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Precise histological evaluation of liver biopsy specimen is indispensable for diagnosis and treatment of acute-onset autoimmune hepatitis

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Background. The diagnosis of acute-onset autoimmune hepatitis (AIH) has been difficult because patients do not always show clinicopathological features typical of AIH. We examined the important requirements for a definitive diagnosis of acute-onset AIH. ***Methods.*** Clinical, biochemical, and pathological features of 18 acute-onset AIH patients (16 women, 2 men; mean age, 54.3 ± 12.3 years) with no history of liver disease and no signs of chronicity were examined. ***Results.*** Mean ALT was 679 ± 431 IU/l, and mean T-Bil was 2.4 ± 2.9 mg/dl. Mean IgG was 1801 ± 446 mg/dl, with 7 patients (39%) showing normal levels. Antinuclear antibody was ≤1:40 in 7 (39%). Liver histology showed severe activity in 17 (94%) of the patients and severe acute hepatitis in 7 (39%). Centrizonal necrosis and plasma cell accumulation were characteristic for acute-onset AIH. AIH score ranged from 7 to 18 (13.2 ± 3.8) before treatment. All patients were diagnosed and treated early and responded completely to therapy. ***Conclusions.*** Histological examination of the liver is necessary for early diagnosis of acute-onset AIH. Moreover, we should evaluate liver biopsy specimens precisely and should be ready for a timely initiation of corticosteroid therapy to improve the prognosis.

Key words: autoimmune hepatitis, acute onset, immunosuppressive therapy, liver biopsy, centrizonal necrosis, plasma cell infiltration

Introduction

Autoimmune hepatitis (AIH) is an unresolving inflammation of the liver of unknown cause.[1] It is characterized by the presence of interface hepatitis and plasma cell infiltration on histological examination, hypergammaglobulinemia, and autoantibodies.[1,2] A prospective study has indicated that as many as 40% of patients with untreated severe disease die within 6 months of diagnosis.[3] Cirrhosis develops in at least 40% of survivors.[4] An acute onset of illness is common,[5–8] and fulminant presentation is possible.[9]

An AIH scoring system based on the clinicopathological features has been proposed by the international AIH group.[10] Although this scoring system has been used as a standard diagnostic tool in clinical practice, there have been unusual patients who do not show typical features and do not fulfill the criteria. AIH with clinical features of acute hepatitis (acute-onset AIH) is one of these conditions.

The diagnosis of acute-onset AIH has been difficult in that patients show acute presentation, such as acute hepatitis, and may not have typical clinicopathological features of AIH. Acute-onset AIH may include two types of AIH patients: AIH with acute presentation of the disease, and AIH with acute exacerbation of underlying chronic disease. In some patients with the former type of AIH, the disease develops into the severe or fulminant form; they are at risk of losing optimal timing to start immunosuppressive therapy, and are sometimes resistant to immunosuppressive therapy and have a poor prognosis.

In the present study, we examined the clinicopathological features of acute-onset AIH patients presenting acute hepatitis clinically and ultrasonographically, and also attempted to determine the essential steps to be taken to reach a more precise diagnosis and begin early administration of immunosuppressive therapy for a better prognosis.

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Patients and methods

Patients

Patients with acute-onset AIH were enrolled between May 2001 and November 2006. Eligibility criteria were as follows: (1) acute-onset liver injury; (2) negativity for possibility of drug-induced liver injury and active viral markers such as hepatitis A, B, and C virus, Epstein–Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV); and (3) liver biopsy findings compatible with AIH within 3 months after onset, consisting of interface hepatitis, centrizonal necrosis, and plasma cell infiltration. Eighteen patients were enrolled in the study. Informed consent was obtained from all patients.

Data obtained from patients were as follows: sex; age at diagnosis; time of onset; complications; serum levels of alanine aminotransferase (ALT), total bilirubin (T-Bil), alkaline phosphatase (ALP), prothrombin time (PT) activity, immunoglobulin G (IgG), immunoglobulin M (IgM), antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), liver kidney microsomal antibody-1 (LKM-1), and antimitochondrial antibody (AMA); types of therapy; and response to therapy. All patients were assigned AIH scores according to the International Autoimmune Hepatitis Group in 1999.[10]

Patients were examined for viral markers such as IgM antihepatitis A virus antibody (IgM-HA), IgM anti-HBc antibody (IgM-HBc), hepatitis B surface antigen (HBsAg), anti-HCV antibody, HCV RNA, IgM anti-EBV antibody (IgM-EBV), IgM anti-HSV antibody (IgM-HSV), and IgM anti-CMV antibody (IgM-CMV). They were also examined for any histories of recent exposure to drugs and chemical agents as well as heavy alcohol consumption (>50 g/day for >5 years). None of the patients had clinical or laboratory evidence of acquired immunodeficiency syndrome.

In acute-onset AIH, early symptoms including fever, general malaise, fatigue, nausea, vomiting, and right upper quadrant discomfort are frequently observed, so we defined the beginning of these symptoms as clinical onset.

Histological examinations

Liver biopsy was performed with a Tru-Cut needle (14 G) under ultrasound guidance before the administration of corticosteroids. Two specialists reviewed the histopathological changes by evaluating the degrees of portal and lobular changes and plasma cell infiltrations on hematoxylin and eosin-stained sections. Staging and grading were evaluated based on the classification of Desmet et al.[11]

Statistical analysis

Differences in proportions among the groups were compared by Fisher's exact probability test, Student's *t* test, and Welch's *t* test ($P < 0.05$ was considered significant).

Results

Patient characteristics

Of the 18 patients fulfilling the criteria, 2 were men and 16 were women. Mean age at the time of diagnosis was 54.3 ± 12.3 years. Fifteen patients (83%) had primary complications and histories of medications: 5 with hypertension, 4 with diabetes mellitus, 3 with rheumatoid arthritis, 2 with hyperthyroidism, 2 with hyperlipidemia, and 1 each with ischemic heart disease, bronchial asthma, Hashimoto disease, chronic hepatitis C, hepatitis A, manic depressive illness, multiple sclerosis, and glioma (Table 1).

The clinical and biochemical features of all patients before initiating treatment are provided in Tables 1 and 2. The mean ALT level was 679 ± 431 IU/l, mean T-Bil 2.4 ± 2.9 mg/dl, and mean PT activity 92% ± 14%.

Mean IgG was 1801 ± 446 mg/dl. The IgG level was normal (<1.0× upper normal value, UNV) in 7 of 18 (39%), 1.0–1.5× UNV in 10 (55%), 1.5–2.0× UNV in 1 (6%), and >2.0× UNV in none. ANA was positive (≥1:40) in 13 of 18 (72%) patients, <1:40 in 5 (28%), 1:40 in 2 (11%), 1:80 in 4 (22%), and >1:80 in 7 (39%). ASMA was positive (≥1:40) in 6 of 15 (40%). One patient was positive for LKM-1, and 1 was positive for AMA, ANA, and ASMA.

No patients were positive for HBsAg. One patient, positive for HCV Ab, HCV RNA, and also for LKM-1, was diagnosed as AIH dominant on the basis of histological findings, and responded to corticosteroid therapy. In one patient with multiple sclerosis, onset was after the withdrawal of steroid pulse therapy.

In another patient with multiple exacerbations, AIH was triggered by hepatitis A. A 36-year-old Japanese man presenting with low-grade fever, diarrhea, and jaundice was admitted to a local hospital in China. Laboratory tests revealed an ALT level of 2119 IU/l and T-Bil level of 10.2 mg/dl. IgM antihepatitis A virus antibody was positive, and he was diagnosed with hepatitis A. After a month of hospitalization, liver function tests improved (ALT 800 IU/l and T-Bil 1.5 mg/dl), and he came back to Japan. Two weeks after his return from China, he was admitted to our hospital presenting with general malaise and itching. Laboratory tests revealed ALT level of 1735 IU/l, T-Bil level of 3.7 mg/dl (peak T-Bil, 8.2 mg/dl), PT 110%, IgG 2190 mg/dl, ANA <40×, and ASMA <40×. Liver histology showed centrilobular

Table 1. Clinical features of 18 patients with acute-onset autoimmune hepatitis (AIH)

Patient	Age (years)/sex	Onset	Complications	Therapy	Response
Histologically acute hepatitis					
1	69/F	2001	HT, HL	CS	CR
2	36/M	2002	Hepatitis A	CS	CR
3	72/F	2004	HT	CS	CR
4	62/F	2006	Basedow	CS	CR
5	51/F	2006	None	CS	CR
6	54/F	2006	None	CS	CR
7	70/F	2006	DM, HL, BA	CS	CR
Histologically chronic hepatitis					
1	35/F	2001	None	CS	CR
2	49/F	2001	HT	CS	CR
3	45/F	2001	HL, MDI	CS	CR
4	65/M	2002	DM	UDCA, SNMC	CR
5	51/F	2002	RA, HT, DM	UDCA, SNMC	CR
6	68/F	2002	DM, IHD	UDCA, SNMC	CR
7	50/F	2002	RA, Hashimoto disease, Chronic hepatitis C	CS	CR
8	50/F	2002	RA	UDCA	CR
9	54/F	2005	Multiple sclerosis	UDCA, SNMC	CR
10	64/F	2005	Glioma	CS	CR
11	33/F	2005	Basedow	CS	CR

HT, hypertension; HL, hyperlipidemia; MDI, manic depressive illness; DM, diabetes mellitus; RA, rheumatoid arthritis; IHD, ischemic heart disease; BA, bronchial asthma; CS, corticosteroid; UDCA, ursodeoxycholic acid; SNMC, stronger neominophagen C; CR, complete response

Table 2. Laboratory data of 18 patients with acute-onset AIH

Patient number	ALT (IU/l)	ALP (IU/l)	T-Bil (mg/dl)	IgG (mg/dl)	PT (%)	ANA	ASMA	LKM-1	AMA	AIH score
Histologically acute hepatitis										
1	797	470	6.2	1800	84	80 fold	<40 fold	–	–	9
2	1735	506	3.7	2190	110	<40 fold	<40 fold	–	–	7
3	700	445	0.5	1760	126	80 fold	ND	–	–	13
4	329	301	0.9	2101	106	320 fold	40 fold	–	–	14
5	1041	589	0.8	1278	97	40 fold	<40 fold	–	–	7
6	744	538	10.1	1789	83	320 fold	ND	–	–	18
7	956	779	0.6	1546	109	<40 fold	<40 fold	–	–	10
Histologically chronic hepatitis										
1	434	211	0.7	1840	86	<40 fold	<40 fold	–	–	15
2	188	408	1.5	2360	86	<40 fold	80 fold	–	640 fold	9
3	1398	513	8.1	2870	91	320 fold	160 fold	–	–	18
4	628	612	0.9	1980	90	320 fold	40 fold	–	–	16
5	255	784	0.7	1480	91	160 fold	<40 fold	–	–	10
6	760	502	1.4	1020	66	40 fold	<40 fold	–	–	15
7	122	113	0.9	2240	82	320 fold	ND	+	–	14
8	402	185	0.5	1530	96	80 fold	<40 fold	–	–	18
9	942	434	4.3	1510	77	<40 fold	40 fold	–	–	15
10	198	308	0.5	1820	97	640 fold	40 fold	–	–	18
11	597	765	0.7	1300	80	80 fold	<40 fold	–	–	11

ND, not done; ALT, alanine aminotransferase; ALP, alkaline phosphatase; T-Bil, total bilirubin; IgG, immunoglobulin; PT, prothrombin time; ANA, antinuclear antibody; ASMA, anti-smooth muscle antigen; LKM, liver kidney microsomal antibody; AMA, antimitochondrial antibody

necrosis and plasma cell accumulation, so we diagnosed his prolonged liver injury as acute onset of autoimmune hepatitis triggered by hepatitis A viral infection. Corticosteroid was introduced, and his liver function tests normalized within 2 weeks.

Although 83% of the patients had primary complications and histories of medications as described above, suspected hepatotoxic drugs were excluded using the drug-induced liver injury diagnostic scale by Maria and Victorino[12] in this study.

Table 3. Histological findings of 18 patients with acute-onset AIH

Patient	Days from onset to biopsy	Histological diagnosis	Interface hepatitis	Centrilobular necrosis	Plasma cell infiltration
Histologically acute hepatitis (AH)					
1	58	AH, severe	–	++	+
2	19	AH, severe	–	++	++
3	16	AH, severe	±	++	++
4	85	AH, severe	–	++	+
5	15	AH, severe	–	++	++
6	14	AH, severe	±	+	++
7	58	AH, severe	–	++	++
Histologically chronic hepatitis (CH)					
1	60	CH (F3, severe)	++	++	+
2	45	CH (F3, severe), Scheuer III	++	++	++ NSDC(+)
3	9	CH (F2, severe)	++	++	++
4	14	CH (F2, severe)	+	+	+
5	7	CH (F3, severe)	+	+	++
6	21	CH (F2, severe)	++	++	+
7	30	CH (F2, severe)	++	+	++
8	22	AH on CH (F1, mild)	±	+	+
9	10	CH (F3, severe)	+	++	++
10	70	CH (F2, severe)	++	++	+
11	30	CH (F2, severe)	++	++	±

NSDC, nonsuppurative destructive cholangitis

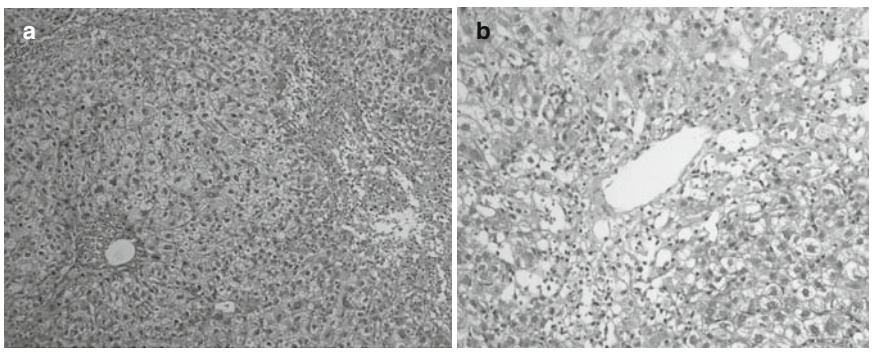

Fig. 1. Severe acute hepatitis (AH 1). A 69-year-old woman with hypertension and hyperlipidemia had a history of multiple medications. **a** Centrilobular hemorrhagic necrosis is shown; significant portal inflammation was not seen. **b** Perivenular hemorrhagic necrosis with marked infiltration of lymphocytes and proliferation of sinusoidal cells, and infiltration of some plasma cells and polymorphonuclear leukocytes on higher-power examination, are observed

Ultrasound showed normal liver in all patients, without signs of chronicity.

Pathological features

The pathological characteristics of the patients are summarized in Table 3. Centrizonal necrosis and plasma cell accumulation in portal and centrilobular areas were characteristic for acute-onset AIH (Figs. 1–3). Seventeen of 18 (94%) patients showed severe activity, with 7 (39%) showing severe acute hepatitis, and 10 (56%) showing severe activity with fibrosis stage 2–3. Only 1 showed mild activity with fibrosis stage 1. One patient had AIH dominant-overlap syndrome with primary biliary cirrhosis stage Scheuer III with nonsuppurative destructive cholangitis, severe centrizonal necrosis, and marked plasma cell infiltration. One was positive for LKM-1 and HCV, and was diagnosed as AIH dominant on the basis of histological findings showing interface hepatitis, centrilobular necrosis, and plasma cell accumulation. One patient with hepatitis A showed acute viral hepatitis with centrizonal necrosis and marked plasma cell infiltration and was diagnosed as acute-onset AIH (Fig. 2).

Patients were analyzed according to their histology, acute hepatitis or chronic hepatitis. The differences in mean age, sex, mean T-Bil level, mean IgG level, and ANA titer were not statistically significant. PT activity

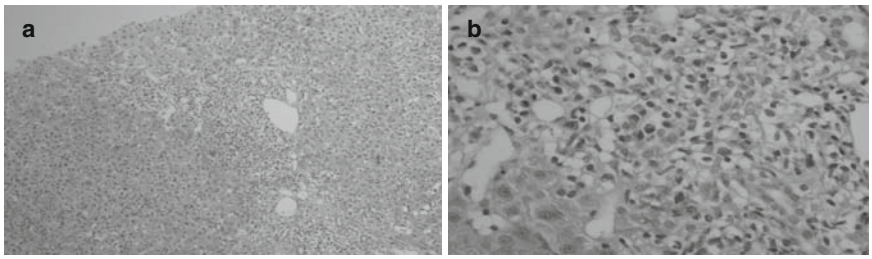

Fig. 2. Severe acute hepatitis (AH 2). A 36-year-old man showed multiple exacerbations in the convalescent phase of hepatitis A. **a** Bridging necrosis. **b** Perivenular necrosis with plasma cell infiltration seen on higher-power examination

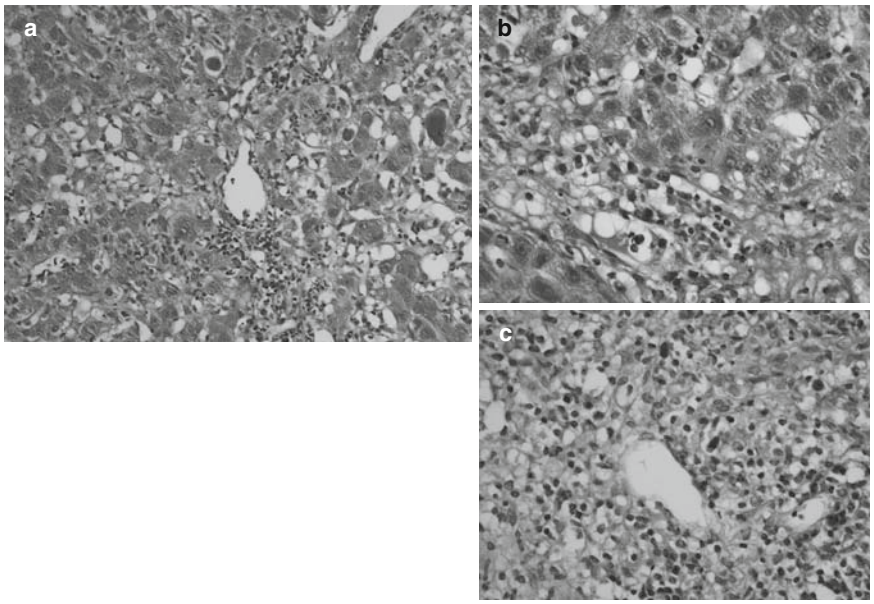

Fig. 3. Severe acute hepatitis (AH 6). A 54-year-old woman was without complications. **a** Centrizonal hemorrhagic necrosis. **b** Perivenular necrosis with plasma cell infiltration observed on higher-power examination. **c** Polymorphonuclear leukocytes seen in perivenular necrosis

Table 4. Comparison of findings at presentation of acute-onset AIH patients between histologically acute and chronic hepatitis

Factor	Acute hepatitis	Chronic hepatitis	*P* value
n	7	11	
Age	59 ± 13	51 ± 11	0.18
Sex (M/F)	1/6	1/10	0.64
ALT (IU/l)	900 ± 432	539 ± 385	0.08
T-Bil (mg/dl)	3.6 ± 3.7	1.8 ± 2.3	0.21
PT (%)	102 ± 15	86 ± 9	0.01
IgG (mg/dl)	1781 ± 311	1814 ± 529	0.88
ANA (≥40 fold)	5/7	8/11	0.73
AIH score	11.1 ± 4.1	14.5 ± 3.2	0.07
Days from onset to biopsy	37.9 ± 28.8	28.9 ± 21.2	0.46

was lower in chronic hepatitis than in acute hepatitis ($P = 0.01$). Mean ALT was higher and mean AIH score was lower in acute hepatitis than in chronic hepatitis, although there were no statistical differences ($P = 0.08$ and $P = 0.07$, respectively) (Table 4). The difference in the duration from onset to liver biopsy was not statistically significant (Tables 3, 4).

AIH scoring system

The provisional scoring system (AIH score) proposed by the International Autoimmune Hepatitis Group[10] was used to score all patients (see Table 1). The AIH score ranged from 7 to 18 (13.2 ± 3.8) before treatment. As already described, the score was 11.1 ± 4.1 and 14.5

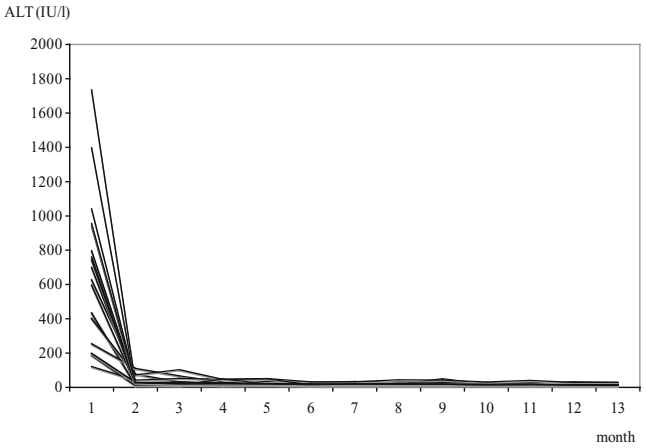

Fig. 4. Changes in alanine aminotransferase (ALT) levels during a year after the start of treatment in all the patients. ALT decreased to normal (<40 IU/l) within a month in 14 of 18 patients, within 2 months in 15, within 3 months in 16, within 5 months in 17, and within 8 months in all patients

± 3.2 in patients whose histological findings showed acute hepatitis and chronic hepatitis, respectively (P = 0.066) (see Table 4). Eight of 18 patients (44%) were diagnosed as definite AIH and 6 (33%) as probable.

Treatment and response

In 13 of 18 (72%) patients, including all 7 with severe acute hepatitis, an initial dose of 40–60 mg prednisolone daily was administered, and all responded completely.

Five (28%) patients were treated with ursodeoxycholic acid (UDCA) and intravenous glycyrrhizin (stronger neominophagen C; SNMC) at 100 ml daily, an aqueous extract of licorice root that is reported to have antiinflammatory activity and has been used for the treatment of chronic viral hepatitis in Japan. All patients responded well to the therapy, and SNMC was then tapered off. ALT levels remained normal thereafter with UDCA monotherapy (see Table 1).

Changes in ALT levels during a year after the start of treatment are shown in Fig. 4. ALT decreased to normal (<40 IU/l) within a month in a majority of the patients. At least 50% improvement of ALT was observed during the first month in all the patients.

Discussion

Acute-onset presentations of AIH have been reported, but the characteristics are yet to be clarified. The clinical features of AIH cover a spectrum from mild, nonspecific symptoms to severe, acute, sometimes even fulminant hepatitis. Acute presentation of AIH shows a picture identical to that of severe hepatitis of other causes. It is important to distinguish this presentation of AIH from that of other acute hepatitis, including viral hepatitis and drug-induced liver injury. However, some AIH patients have no autoantibodies and no hypergammaglobulinemia, and some of them at present are being diagnosed as cryptogenic hepatitis.

In our study, ANA was negative (<1:40) in 5 of 18 (28%) patients, ASMA was negative (<1:40) in 9 of 15 (60%), and 3 of 18 (17%) were negative for both. In Japanese studies of acute-onset AIH, 4%[13] and 0%[14] were negative for ANA, and 56%[13] and 33%[14] were negative for ASMA. In the Italian study of acute-onset AIH, 27% was negative for ANA, 18% was negative for ASMA, and 9% was negative for both.[15] In the U.S. study of acute-onset AIH, 31% was negative for ANA, 15% was negative for ASMA, and 4% was negative for both.[16] Thus, our negativity of ANA and ASMA was about the same as other reports of acute-onset AIH.

Kaymakoglu et al. reported that severe cryptogenic chronic hepatitis was similar to autoimmune hepatitis in clinical, biochemical, and histological features as well as responsiveness to immunosuppressive therapy, and severe cryptogenic chronic hepatitis patients might have an autoimmune liver disease with no identified immunoserological marker.[17] It was reported that 25% of AIH patients have an acute presentation resembling viral hepatitis.[15] Potthoff et al. suggested that steroids have to be considered in the therapy for severe acute cryptogenic hepatitis, and the response to steroid treatment could be indicative for an autoimmune genesis of the disease.[18] In our patients, we compared the histology between those whose ANA was less than 40× and those whose ANA was more than 80×. The former showed 3 AH and 4 CH, and the latter 4 AH and 7 CH. Comparing the histology between those whose IgG was normal and those whose IgG was above normal, the former showed 2 AH and 5 CH and the latter 5 AH and 6 CH, respectively. Then, comparing the histology between those whose ANA was less than 40× and IgG was normal and those whose ANA was more than 80× and IgG was above normal, the former showed 2 AH and 2 CH and the latter 5 AH and 9 CH. There were no differences, statistically and histologically, and the responses to corticosteroids were good in each comparison.

In this study, none of the patients had any signs of chronicity on the basis of physical examination, laboratory data, and ultrasound, so they were diagnosed as acute hepatitis on admission. The main ultrasound findings of normal liver are sharp edge, smooth surface, and homogeneous parenchyma. We supposed that patients whose histology revealed chronic hepatitis showed normal liver on ultrasound because they did not have thick fibrosis and deformity of the liver.

Without histological findings by liver biopsy, we could not have diagnosed and treated them adequately.

Although PT activity was maintained in our patients, liver histology showed severe activity with zonal necrosis in 94% of them. Therefore, AIH with prolonged PT activity must have very severe and advanced histology (submassive to massive necrosis) and present impaired hepatocellular regeneration, which may be associated with resistance to immunosuppressive therapy. Centrizonal necrosis and plasma cell accumulation were characteristic for acute-onset AIH. In histologically acute hepatitis, the ALT level was higher and the AIH score was lower than in histologically chronic hepatitis, although there were no statistical differences ($P = 0.08$ and $P = 0.07$, respectively) (see Table 4).

There are no morphological features that are pathognomonic of AIH, but the characteristic histological picture is that of an interface hepatitis with predominantly lymphoplasmacytic necroinflammatory infiltrates, with or without lobular involvement and bridging necrosis, often with the formation of liver cell rosettes.[10]

There are only a few reports on the histological features of acute-onset AIH. Lefkowitch et al. first reported AIH cases presenting histologically acute hepatitis.[19] In a Japanese nationwide survey study, 5.6% of patients with AIH were found to have a feature of acute hepatitis upon histological examination.[20]

Nikias et al. reported that lobular hepatitis is an important histological feature in AIH with an acute presentation.[8] Singh et al. suggested that the pattern of predominant centrizonal injury might be an early presentation of AIH according to sequential liver biopsy findings.[21] Centrilobular necrosis (CN) is associated with an acute clinical presentation and might reflect an early lesion preceding portal involvement, although CN with sparing of the portal areas represents a rare histological pattern in AIH. Recognition of this particular histological appearance enables early diagnosis of AIH and a timely initiation of immunosuppressive therapy.[22] The histological characteristics of the acute presentation of AIH revealed centrilobular necrosis, no or mild inflammatory infiltration in the portal area, and no portal fibrosis.[14]

On the other hand, Burgart et al. reported that only 4% of recent-onset AIH patients showed lobular hepatitis without portal inflammation, concluding that most patients with recent-onset AIH had histological evidence of chronic hepatitis.[16] Ferrari et al. also reported that histological grade and stage were comparable in acute, chronic, and asymptomatic AIH groups.[15] The reasons for these discrepancies are not clear.

In a murine model of experimental autoimmune hepatitis, the histological findings of initial lesions were characterized by infiltrates of polymorphonuclear leukocytes with some lymphocytes localized mainly in the centrilobular or portal area. Liver injury at the peak of hepatitis consisted of areas of liver cell necrosis randomly distributed, and the inflammatory infiltrates were densely distributed throughout the lobule, with a preference for the area around the central vein.[23] It seems that these findings were similar to our findings of human acute-onset AIH.

The actual numbers of acute-onset AIH have possibly been underestimated because diagnosis of acute-onset AIH is sometimes very difficult by the AIH scoring system, and understanding of the pathological features is lacking. Recently, Abe et al. described the clinicopathological features of 23 histologically acute AIH, the greatest number of patients so far reported.[13] The mean AIH score of all our patients was 13.2 ± 3.8, a somewhat lower score than that of the patients (14.0 ± 2.8) reported by Abe et al. In our patients, the AIH score was lower, although not significantly so, in acute hepatitis (11.1 ± 3.8) than in chronic hepatitis (14.5 ± 3.2) ($P = 0.066$). Therefore, the diagnosis of our patients was even more difficult than in those so far reported.

Abe et al. also reported that the histological findings are very useful for differentiating between acute AIH and acute hepatitis as a result of other causes, because the former showed plasma cell infiltration, zonal necrosis, and early cell infiltration into portal areas, features absent in the latter, and that early histological diagnosis and treatment might be important for patients with acute AIH.[13] Precise pathological evaluation plays an important role in the differential diagnosis. We should study and recognize the pathological characteristics of acute-onset AIH.

In this study, most patients had primary complications and histories of medications. In our 18 patients, 15 (83%) had primary complications, suggesting the relatively high frequency of complications in these patients. Seven autoimmune-associated complications (3 with rheumatoid arthritis, 2 with hyperthyroidism, 1 with Hashimoto disease, and 1 with multiple sclerosis) were found in 6 patients (33%). Four had type 2 diabetes mellitus. It seems that autoimmune-associated complications are rather common in these patients.

In some patients, it was difficult to distinguish drug-induced liver injury (DILI) from the early stage of acute-onset AIH pathologically. We needed follow-up periods to arrive at a differential diagnosis for these patients, and especially for those with DILI without typical histories and extrahepatic manifestations (rash, fever, arthralgia, eosinophilia, and cytopenia). Moreover, other possible causes such as unidentified viruses could not be completely ruled out.

In AIH, there are two forms by HLA-DR differences. In Japan, almost all AIH patients do not have HLA-DR3. Therefore, it might be worth examining the HLA-DR backgrounds, although we could not do so because

examination of HLA is not covered by the Japanese National Health Insurance.

All our patients responded well to the therapies. In our study, 94% of patients showed severe activity, with 39% having severe "acute" AIH and 61% "chronic" AIH. Corticosteroids were administered for all acute AIH case and 55% of chronic AIH cases to avoid progression to liver failure. Interestingly, in 45% of chronic AIH (28% of all patients), ALT levels remained normal with UDCA monotherapy without immunosuppressive therapy after SNMC was tapered off. Further studies and longer-term follow-up are necessary for this category of patients.

In conclusion, we should be aware of the possibility that there are acute-onset AIH patients who do not have hypergammaglobulinemia or autoantibodies, and that this condition can cause severe hepatitis and fulminant hepatic failure with a poor prognosis. Histological examination of the liver is necessary for early diagnosis, and prognosis might indeed be improved by getting a head start on corticosteroid therapy. We should evaluate liver biopsy specimens precisely, and we should not miss the chance of starting corticosteroid therapy as soon as possible. Multicenter studies are also needed to clarify the features of acute-onset AIH and define the treatment strategies.

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