【 CASE REPORT 】

IgG4-related Autoimmune Hepatitis with a Suspected Drug-induced Etiology

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Abstract:
   A 69-year-old man was referred to our department with acute hepatitis. He had been newly treated with benidipine hydrochloride for two months. His blood test results were as follows: aspartate aminotransferase, 1,614 IU/L; alanine aminotransferase, 1,091 IU/L and anti-smooth muscle antibody, ×80. Needle liver biopsy specimen showed interface hepatitis with mainly lymphocytic infiltration and bridging fibrosis in the periportal area. Immunohistochemistry revealed lymphocytic infiltration positive for IgG4. We diagnosed him with IgG4-related AIH with an etiology that was suspected of being drug-induced. Oral prednisolone was started and then tapered after achieving biochemical remission. Hepatitis recurred after the cessation of steroids; however, remission was achieved with ursodeoxycholic acid.

Key words: drug-induced, IgG4, autoimmune hepatitis

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Introduction

   Drug-induced liver injury (DILI) is a rare event, with an estimated incidence of 1 per 10,000 to 1 per 100,000 treated patients (1). Several drugs can induce autoimmune hepatitis (AIH), a condition that is referred to as drug-induced AIH (DIAIH) and identified in approximately 9% of patients with AIH (2). de Boer et al. reported that autoimmune-like hepatitis occurred in most patients with nitrofurantoin- and minocycline-induced liver injury and in approximately half of patients with methyldopa and hydralazine injury (3). At least three clinical scenarios have been proposed for drug-induced autoimmune liver disease: AIH with DILI, DIAIH, and immune-mediated DILI (IM-DILI) (4, 5). However, the differentiation between these conditions is challenging, especially between DIAIH and IM-DILI. They show similar clinical manifestations, histological findings, and corticosteroid responsiveness and are often indistinguishable.

   In contrast, it was recently proposed that autoimmune hepatitis (AIH) with an increased serum immunoglobulin G4 (IgG4) level and abundant IgG4-positive plasma cell infiltration in the liver should be termed "IgG4-related AIH," implying a form of hepatic involvement in IgG4-related disease (IgG4-RD) (6, 7). However, the clinical course and the pathological significance of IgG4-related AIH remain unclear because a very limited number of cases are found in patients with AIH (3%) (6, 7). Furthermore, the characteristics of drug-induced IgG4-related AIH have not been investigated.

   We herein report the first case of IgG4-related AIH wherein the etiology was suspected to be drug-induced.

Case Report

   A 69-year-old man who had taken medication for type 2 diabetes mellitus and hyperuricemia that had persisted for 1 year was referred to our department with asymptomatic acute hepatitis in June 2016. Two months prior to the onset of the patient's clinical manifestation, he had been treated

Table.   Laboratory Findings of the Present Case on Admission.

Hematology		Blood chemistry		Virus markers	
WBC	8,520 /μL	T-Bil	2.7 mg/dL	HBs Ag	(-)
RBC	405 ×10⁴/μL	D-Bil	0.3 mg/dL	HCV Ab	(-)
Hemoglobin	12.8 g/dL	AST	1,614 IU/L	HA IgM	(-)
Hematocrit	36.6 %	ALT	1,091 IU/L	CMV IgM	(-)
Platelets	21.6 ×10⁴/μL	LDH	1,255 IU/L	EBV VCA IgG	×1,280
Eosinophils	19 %	ALP	1,617 IU/L	EBV VCA IgM	<×10
		γ-GTP	200 IU/L	EBV EBNA IgG	×40
Coagulation		ChE	159 U/L		
PT	59.7 %	Amylase	26 U/L	Tumor markers	
PT-INR	1.26	BUN	32.9 mg/dL	CEA	2.0 ng/mL
		Creatinine	1.55 mg/dL	CA19-9	7.2 ng/mL
Immunology		CRP	1.68 mg/dL	AFP	4.6 ng/mL
ANA	<×40	IgG	3,158 mg/dL	PIVKA-II	14 mAU/mL
ASMA	×80	IgG4	703 mg/dL		
AMA-M2	(-)	IgA	231 mg/dL		
		IgM	33 mg/dL		

WBC: white blood cell count, RBC: red blood cell count, PT: prothrombin time, PT-INR: PT-international normalized ratio, ANA: anti-nuclear antibody, ASMA: anti-smooth muscle antibody, AMA: anti-mitochondrial antibody, T-Bil: total bilirubin, D-Bil: direct-Bil, AST: aspartate aminotransferase, ALT: alanine transaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transferase, ChE: cholinesterase, BUN: blood urea nitrogen, CRP: C-reactive protein, HBs Ag: anti-hepatitis B virus surface antigen, HCV Ab: anti-hepatitis C virus antibody, HA: anti-hepatitis A Ab, CMV: cytomegalovirus, EBV VCA: Epstein-Barr viral capsid Ag Ab, EBV EBNA: EB nuclear Ag Ab, CEA: carcinoembryonic antigen, CA: carbohydrate antigen, AFP: α-fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonist-II
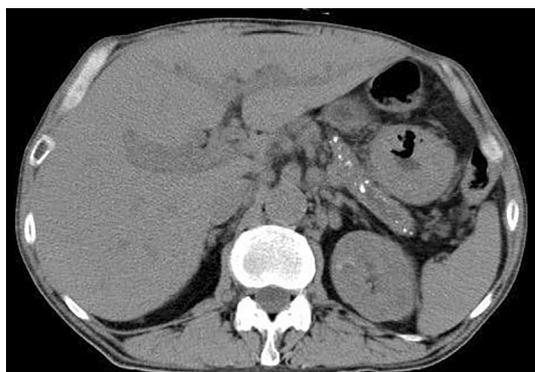
Figure 1.   Computed tomography revealed no mass lesions, stones or biliary duct dilatation.

with benidipine hydrochloride for hypertension. His medical history included calculous chronic pancreatitis and diabetic nephropathy. He had been a heavy drinker but had reduced his alcohol intake to 350-700 mL of beer per day for the last year, and he convincingly denied any recent harmful alcohol consumption. His regularly prescribed medications included sitagliptin phosphate hydrate, febuxostat, and insulin glargine. He had no recent history of taking any other drugs, supplements or having any allergic diseases.

He had undergone blood tests, including liver enzyme tests, every two months, and his liver enzyme levels had previously been within normal limits. His blood test results were as follows: total bilirubin, 2.7 mg/dL; aspartate aminotransferase, 1,614 IU/L; alanine aminotransferase, 1,091 IU/L; alkaline phosphatase, 1,617 IU/L; γ-glutamyl transpeptidase, 200 IU/L; and white blood cell count, 8,520 μL (eosinocytes 19%). Viral hepatitis serology was negative. Other relevant data were as follows: IgG concentration, 3,158 mg/dL; IgG4 concentration, 703 mg/dL; anti-nuclear antibody (ANA) titer, <×40, and anti-smooth muscle antibody (ASMA) titer, ×80 (Table). Other laboratory findings, including the renal function and pancreatic enzymes revealed no remarkable changes in comparison to the previous data.

Computed tomography and magnetic resonance cholangiopancreatography revealed no mass lesions, stones or biliary duct dilatation (Fig. 1). A needle liver biopsy specimen showed interface hepatitis with mainly lymphocytic infiltration and occasional bridging fibrosis in the periportal area, indicating chronic active hepatitis due to AIH (Fig. 2a, b). No histological findings suggesting alcoholic hepatitis, such as ballooning or Mallory body, were observed. Furthermore, no lymphocytic or plasmacytic infiltration was found in the bile ducts. The patient's respective scores on the 1999 revised original AIH scoring system (8) and the simplified criteria for the diagnosis of AIH (9) were 14 and 8, indicating a probable and definite diagnosis of AIH, respectively. Furthermore, immunohistochemistry revealed lymphocytic infiltration that was positive for IgG4 [140 cells per high-powered field (HPF)] with an IgG4/IgG-positive cell ratio of 60%, which suggested the IgG4-related type (Fig. 2c). In contrast, the DDW-J2004 DILI workshop score (10) for benidipine was 'probable' (score 7), although the patient refused to undergo a drug lymphocyte stimulation test. We therefore diagnosed the condition as IgG4-related AIH with
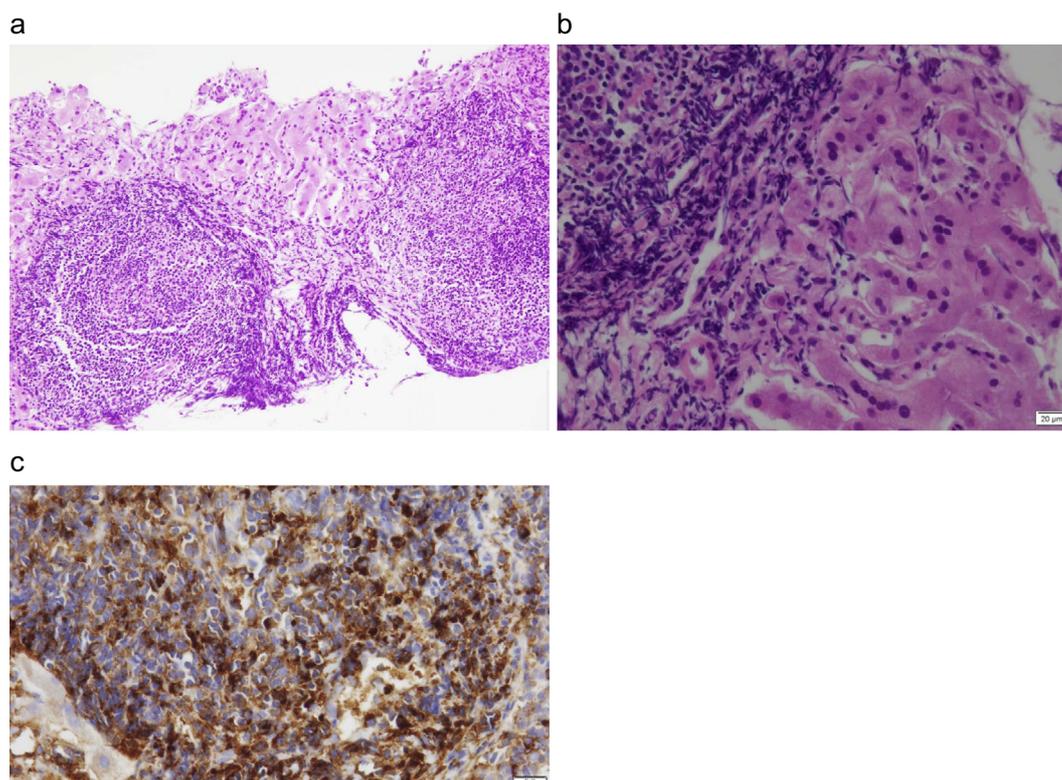
Figure 2.   a, b: A needle liver biopsy specimen showing interface hepatitis with mainly lymphocytic infiltration and occasional bridging fibrosis in the periportal area, indicating chronic active hepatitis due to AIH (Hematoxylin and Eosin staining, a: ×100, b: ×400). c: Immunohistochemistry showing lymphocytic infiltration lymphocytic infiltration that was positive for IgG4 (140 cells per high-powered field) with an IgG4/IgG-positive cell ratio of 60%, which suggested the IgG4-related type. AIH: autoimmune hepatitis

an etiology suspected of being drug-induced.

Oral prednisolone (40 mg/day) was started based on this diagnosis because the patient's liver dysfunction had not improved at 2 weeks after the cessation of benidipine hydrochloride. Following a rapid biochemical improvement, steroids were tapered at five months of treatment, after achieving biochemical remission. At two weeks after the cessation of steroids, there was a mild increase in his transaminase levels, indicating the recurrence of hepatitis. Ursodeoxycholic acid (600 mg, daily) was started, which led to remission. The patient has sustained remission since then (Fig. 3).

Discussion

We experienced a case of DILI that met the criteria for AIH; however, serum IgG4 elevation was detected, and immunohistochemical staining of IgG4 was positive, which indicates a diagnosis of IgG4-related AIH with a suspected drug-induced etiology.

According to the attached document for benidipine hydrochloride, the adverse event of liver dysfunction occurs in less than 0.5-5% of patients; however, we found no reports describing DILI due to benidipine hydrochloride. Another kind of dihydropyridine calcium channel blocker, nifedipine, also rarely but occasionally induces hepatic injury, as has been described in 10 case reports (11). The disease can pre-

sent acutely (within days) or subacutely (within four to eight weeks after medication start), and the initial pattern of liver injury is the profound elevation of liver enzymes and conjugated bilirubin, characteristics that were similar to our present case. In contrast, immunological markers of autoimmune hepatitis are typically negative or inconclusive. These data suggest that benidipine-hydrochloride-induced AIH rarely occurs although data are scarce at present.

In clinical practice, the differentiation between idiosyncratic DILI and drug-induced AIH may be challenging. Bernal et al. showed that autoantibodies typically seen in AIH were present in 32% of patients with acute liver injury due to various etiologies, including DILI. Even histologically, it may be very difficult to differentiate drug-induced AIH from idiosyncratic DILI in the real-world setting (12). Furthermore, the discrimination of drug-induced autoimmune liver disease is often difficult, and the same was true of our present case. We were able to diagnose the patient with DIAIH because he not only met the criteria of AIH but also experienced a relapse after the withdrawal of prednisolone, which is one of the only specific characteristics that differentiates DIAIH from IM-DILI. In our present case, latent AIH may have become apparent due to benidipine hydrochloride, as histological findings of chronic hepatitis had already been observed in the liver biopsy specimen. However, he also presented eosinophilia, which suggested IM-DILI (4, 5).
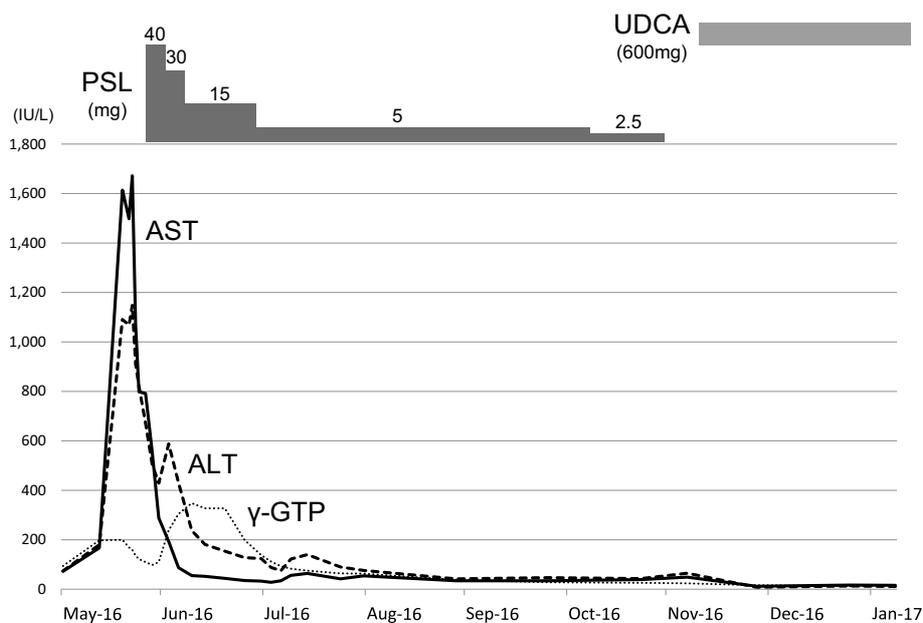
Figure 3.   **Clinical course. AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, PSL: prednisolone, UDCA: ursodeoxycholic acid**

Our present case showed seropositivity for ASMA but not ANA. The proportion of DIAIH patients positive for ASMA was reported to be 16-50%, which was similar to the proportion of positive AIH patients (2, 13). Martínez-Casas et al. (13) described the individual clinical characteristics of 12 patients with DIAIH. Four of those 12 patients had seropositivity for SAMS (titer, 1:20-160). Compared with the SAMS-negative patients, the SAMS-positive patients seemed to be younger (median age, 25 vs. 63 years old), have an acute course (100% vs. 50%), and show more severe liver damage (median AST level, 1,271 vs. 557 U/L), whereas the phenotypes of female predominance, nitrofurantoin-induced predominance, and a preferable response to immunosuppressive therapy seemed to be similar, although no statistical analyses were performed. The accumulation of further cases is needed in order to clarify the characteristics of SAMS-positive DIAIH.

Umemura et al. reported that IgG4-associated AIH, which was defined as a high serum IgG4 concentration (≥135 mg/dL) and IgG4-bearing plasma cell infiltration in the liver (≥10/HPF) was found in 2 of 60 (3.3%) patients with type 1 AIH (6). Chung et al. showed that the number of T cells, B cells, and plasma cells were significantly higher in the livers of patients with IgG4-positive AIH than in those with IgG4-negative AIH (14). Furthermore, they revealed that patients with IgG4-positive AIH showed a marked response to prednisolone therapy. The IgG4-related type was diagnosed in the present case because the patient also showed both a high serum IgG4 concentration and dense lymphocytic infiltration in the periportal area that was positive for IgG4. To our knowledge, no other reports have described drug-induced IgG4-related AIH. Clinically, drug-induced IgG4-related AIH may affect other specific organs, including the pan-

creas, biliary tracts, salivary glands, and thyroid glands, among others. Therefore, a systemic diagnostic investigation and careful follow-up after discontinuation of immunosuppressive therapy should be performed.

In conclusion, we experienced a case of IgG4-related AIH wherein the etiology was suspected to be drug-induced. The accumulation of further cases will be necessary to investigate and clarify the specific characteristics that are useful for the diagnosis and treatment of this entity.

Written informed consent was obtained from the patient.

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

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