A rare case of carbimazole-induced hepatitis in a patient with Graves’ disease

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Lesson
Although carbimazole-induced hepatitis is rare, clinicians should be aware of this potential complication and offer alternative treatment early.

Keywords
drugs, endocrine system, liver disease, thyroid disease

Case report
A 55-year-old lady was diagnosed with Graves’ disease in July 2011. At diagnosis, the biochemistry was: thyroid-stimulating hormone <0.01 (0.27–4.20 mU/L), free thyroxine (FT4) 38 (12–22 pmol/L) and free triiodothyronine (FT3) 16.2 (3.1–6.8 pmol/L). She had positive thyroid peroxidase and thyrotropin receptor antibodies. Apart from coeliac disease, she had no other medical problems and had never smoked. She was commenced on carbimazole at a dose of 20 mg once daily. She tolerated carbimazole which was continued on the same dose until January 2012, when it was reduced to a maintenance dose of 10 mg once daily and then stopped a month later as her thyroid-stimulating hormone levels increased to 22.8 mU/L on treatment. She relapsed in October 2012, six months after carbimazole had stopped, and she had remained euthyroid. On this occasion, she was started on 40 mg carbimazole. She declined radio-iodine treatment. In April 2013, she developed jaundice with bilirubin 123 (<21 µmol/L), alanine transaminase 1514 (<41 U/L), alkaline phosphatase 247 (20–130 U/L) and Gamma GT 132 (<45 U/L). At that time, the thyroid function were thyroid-stimulating hormone <0.01, FT4 27 and FT3 8.7. There was no history of recent travel or for blood transfusion. Hepatitis serology was negative for viral hepatitis and for auto-immune hepatitis, the possibility of drug-induced (carbimazole) hepatitis was considered. The histological changes were that of portal and lobular inflammation with ballooning degeneration of liver cells, frequent individual cell necrosis and focal bilirubinostasis. Stains for iron, hepatitis B surface-antigen were negative (Figures 1 and 2). All anti-thyroid medications were withdrawn and the patient was commenced on Nadolol (β-blocker) to control symptoms and given radio-iodine once her thyroid function tests had improved four months later.

Discussion
Graves’ disease is the most common form of hyperthyroidism. The three treatment options for Graves’ disease, anti-thyroid drugs, radioactive iodine and surgery are equally effective in lowering thyroid hormone levels within six weeks of therapy,¹ but anti-thyroid drugs are associated with higher rate of relapse compared to radioactive iodine or surgery.² The anti-thyroid drugs carbimazole and propylthiouracil are often used as first-line treatment in the UK. Carbimazole is preferred because of its longer duration of action allowing once-daily dosing, more rapid efficacy and lower incidence of side-effects. Hepatotoxicity is a rare complication of treatment with anti-thyroid drugs. Propylthiouracil is associated with elevation of transaminases in up to a third of patients. Reports of liver necrosis and liver failure associated with propylthiouracil are rare and estimated to occur in 1:10,000 adults and 1:2000 children.³ Carbimazole which is metabolised completely to methimazole has been rarely associated with intrahepatic cholestasis. There have been only a few reports of carbimazole-induced liver damage in the medical literature; almost all cases had reviewed independently by two consultant histopathologists, and diagnosis of active hepatitis was made. In the light of negative serological investigations for viral hepatitis and for autoimmune hepatitis, the possibility of drug-induced (carbimazole) hepatitis was considered. The histological changes were that of portal and lobular inflammation with ballooning degeneration of liver cells, frequent individual cell necrosis and focal bilirubinostasis. Stains for iron, hepatitis B surface-antigen were negative (Figures 1 and 2). All anti-thyroid medications were withdrawn and the patient was commenced on Nadolol (β-blocker) to control symptoms and given radio-iodine once her thyroid function tests had improved four months later.

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The above case highlights the need for clinicians to be aware that hepatitis may rarely occur with carbimazole and to swiftly consider an alternative treatment strategy such as surgery or radioiodine instead of switching to another drug. Early referral and investigations are required for a prompt diagnosis. Given the uncommon nature of this condition, histological confirmation may be necessary from another histopathologist independently. Routine tests for liver function in patients on anti-thyroid drugs would not seem unreasonable.

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**Guarantor:** AB

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