Acute Pancreatitis, Hepatic Cholestasis, and Erythema Nodosum Induced by Carbimazole Treatment for Graves' Disease

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Abstract. A 33-year old female was diagnosed as Graves' disease and started on carbimazole. One month later when she was already euthyroid only on carbimazole therapy, she developed acute pancreatitis associated with mild cholestatic hepatitis and erythema nodosum. Carbimazole therapy was interrupted, pancreatic and liver function gradually improved and become normalized two weeks later. Other potential etiological causes of acute pancreatitis, hepatitis and erythema nodosum were excluded. Rechallenge with a single dose of carbimazole led to a new episode of acute pancreatitis and cholestatic hepatitis one day later. The appearance of different hypersensitivity reactions including pancreatitis, hepatitis and erythema nodosum, together with the observation that the interval between drug intake and onset of symptoms became shorter with repeated exposure to carbimazole, point to an immune-mediated mechanism. Carbimazole has to be added to the list of drugs capable of inducing acute pancreatitis, and should be emphasized the need to discontinue this medication as soon as there is evidence of pancreatic dysfunction.

Key words: Acute pancreatitis, Hepatic cholestasis, Erythema nodosum, Carbimazole, Graves' disease

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CARBIMAZOLE is an effective and generally safe antithyroid drug, widely prescribed for the treatment of hyperthyroidism. It is a 3-carbethoxy methimazole derivative, metabolized to methimazole in the liver. It has been associated with various minor sensitivity reactions in a small percentage of patients including skin rashes, arthralgias, fever, transient leukopenia or lymph node enlargement. In addition, serious adverse reactions, sometimes fatal, such as agranulocytosis and severe hepatitis can rarely occur with carbimazole therapy [1], although they are less common than with methimazole therapy, despite a common structural formula [2]. Here we report new side effects of carbimazole: acute pancreatitis and erythema nodosum (EN), which appeared combined with mild hepatitis.

Case Report

In September 1997, a 33 year-old female patient was diagnosed as Graves' disease (GD) with a florid clinical picture of thyrotoxicosis. Serum total T4 level was 21 μg/dl (normal 4.5-12), total T3 2.8 ng/ml (normal 0.9-2.1), TSH < 0.05 μU/ml (normal 0.5-5.5), and she had a positive TSH receptor antibody titre (TBI 39%, normal < 10%). A 50% 24-hour radioactive iodine uptake (RAIU) was found. She started therapy with carbimazole at a dose of 45 mg daily. One month later, when she was already clinically and biochemically euthyroid on carbimazole therapy, she complained of weakness, vomit-
ing and intense abdominal pain of 24 hour duration. She also referred tender red nodules in both lower extremities, which had appeared two days before. Past medical history was unremarkable and she had no previous history of allergy or adverse reactions to drugs. She denied alcohol ingestion and she was not taking any other medications at the time of admission.

On examination she had a tender abdomen with positive Blumberg and a 3 cm enlarged liver. She had no ascites. In addition, on the anterior aspect of both lower extremities bilateral, slightly elevated, red tender nodules characteristic of EN were found.

Laboratory tests revealed a white blood cell count of 18,300 with 86% of neutrophils. There was no eosinophilia. Platelet count was 199,000, with normal coagulation. Serum amylase was elevated to 454 U/L (normal, <110), serum lipase to 2280 U/L (normal, 23–270) and urine amylase was 1770 U/24 h (normal, negative) (Table 1). Liver function tests demonstrated a slight increase in aspartate aminotransferase, alanine aminotransferase, with a greater increase in alkaline phosphatase 632 U/L (normal, 80–270) and γ-glutamyl-transferase 915 U/L (normal, 0–50) and a normal bilirubin (Table 1). Levels of electrolytes, ionized calcium, cholesterol, triglycerides, elastase, alpha-1-antitrypsin and thyroid function tests were normal. Hepatitis virus A, B and C serologies were all negative. Antinuclear, antimitochondrial, and anti-smooth muscle antibodies were negative. There was no evidence of serum antibodies for viruses or bacteria that could induce pancreatitis, hepatitis or EN including mumps, para-influenza, influenza, and Coxsackie virus. Serum levels of IgG, IgA, IgM, and IgE were all in normal range and did not alter during the acute episode. An abdominal ultrasound and a CT scan showed no biliary tract or gallbladder abnormalities. The pancreas was enlarged and hypoechoogenic. A cutaneous biopsy of the lower extremities lesions was diagnostic of EN. She had a negative Mantoux test, a negative throat culture with normal antistreptolysin-O titres, and a normal chest X-ray.

The diagnosis of acute pancreatitis, mild intrahepatic cholestasis and EN was made. The patient improved with conservative management with fluids and analgesics, and three days after discontinuing carmbimazole she had no abdominal signs or symptoms. Serum amylase and lipase levels, and liver function tests gradually decreased and she was discharged on the tenth day of hospitalization. Seven days later, after complete resolution of her symptoms, because there had not been any previous report in the literature of antithyroid drug-induced pancreatitis in the literature, with the patient’s consent, carmbimazole was reintroduced at a single dose of 10 mg. Twenty-four hours after receiving the first tablet the patient repeated the clinical and analytical picture of acute pancreatitis. Laboratory tests revealed a serum amylase of 415 U/L and a urine amylase of 5770 U/L. Liver function tests were mildly increased (Table 1). A new abdominal ultrasound examination showed a diffusely enlarged hypochoic pancreas consistent with acute pancreatitis. Endoscopic retrograde cholangio-pancreatogram (ERCP) performed after recovery from the second episode confirmed the absence of organic disease. Symptoms and analytical abnormalities disappeared four

<table>
<thead>
<tr>
<th>Units</th>
<th>Reference range</th>
<th>1st episode pancreatitis</th>
<th>Recovery 1st episode</th>
<th>1 day after rechallenge</th>
<th>Recovery 2nd episode</th>
<th>2 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase blood</td>
<td>IU/L</td>
<td>&lt;110</td>
<td>454</td>
<td>227</td>
<td>415</td>
<td>75 8</td>
</tr>
<tr>
<td>Amylase urine</td>
<td>IU/24 h</td>
<td>23–270</td>
<td>2280</td>
<td>775</td>
<td>775</td>
<td>257 91</td>
</tr>
<tr>
<td>Lipase</td>
<td>IU/L</td>
<td>0–37</td>
<td>47</td>
<td>12</td>
<td>47</td>
<td>22 27</td>
</tr>
<tr>
<td>ALT</td>
<td>IU/L</td>
<td>0–40</td>
<td>85</td>
<td>20</td>
<td>85</td>
<td>28 36</td>
</tr>
<tr>
<td>ALP</td>
<td>IU/L</td>
<td>0–50</td>
<td>915</td>
<td>471</td>
<td>915</td>
<td>180 60</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>mg/dl</td>
<td>0.1–1.2</td>
<td>0.8</td>
<td>0.6</td>
<td>0.8</td>
<td>0.8 0.9</td>
</tr>
<tr>
<td>WBC</td>
<td>×10⁹ cells/l</td>
<td>3.2–7.9</td>
<td>18.3</td>
<td>6.0</td>
<td>18.3</td>
<td>5.2 6.7</td>
</tr>
<tr>
<td>ESR</td>
<td>mm/h</td>
<td>&lt;20</td>
<td>92</td>
<td>54</td>
<td>92</td>
<td>34 38</td>
</tr>
</tbody>
</table>
days after stopping carbimazole.

One month later, receiving no therapy, amylase and liver function tests were normal, but she remained hyperthyroid (FT4: 2.58 ng/dl, normal 0.8-2). The patient was treated with an ablative dose of radioiodine with resolution of symptoms. She developed post-radioiodine hypothyroidism and has been followed up on thyroxine therapy for five years without recurrence of pancreatitis, hepatitis or EN.

**Discussion**

We report a patient who developed a clinical picture of pancreatitis after receiving carbimazole therapy for one month. Drug-induced pancreatitis is a rare entity and often difficult to prove. Although a number of therapeutic agents have been associated with acute pancreatitis, most reports are based on anecdotal evidence and are hampered by the facts that the patients have been exposed, at the same time, to different drugs and that the illness for which a drug was administered might cause acute pancreatitis. Carefully documented cases showing a recurrence of pancreatitis after reexposure are few. Pancreatitis in our patient can be reasonably ascribed to carbimazole, because clinical course and laboratory findings fulfilled all the diagnostic criteria of drug-induced pancreatitis [3], including: 1) the temporal relationship of the first episode of acute pancreatitis to the administration of carbimazole, 2) rapid reversal of abnormal pancreatic function test results upon withdrawal of carbimazole, 3) prompt rechallenge after reexposure to the drug 24 hours later, 4) absence of other causes of pancreatitis such as cholecystitis, cholelithiasis, alcohol ingestion, viruses, hypertriglycerideremia or other pharmacological agents, and 5) normal endoscopic retrograde cholangiography. To our knowledge, this is the second report in which thionamide drugs have been implicated as a cause of pancreatitis. In a recent report acute pancreatitis and parotitis have been associated with methimazole therapy and confirmed by rechallenge [4].

In addition, our patient had EN, which is characterized by painful, non-suppurative, red cutaneous nodules that usually occur over the extensor surface of the lower extremities. Individual nodules last several weeks before disappearing spontaneously. Although acute pancreatitis has been associated with nodular panniculitis, in our patient this diagnosis was excluded by distinct clinical features and skin biopsy. The EN syndrome is a distinctive hypersensitivity reaction, which has been associated with different unrelated disorders mostly sarcoidosis, infections and drugs including penicillin, sulfonamides or iodides. Although there have been few cases in the literature [5] associating sarcoidosis, EN, and thyroid disease, in none were they related to any drug treatment. In a previous report EN has been associated chronologically to propylthiouracil (PTU) treatment for thyrotoxicosis [6].

Hepatic adverse effects have been associated to hyperthyroidism and rarely to thionamide administration. During hyperthyroidism increases in serum alkaline phosphatase and gammaglutamyl transferase have been observed in about half of the patients, and gradually disappear with normalization of thyroid hormone levels [7]. Drug-induced hepatitis is a well-known side effect of antithyroid drugs, while PTU produces predominantly hepatocellular necrosis, methimazole and carbimazole mainly cause cholestatic damage [7]. Hepatotoxicity is more infrequent during treatment with methimazole when compared to carbimazole [2] and only five cases of jaundice associated with carbimazole have been reported. In addition to these severe hepatic side effects related to thionamides, more mild hepatic effects have been recognized [8]. In this regard, PTU therapy has been associated with elevations in liver enzymes, with no elevation in bilirubin, in 30% of patients after two months of therapy [9]. Despite continuation of PTU treatment, liver enzymes normalized by five months. Mild hepatic side effects associated with methimazole and carbimazole therapy have been less well studied. Our patient’s hepatic abnormalities point to carbimazole-induced hepatotoxicity, as she had normal thyroid function, no clinical, biochemical, or histological evidence of alcoholism or previous chronic liver disease, absence of viral infection or cholecystitis, and a normal ERCP.

The coincidence of pancreatitis, EN and hepatotoxicity associated to carbimazole treatment for GD in our patient is noteworthy. All these abnormalities can be secondary to hypersensitivity reactions to drugs. These reactions develop in a small segment of the drug-exposed population, are not dose-dependent, have a variable latent period of exposure and evoke prompt signs and symptoms of the disease.
upon rechallenge. These disturbances are mediated by immune mechanisms that may develop in response to a number of antigenic stimuli. Although the mechanism of carbimazole-induced pancreatitis is unknown, carbimazole-induced hepatotoxicity appears to be an idiosyncratic event related to cell-mediated immunity [8]. In our patient, the clinical observation of the intervals between drug intake and start of symptoms of acute pancreatitis becoming shorter with repeated exposure, together with the rapid improvement after cessation of treatment, as well as the association of hepatitis and EN, point to a hypersensitivity reaction as the pathogenic mechanism.

The possible component of the thionamide to which the hypersensitivity reaction is directed could be the sulphhydryl group. Sulphonamides have been described as a definite cause of pancreatitis, probably secondary to an allergic drug reaction [10] and a cause of EN. In addition, another immunological disorder, the insulin autoimmune syndrome, has been associated with drugs containing sulphhydryl compounds, such as carbimazole [11].

In conclusion, our patient presented with pancreatitis, cholestatic hepatitis and EN probably secondary to immune-mediated reaction to carbimazole. Although pancreatitis secondary to carbimazole is probably a rare complication in view of the widespread use of antithyroid drugs, the potential danger of this complication should be kept in mind. While we do not recommend clinical and biochemical monitoring in all patients on carbimazole therapy, we emphasize the need of evaluation for acute pancreatitis in any patient who develops abdominal distress and/or abnormal liver function tests while receiving methimazole and/or carbimazole.

References