Case Report

Acute icteric hepatitis as the main manifestation of hyperthyroidism

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SUMMARY

Thyroid storm is a rare (<1%) cause of acute icteric hepatitis. We present the case of a 32-year-old white female who was admitted to hospital due to acute hepatitis with jaundice, as a result of development of hyperthyroidism due to Graves' disease. Clinical examination, serological tests, radiological and cardiovascular investigations excluded other causes of acute hepatitis. The hepatitis reversed a few days after initiation of hyperthyroidism treatment. In conclusion, acute icteric hepatitis can be the presenting symptom of hyperthyroidism, thus creating difficulties in differential diagnosis and management.

Key words: Jaundice, acute hepatitis, hyperthyroidism, Graves' disease

INTRODUCTION

Thyroid storm or thyrotoxic crisis is a form of hyperthyroidism, characterised by the presence of life-threatening clinical features. Clinical manifestations, include fever, cardiovascular disorders (tachycardia, arrhythmias or the acute development of heart failure), central nervous system manifestations (psychosis, agitation, somnolence, coma) and gastrointestinal disorders (abdominal pain, diarrhoea, vomiting or jaundice). Laboratory findings may include elevated hepatic enzyme and bilirubin levels, anaemia, leukopenia with relevant lymphocytosis, hyponatriaemia and hypercalcaemia.[1] The development of acute icteric hepatitis is a very rare feature of thyroid storm, presenting in less than 1% of cases.[2]

We present the case of a 34-year-old patient with acute icteric hepatitis as the main manifestation of thyroid storm, which created difficulties in differential diagnosis and management.

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CASE REPORT

A 34-year-old Caucasian housewife was referred by her general practitioner for admission to the local hospital due to acute icteric hepatitis. Four years prior to admission, hyperthyroidism due to Graves' disease was diagnosed and the patient was treated with carbimazole, which was substituted by propylthiouracil one month later due to a referred allergic reaction to the former drug. Therapy was discontinued after 20 days on the patient's request. Three years later, due to recurrence of hyperthyroidism, the patient was treated with carbimazole followed by propylthiouracil and once more therapy was discontinued on her request. One week prior to admission to our hospital, the patient's symptoms (excess sweating, agitated tiredness, hyperactivity, insomnia, palpitations, dyspnea in exertion) became more intense and she was admitted to another hospital. On clinical examination, the patient had a temperature of 38ºC. An electrocardiogram revealed atrial fibrillation with a rapid ventricular response. Laboratory values included: haematocrit (Ht) 39.9%, white blood count (WBC) 3,850 mm3 (59% neutrophils, 25% lymphocytes, 14% monocytes, 2% eosinophils), platelets (PLT) 112,000 mm3, glucose 146 mg/dl, urea 18 mg/dl, creatinine 0,7 mg/dl, aspartate aminotransferase (AST) 110 U/L (normal values 10-40), alanine aminotransferase (ALT) 79 U/L (normal values 10-40), γ-Glutamyl-transferase (γGT) 20 U/L, alkaline phosphatase (ALP) 95 U/L, lactate dehydrogenase

(LDH) 165 U/L, total bilirubin (TBil) 1.20 mg/dl, conjugated (direct) bilirubin (DBil) 0.47 mg/dl, sodium (Na) 134.8 mEq/l, potassium (K) 4.54 mEq/l, free triiodothyronine (FT3) 24.2 pg/ml (normal values 1.64-3.45), free thyroxin (FT4) >6.0 ng/ml (normal values 0.71-1.85), triiodothyronine 5.94 ng/ml (normal values 0.8-2.0), thyroxin >24 μg/ml (normal values 4.5-12.0), thyrotropin (TSH) 0.02 mIU/ml (normal values 0.32-5.0). During the first hospital day, the patient was treated with a daily dose of 600 mg propylthiouracil, digitalis, ampicilline with sulbactam and acenocoumarol. The following day, laboratory tests revealed: AST 646 U/L, ALT 306 U/L, ALP 135 U/L, TBil 4.10 mg/dl (figure) and the patient was referred to our hospital for further evaluation and treatment of the acute icteric hepatitis.

The patient had a history of recurrent menorrhagias. She was allergic to detergents. She reported no alcohol abuse and had a 10 pack-year history of tobacco smoking.

On clinical examination, she was nervous and had excessive perspiration. Blood pressure was 150/90 mmHg, her pulse rate was 140/min and irregular. Her temperature was 38.4°C. Bilateral exophthalmos, icteric pigmentation of skin and sclera and a diffuse enlargement of the thyroid gland were apparent. The spleen was nontender and palpable 3cm below the left costal margin.

Laboratory values revealed: Ht 36.8%, Hb 12.2 g/dl, mean corpuscular haemoglobin 26.3 pg, mean corpuscular haemoglobin concentration 34 g/dl, mean corpuscular volume 77.3 fl, WBC 2,000 mm3 (neutrophils 70%, lymphocytes 22%, monocytes 7%, eosinophils 1%), PLT 130,000 mm3, erythrocyte sedimentation rate 48 mm/h, glucose 154 mg/dl, urea 34 mg/dl, creatinine 0.7 mg/dl, cholesterol 99 mg/dl, triglycerides 114 mg/dl, serum total protein 6.9 g/dl, albumin 3.7 g/dl, AST 646 U/L, ALT 306 U/L, γGT 97 U/L, ALP 135 U/L, LDH 670 U/L, creatine kinase 60 mU/ml, serum amylase 31 U/L, TBil 4.1 mg/dl, DBil 2.45 mg/dl, Na 136 mEq/l, K 4.2 mEq/l, calcium 9.8 mg/dl, phosphorus 2.2 mg/dl. Prothrombin time was 11.9" (with an international normalised ratio of 0.99), activated partial thromboplastine time 40", fibrinogen 280 mg/dl, D-Dimers<0.25 and fibrinogen split products negative. Serum protein electrophoresis revealed: albumin 42%, α1 6.2%, α2 9.5%, β 14.4%, γ 27.8%. Serum immunoglobulin levels were: IgG 1550 mg% (normal values 694-1618), IgA 179 mg% (normal values 68-378), IgM 246 mg% (normal values 60-263), κ: 1410 mg% (normal values 574-1276), λ 762 mg% (normal values 269-638), a2m 224 mg% (normal values 131-293). HBsAg, anti-HBs, anti-HBc, anti-HAV IgM, HCV RNA (by PCR) anti-HBc IgM and anti-HCV were negative, as were ANA, AMA and anti-DNA autoantibodies. SMA autoantibodies were positive in a low titre (1/80). C-reactive protein was 3 mg/dl. FT3 was 13.4 pmol/L (normal values 3.4-8.5), FT4 125.0 pmol/L (normal values 10-25), TSH <0.01 μIU/ml (normal values 0.54-4.58), thyroglobulin 401.0 ng/ml (normal values 2.0-70.0), thyroglobulin antibodies were negative (normal, <60 U/ml) and antimicrosomal antibodies (ATPO) were positive (2732.0 U/ml, normal <60). Urinalysis was normal, urine and blood cultires were negative. Electrocardiography revealed atrial fibrillation. A chest x-ray was normal.

Abdominal ultrasonography revealed a liver of normal size and increased echogenicity, without identification of focal lesions. The spleen was enlarged (length 17.5 cm). Thyroid ultrasonography demonstrated an enlargement of the thyroid, without identification of nodules.

The patient was treated with thiamazole (60mg per day), a potassium iodine solution, propranolol (120mg per day), hydrocortisone (200mg per day) and diazepam. Jaundice reversed and the aminotransferase levels returned to normal within a few days after commencement of hyperthyroidism treatment (table). The spleen returned to normal size (by ultrasonography) one month after initiation of therapy.

DISCUSSION

Clinical hepatic features in patients with hyperthyroidism may be attributed to the endocrine syndrome itself,[3] to coexisting congestive heart failure, to diseases of the liver associated with Graves' disease (such as autoimmune hepatitis, or primary biliary cirrhosis,[4] which may be transiently aggravated) or to merely co-inciding liver disease.[5] Unconjugated hyperbilirubinaemia may be aggravated in patients with Gilbert's syndrome and hyperthyroidism. Patients with hyperthyroidism without congestive heart failure often present with hepatomegaly (18-33%), splenomegaly, jaundice (elevation of conjugated bilirubin in 5.3-50% of cases) and increased aminotransferase (25-76%), ALP (64,2%) and γ-GT (16,8%) levels.[6-8] Aminotransferase levels exceed 250 U/L in only 3% of cases.[9] Acute icteric hepatocyte damage occurs in less than 1% of cases[2]. The varying elevation of conjugated bilirubin and hepatic enzyme levels is attributed to the excess amounts of thyroid hormones and to hepatic tissue hypoxia, due to increased visceral consumption of oxygen, combined with increased oxygen needs by the hepatocytes.[10] The above metabolic disorders are rapidly improved after start of hyperthyroidism treat-

ment. Histopathology of the liver is non-specific (steatosis with or without fibrosis) and does not contribute to differential diagnosis[9]. Elevation of ALP levels does not always reflect hepatobiliary damage because hyperthyroidism may cause increased osteoblastic activity, resulting in an elevation of the bone isoenzyme of ALP[2].

The reported patient presented with acute icteric hepatitis as a result of thyroid storm, due to untreated Graves' disease. This is a rare cause of acute hepatitis demanding differential diagnosis with viral hepatitis, ischaemic hepatitis, drug-induced and autoimmune diseases. There were no features of congestive heart failure or ischaemic hepatitis, wihich could also be the cause of acute icteric hepatocyte damage. The liver was of normal size, there was no hepatojugular reflux, ultrasonography did not demonstrate distension of hepatic veins, nor did the patient present a drop in arterial blood pressure. LDH was not disproportionately elevated in comparison to the aminotransferases, which could indicate ischaemic hepatitis. Serologic testing excluded the usual causes of viral hepatitis. The rapid development of acute icteric hepatocyte damage with elevation of aminotransferases and bilirubin, within a period of 24 hours (figure) was attributed to the thyroid storm. During the following days jaundice reversed and hepatic enzymes dropped towards normal levels, despite persistence of hyperthyroidism, probably due to haemodynamic improvement and reverse of hypoxia of hepatic tissue, as a result of therapy (potassium iodide, propranolol and hydrocortisone). Splenomegaly and polyclonal hypergammaglobu-linaemia were attributed to reticuloendothelial hyperplasia, due to hyperthyroidism11 and resolved the following weeks, after normalisation of thyroid hormone levels.

The patient was initially treated with prophylthiouracil, but was referred to our hospital due to aggravation of jaundice, with the clinical suspicion of drug-induced acute icteric hepatitis. Drugs are the cause of 2-5% of episodes of jaundice treated in hospital, 25% of fulminant hepatic failure and up to 66% of chronic liver diseases.[12] Prophylthiouracil may cause an increase of aminotransferase levels (28%), which however is asymptomatic, transient and self-localised, despite continuance of therapy, usually 2 months after administration of the drug.[13] Some cases of fulminant hepatic failure have been reported, which were attributed to idiosyncratic reactions to propylthiouracil, but have all occurred at least after 12 days of therapy.[14] Carbimazole may also cause fulminant hepatitis, usually 6 weeks after administration of the drug.[15] In the reported patient, aminotransferase level elevation preceded the administration of the drugs and aggravation of hepatocyte damage was very rapid/occuring (in a 1-2 day period).

In conclusion, thyroid storm can rarely present as acute icteric hepatitis, leading to differential diagnosis difficulties from viral, ischaemic, drug-induced or autoimmune causes of acute hepatocyte damage.

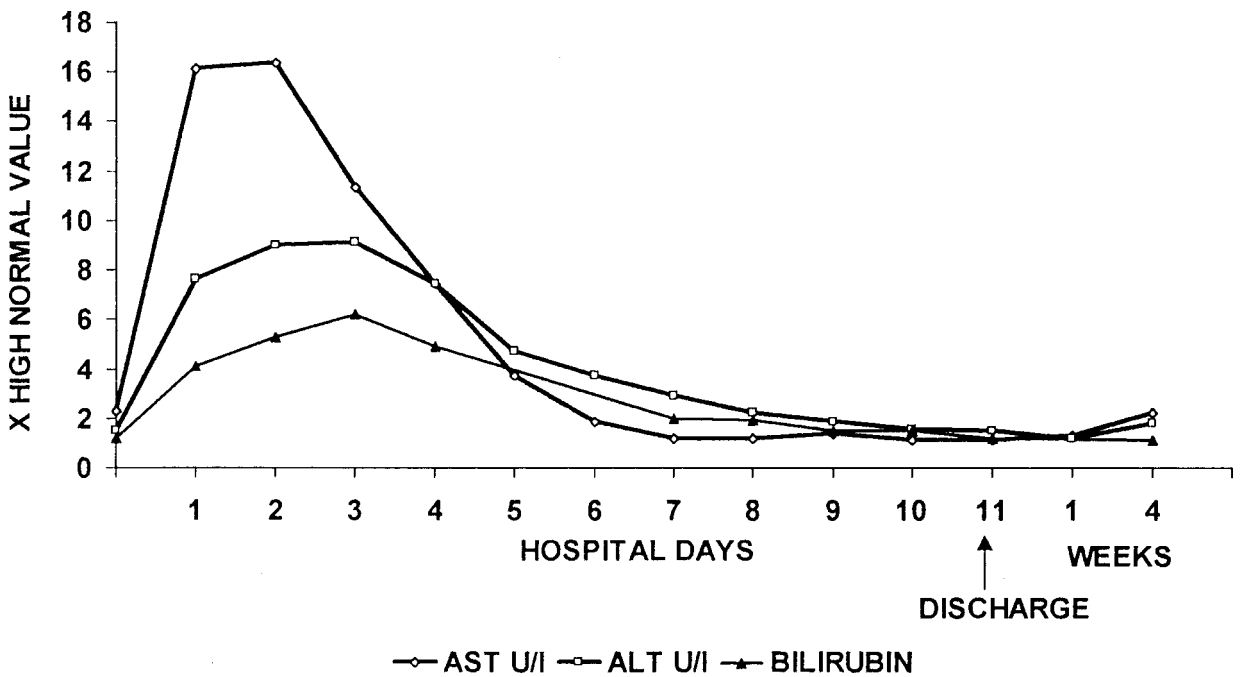

Figure. Billirubin and aminotransferase levels during hospitalization

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