Cholestatic hepatitis in patient treated by carbimazole:
A case report

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Abstract: Antithyroid drugs are the treatment option for toxic multinodular goiter (TNG). Carbimazole is generally the drug of choice except in pregnancy where propylthiouracil is used. It is well tolerated and common side effects include allergy, gastrointestinal disorder, and rarely agranulocytosis. Hepatitis is another rare but serious complication. We reported a case of 43 years female diagnosed as hyperthyroidism, who developed cholestatic hepatitis and skin manifestation after carbimazole treatment for 2 months. She recovered completely following withdrawal of the drug and steroid therapy.

Keywords: Cholestasis, Hyperthyroidism and antithyroid drugs.

Introduction
Hyperthyroidisms refer to an un-stoppable overproduction of thyroid hormones, by all or just a part of the thyroid gland. The etiologies are several but stay behind Graves’ disease. It is liable for about 80% - 90% hyperthyroidism cases in India, 70% of hyperthyroidism in France, and 82% of cases in Cameroon. In Senegal, it represents 72% of the patients treated for hyper-thyroidism. Graves’ disease is the most common specific organ autoimmune disease. Its diagnosis is usually set up when occur clinical and biological symptoms of hyperthyroidism with homogeneous goiter and mostly an ophthalmopathy. Antithyroid is still used for symptomatic relief in patients waiting for surgery. It has a number of side effects. The majorities are mild and include allergic reactions and upper gastrointestinal intolerance. Other side effects include agranulocytosis and vasculitis-like reaction mainly with propylthiouracil (PTU). Hepatotoxicity is rare, but serious side effects with both carbimazole and PTU. Fatal cases have been documented with both drugs. The hepatic histopathology with PTU is toxic hepatitis and necrosis and it is cholestatic hepatitis with carbimazole. We present a case of carbimazole-induced cholestatic hepatitis in a patient with TNG. Clinical and biochemical findings in this patient with relevant review of literature are presented.

Case Report
A 43 years woman presented at our hospital (Damietta gastroenterology and fever hospital) with yellow eyes, dark urine and skin itching for 2 weeks ago. She had no history of liver disease and diabetes. She was neither a smoker nor an alcohol consumer and no history of taking any other medications apart from antithyroid drugs. The patient weight was 63 kg and the height is 169 cm. The BMI was 22.1kg/m². Her vital signs were stable and systemic examination unremarkable except, heptomegaly. Liver function tests were suggestive of cholestatic hepatitis (total bilirubin was 8.8 mg/dL, direct bilirubin was 7.5 mg/dL, ALT was 78 IU/L, AST was 75 IU/L, ALP was 435 IU/L). She was suspected to have viral hepatitis and was worked up in the same day. HAV IgM, HBsAg, IgM Anti-HBcAb, anti -HCV, HCV PCR, HEV IgM were negative. ANA, ASMA, IgG, AMA profile of autoimmune hepatitis was also negative. The serum cerulloplasmine were negative. The lipid profile within normal. Abdomen ultrasound showed features of chronic non-calculous cholecystitis, MRCP showed no obstruction. She was started on a trial of ursodeoxycholic acid, but this did not improve symptoms and subsequent the liver function tests showed that (total bilirubin (TB) was 12.5 mg/dL, DB was 11.2 mg/dL, ALT was 60 IU/L, AST was 55 IU/L). By the history she was diagnosed hyperthyroidism and received neomercazole two months ago but, after the appearance of jaundice the neomercazole was stopped. After four days repeat the serum bilirubin was (TB was 18.5 mg/dL, DB was 16 mg/dL). A provisional diagnosis of neomercazole-induced cholestasis was made and after stoppage of neomercazole for 2 weeks the cholestatic condition not improved, then we started steroid as therapeutic treatment for toxic hepatitis by 40 mg/day for 5 days. The subsequent investigation after steroid therapy showed improvement (TB was 10 mg/dL; DB was 9 mg /dL, ALT was 42 IU/L, AST was IU/L) then the steroid tapered until complete stoppage, and liver function done every 2 weeks which showed the improvement till the (TB 1.0 mg/dL, DB 0.3 mg/dL, ALT 27 IU/L, AST 25 IU/L) and followup for 2 month after the stoppage of the steroid showed normal liver function test.
Table 1. Serial liver function reports during the course of illness.

<table>
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<tr>
<th>Date</th>
<th>Total bilirubin mg/dL</th>
<th>Direct bilirubin mg/dL</th>
<th>ALT IU/L</th>
<th>AST IU/L</th>
<th>Alk p IU/L</th>
<th>GGT U/L</th>
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<td>75</td>
<td>438</td>
<td>143</td>
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<tr>
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<td>11.2</td>
<td>60</td>
<td>55</td>
<td>162</td>
<td>137</td>
</tr>
<tr>
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<td>160</td>
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<td>46</td>
<td>154</td>
<td>123</td>
</tr>
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<td>130</td>
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<td>143</td>
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</tr>
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<td>28</td>
<td>27</td>
<td>152</td>
<td>128</td>
</tr>
</tbody>
</table>

ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: γ-glutamyl transferase.

Discussion
The incidence of drug-induced hepatitis is estimated to 13.4-24/1000000[7]. Common drugs casing hepatitis are drug like methotrexate, amiodarone, statin, halothane, isoniazid, rifampicin and pyrazinamide[8,9]. Common histopathology of drug induced hepatitis is similar to that of acute viral hepatitis, however some drugs like erythromycin show a cholestatic picture[10]. The anti-thyroid drugs carbimazole and propylthiouracil are frequently used as a first-line treatment in Graves’ disease which is the most common type of hyper-thyroidism in the UK. Carbimazole is favored because of its longer duration of action allowing once-daily dosing, more rapid efficacy and lesser 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 one third of patients. Reports of liver necrosis and liver failure associated with propylthiouracil are rare and estimated to occur in 1:10,000 in adults and 1:2000 in children[11]. Neomercazole which is metabolized completely to methimazole has been rarely associated with intrahepatic cholestasis. There have been only a few reports of neomercazole -induced liver damage in the medical literature; nearly all cases had histological changes consistent with cholestasis[12]. Our patient developed acute cholestatic hepatitis two months after initiation of treatment with carbimazole. Although the hepatitis developed after a dose increase from 20 mg to 40 mg of neomercazole, it is unclear whether the higher dose may have been a trigger factor[13]. Currently, the most effective treatment for drug induced liver injury (DILI) is to suspend the offending drug(s) and to avoid re-exposure, with no definitive therapy available for idiosyncratic DILI with or without acute liver failure. Given the anti-inflammatory effects of corticosteroids, they have been widely used in DILI in clinical practice, although their efficacy remains controversial.

Conclusion
Hepatic toxicity is a rare, but serious side effect of antithyroid medications. Though very rare; neomercazole can cause a dose- dependent hepatitis. This hepatitis is usually due to an allergic mechanism and has a cholestatic picture on histopathology. With a few exceptions, the hepatitis is mild and resolves within a few weeks of stopping the drug the anti-inflammatory effects of corticosteroids, they have been widely used in DILI in clinical practice, although their efficacy remains controversial.

Reference


