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CASE REPORT

그레이브스 병에 합병된 자가면역성 간염의 증례 보고

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A Case of Autoimmune Hepatitis Combined with Graves' Disease

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A 25-year-old woman presented with jaundice, palpitation, and weight loss of 5 kg during a period of 2 weeks. Laboratory tests showed elevated levels of liver enzymes (AST 1,282 IU/L, ALT 1,119 IU/L) and total bilirubin (6.4 mg/dL); negative for hepatitis virus infection; elevated serum levels of triiodothyronine (T3, 3.60 ng/dL), free thyroxine (fT4, 3.82 ng/dL), and lowered serum level of thyroid stimulating hormone (TSH, <0.025 μIU/mL); and positive for thyroid stimulating antibody and anti-mitochondrial antibody (AMA). The liver biopsy findings were consistent with autoimmune hepatitis (AIH). Accordingly, oral steroid therapy was started with 60 mg of prednisolone under the impression of AIH associated with Graves' disease. After a week of steroid therapy, the clinical manifestation showed significant improvement, with normalization of both liver and thyroid functions. Diagnosis of the liver condition of patients who present with hyperthyroidism and liver dysfunction is important, so that appropriate therapy can be promptly initiated. **(Korean J Gastroenterol 2015;65:48-51)**

Key Words: Autoimmune hepatitis; Graves disease; Steroid

INTRODUCTION

Graves' disease is an autoimmune disease characterized by the presence of activating autoantibodies against thyroid stimulating hormone (TSH) receptor. The clinical manifestations of hyperthyroidism are largely diverse, including liver function abnormalities. Autoimmune hepatitis (AIH) is a chronic hepatitis of unknown etiology characterized by the presence of circulating autoantibodies, hyperglobulinemia, and inflammatory changes on liver histology in the absence of other causes of hepatitis. In acute hepatitis combined with Graves' disease, it is important to make a differential diagnosis of the cause of hepatitis. Here, we report on a case of a young woman who developed AIH combined with Graves' disease.

CASE REPORT

A 25-year-old woman presented with jaundice, palpitation, and weight loss of 5 kg during a period of 2 weeks. There was no history of drug or alcohol abuse, and no family history of liver disease.

Physical examination findings were not remarkable except her sclera was icteric. There was no evidence of exophthalmos, hepatomegaly, splenomegaly, ascites, pretibial edema, or skin rash.

Laboratory tests showed elevated levels of aminotrans-

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ferases (AST 1,282 IU/L, ALT 1,119 IU/L) and total bilirubin (6.4 mg/dL) without evidence of hepatitis virus infection (negative for HBsAg, anti-HCV, and IgM anti-HAV). IgM anti-HAV was still negative after peak level of ALT. Thyroid function test was consistent with hyperthyroidism (T3 3.60 ng/dL, fT4 3.82 ng/dL and TSH < 0.025 μIU/mL) with positive thyroid stimulating antibody, highly suggestive of Graves' disease. Serological tests for anti-nuclear antibodies (ANA), anti-liver/kidney microsomal type 1 (anti-LKM), and anti-smooth muscle antibody (SM) were negative, whereas anti-mitochondrial antibody (AMA) was positive. The serum levels of IgG (1,221 mg/dL), IgA (137.0 mg/dL), and IgM (214.0 mg/dL) were within normal range (Table 1).

Abdominal CT and liver biopsies were performed for differential diagnosis of other possible causes of aggravated liver function. Abdominal CT findings were consistent with acute hepatitis without hepatic or biliary lesions. The histologic findings of liver biopsies showed lobular hepatitis with marked infiltration of lymphoplasma cells in the portal area, with occasional eosinophils and mild ductular proliferation (Fig. 1).

Accordingly, the patient was clinically diagnosed with Graves' disease and the co-morbid acute hepatitis was considered a liver dysfunction associated with underlying uncontrolled Graves' disease. Initially, the patient was treated with methimazole for treatment of hyperthyroidism from Graves' disease; however, there was no improvement in the clinical course of hepatitis. Thus oral steroid therapy was administered. After one week of oral steroid treatment with 60 mg of prednisolone, the clinical manifestation showed significant improvement, with normalization of both liver and thyroid functions (Fig. 2).

Table 1. Laboratory Data on Admission

Laboratory data	Result
Liver function test	
AST (IU/L)	1,282
ALT (IU/L)	1,119
Total bilirubin (mg/dL)	6.4
Direct bilirubin (mg/dL)	5.4
GGT (mg/dL)	150
ALP (IU/L)	136
Albumin (g/dL)	4.0
PT (INR)	1.05
Viral markers	
IgM anti-HAV	Negative
HBsAg	Negative
Anti-HBc	Negative
Anti-HBs	Negative
Anti-HCV	Negative
Thyroid function test	
TSH	< 0.025
Free T4	3.82
T3	421.5
Autoantibodies	
Thyroid stimulating antibody	Positive
Anti-LKM	Negative
ANA	1 : 40 negative
Anti-smooth muscle antibody	Negative
AMA	Positive

TSH, thyroid stimulating hormone; Anti-LKM, anti-liver/kidney microsomal type 1; ANA, anti-nuclear antibodies.

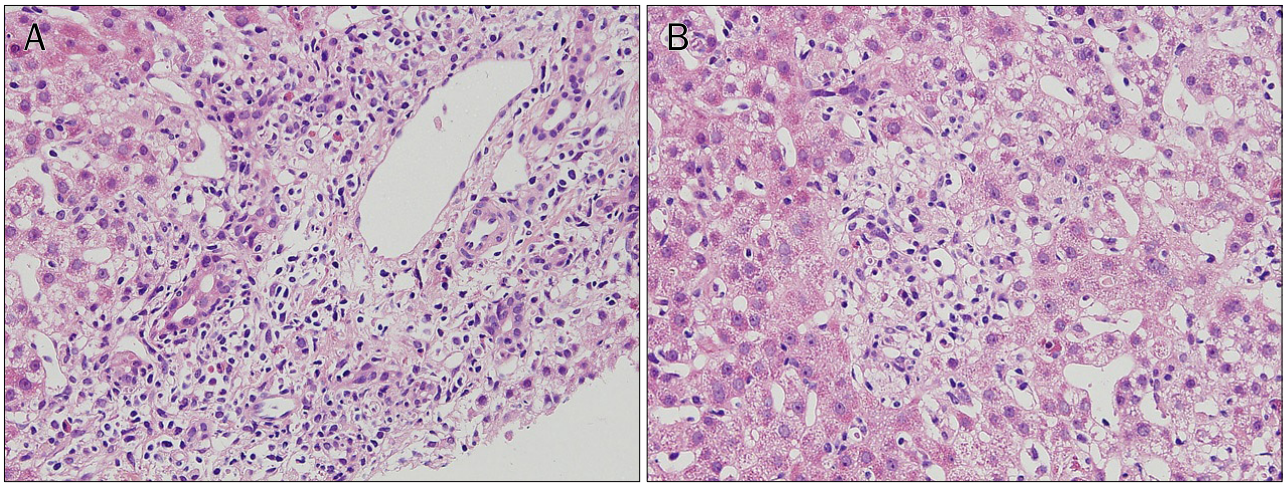

Fig. 1. Histologic findings of liver biopsies are consistent with autoimmune hepatitis (H&E, ×200). (A) Severe necroinflammatory activity with marked portal lymphoplasma cell infiltration with occasional eosinophils and mild ductular proliferation are seen within the portal tract. (B) Local infiltration of inflammatory cells within the lobules and damaged hepatocytes are seen, indicating lobular hepatitis.

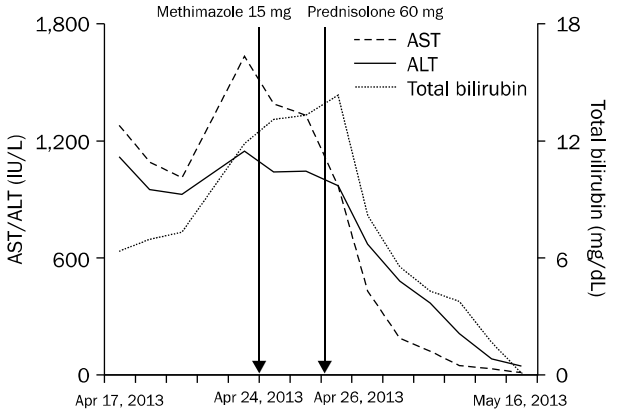

Fig. 2. Clinical course of the patient.

Table 2. Simplified Diagnostic Criteria for AIH[15]

Variable	Cutoff[a]	Points
ANA or SM	≥1 : 40	1
ANA or SM	≥1 : 80	
Anti-LKM	≥1 : 40	2
Soluble liver antibody	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2

AIH, autoimmune hepatitis; ANA, anti-nuclear antibodies; SM, anti-smooth muscle antibodies; Anti-LKM, anti-liver/kidney microsomal type 1.
[a]≥6, probable autoimmune hepatitis; ≥7, definite autoimmune hepatitis.

DISCUSSION

AIH is an autoimmune disease characterized by chronic inflammation of unknown cause.[1,2] Distinguishing AIH from other forms of hepatitis is important, because most cases of AIH respond to anti-inflammatory or immunosuppressive therapy.[3,4] Treatment should be initiated promptly upon diagnosis. If left untreated, AIH usually progresses to liver failure requiring transplantation.[5,6] The diagnosis is based on characteristic clinical and biochemical findings, histologic abnormalities, abnormal levels of serum globulins including autoantibodies, immunogenetic background such as other autoimmune disorders and appropriate investigation to exclude other possible causes of the liver disease, such as viral hepatitis, drug or ethanol-induced hepatitis, primary biliary cirrhosis, Wilson's disease, and hemochromatosis.[7,8] The clinical findings of AIH are heterogeneous, and the clinical course may be characterized by periods of decreased or increased activity; thus, clinical manifestations are variable. The spectrum of presentation ranges from no symptoms to debilitating symptoms and even fulminant hepatic failure.[1,9] One clue to diagnosing AIH is the presence of other diseases with autoimmune features. AIH is associated with other autoimmune diseases, including rheumatoid arthritis, Sjogren's syndrome, and Graves' disease.[10-13] In laboratory testing, aminotransferase elevations are more striking than abnormalities in bilirubin and ALP levels in patients with AIH.[1] The characteristic circulating autoantibodies seen in AIH include ANA, SM, and anti-LKM, while up to 20% have none of these antibodies.[8,14] AMA is sometimes present in patients with AIH. However, it should be noted that autoantibodies are found in various liver diseases, and their presence is not diagnostic of AIH.[1] Liver biopsy is essential to confirming the diagnosis of AIH and in evaluating the severity of liver damage. Characteristic histological picture of AIH is that of an interface (periportal or periseptal) hepatitis with a predominantly lymphoplasmacytic necroinflammatory infiltrate, with or without lobular (intra-acinar) involvement and portal-portal or central-portal bridging necrosis.[7] Histologic features are typical for AIH but serologic findings characteristic of primary biliary cirrhosis, such as an isolated positive AMA, would be indicative of the overlap syndrome, or AMA-positive AIH. The clinical course and response to therapy in this syndrome appear to be identical to those in classic AIH.[1] The International Autoimmune Hepatitis Group (IAIHG) proposed diagnostic criteria, which were revised in 1999.[7] These criteria were devised primarily by expert consensus and introduced to enable comparison of studies from different centers. Due to the complexity of these criteria, the IAIHG have proposed and evaluated a simplified scoring system for diagnosis of AIH that can be easily applied in daily clinical practice in 2008. Simplified diagnostic criteria for AIH are shown in Table 2.[15] In this case, the score was 4 points (2 points for typical histologic findings and another 2 points for absence of viral hepatitis). Although the score is insufficient to directly make a diagnosis of AIH, typical findings of histology and positive result of AMA indicate that this case could be diagnosed as AIH with overlap syndrome.

Graves' disease is an autoimmune disease characterized by the presence of activating autoantibodies against TSH

receptor. The diagnosis of Graves' disease is based on the clinical and biochemical manifestations of hyperthyroidism and on the clinical and laboratory features that confirm the cause. Measurement of serum TSH and fT4 is a useful screening test for the presence of hyperthyroidism. The signs of ophthalmopathy or dermopathy and detectable antibodies against the TSH receptor in the serum are sufficient to confirm the diagnosis of Graves' disease.[16] The clinical manifestations of hyperthyroidism are largely diverse, including liver function abnormalities.[17-19] There are several mechanisms of liver dysfunction in the setting of hyperthyroidism, including liver abnormalities due to hyperthyroidism alone, liver damage related to heart failure and hyperthyroidism, and concomitant liver disease in the setting of hyperthyroidism.[20] To make a differential diagnosis for liver function abnormality in hyperthyroidism, evaluation of the systemic cause and exclusion of drug induced hepatitis or viral hepatitis is necessary. Autoimmune markers and liver biopsy should also be considered.

In this case, the patient presented with liver dysfunction combined with Graves' disease. Histologic findings and combination of other autoimmune disorders were the key points for making a prompt diagnosis of AIH.

In conclusion, diagnosis of the liver condition is important in patients who present with hyperthyroidism and liver dysfunction, so that appropriate therapy can be promptly initiated. In this case, prompt diagnosis of AIH combined with Graves' disease was made and oral steroid therapy was started immediately, which resulted in complete remission of liver dysfunction.

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