

A case of severe cholestatic jaundice associated with Graves' disease

Şiddetli kolestatik sarılığın eşlik ettiği Graves hastalığı olgusu

To the Editor

Liver injury caused by thyrotoxicosis is relatively common and can be conveniently divided into hepatic or cholestatic types (1).

A 49-year-old man with jaundice, nausea, vomiting and palpitation was admitted to our clinic. His past medical history was unremarkable.

Physical examination revealed severe jaundice. There were no signs of chronic liver disease. He was afebrile with a regular pulse rate of 100 beats per minute and normal blood pressure. He had no signs of thyroid eye disease and no external goiter. Respiratory and cardiovascular examinations were normal. Chest radiography and echocardiography excluded any kinds of cardiac failure. There was no hepatomegaly or lymphadenopathy but the spleen was enlarged 3 cm below the costal margin and was smooth and nontender.

Laboratory investigations revealed abnormally high serum free T4 (6.07 ng/dl) and free T3 (17.90 pg/dl) and low serum thyroid stimulating hormone (TSH) (0.001 IU/L). Autoantibody profile included anti-thyroglobulin antibody >500.0 IU/ml (NR: 0 to 60 IU/ml), antimicrosomal antibody (anti-thyroid peroxidase) >1300 IU/ml (NR: 0 to 60 IU/ml) and anti TSH receptor antibody 8.8 U/L (NR: <1.5 U/L). Cervical ultrasound showed the thyroid gland was enlarged to the retrosternal area and the parenchyma was heterogeneous without a nodule formation. Thyroid radioisotope scan demonstrated diffuse tracer uptake suggesting primary hyperthyroidism (Graves' disease).

Hepatic function tests revealed total bilirubin 27.7 mg/dl, direct bilirubin 19.7 mg/dl, alkaline phosphatase 192 U/L (NR: 40 to 140 U/L), gamma-glutamyl transferase (GGT) 110 U/L (NR: 9.0 to 64.0 U/L), aspartate aminotransferase (AST) 50 U/L, and alanine aminotransferase (ALT) 100 U/L; al-

bumin and prothrombin time were normal. Serology for hepatitis A,B,C, Epstein-Barr and cytomegalovirus (CMV), group agglutination test for typhoid fever, and direct globulin test for Brucella melitensis were all negative. Serum high sensitivity C-reactive protein (hsCRP), ferritin, ceruloplasmin, copper and alpha-1-antitrypsin levels were normal. Autoantibody profiles for ASMA, LKM, AMA, mpo-ANCA and anti-dsDNA were negative; ANA showed a borderline positive level of 1/80 of nucleolar pattern. Serum protein electrophoresis showed a mild elevation in gammaglobulin level with serum Ig G 1980 mg/dl (NR: 540 to 1822 mg/dl), Ig M 189 mg/dl (NR: 22 to 240 mg/dl) and Ig A 360 mg/dl (NR: 63 to 484 mg/dl).

The size and the parenchyma of the liver were normal and no ascites was found on the abdominal ultrasound. The spleen was enlarged. There was no evidence of intra- or extra- hepatic biliary tract dilatation on the magnetic resonance (MR) cholangiopancreatography.

Percutaneous liver biopsy showed a mild centrilobular cholestasis with focal hepatic steatosis and nonspecific focal necrosis. There was no evidence of hepatitis or granulomata (Figures 1, 2).

A thyrostatic drug, methimazole, 30 mg/day and a β -adrenergic blocking agent, propranolol, 40 mg/day were started. In four weeks, liver function tests became almost normal without specific treatment directed to the clinical or biochemical features of liver impairment. After five months, free T4 was 0.96 ng/dl, free T3 was 2.93 pg/ml and TSH increased to 0.01 IU/ml. He presented to the surgeon and a total thyroidectomy was applied. Four weeks after the operation he started to use L-thyroxine 100 mg/day. He is now being followed as an outpatient.

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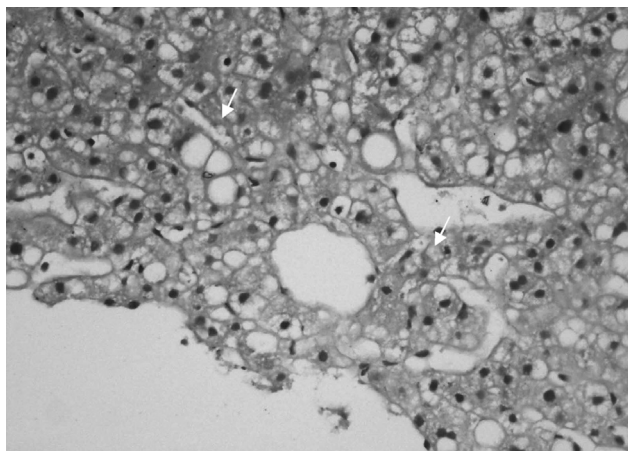


Figure 1. Liver biopsy shows mild centrilobular cholestasis (white arrows) and steatosis (Hematoxylin and eosin stain, original magnification x200).

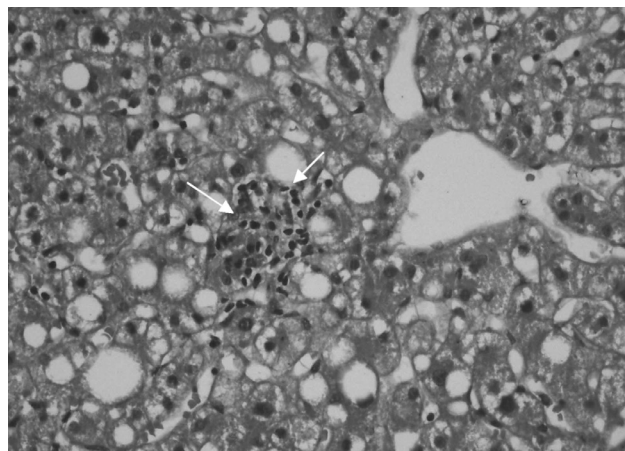


Figure 2. Liver biopsy shows focal necrosis (white arrows) (Hematoxylin and eosin stain, original magnification x200).

In spite of severe jaundice with mild elevation of serum transaminases, alkaline phosphatase and GGT, there was no evidence of autoimmune hepatitis nor typical histological findings in the biopsy specimen except for hypergammaglobulinemia with selective elevation of serum Ig G (2, 3) in our patient. Appropriate investigation excluded viral hepatitis, primary biliary cirrhosis, Wilson's disease and hemochromatosis, and there was no history of alcohol abuse or of any type of medication. The borderline ANA positivity with mild elevation of serum Ig G level was related to Graves' disease (4, 5). There was no evidence of biliary tract dilatation, biliary colic or fever.

In fact, abnormal results of liver function tests are relatively common in Graves' disease, but cholestasis and jaundice are far less common than mild enzyme abnormalities and make the diagnosis difficult until the euthyroid state has been established (1,6-9). Treatment with antithyroid drugs resulting in dramatic decreases in patients' bilirubin

levels were mentioned in cases previously (2, 6-10).

A number of hypotheses have been put forward to explain the cholestasis in hyperthyroidism in the absence of cardiac failure. It has been suggested that the hypermetabolic state in thyrotoxicosis increases hepatic oxygen consumption without an appropriate increase in hepatic blood flow and lowers the oxygen tension in the centrilobular zones leading to cholestasis (1, 7-10). Jaundice is uncommon, but when it does occur, complications of thyrotoxicosis (cardiac failure/sepsis) or intrinsic liver disease need to be excluded (1).

Drug therapy may also predispose or contribute to cholestasis with severe cholestatic jaundice in hyperthyroidism (1,9). Abnormalities of liver function are much less common with methimazole and it induces cholestasis as an idiosyncratic reaction to the drug (1, 7). In our case, the severity of jaundice and high levels of serum bilirubins returned to normal as soon as special treatment was started with methimazole.

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