


Clinical features of autoimmune hepatitis with acute presentation: a Japanese nationwide survey

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Abstract

Background Autoimmune hepatitis (AIH) is characterized by progressive inflammation and necrosis of hepatocytes and eventually leads to a variety of phenotypes, including acute liver dysfunction, chronic progressive liver disease, and fulminant hepatic failure. Although the precise mechanisms of AIH are unknown, environmental factors may trigger disease onset in genetically predisposed individuals. Patients with the recently established entity of AIH with acute presentation often display atypical clinical features that mimic those of acute hepatitis forms even though AIH

is categorized as a chronic liver disease. The aim of this study was to identify the precise clinical features of AIH with acute presentation.

Methods Eighty-six AIH patients with acute presentation were retrospectively enrolled from facilities across Japan and analyzed for clinical features, histopathological findings, and disease outcomes.

Results Seventy-five patients were female and 11 were male. Patient age ranged from adolescent to over 80 years old, with a median age of 55 years. Median alanine transaminase (ALT) was 776 U/L and median

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immunoglobulin G (IgG) was 1671 mg/dL. There were no significant differences between genders in terms of ALT ($P = 0.27$) or IgG ($P = 0.51$). The number of patients without and with histopathological fibrosis was 29 and 57, respectively. The patients with fibrosis were significantly older than those without ($P = 0.015$), but no other differences in clinical or histopathological findings were observed. Moreover, antinuclear antibody (ANA)-positive (defined as $\times 40$, $N = 63$) and -negative ($N = 23$) patients showed no significant differences in clinical or histopathological findings or disease outcomes. Twenty-five patients experienced disease relapse and two patients died during the study period. ALP ≥ 500 U/L [odds ratio (OR) 3.20; 95% confidence interval (CI) 1.12–9.10; $P < 0.030$] and GGT ≥ 200 U/L (OR 2.98; 95% CI 1.01–8.77; $P = 0.047$) were identified as independent risk factors of disease relapse.

Conclusions AIH with acute presentation is a newly recognized disease entity for which diagnostic hallmarks, such as ALT, fibrosis, and ANA, are needed. Further investigation is also required on the mechanisms of this disorder. Clinicians should be mindful of disease relapse during patient care.

Keywords Autoimmune hepatitis · Antinuclear antibody · Immunoglobulin G · Fibrosis · Histopathology

Introduction

Autoimmune hepatitis (AIH) is a chronic liver disease characterized by immunologic and autoimmunologic features, generally including the presence of circulating autoantibodies and high levels of immunoglobulin G (IgG) [1]. Although autoantibodies are present in the vast majority of patients with AIH, there is little evidence supporting their involvement in AIH pathogenesis or predictive ability of histologic severity or treatment response [2]. Most cases of AIH respond to anti-inflammatory or immunosuppressive therapy. However, some show rapid progression to fulminant hepatic failure, cirrhosis, or complicating hepatocellular carcinoma over time. The precise cause of AIH remains unknown, but one theory is that environmental factors can trigger disease onset in genetically predisposed individuals. In support of this hypothesis, human leukocyte antigen (HLA) loci displayed the highest susceptibility or protectivity to AIH across ethnicities [3–5], along with several genes on non-HLA loci [6–8]. Moreover, a recent genome-wide association study identified variants of SH2B3 on chromosome 12 [9] and CARD 10 on chromosome 22 in addition to other HLA regions [9].

The incidence of AIH has been estimated as 1.1 per 100,000 individuals in the Netherlands [10], 1.68 in Denmark [11], and 1.52 in Japan [12], with a prevalence of 18.3, 23.9, and 15.0, respectively. The clinical manifestations of AIH patients are diverse and range from asymptomatic to fulminant hepatic failure. There have recently been rare, but remarkable, AIH cases with acute presentation [13, 14] since a first report in 1984 [15]. The incidence of AIH with acute presentation has increased over the last 2 decades [16]. As patients with AIH are becoming older while serum IgG levels are decreasing in Japan [16], it appears that atypical cases of AIH are expanding and the disease is more diverse than expected. In the diagnosis of AIH, guidelines from the European Association for the Study of the Liver [17] and the Japan Society of Hepatology [18] require liver biopsy as part of the evaluation. Regarding the histopathological features of AIH with acute presentation, we recently reported that the presence of prominent lobular and perivenular necroinflammatory activity, pigmented macrophages, and cobblestone appearance of hepatocytes were useful for diagnosis in addition to the classic AIH features of plasma cell infiltration and emperipolesis [19]. However, as the clinical features of AIH with acute presentation have not been conclusively elucidated, the present study examined the clinical characteristics of this disorder.

Patients and methods

The Japan Autoimmune Hepatitis Study Group (JAIHG) conducted this multicenter retrospective survey among eight hospitals (Shinshu Ueda Medical Center, Fukushima Medical University Hospital, Ehime University Hospital, Jikei University Hospital, Okayama University Hospital, Teine Keijinkai Hospital, Chiba University Hospital, and Kurume University Hospital). Eighty-seven patients who were diagnosed as having AIH with acute presentation of the acute hepatitis phase after ruling out AIH of the acute exacerbation phase by liver specialists between 2005 and 2014 were initially registered in this study. One subject exhibited histological disease progression with fibrosis stage 3 and was therefore excluded. Ultimately, a total of 86 patients having AIH with acute presentation were analyzed. The diagnosis of AIH with acute presentation was based on criteria from the International AIH Group (IAIHG) (1999) [20] as well as guidelines from the Japan Society of Hepatology [18], with scoring for definite or probable AIH and/or empirical judgements by experienced hepatologists on the basis of combined clinical, laboratory, serological, and histological data, as reported previously [19].

No patient had a history of organ transplantation or concurrent use of immunomodulatory drugs or corticosteroids, and none were coinfecting with the hepatitis C virus (HCV) confirmed with the HCV antibody, hepatitis B virus confirmed with the HBs antigen, or human immunodeficiency virus type 1 confirmed with the HIV antibody. No subject exhibited evidence of other liver diseases, such as alcoholic liver disease or non-alcoholic fatty liver disease.

This study was reviewed and approved by the head of the Institutional Review Board of Fukushima Medical University School of Medicine, Fukushima, Japan (Approval number: 2099) and the ethics committees of the other participating institutions. Written informed consent was obtained from all participating subjects. This study was conducted in accordance with the principles of the 1975 Declaration of Helsinki.

Laboratory testing

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (upper limit of normal: 330 U/L), IgG (upper limit of normal: 1700 mg/dL) and other relevant biochemical and serological evaluations were performed using standard methods at the time of liver biopsy at respective institutions.

Histological evaluation

Liver biopsies were performed on all patients and formalin-fixed, paraffin-embedded specimens were prepared and used for subsequent histopathological studies. Sections were stained with hematoxylin and eosin and connective tissue staining, including Masson's trichrome and reticulin stainings. All liver biopsy samples were independently evaluated by five experienced pathologists who were blinded to clinical data by means of identical histological scoring sheets covering several parameters that included fibrosis, central zone necrosis, perivenular necroinflammatory activity, lobular necrosis/inflammation, cobblestone appearance, plasma cell infiltration, and emperipolesis, as reported previously [19].

Statistical analysis

Statistical analysis and data visualization were carried out using StatFlex version 6.0 (Artech Co., Ltd., Osaka, Japan) and IBM SPSS Statistics version 23.0 (IBM, Chicago, IL) software. Data are presented as the median \pm interquartile range for continuous variables. Linear data were compared using the Mann–Whitney *U* test. Groups were compared using the Chi-square test for categorical variables. This model was checked by regression diagnostic plots to verify normality, linearity of the data, and constant variance.

Stepwise logistic regression analysis with a forward approach was performed to identify independent factors associated with disease relapse after continuous variables were separated into two categorical variables by the nearest clinically applicable value to the cutoff, being considered as the optimal cutoff value for clinical convenience. All statistical tests were two-sided and evaluated at the 0.05 level of significance.

Results

Baseline clinical characteristics

The baseline clinical characteristics in this study are summarized in Table 1. Of the 86 enrolled patients, 75 were female and 11 were male. Median age was 55 years and was distributed from adolescence to over 80 years (Fig. 1a). Median ALT and IgG levels were 776 U/L and 1671 mg/dL, respectively, and were comparable between genders ($P = 0.27$ and $P = 0.51$) (Fig. 2a, b). Twenty-three patients (27%) were antinuclear antibody (ANA)-negative (Fig. 1b). Sixty-three patients (73%) were ANA-positive ($\times 40$) at diagnosis, with similar rates between men and women (Fig. 2c). The median duration between the onset of AIH with acute presentation, which was defined as when clinicians predicted based on medical interview and clinical findings, and liver biopsy was 21 days. Based on histological findings, the number of patients with fibrosis stage 0, 1, 2, 3, and 4 was 29, 38, 19, 0, and 0, respectively. One patient succumbed to lung cancer and the other did to disease-related death. We next analyzed several parameters to elucidate the clinical features of AIH with acute presentation.

Comparisons according fibrosis 0 and fibrosis 1–2 stages

Although all patients met the criteria of AIH with acute presentation, 29 (34%) showed no fibrosis and 57 (66%) exhibited early or significant fibrosis. The median age of patients with fibrosis was significantly higher than that of patients without ($P = 0.015$). Moreover, the median duration between disease onset and liver biopsy was markedly longer in the F1-2 group (29 days) than in the F0 group (15 days) ($P = 0.052$). There were no significant differences in laboratory data, pathological findings, or disease outcomes between the groups (Table 2).

Comparisons according to IgG level

Median IgG level was 1671 mg/dL, indicating that more than half of patients had IgG levels below the upper limit of

Table 1 Baseline clinical characteristics of 86 AIH patients with acute presentation

	Median	IQR
Age	55	(43–63)
Gender (female)	75 (87)	
Laboratory data		
Albumin (g/dL)	3.8	(3.4–4.1)
T-bilirubin (mg/dL)	3.95	(1.2–8.7)
AST (U/L)	575	(262–930)
ALT (U/L)	776	(395–1186)
GGT (U/L)	183	(120–283)
ALP (U/L)	472	(326–702)
IgG (mg/dL)	1671	(1436–2232)
IgM (mg/dL)	128.5	(77.3–195.5)
Platelet count, $\times 10^4/\mu\text{L}$	19.7	(14.6–23.9)
Prothrombin time, %	80	(68.7–94.4)
ANA $\geq \times 40$	63 (73)	
ANA $\geq \times 80$	52 (61)	
ASMA	15/53 (28)	
AMA-M2	11/83 (13)	
HBcAb	10/64 (16)	
Scoring		
IAIHG score	15	(12–17)
Simplified score	5	(5–7)
Duration between onset and liver biopsy (days)	21	(10–60)
Pathological findings		
Fibrosis 0/1/2	29/38/19	
Rosette formation	45 (52)	
Central zone necrosis	47 (55)	
Perivenular necroinflammatory activity	67(78)	
Lobular necrosis/inflammation 0/1/2/3	3/44/30/9	
Cobblestone appearance 0/1/2/3	16/41/19/10	
Plasma cell infiltration 0/1/2/3	13/57/11/4	
Emperipolesis	78 (88)	
Clinical outcomes		
Relapse	25 (29)	
Prognosis (death)	2 (2)	
Complication of other autoimmune diseases	18 (21)	

Data are expressed as number (%) or median (first-third quartiles)

AIH autoimmune hepatitis, IQR interquartile range, AST aspartate aminotransferase, ALT alanine aminotransferase; GGT gamma-glutamyl transpeptidase, ALP alkaline phosphatase, IgG immunoglobulin G, IgM immunoglobulin M, ANA antinuclear antibody, ASMA anti-smooth muscle antibody, AMA-M2 anti-mitochondrial antibody specific for the pyruvate dehydrogenase complex-E2 component, HBcAb hepatitis B core antibody, IAIHG International Autoimmune Hepatitis Group

normal (1700 mg/dL). After stratification according to this limit, the higher IgG group was significantly older than the lower IgG group (Table 3). Anti-smooth muscle antibody (ASMA) positivity was significantly higher in the higher IgG group ($P = 0.005$) along with IAIHG and simplified scores ($P = 0.002$ and $P < 0.001$). No other biochemical parameters or histopathological findings differed significantly between the groups.

Comparisons according to ANA status

Overall, 73% of patients were ANA-positive, defined as ANA $\geq \times 40$. The ANA-positive group showed significantly higher IgG levels than did the ANA-negative group ($P < 0.001$) (Table 4). Both IAIHG and simplified scores were significantly higher in the ANA-positive group ($P = 0.004$ and $P < 0.001$), although other biochemical

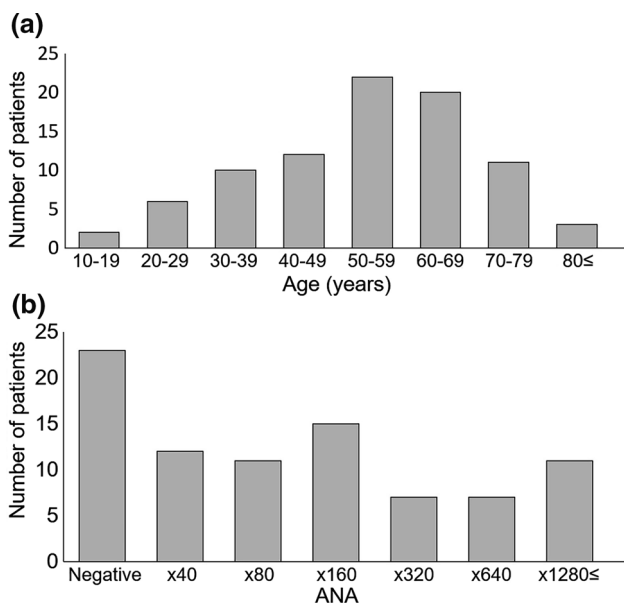


Fig. 1 **a** Age distribution of AIH patients with acute presentation (median age: 55 years). **b** Distribution of patients based on ANA positivity. ANA antinuclear antibody

parameters and histopathological findings were comparable between the groups.

Treatment

The vast majority of patients with AIH acute presentation were initially treated with prednisolone at an oral dosage of 20-50 mg/day that was gradually tapered after remission.

Clinical outcomes of AIH with acute presentation

Overall, 25 patients (30%) experienced AIH relapse (Fig. 3). The median levels of gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) in the disease relapse group were significantly higher than those in the disease non-relapse group ($P = 0.002$ and $P < 0.001$, respectively) (Table 5). No other biochemical parameters

or histopathological findings differed remarkably between the groups. A stepwise logistic regression model to determine independent risk factors associated with disease relapse showed that $ALP \geq 500$ U/L [nearly 1.5 times the upper limit of normal; odds ratio (OR) 3.20; 95% confidence interval (CI) 1.12–9.10; $P < 0.030$] and $GGT \geq 200$ U/L (nearly 4 times the upper limit of normal; OR 2.98; 95% CI 1.01–8.77; $P = 0.047$) were independent risk factors of disease relapse in AIH with acute presentation after adjustment by age and gender.

One patient ultimately died of lung cancer and one patient succumbed to disease-related death due to unresponsiveness to immune-mediated therapy.

Discussion

This study revealed the following clinical features of AIH with acute presentation: (1) afflicted patients showed elevated levels of ALT, which was compatible with acute hepatitis, while more than half displayed IgG levels lower than the upper limit of normal, unlike AIH with chronic hepatitis; (2) less than half of patients showed no fibrosis, with the remainder exhibiting histologically proven early or significant fibrosis stages; (3) a quarter of patients showed ANA negativity, which is a reminder for clinicians to consider AIH with acute presentation even when patients are ANA-negative; and (4) GGT and ALP were independent risk factors of disease relapse in AIH with acute presentation.

As AIH with acute presentation exhibits higher ALT levels than does chronic hepatitis [16, 21, 22], the diagnosis of acute hepatitis can be easily made in the clinical setting. Moreover, AIH patients with chronic hepatitis typically show high levels of IgG, which can help clinicians with diagnosis; indeed, IgG is included in both IAIHG scoring [20] and the simplified criteria for diagnosing AIH [23]. If scoring systems are relied on, however, there is a risk of underestimating the number of AIH patients with acute

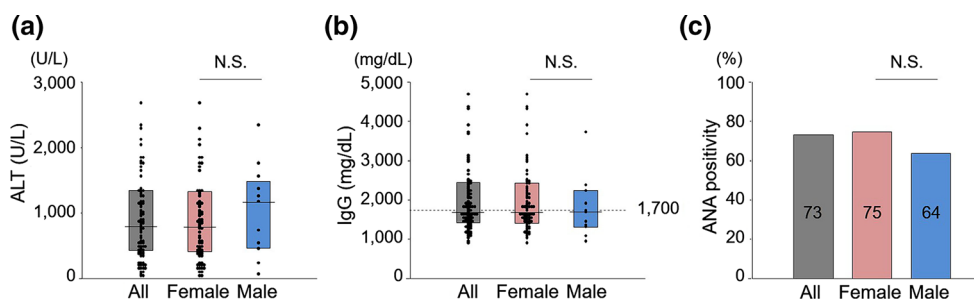


Fig. 2 **a** ALT levels in all, female, and male AIH patients with acute presentation. No significant differences were found. **b** IgG levels in all, female, and male AIH patients with acute presentation. Dotted line indicates the upper normal limit of IgG level. No significant

differences were found. **c** ANA positivity in all, female, and male AIH patients with acute presentation. No significant differences were found. ALT alanine aminotransferase, IgG immunoglobulin G, ANA antinuclear antibody, N.S. not significant

Table 2 Comparisons of clinical markers according to histological fibrosis 0 and fibrosis 1–2 stages

	F0 (<i>N</i> = 29)	F1-2 (<i>N</i> = 57)	<i>P</i> value
Age	50	58	0.015
Gender (female)	24/5	51/6	N.S.
Laboratory data			
Albumin (g/dL)	3.8	3.8	N.S.
T-bilirubin (mg/dL)	3.52	5.3	N.S.
AST (U/L)	577	571	N.S.
ALT (U/L)	847	766	N.S.
GGT (U/L)	152	207	N.S.
ALP (U/L)	543	453	N.S.
IgG (mg/dL)	1620	1785	N.S.
IgM (mg/dL)	118	144	N.S.
Platelet count, × 10 ⁴ /μL	21.3	17.9	N.S.
Prothrombin time, %	81	80	N.S.
ANA ≥ × 40	75%	74%	N.S.
ANA ≥ × 80	61%	61%	N.S.
ASMA	26%	29%	N.S.
AMA-M2	15%	12%	N.S.
Scoring			
IAIHG score	14	16	N.S.
Simplified score	5	5	N.S.
Duration between onset and liver biopsy (days)	15	29	0.052
Pathological findings			
Rosette formation	45%	56%	N.S.
Central zone necrosis	41%	61%	N.S.
Perivenular necroinflammatory activity	71%	81%	N.S.
Lobular necrosis/inflammation 0/1/2/3	3/59/24/14%	4/47/40/9%	N.S.
Cobblestone appearance 0/1/2/3	28/38/21/14%	14/53/23/11%	N.S.
Plasma cell infiltration 0/1/2/3	17/72/7/3%	14/64/16/5%	N.S.
Emperipolesis	93%	86%	N.S.
Clinical outcomes			
Relapse	31%	28%	N.S.
Prognosis (death)	4%	2%	N.S.
Complication of other autoimmune diseases	24%	19%	N.S.

Data are expressed as number, %, or median

AST aspartate aminotransferase, ALT alanine aminotransferase, GGT gamma-glutamyl transpeptidase, ALP alkaline phosphatase, IgG immunoglobulin G, IgM, immunoglobulin M, ANA antinuclear antibody, ASMA anti-smooth muscle antibody, AMA-M2 anti-mitochondrial antibody specific for the pyruvate dehydrogenase complex-E2 component, IAIHG International Autoimmune Hepatitis Group, N.S. not significant

presentation. We therefore examined for the clinical characteristics of AIH with acute hepatitis in terms of IgG level but uncovered no significant differences apart from age, ASMA positivity, and the frequency of complicating autoimmune diseases. Moreover, no significant differences between definite and probable AIH groups were found in terms of clinical or histological features. These findings indicated that our cohort was uniform and hence the diagnosis of AIH with acute presentation is challenging. It can also be stated that diagnostic hallmarks for AIH with acute presentation are urgently needed in the clinical

setting because treatment strategies differ among types of acute hepatitis, such as AIH patients better responding to corticosteroids.

Centrilobular necrosis without portal inflammation is a particular histopathological finding in AIH with acute presentation [13]. However, it was also reported that the disorder was associated with a variety of histological changes, and that lobular necrosis/inflammation, particularly centrilobular necrosis, plasma cell infiltration, emperipolesis, and pigmented macrophages, were common [19]. Specifically, emperipolesis and rosette formation

Table 3 Comparisons of clinical markers according to IgG level

	< 1700 mg/dL (N = 44)	≥ 1700 mg/dL (N = 42)	P value
Age	52	58.5	0.038
Gender (female)	86%	88%	N.S.
Laboratory data			
Albumin (g/dL)	3.75	3.8	N.S.
T-bilirubin (mg/dL)	3.86	3.95	N.S.
AST (U/L)	599.5	536	N.S.
ALT (U/L)	849	648	N.S.
GGT (U/L)	151	207.5	N.S.
ALP (U/L)	463	498.5	N.S.
IgM (mg/dL)	122	143	N.S.
Platelet count, × 10 ⁴ /μL	21.3	18.95	N.S.
Prothrombin time, %	85.65	77.2	N.S.
ANA ≥ × 40	63%	86%	N.S.
ANA ≥ × 80	49%	74%	N.S.
ASMA	11%	46%	0.005
AMA-M2	15%	12%	N.S.
Scoring			
IAIHG score	14	17	0.002
Simplified score	5	7	< 0.001
Duration between onset and liver biopsy (days)	19	26	N.S.
Pathological findings			
Fibrosis 0/1/2	39/39/22	29/50/21	N.S.
Rosette formation	47%	57%	N.S.
Central zone necrosis	61%	48%	N.S.
Perivenular necroinflammatory activity	77%	79%	N.S.
Lobular necrosis/inflammation 0/1/2/3	2/59/30/9%	5/43/40/12%	N.S.
Cobblestone appearance 0/1/2/3	23/54/16/7%	14/40/29/17%	N.S.
Plasma cell infiltration 0/1/2/3	21/61/16/2%	10/74/9/7%	N.S.
Emperipolesis	89%	89%	N.S.
Clinical outcomes			
Relapse	25%	33%	N.S.
Prognosis (death)	2%	2%	N.S.
Complication of other autoimmune diseases	9%	33%	0.006

Data are expressed as number, %, or median

IgG immunoglobulin G, AST aspartate aminotransferase, ALT alanine aminotransferase, GGT gamma-glutamyl transpeptidase, ALP alkaline phosphatase, IgM immunoglobulin M, ANA antinuclear antibody, ASMA anti-smooth muscle antibody, AMA-M2 anti-mitochondrial antibody specific for the pyruvate dehydrogenase complex-E2 component, IAIHG International Autoimmune Hepatitis Group, N.S. not significant

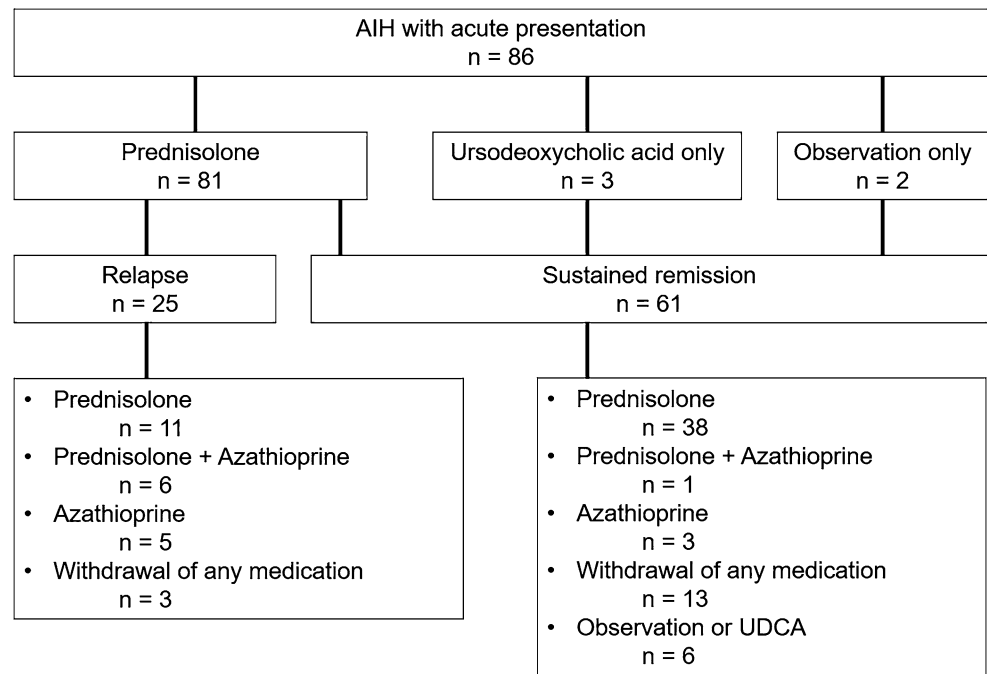
Table 4 Comparisons of clinical markers according to ANA status

	ANA-negative (N = 22)	ANA-positive* (N = 64)	P value
Age	57	54	N.S.
Gender (female)	82%	89%	N.S.
Laboratory data			
Albumin (g/dL)	3.5	3.8	N.S.
T-bilirubin (mg/dL)	5.6	3.7	N.S.
AST (U/L)	600	566	N.S.
ALT (U/L)	899	727	N.S.
GGT (U/L)	207	165	N.S.
ALP (U/L)	540	459	N.S.
IgG (mg/dL)	1418	1822	< 0.001
IgM (mg/dL)	112	135	N.S.
Platelet count, × 10 ⁴ /μL	20.5	19.7	N.S.
Prothrombin time, %	79	80	N.S.
ASMA	25%	30%	N.S.
AMA-M2	14%	12%	N.S.
Scoring			
IAIHG score	14	16	0.004
Simplified score	4	6	< 0.001
Duration between onset and liver biopsy (days)	29	20	N.S.
Pathological findings			
Fibrosis 0/1/2	32/36/32	33/48/19	N.S.
Rosette formation	44%	56%	N.S.
Central zone necrosis	64%	52%	N.S.
Perivenular necroinflammatory activity	77%	78%	N.S.
Lobular necrosis/inflammation 0/1/2/3	5/41/36/18%	2/56/33/8%	N.S.
Cobblestone appearance 0/1/2/3	27/59/9/5%	14/44/27/15%	N.S.
Plasma cell infiltration 0/1/2/3	14/73/9/4%	16/65/15/4%	N.S.
Emperipolesis	82%	91%	N.S.
Clinical outcomes			
Relapse	26%	30%	N.S.
Prognosis (death)	4.5%	2.0%	N.S.
Complication of other autoimmune diseases	9%	25%	0.006

Data are expressed as number, %, or median

ANA antinuclear antibody, AST aspartate aminotransferase, ALT alanine aminotransferase, GGT gamma-glutamyl transpeptidase, ALP alkaline phosphatase, IgG immunoglobulin G, IgM immunoglobulin M, ASMA anti-smooth muscle antibody, AMA-M2 anti-mitochondrial antibody specific for the pyruvate dehydrogenase complex-E2 component, IAIHG International Autoimmune Hepatitis Group, N.S. not significant

*Defined as greater than × 40

Fig. 3 Schematic of patient selection in this study

appear superior to interface hepatitis and plasma cell-rich infiltration as histological predictors of adult AIH with chronic hepatitis [24]. The present study demonstrated no significant differences between patients with and without fibrosis in terms of laboratory findings, histopathological findings, or disease outcomes, including AIH relapse. Although the median duration between disease onset and liver biopsy was markedly longer in the F1-2 group (29 days) than in the F0 group (15 days) ($P = 0.052$), we were unable to objectively ascertain fibrosis progression rate. However, all cases of clinically diagnosed AIH with acute presentation were confirmed as having fibrosis stage 0, 1, or 2 except for one subsequently excluded patient with stage 3. Since there were no cases of AIH with acute presentation with severe fibrosis, we surmised a predominance of AIH with chronic hepatitis in this group.

ANAs are the most common circulating autoantibodies in AIH and are serologic hallmarks for systemic and organ-specific autoimmune diseases. ANAs are not believed to be involved in AIH pathogenesis and are not predictive of histologic severity or treatment response [2], but are included in both IAIHG scoring [20] and the simplified criteria for AIH diagnosis [23]. As a quarter of patients in this study were ANA-negative, we looked for clinical differences between ANA-negative and -positive groups and observed that IgG level and the frequency of complications with other autoimmune diseases were significantly higher in the ANA-positive group. Further study is required to clarify this intriguing significance of ANA positivity with

AIH with acute presentation. Taken together, our findings indicated that ANA, IgG, and complicating autoimmune diseases may be hallmarks of AIH with acute presentation as well as AIH with chronic hepatitis. It was noteworthy that 13% of patients were positive for anti-mitochondrial antibody (AMA), which is a specific and sensitive marker for primary biliary cholangitis (PBC). This was consistent with a previous study revealing an association of AMA positivity with AIH/PBC overlap syndrome [25], wherein no AMA-positive AIH patients progressed to PBC over long-term follow-up. Clarification of the clinical significance of AMA positivity in AIH patients with acute presentation is needed.

Overall, 26 of 86 patients (30%) experienced disease relapse in this study, which was statistically comparable to the incidence in a previous study of 48 of 203 (24%) AIH patients in the chronic phase ($P = 0.241$) [26], indicating that disease relapse should be always considered both in AIH with acute presentation and AIH in the chronic phase. Comparisons of clinical markers between relapse and non-relapse groups identified two independent risk factors associated with disease relapse. Since relapse was reportedly associated with certain human leukocyte antigen (HLA) types in chronic phase AIH, including HLA-A1, HLA-B8, and HLA-DR3 [27], HLA typing might help uncover additional risk factors associated with disease relapse in AIH with acute presentation as well. Higher gamma globulin levels can also predict relapse after initial treatment [28], but there were no remarkable differences in

Table 5 Comparisons of clinical markers according to disease relapse

	Relapse (<i>N</i> = 26)	Non-relapse (<i>N</i> = 60)	<i>P</i> value
Age	52	57	N.S.
Gender (female)	88%	87%	N.S.
Laboratory data			
Albumin (g/dL)	3.8	3.8	N.S.
T-bilirubin (mg/dL)	5.3	3.1	N.S.
AST (U/L)	674	487	N.S.
ALT (U/L)	857	657	N.S.
GGT (U/L)	249	154	0.039
ALP (U/L)	613	446	0.008
IgG (mg/dL)	1822	1636	N.S.
IgM (mg/dL)	164	126	N.S.
Platelet count, × 10 ⁴ /μL	21.0	19.0	N.S.
Prothrombin time, %	80	84	N.S.
ANA ≥ × 40	76	72	N.S.
ASMA	35%	25%	N.S.
AMA-M2	20%	10%	N.S.
Scoring			
IAIHG score	14	15	N.S.
Simplified score	5	5	N.S.
Duration between onset and liver biopsy (days)	31	18	N.S.
Pathological findings			
Fibrosis 0/1/2	9/12/4	20/26/15	N.S.
Rosette formation	53%	52%	N.S.
Central zone necrosis	44%	59%	N.S.
Perivenular necroinflammatory activity	84%	75%	N.S.
Lobular necrosis/inflammation 0/1/2/3	4/40/40/16%	3/56/33/8%	N.S.
Cobblestone appearance 0/1/2/3	8/48/24/20%	23/48/21/8%	N.S.
Plasma cell infiltration 0/1/2/3	8/68/12/12%	18/67/13/2%	N.S.
Emperipolesis	96%	85%	N.S.

Data are expressed as number, %, or median

ANA antinuclear antibody, AST aspartate aminotransferase, ALT alanine aminotransferase, GGT gamma-glutamyl transpeptidase, ALP alkaline phosphatase, IgG immunoglobulin G, IgM immunoglobulin M, ASMA anti-smooth muscle antibody, AMA-M2 anti-mitochondrial antibody specific for the pyruvate dehydrogenase complex-E2 component, IAIHG International Autoimmune Hepatitis Group, N.S. not significant

IgG in this study. Rather, GGT and ALP were independent risk factors of disease relapse in AIH with acute presentation and might assist in disease treatment.

The present study has several limitations. Although multicenter, it was retrospective in nature and of a limited sample size due to our selection of only histopathologically proven cases. Liver biopsy for evaluating the degree of liver fibrosis was prone to sampling error. Some cases exhibited disease relapse. A longitudinal investigation of AIH patients with acute presentation is warranted as well. The environmental factors associated with disease onset according to prior studies on AIH pathogenesis should also be addressed by gathering detailed information in a larger cohort [29].

Conclusions

AIH with acute presentation is a newly recognized disease entity with apparent associations with ALT, fibrosis, ANA, and other clinical characteristics. Clinicians should be mindful of disease relapse, especially with patients exhibiting the above risk factors. Further studies are needed to clarify the diagnostic hallmarks and mechanisms of AIH with acute presentation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have nothing to disclose regarding funding from industries or other conflicts of interest with respect to this manuscript.

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