occurred.

The successful use of steroid has been reported for fulminant hepatitis caused by antithyroid agents. The underlying mechanism of the hepatotoxicity may be immune-mediated, as evidenced by the observation that toxic symptoms occurred at an accelerated rate on rechallenge with antithyroid drugs. In addition, peripheral lymphocyte sensitisation to propylthiouracil has been demonstrated in vitro. However, the type of hepatic injury was hepatocellular in those steroid-responsive cases.
The use of steroid has not been reported before in patients with cholestatic hepatotoxicity.

The type of liver injury in patients receiving propylthiouracil and carbimazole reported previously was usually hepatic or mixed cholestatic hepatitis. Liver biopsy often revealed portal inflammatory changes and hepatocyte necrosis, with or without intranuclear cholestasis. Cholestasis with minimal inflammation and absent apoptotic bodies has not been reported previously, and this is also the first reported case demonstrating numerous glycogen inclusion bodies in the liver biopsy specimen from a patient receiving antithyroidal drugs.

Glycogen inclusion bodies in drug-induced hepatotoxicity have been reported in patients taking anabolic steroids, trimethoprim or sulfamethoxazole, 6-mercaptopurine, methotrexate, nitrofurantoin, or vitamin A. Whether carbimazole or propylthiouracil is the cause of the increase in glycogen inclusion bodies cannot be ascertained. The reported features of liver biopsies in patients with hepatotoxicities because of carbimazole and propylthiouracil are summarised in the Table.

The cause of the lung injury in this patient could be ascertained. We postulate that it was due to superimposed opportunistic infection during steroid treatment, or due to a generalised immune-mediated reaction involving the liver, as well as the lung. Hence, extreme caution should be taken when a patient develops hepatotoxicity in response to one type of antithyroidal agent, because cross-reactivity may develop in response to a second type of antithyroidal drug. The use of steroid in this condition is still uncertain. Further studies are needed on the mechanisms of antithyroid drugs causing hepatotoxicity and on the use of steroid in these conditions.

### Table. Summary of histological findings in published adult cases of carbimazole- and propylthiouracil-induced cholestasis since 1980

<table>
<thead>
<tr>
<th>Report</th>
<th>Age (years)/sex</th>
<th>Drug</th>
<th>Time to onset of cholestasis</th>
<th>Histological findings</th>
<th>Outcome</th>
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<tr>
<td>Dinsmore et al., 1983</td>
<td>24/F</td>
<td>Carbimazole</td>
<td>3 months</td>
<td>Intranuclear cholestasis, occasional bile thrombi, portal infiltration</td>
<td>Recovered</td>
</tr>
<tr>
<td>Blom et al., 1985</td>
<td>81/F</td>
<td>Carbimazole</td>
<td>6 weeks</td>
<td>Intranuclear cholestasis, piecemeal necrosis, portal infiltration</td>
<td>Recovered</td>
</tr>
<tr>
<td>Ayensa et al., 1986</td>
<td>45/F</td>
<td>Carbimazole</td>
<td>10 days</td>
<td>Intranuclear cholestasis, portal infiltration</td>
<td>Recovered</td>
</tr>
<tr>
<td>Ozenne et al., 1989</td>
<td>70/F</td>
<td>Carbimazole</td>
<td>10 days</td>
<td>Cholestasis: centrilobular, normal portal tract</td>
<td>Recovered</td>
</tr>
<tr>
<td>This report, 1999</td>
<td>36/M</td>
<td>Carbimazole, propylthiouracil</td>
<td>4 weeks</td>
<td>Intranuclear cholestasis, glycogen inclusion bodies, minimal inflammation</td>
<td>Died</td>
</tr>
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### References