CASE REPORT

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A CASE OF AUTOIMMUNE HEPATITIS WITH GRAVES' DISEASE TREATED BY PROPYLTHIOURACIL

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ABSTRACT

A 58-year-old woman was referred to our hospital because of liver dysfunction. Her serum levels of AST (619 IU/l) and ALT (603 IU/l) had increased. Histological findings in the liver biopsy were compatible to autoimmune hepatitis (AIH), and the diagnosis of AIH was confirmed by the diagnostic criteria. She was admitted to a nearby hospital 3 years ago, and diagnosed with Graves' disease. She received methimazole (MMI) at first, which was discontinued due to liver injury in one month, then propylthiouracil (PTU) was administered. One year later, transaminase increased and was decreased by stopping PTU administration. PTU was restarted after her transaminase decreased, but a recurrence of hepatotoxicity was observed, and she was referred to our hospital. Oral prednisolone decreased liver function immediately. In this case, PTU-induced liver injury was suspected as a possible trigger of AIH. While PTU remains a commonly used drug in the treatment of hyperthyroidism, severe liver injury is reported in some cases. If liver injury is observed in patients treated with PTU, rechallenge is not recommended in order to avoid severe hepatotoxicity.

Key Words: Graves' disease, Propylthiouracil, Autoimmune hepatitis

INTRODUCTION

Propylthiouracil (PTU), a thiourea derivative, is widely used for the treatment of Graves' disease. The adverse effects of PTU include rash, arthralgia, fever, and transient leukocytopenia.[1)] Although elevated transaminases are usually transient by discontinuing medication, severe liver dysfunction is reported in some cases.[1,2)] Autoimmune hepatitis (AIH) is generally a progressive chronic hepatitis with increased immunoglobulins and auto antibodies, which primarily responds to immunosuppression.[3)] Some cases with Graves' disease concomitant with AIH have been reported in the literature.[4-6)] and PTU-induced liver injury is suggested to be a possible trigger of AIH.[7,8)]

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CASE REPORT

A 58-year-old woman was referred to our hospital because of liver dysfunction. She was admitted to a nearby hospital three years ago, and diagnosed with Graves' disease. She started methimazole (MMI) at first, which was discontinued in one month due to elevation of serum transaminase. A drug-stimulated lymphocyte test (DLST) showed positive for MMI, and drug-induced hepatitis by MMI was suspected. MMI was discontinued, and she was further treated by PTU. During the following month, liver function test results returned to normal, and PTU administration was continued. One year later, her transaminases increased again. As her thyroid function was within the normal range, PTU administration was discontinued, and her transaminases returned to the normal range at that time, suggesting liver injury was induced by PTU. Two months later, PTU was rechallenged because of a recurrence of hyperthyroidism. A recurrence of hepatotoxicity was observed, and she was referred to our hospital. Her height was 163 cm and body weight was 52 kg. Blood pressure was 120/70 mmHg. She had no history of alcohol intake. Her serum IgG concentration increased. She exhibited positive anti-nuclear antibody, and negative anti-mitochondria antibody. Her hepatitis virus markers were negative. Other laboratory data on admission are summarized in Table 1. As her transaminases increased further even after discontinuing PTU administration, drug-induced liver injury was not suspected (Fig. 1). She was then referred to the Department of Gastroenterology. 40 mg/day oral prednisolone was started after liver biopsy, and her liver function test results decreased immediately (Fig. 1). The histologic features of liver biopsy were compatible with AIH, and the diagnosis of AIH was confirmed by the criteria of the International Autoimmune Hepatitis Scoring System.[9)]

TABLE 1 Laboratory Data on Admission

CBC			Thyroid		
WBC	3.7×10^3	/mm^3	fT3	4.40	pg/mL
Monocyte	5.7%		fT4	1.65	ng/dL
Neutrocyte	46.1%		TSH	0.01	μU/mL
Eosinocyte	1.1%		TRAb	4.9	U/L
Lymphocyte	44.7%		Thyroid test	(+)	
RBC	344×10^4	/mm^3	Microsome test	(+)	
Hg	11.1	g/dL			
Plat	13.7×10^4	/mm^3			
Chemistry			**Serology**		
TP	7.1	g/dL	HBs-Ag	(-)	
Alb	3.0	g/dL	HCV-Ab	(-)	
AST	619	IU/L	IgG	2877	mg/dL
ALT	603	IU/L	IgA	415	mg/dL
g-GTP	68	IU/L	IgM	42	mg/dL
ALP	445	IU/L	Rheumatoid factor		(-)
CPK	53	U/L	Anti-nuclear antibody		(+)
BUN	13.5	mg/dL	Anti-mitochondria antibody		(-)
Creat	0.50	mg/dL	Anti-glutamic acid decarboxylase antibody		(-)
UA	4.3	mg/dL			

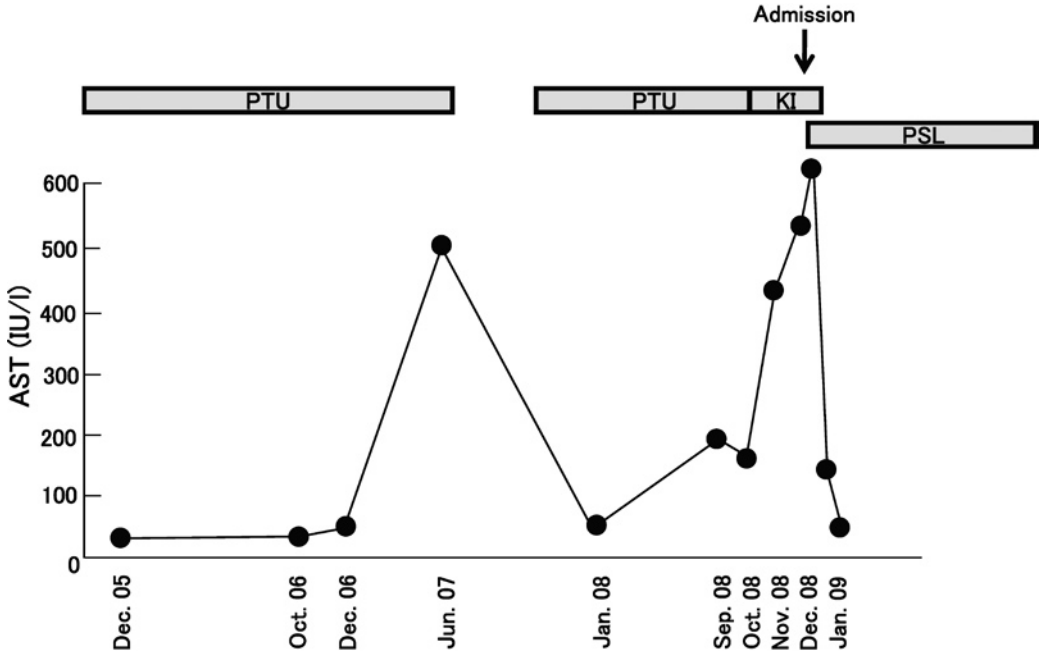

Fig. 1 Clinical course of serum AST level of the present case. PTU administration increased AST level, and PSL decreased AST level. PTU, propythiouracil; KI, potassium iodide; PSL, prednisolone

DISCUSSION

AIH is an autoimmune disease with unresolving hepatocellular inflammation of unknown cause. While some cases of AIH are associated with autoimmune diseases, such as rheumatoid arthritis and Sjogren's syndrome,[10] AIH associated with Graves' disease is rare. On the other hand, certain drugs, including methyldopa, interferon, minocycline, and atorvastatin are known to induce hepatocellular injury that mimics AIH.[3] Elevated transaminase are a common side effect in patients treated with PTU. While the pathogenesis of PTU-induced liver injury is not known, immunologic mechanisms have been suspected to be responsible. At this point, the pathogenesis of PTU-induced liver damage and AIH are thought to be similar, and it is difficult to make a differential diagnosis between the two.[7] Liver dysfunction in our case was reversed by discontinuing PTU the first time. This suggests drug-induced liver injury. However, rechallenge of PTU worsened liver function again, and was not reversed by discontinuing PTU a second time. Thus, drug-induced liver injury was not suspected. Given a compatible histologic picture, the diagnosis of AIH is based on characteristic clinical and biochemical findings, circulating autoantibodies, and abnormal levels of serum globulins.[3] In our patient, elevation of serum IgG concentration and high titer of anti-nuclear antibody are characteristic laboratory features of AIH. Such features are not explained by drug-induced liver injury, and the histological findings of high activity hepatitis (A3) obtained by liver biopsy 2 months after quitting medication, were not similar to drug-induced liver injury.

As shown in Figure 2, histological findings show interface hepatitis and rosette formation, which demonstrate AIH. There are also few plasma cells and some eosinophils among the findings. Although these are different from diagnostic criteria and the findings may suggest that

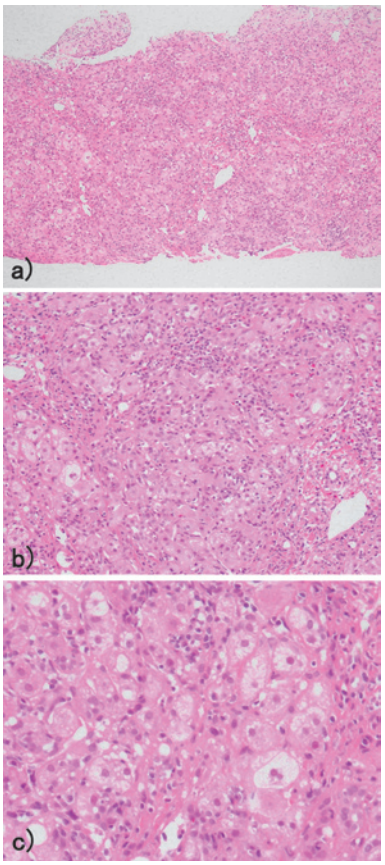

Fig. 2 Histological findings of liver biopsy. a) Portal areas are expanded by fibrosis and infiltration. b) Explant reveals bridging necroses and inflammatory infiltration, including lymphocytes, plasma cells and some eosinophils. c) interface hepatitis findings and rossette formation.

allergic response might play an important role of pathogenesis as usual, Manns et al. demonstrated that plasma cells and eosinophils may be present in the histological sample of an AIH patient.[11] Our patient was then diagnosed with AIH, suggesting the possibility that PTU-induced liver injury triggered AIH.

When treating patients with PTU, occasional monitoring of liver function is needed, and if liver injury is suspected, it is important to promptly discontinue PTU therapy. Rechallenge of affected individuals is not recommended to avoid severe hepatotoxicity.

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