Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9728-17
Intern Med 57: 1591-1596, 2018
http://internmed.jp

【 CASE REPORT 】

Acute-onset Autoimmune Hepatitis in a Young Woman with Type 1 Diabetes Mellitus

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Abstract:
Autoimmune hepatitis (AIH) and type 1 diabetes mellitus (T1DM) are thought to be induced by autoimmunity, but their coexistence has rarely been reported. We herein report a case in which a patient with T1DM developed acute-onset AIH. A 26-year-old woman, who had been diagnosed with T1DM in childhood, was transferred to our hospital because of acute liver failure of unknown etiology. The administration of corticosteroids including steroid pulse therapy was effective. Based on the histological finding of massive centrilobular necrosis and a good response to steroid therapy, we diagnosed the patient with acute-onset AIH. This case indicates that AIH can occur in young T1DM patients.

Key words: AIH, T1DM, HLA, corticosteroid

(Intern Med 57: 1591-1596, 2018)
(DOI: 10.2169/internalmedicine.9728-17)

Introduction

Autoimmune hepatitis (AIH) is a chronic liver disease that is characterized by autoantibodies and hypergammaglobulinemia. It can lead to liver cirrhosis if untreated; however, most patients show a good response to immunosuppressive therapies, including corticosteroids. AIH predominantly occurs in middle-aged and elderly women and is sometimes accompanied by autoimmune diseases such as rheumatoid arthritis, Sjögren syndrome, and chronic thyroiditis (1). Type 1 diabetes mellitus (T1DM), which is the predominant form of DM in children, is considered to be associated with autoimmunity against pancreatic islet cells (2). However, there are few reports describing cases with both T1DM and AIH, and the genetic background and disease phenotypes of such cases are not fully understood. We herein describe the case of a T1DM patient who experienced acute-onset AIH 20 years after the onset of T1DM, and discuss the characteristics of patients with both T1DM and AIH, together with previously reported cases.

Case Report

A 26-year-old Japanese woman was hospitalized at a local hospital because of liver dysfunction that was detected at a regular visit for the management of T1DM. She was admitted to the hospital and her liver function had worsened without a specific diagnosis; she was transferred to our hospital 11 days after admission. She had been diagnosed as T1DM when she was 2 years of age, and had continued insulin therapy. With regard to autoantibodies associated with T1DM, she was positive for anti-glutamic acid decarboxylase (GAD) antibody and anti-islet cell antigen 2 (IA-2) antibody (18.6 U/mL and 1.6 U/mL, respectively, on admission). With regard to her history, she had developed acute hepatitis of unknown etiology when she was 3 years of age, and her liver function recovered without any specific therapy. After recovery from acute hepatitis, her liver function tests had been normal until this time. She had no history of travelling abroad within the previous year, intravenous drug use, and did not regularly consume alcohol. She did not take any medicines or supplements regularly, and took ibuprofen and acetaminophen occasionally to obtain relief from menstrual pain.

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Received: June 27, 2017; Accepted: October 17, 2017; Advance Publication by J-STAGE: January 11, 2018
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Table 1. The Clinical Parameters on Admission to Our Hospital.

WBC	4,700 /μL	NH3	16 μg/dL
RBC	426×10⁴ /μL	Fe	196 μg/dL
Hb	12.6 g/dL	Ferritin	405.9 ng/mL
Platelets	17.8×10⁴ /μL	Alpha-fetoprotein	2.9 ng/mL
T. bil	4.7 mg/dL	IgG	1,527 mg/dL
D. bil	2.2 mg/dL	IgA	292 mg/dL
ALP	532 U/L	IgM	111 mg/dL
γ-GTP	138 U/L	PT	37.7 %, 1.54 INR
AST	969 U/L	APTT	53.5 sec
ALT	1,452 U/L	Ceruloplasmin	15.8 mg/dL
LDH	365 U/L	Free T3	2.19 pg/mL
Cholinesterase	141 U/L	Free T4	1.46 ng/dL
Amylase	75 U/L	TSH	0.893 μIU/mL
BUN	11 mg/dL	ANA	×80
Creatinine	0.70 mg/dL	Anti-LKM1	5.0 index
Uric acid	1.8 mg/dL	AMA	(-)
Total protein	6.5 g/dL	IgM anti-HAV	(-)
Albumin	3.7 g/dL	HBsAg	(-)
Na	136 mEq/L	IgM anti-HBc	(-)
K	4.1 mEq/L	HBV DNA	(-)
Cl	101 mEq/L	HCV RNA	(-)
Ca	8.7 mg/dL	IgA anti-HEV	(-)
Triglycerides	112 mg/dL	IgM anti-PVB19	(-)
Total cholesterol	46 mg/dL	IgM anti-CMV	(-)
Glucose	257 mg/dL	IgG anti-EBV VCA	×160
HbA1c	7.6 %	IgM anti-EBV VCA	(-)
CRP	0.1 mg/dL	Anti-EBNA	×160

WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, T. bil: total bilirubin, D. bil: direct bilirubin, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltransferase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, CRP: C-reactive protein, PT: prothrombin time, APTT: activated partial thromboplastin time, TSH: thyroid-stimulating hormone, ANA: anti-nuclear antibody, LKM1: liver kidney microsome 1, AMA: anti-mitochondrial antibody, HAV: hepatitis A virus, HBsAg: hepatitis B surface antigen, HBc: hepatitis B core, HCV: hepatitis C virus, HEV: hepatitis E virus, PVB19: parvovirus B19, CMV: cytomegalovirus, EBV: Ebstein-Barr virus, VCA: virus capsid antigen, EBNA: EBV nuclear antigen

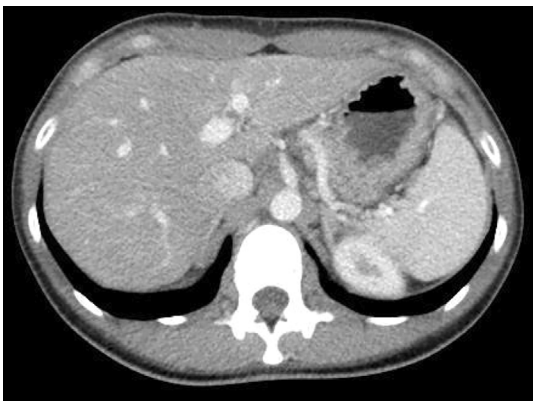

Figure 1. An abdominal contrast enhanced computed tomography scan. There were no signs of liver atrophy, ascites, or dilatation of the bile duct.

On admission to our hospital, she was 155.6 cm in height, 46.1 kg in weight, and her blood pressure was 94/54 mmHg. She did not have abdominal pain, nausea, or fever and her consciousness was clear. A liver function test revealed remarkably elevated levels of total bilirubin (T. bil, 4.7 mg/dL) and alanine aminotransferase (ALT, 1,452 U/L), and a severely decreased prothrombin time (PT, 37.7%) (Table 1). She was negative for IgM anti-hepatitis A virus (HAV), hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and IgA-hepatitis E virus (HEV), but positive for anti-nuclear antibody (ANA, x80, homogenous and speckled types). Her IgG level was within the normal range. An abdominal computed tomography (CT) scan and an ultrasound (US) examination revealed no specific findings of liver dysfunction (Fig. 1). Her liver was not atrophic and there was no ascites. The histological examination of a liver specimen obtained by a US-guided biopsy, which was performed by a physician at the local hospital before the development of coagulopathy, showed mild fibrotic expansion of the portal areas and the infiltration of lymphocytes with interface hepatitis (Fig. 2A). The hepatocytes around the cen-

tral vein area were collapsed, and necrosis and mild ballooning were observed. It was thought that these findings were not typical for classical AIH. There was no evidence of bile duct injury.

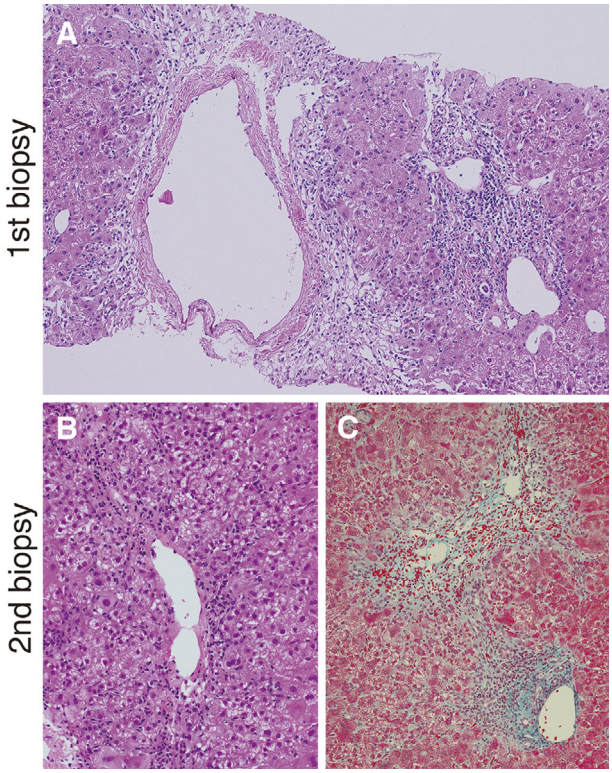

Figure 2. **The liver histology. (A) An image of a liver biopsy specimen [Hematoxylin and Eosin (H&E) staining] that was obtained at the local hospital. Massive collapse and necrosis in the cenrtilobular zone 3 area as well as interface hepatitis in the portal area were observed. (B,C) Images of the second liver specimen that was obtained at our hospital after the recovery of coagulopathy. H&E staining (B) and Elastica-Masson staining (C). The findings of collapse, necrosis, and inflammation became milder.**

The patient was diagnosed with acute liver failure of unknown etiology, and steroid therapy with methylprednisolone (mPSL; 1,000 mg/day for 3 days) was administered; the dose was then tapered (Fig. 3). Blood transfusion with fresh frozen plasma was performed several times for the maintenance of coagulopathy. During the tapering of the corticosteroid dose, ursodeoxycholic acid (UDCA) was added and the liver function gradually recovered. After the recovery of coagulopathy, US-guided liver biopsy was reperformed. The examination of the second biopsy specimen revealed that the inflammation had become milder and that the fibrosis had not progressed (Fig. 2B and C). We considered that the histological findings might correspond to features related to the acute onset of AIH. On the 56th day after admission, the patient was discharged with prednisolone (PSL; 10 mg/day) and UDCA (600 mg/day). We diagnosed the patient with AIH based on the revised scoring system of the International Autoimmune Hepatitis Group (IAIHG); her score was 19 points (3). Furthermore, the patient fulfilled 4 of the 5 items of the Japan AIH guidelines of 2013 (4). After discharge, the patient's liver function was stable and the administration of PSL (5 mg/day) and UDCA was continued.

Because it has been suggested that both AIH and T1DM might be associated with a genetic background and that some human leukocyte antigen (HLA) types were reported to be risk factors for such diseases, we determined the HLA haplotypes and compared them with those of previous Japanese reports (Table 2). This analysis revealed that she had DRB1*0901 and DQB1*0303, which are reported to be associated with T1DM (5). However, she did not possess any of the HLA types that have frequently been found in patients with AIH (6-9).

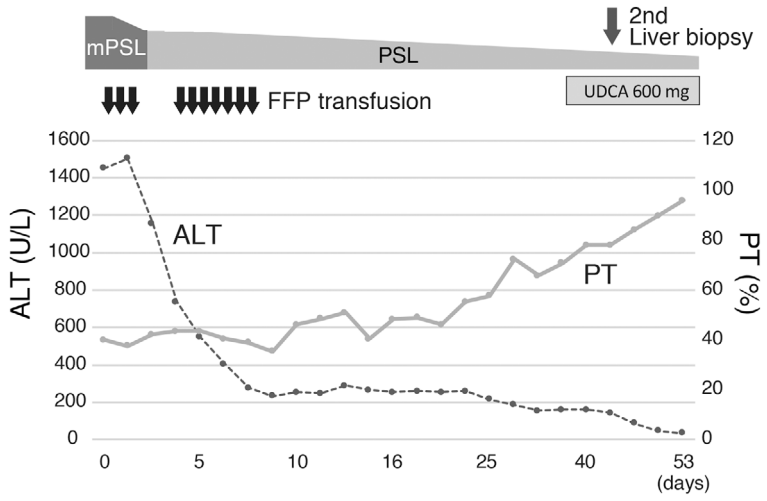

Figure 3. **The clinical course of the present case. mPSL: methylprednisolone, PSL: prednisolone, FFP: fresh frozen plasma, UDCA: ursodeoxycholic acid, ALT: alanine aminotransferase, PT: prothrombin time**

Table 2. The HLA Types of the Present Case and Those of Previously Reported Japanese Patients with Autoimmune Hepatitis (AIH) or Type 1 Diabetes Mellitus (T1DM).

HLA locus	Present case	Previous Japanese reports		
		AIH	T1DM	References
A	A*0201, A*2402			
B	B*1301, B*5201		B54	(25)
C	C*0304, C*1202			
DR	DRB1*0901, DRB1*1202	DR4, DRB1*0405	DRB1*0405, DRB1*0802, **DRB1*0901**	(5-9)
DQ	DQA1*0302, DQA1*0601, DQB1*0301, DQB1*0303	DQB1*0201, DQB1*0401	DQB1*0302, **DQB1*0303**, DQB1*0401	(5, 8, 9)
DP	DPB1*0201, DPB1*0501			

Bold typeface indicates HLA types that match the present case.

Discussion

Although the detailed mechanism of AIH development has not been clarified, it has been considered that AIH is induced by a deficiency of suppressor T cells, which leads to the production of auto-antibodies against the ligands expressed on hepatocytes (10). AIH is classified into types 1 to 3 according to the types of auto-antibodies that are detected (11). It is a relatively rare disease and the number of patients in Japan is estimated to be approximately 10,000. Corticosteroids are administered as the first-line therapy; if the effect is insufficient, other immunosuppressants including azathioprine and cyclosporine should be considered. If a patient has diabetes mellitus, the blood sugar levels may be affected by corticosteroids and it is sometimes difficult to control both diseases.

The clinical presentations of AIH at the time of the diagnosis are various. Chronic liver diseases, including liver cirrhosis, are common, but acute onset disease (including acute liver failure) it is rarely diagnosed (12). It is known that the serological features of acute-onset AIH may not be typical: the IgG and ANA levels may not be reliable (13). Furthermore, the histological features differ from chronic AIH, and Stravitz et al. reported that centrilobular zonal necrosis was a predominant feature of autoimmune acute liver failure (14), which was also found in the present case. Thus, the conventional scoring systems for AIH may be unreliable for such patients. The present case fulfilled the revised IAIHG score but not the simplified IAIHG score (15). Recently, Nguyen et al. showed the frequencies of the histological features found in cases of acute-onset AIH (16): lobular necrosis/inflammation, 97.7%; plasma cell infiltration, 96.4%; emperipolesis, 89.3%; pigmented macrophage, 84.5%; cobblestone appearance of hepatocytes, 82.6%; perivenular necroinflammatory activity, 81.4%. Most of these features (with the exception of emperipolesis and cobblestone appearance of hepatocytes) were found in the present case.

There are some case reports of AIH with autoimmune polygrandular syndrome (APS). APS was reported first by Schmidt et al. in 1926 as a co-occurrence of Addison disease and chronic thyroiditis (17). It affects multiple endocrine functions and is classified into 3 major types: APS-1, APS-2, and IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) (18). APS can be accompanied by T1DM (18%, 20%, and >50% in APS-1, APS-2, and IPEX, respectively) (18), and AIH is rarely observed in APS-1 (19). In the present case, there was no endocrine dysfunction (other than insulin); however, careful attention should be paid to the occurrence of other endocrine disorders.

Cases with both AIH and T1DM have been reported from several countries. Homberg et al. reported that T1DM was found in 4 of 65 (6.2%) AIH patients with liver kidney microsome (LKM)-1 antibodies and in 1 of 60 (1.7%) patients without LKM-1 antibodies (20). A report from Germany showed that T1DM was found in 2 of 278 (0.7%) AIH patients (21), and another report from England showed that there were no T1DM patients among 20 AIH patients with LKM-1 antibodies (22). With regard to the detection of autoantibodies, a report from Saudi Arabia showed that 8 of 106 (7.5%) T1DM children were positive for ANA and that 1 was positive for LKM-1 antibodies. Furthermore, da Silva et al. surveyed children with AIH in Brazil and showed that 60.7%, 18.5%, 3.6% were positive for anti-islet cell antibodies, insulin autoantibodies, and anti-GAD antibodies, respectively. These data suggest that the autoantibodies associated with AIH and T1DM might emerge concurrently, although the development of both diseases is relatively rare. A search of the PubMed database using the key words 'autoimmune hepatitis' and 'type 1 diabetes', revealed 50 publications. After the removal of the reports on APS or other diseases, 10 publications were found. To find reports on Japanese pa-

Table 3. The Previously Reported Cases Involving Patients with Both AIH and T1DM (Excluding Autoimmune Polyglandular Syndrome).

Case no.	Gender	Age at diagnosis (year)		Autoantibody	HLA	References
		T1DM	AIH			
1	Female	78	79	Acetylcholine, DNA, GAD, islet cell		(26)
2	Female	2	2	Islet cell, LKM1	A3/29, B35/40, DRB 1502/1401	(27)
3	Male	20	29	Intrinsic factor, insulin, LKM, parietal cell, thyroid peroxidase		(28)
4	Female	11	12	GAD, insulin, smooth muscle	DRB1 0301/07, DQA1 0201/0501, DQB1 02	(29)
5	Male	2	2			(30)
6	Female	1	2		DRB1 01/03, DQB1 02/05	(31)
7	Female	6	16	DNA, GAD, nucleus	A24/31, B59/35, Cw3/1, DR9/8	(23)
8	Female	2	26	GAD, IA-2, nucleus	(Table 2)	Present case

GAD: glutamic acid decarboxylase, IA-2: islet cell antigen 2

tients with both AIH and T1DM, we searched the previous publications in Japanese using Ichushi Web and found 10 reports. After the removal of reports on APS or other diseases, only one pediatric case remained (23). A list of the cases, in which the patient's gender and age at the time of the diagnosis were reported, is shown in Table 3.

It has been suggested that the development of AIH might be associated with the type of HLA, and HLA-DR4 was reported to be found frequently in Japanese AIH patients (6). It is known that associations between the HLA type and disease susceptibility differ among races, and associations between AIH and other types of HLA-DR and DQ have been reported from areas other than Japan (9). Furthermore, several HLA types were shown to be risk factors for T1DM (24, 25). The present case had HLA-DR/DQ types that were reported to be associated with T1DM in Japan (5), but did not have types that have been reported to be associated with AIH. Because the HLA types of patients with both AIH and T1DM have not been reported, the further accumulation of such patients is needed.

Generally, the peak age for AIH is 50-60 (7); at 26 years of age, the patient in the present case was relatively young; however, with the exception of one case, all of the previous cases in which AIH and T1DM co-occurred involved patients who were under 30 years of age (Table 3). Thus, although rare, AIH should be considered in the differential diagnosis if a young T1DM patient develops liver dysfunction. The patient in the present case experienced acute hepatitis when she was a child and it is possible that the hepatitis at that time might have been associated with autoimmunity.

In summary, we reported the case of a young woman who developed acute-onset AIH during insulin therapy for T1DM. She developed acute liver failure; however, corticosteroid treatment was effective, and the AIH was well-controlled. Although the co-existence of AIH and T1DM is rare, it should be considered that acute liver injury may be induced by autoimmunity in T1DM patients, regardless of their age.

The authors state that they have no Conflict of Interest (COI).

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