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ORIGINAL ARTICLE

Long-term observation of acute-onset autoimmune hepatitis presenting clinically and radiologically as acute hepatitis

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Abstract

Background There is yet no gold standard for the diagnosis of acute-onset autoimmune hepatitis (A-AIH), especially histologically acute AIH. As a result, long-term observation of A-AIH has been difficult and the nature is not well known. We retrospectively analyzed the clinicopathological features of A-AIH over a long prospective follow-up period.

Methods Clinical, biochemical, immunological and pathological features of 30 patients (21 female, mean age 55.1 ± 13.1 years) with non-severe A-AIH "without signs of clinical and radiological chronicity" admitted to a community hospital between 2001 and 2015 who were prospectively followed for more than 2 years were analyzed retrospectively.

Results Liver histology of 45% showed acute and 55% chronic hepatitis. Mean age was older, prothrombin time activity was higher, AIH scores before treatment were lower in histologically acute hepatitis than histologically chronic hepatitis significantly. Liver fibrosis was not coarse, but delicate with severe activity in most patients showing chronic hepatitis defined by our strict criteria. Median (range) follow-up period was 6.9 (2.1–16.2) years. Six (20%) patients experienced episode of relapses. All were alive at the last follow-up point. Corticosteroid was continued at 2.5–5 mg/day until the study end point without serious side effects in most patients. Serial change of alanine aminotransferase levels, immunoglobulin G levels and anti-nuclear antibody titers did not show statistical difference between histologically acute and chronic hepatitis.

Conclusion Rapid progression of fibrosis could occur in A-AIH. Treatment response and long-term prognosis were good, and not different between patients with histologically acute and chronic hepatitis.

Keywords Autoimmune hepatitis · Acute presentation · Non-severe · Long-term observation · Histology

Abbreviations

AIH	Autoimmune hepatitis
A-AIH	Acute-onset autoimmune hepatitis
ALT	Alanine aminotransferase
IgG	Immunoglobulin G
ANA	Anti-nuclear antibody
CS	Corticosteroid

Introduction

An acute presentation occurs in 25–75% of patients with autoimmune hepatitis (AIH) [1, 2], but the diagnosis of acute-onset AIH has been difficult in that, patients show acute presentation like acute hepatitis and may not have typical clinicopathological features of AIH. Therefore, patients with acute-onset AIH are at risk of losing the timing of starting immunosuppressive therapy, and some of them develop into the severe or fulminant form in the "subacute" clinical course and are sometimes resistant to immunosuppressive therapy and have poor prognosis [3].

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The number of patients with AIH showing histological features of acute hepatitis has been increasing in a recent Japanese nationwide survey [4], and acute liver failure (ALF) Study Group of the United States reported that 58% of indeterminate ALF were considered to be AIH by histological analysis [5]. Thus, AIH is a major etiology of acute liver injury in Japan and the USA, if precise evaluation of the histology is done.

There are two types of acute presentation based on histology: newly developed disease without fibrosis (histologically acute AIH) and exacerbated pre-existent one with fibrosis (histologically chronic AIH). Many reports on acute-onset AIH have been published for more than two decades and we also have reported the clinicopathological features of "strict" acute-onset AIH patients presenting acute hepatitis clinically and radiologically with one of the aims of improving the prognosis of ALF and intractable liver diseases. Nevertheless, there is yet no gold standard for the diagnosis of acute-onset AIH. As a result, long-term observation of histologically acute AIH has been difficult and the nature is not well known, including the differences from typical chronic AIH and acute-onset AIH showing histologically chronic hepatitis.

In the present study, we retrospectively analyzed the clinicopathological features of acute-onset AIH over a long prospective follow-up period.

Patients and methods

Selection criteria of patients

Patients with non-severe acute-onset AIH in a community hospital for more than 2 years of follow-up period were enrolled between 2001 and 2015. All patients showed INR less than 1.5 or prothrombin time (PT) activity more than 40%. The work described in this study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). This study was approved by the Ethics Committee of Chiba University (2153). Informed consent was obtained from all patients or appropriate family members.

We selected non-severe patients because liver biopsies were performed before the treatment and histological findings were not influenced by the treatment. We also selected those in a single community hospital (Seikeikai Chiba Medical Center) where the diagnoses and treatment protocols were uniform.

A diagnosis of AIH was made based on the revised original criteria of the International AIH Group (IAIHG) in 1999 defining the score for probable or definite AIH [6] and/or on liver histological findings compatible with AIH [6–13].

Eligibility criteria of clinically "acute-onset" AIH were as follows in addition to the AIH criteria described above: (1) acute-onset liver injury, (2) no histories of chronic liver injury, (3) negativity of active viral markers such as hepatitis A, B, C and E viruses, Epstein–Barr virus (EBV), cytomegalovirus (CMV) and herpes simplex virus (HSV), drug-induced liver injury, toxic and metabolic disorders and (4) no signs of chronicity on the basis of physical examination, laboratory data and abdominal radiological findings (ultrasound and/or computed tomography). 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).

Clinical, biochemical, immunological and radiological analysis

Data obtained from patients were as follows: sex; age at diagnosis; time of onset, liver biopsy and the start of treatment; type and dose of corticosteroid; liver histology; serum levels of alanine aminotransferase (ALT), total bilirubin (T-Bil), alkaline phosphatase (ALP), PT activity, immunoglobulin G (IgG), immunoglobulin M (IgM), antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), liver kidney microsomal antibody-1 (LKM-1) and anti-mitochondrial antibody (AMA) at diagnosis; serial changes of ALT, IgG and ANA; occurrence of relapse; occurrence of hepatocellular carcinoma (HCC). ANA was examined by a fluorescent antibody method using HEp2 cells, ASMA by a fluorescent antibody method and AMA by a fluorescent antibody method or an enzyme-linked immunosorbent assay (ELISA), and LKM-1 by ELISA. All patients were assigned AIH scores according to revised original AIH score [6] and simplified AIH score [14] by the International AIH Group.

A relapse of AIH was defined as an increase in serum ALT level to more than twice the upper limit of normal (ULN) (> 80 U/L). The maintenance of serum ALT levels of less than twice the ULN during follow-up constituted a sustained remission.

Histological examination

Liver biopsy was performed using Tru-Cut needle (14–18G) under ultrasound guidance before the administration of corticosteroids. Two specialists (KF and MN) reviewed the histopathological changes by evaluating the degrees of portal and lobular changes on Victoria blue and hematoxylin–eosin staining and immunohistochemistry for cytokeratin 7 [12]. Staging and grading were evaluated based on the classification of Desmet et al. [15]. Histological features including interface hepatitis, lymphoplasmocytic infiltration, rosette formation, cobblestone

appearance and centrilobular necrosis/collapse were examined for the diagnosis of acute-onset AIH [6–13].

Statistical analysis

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

Results

Clinical, biochemical and immunological features of patients at admission

Clinical, biochemical and immunological features of patients at admission are shown in Table 1. The IgG level was normal (< 1.0 × ULN) in 8 (27%), 1.0–1.5 × ULN in 16 (53%), 1.5–2.0 × ULN in 3 (10%) and > 2.0 × ULN in 3 (10%). ANA was positive (≥ × 40) in 24 (80%) patients. ASMA was positive in eight patients, AMA in five and LKM-1 in none. One was triggered by hepatitis A.

Ultrasound and/or computed tomography (CT) did not show signs of chronicity in all patients. In our previous reports, severe and fulminant AIH often showed radiological heterogeneity: heterogeneous hypoattenuating areas on unenhanced CT, which are hypoechoic areas on ultrasound, reflecting heterogeneous distribution of massive hepatic necrosis in contrast to diffuse hypoattenuating areas of viral necrosis with significant difference [3, 11, 16–18]. In the present study of non-severe patients, only one showed radiological heterogeneity [19].

Table 1 Clinical, biochemical and immunological features of patients

n	30
Sex (male/female)	9/21
Age (years)[a]	55.1 ± 13.1
PT (%)[a]	91 ± 15
ALT (U/L)[a]	825 ± 486
ALP (U/L)[a]	504 ± 167
T-BIL (mg/dL)[a]	4.2 ± 4.2
ANA	
< × 40	5
× 40	4
× 80	5
> × 80	16
IgG (mg/dL)[a]	2146 ± 720
IgM (mg/dL)[a]	203 ± 146
Revised original score before treatment[a]	13.9 ± 4.0
Simplified score before treatment[a]	5.4 ± 1.5
Duration from onset to liver biopsy (days)[a]	51.1 ± 45.0

PT prothrombin time, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *T-BIL* total bilirubin, *ANA* anti-nuclear antibody, *IgG* immunoglobulin G, *IgM* immunoglobulin M

[a]Values are mean ± SD

Histological analysis

Histological examination was performed in 29 of 30 patients. Histological findings were compatible with acute-onset AIH in all 29 examined. Thirteen (45%) showed acute form, 4 acute hepatitis, 8 acute severe hepatitis and 1 acute severe hepatitis with massive necrosis. Acute hepatitis included centrilobular necrosis/collapse and/or plasma cell infiltration. Histological findings of a patient showing acute hepatitis are presented in Fig. 1.

Sixteen patients (55%) showed the chronic form, 1 with F1 and mild activity, 2 with F1 and moderate activity, 2 with F1 and severe activity, 1 with F2 and moderate activity, 7 with F2 and severe activity, and 3 with F3 and severe activity. Chronic hepatitis included interface hepatitis and/or plasma cell infiltration. Five patients showed primary biliary cholangitis (PBC) and AIH overlap. Histological findings of a patient showing chronic hepatitis are presented in Fig. 2.

AIH score before treatment

The mean revised original score before treatment was 13.9 ± 4.0, with 41% of definite diagnosis, 38% of probable diagnosis and 21% of non-diagnosis. The mean simplified score before treatment was 5.4 ± 1.5, with 31% of definite diagnosis, 21% of probable diagnosis and 48% of non-diagnosis.

Comparison of findings of patients between histologically acute and chronic hepatitis at the start of treatment

The mean age was older and PT activity was higher significantly in histologically acute hepatitis than chronic hepatitis (Table 2). The revised original score and simplified score before treatment were significantly lower in the former than the latter. Sex, ALT, ALP, T-BIL, ANA, IgG, IgM and duration from onset to liver biopsy were not statistically different between patients with histologically acute and chronic hepatitis (Table 2).

Treatment and initial response

The loading dose of prednisolone (PSL) was 60 mg in 1 patient, 50 mg in 1, 40 mg in 19, 30 mg in 5 and 25 mg in 1. 1.5 mg of dexamethasone was administered to one for

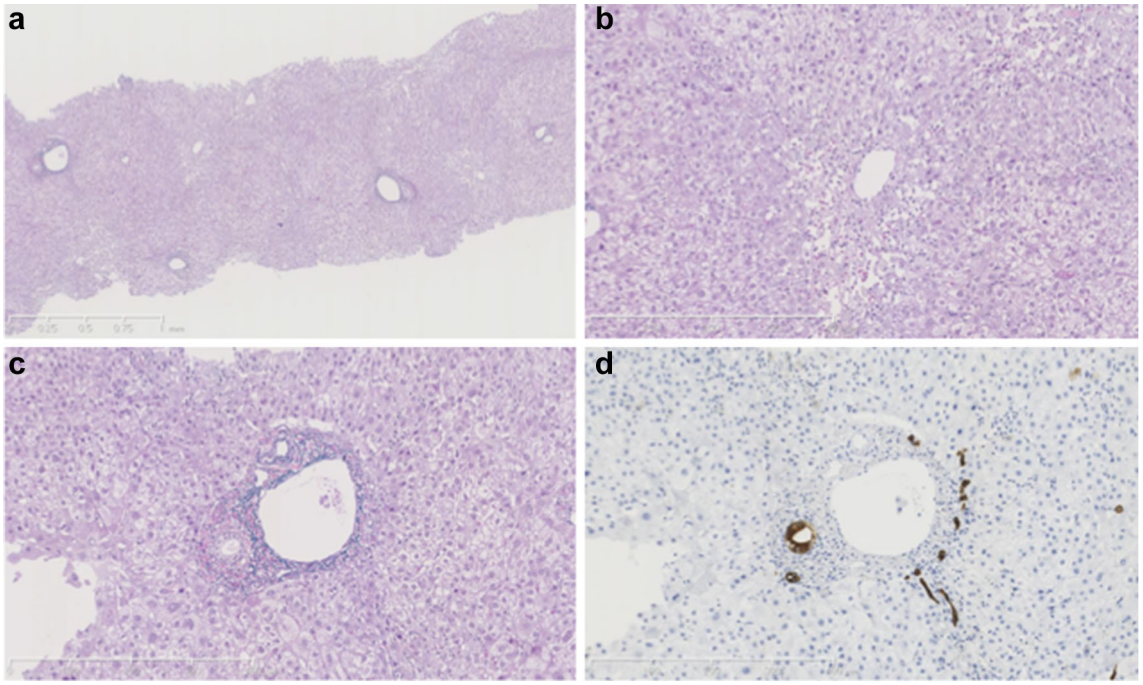

Fig. 1 Histological findings of a 69-year-old female patient with acute hepatitis, 33 days after clinical onset. She had nausea and jaundice. Laboratory tests on histological examination revealed alanine aminotransaminase of 797 U/L, alkaline phosphatase of 470 U/L, total bilirubin of 6.2 mg/dL and prothrombin time activity of 84% of the control. Hepatotropic viruses were all negative. Antinuclear antibody was 1:80 and immunoglobulin G was 1800 mg/dL. Other etiological factors including drugs and metabolic diseases were negative. **a** Victoria blue and hematoxylin–eosin staining. **b** Centrilobular necrosis with collapse and lymphoplasmocytic infiltrates. **c** Pre-existing coarse elastic fibers within normal amount are observed in the periportal area without newly formed, delicate elastic fibers. **d** Immunohistochemistry for cytokeratin 7 shows bile ducts and some progenitor cells

the treatment of scleritis, thereafter replaced by PSL. During the tapering process of CS, ursodeoxycholic acid (UDCA) was added. All achieved initial remission within 3 months of CS treatment.

Two patients were treated with UDCA and intravenous glycyrrhizin (IVGL) 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 acute and chronic hepatitis in Japan [20]. They responded well to the therapy, and IVGL was then tapered off. ALT levels remained normal thereafter with UDCA monotherapy.

Observation during the follow-up period

The mean follow-up period was 8.1 ± 5.3 years, ranging from 2.1 to 16.2 years: 5.8 ± 3.9 years, ranging from 2.2 to 12.1 years in histologically acute hepatitis, and 10.8 ± 5.8 years, ranging from 2.1 to 16.2 years in histologically chronic hepatitis patients ($p = 0.034$).

Six (20%) patients experienced episode of relapses, one with three relapses, two with two relapses and three with one relapse. Two experienced relapses before being transferred to our unit. In four patients, relapses occurred after CS was discontinued by themselves or by doctors, and in two during tapering of CS. Azathioprine was administered to three patients with two and three relapses. The occurrence of relapse did not differ between histologically acute and chronic hepatitis patients ($p = 1.00$).

CS was successfully withdrawn without relapse in three patients, for 2, 4 and 8 years, respectively. In the remaining patients, CS was continued at 2.5–5 mg/day until the study end point without serious side effects.

During the follow-up period, occurrence of HCC was found in none. One suffered from heart tumor and one from myelodysplastic syndrome. All were alive at the last follow-up point.

Serial change of ALT levels during the follow-up period

Serial change of ALT levels during the follow-up period is shown in Fig. 3a, b. Mean ALT levels in each point of the follow-up period were not different between patients with histologically acute and chronic hepatitis. As described above, six patients showed relapses, but ALT levels were under control in the last follow-up point.

In patients without relapses, maximum ALT level during remission was normal (< 1.0 × ULN) in 83% and 1–2 × ULN in 17%. It was normal in 82% and 1–2 × ULN in 18% in histologically acute hepatitis, and

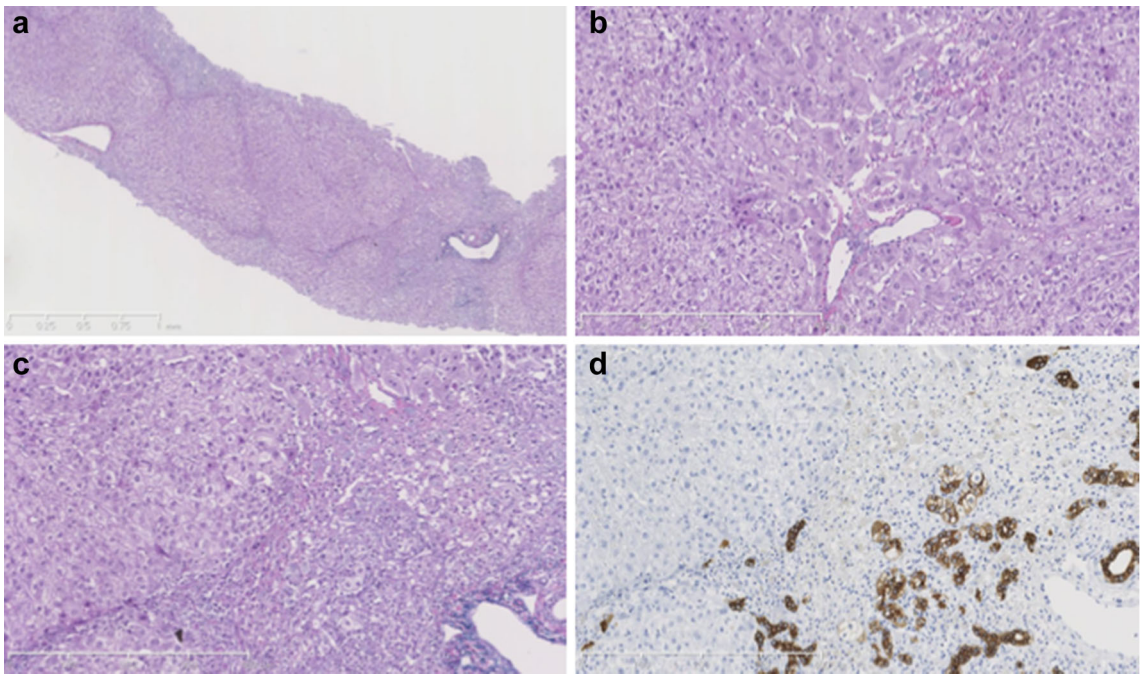

Fig. 2 Histological findings of a 33-year-old female patient showing chronic hepatitis, 86 days after clinical onset. The clinical course of the patient is presented in Fig. 4. **a** Victoria blue and hematoxylin–eosin staining. **b** Centrilobular necrosis. **c** Newly formed, delicate elastic fibers are observed in the zonal necrotic area with lymphoplasmocytic infiltrates and hepatocellular dropout without pre-existing coarse fibers. **d** Immunohistochemistry for cytokeratin 7 shows many of the hepatocellular dropout in the periportal area to be intermediate hepatocytes (ductular hepatocytes) which are transformed into mature hepatocytes after massive necrosis

was normal in 83% and 1–2 × ULN in 17% in histologically chronic hepatitis ($p = 1.00$).

Serial change of IgG levels during the follow-up period

Serial change of IgG levels during the follow-up period is shown in Fig. 3c, d. IgG levels were not often examined after the dose of CS reached the maintenance level, when levels of ALT and IgG were normal. During the 2 years after the start of treatment when IgG levels were periodically examined in almost all patients, IgG levels were not different between patients with histologically acute and chronic hepatitis. In four patients with relapses during the follow-up period, IgG levels were normal during the relapses but slightly elevated compared with those before the relapses.

Serial change of ANA titers during the follow-up period

Serial change of ANA titers during the follow-up period is shown in Supporting Figure 1. Examination of ANA titers was more often missed than that of IgG levels after the dose of CS reached the maintenance level, when levels of ALT and IgG were normal. ANA titers were not different before, during and after the relapses in four patients with relapses during the follow-up period.

Discussion

Precise histological evaluation of liver biopsy specimen is important for the diagnosis and treatment of AIH, which is even more important for atypical patients with acute-onset AIH (A-AIH) without hypergammaglobulinemia and autoantibodies. It has been reported that centrilobular necrosis/collapse is one of the diagnostic features of A-AIH as described above. However, liver injuries due to other etiologies could also show similar histological patterns [21]. Therefore, diagnostic histological features should be applied only to patients whom hepatologists consider to have AIH clinically for avoiding overdiagnosis and misdiagnosis. Along with histological features, it is essential to evaluate the aging of fibrosis for the differential diagnosis between newly formed A-AIH and exacerbated pre-existent one. Accordingly, first of all, we discuss the evaluation of liver fibrosis.

Elastic fibers are stained by orcein and Victoria blue, which are valuable in differentiating between the two kinds: pre-existing and newly formed fibers [22]. Horiuchi et al. [23] reported that elastic fibers are easily stained by

Table 2 Comparison of findings of patients between histologically acute and chronic hepatitis at the start of treatment

	Histologically acute hepatitis	Histologically chronic hepatitis	*p*
n	13	16	
Sex (male/female)	4/9	4/12	0.53[b]
Age (years)[a]	59.6 ± 13.1	50.3 ± 10.6	0.049[c]
PT (%)[a]	98 ± 14	85 ± 13	0.019[c]
ALT (U/L)[a]	992 ± 561	690 ± 402	0.10[c]
ALP (U/L)[a]	542 ± 166	471 ± 171	0.27[c]
T-BIL (mg/dL)[a]	5.2 ± 5.1	3.0 ± 3.0	0.16[c]
ANA			0.70[d]
< × 40	3	2	
× 40	2	2	
× 80	3	2	
> × 80	5	10	
IgG (mg/dL)[a]	1931 ± 485	2322 ± 871	0.16[c]
IgM (mg/dL)[a]	193 ± 191	217 ± 102	0.69[c]
Revised original score before treatment[a]	12.1 ± 4.5	15.6 ± 3.4	0.019[c]
Simplified score before treatment[a]	4.5 ± 1.5	6.1 ± 1.2	0.0029[c]
Duration from onset to liver biopsy (days)[a]	37.2 ± 27.7	62.3 ± 53.5	0.14[c]

PT prothrombin time, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *T-BIL* total bilirubin, *NA* anti-nuclear antibody, *IgG* immunoglobulin G, *IgM* immunoglobulin M

[a]Values are mean ± SD

[b]Fisher's exact probability test

[c]Student's *t* test

[d]Chi squared test

Victoria blue and that pre-existing fibers are coarse (1–2 μm in thickness) and newly-formed ones are delicate and reticular (0.2–0.7 μm). The pre-existing elastic fibers are confined to portal tracts and thin rims surrounding central and sublobular veins; in contrast, the newly formed ones occur in areas of hepatocellular necrosis. The newly formed elastic fibers could occur at 1 month after the onset of severe acute hepatitis at the area of collapse. Staining of elastic fibers may be valuable to differentiate between collapse and fibrosis and to judge the rough aging of fibrosis [23].

We have recently reported that high level of liver inflammation persists long in many patients with A-AIH before the diagnosis and treatment, which is different from transient viral infection [19]. We speculate that rapid histological progression of fibrosis could occur, because fibrosis observed in most patients with A-AIH without radiological chronicity is not dense but sparse with severe activity. The clinical course of a patient whose histology showed chronic hepatitis (Fig. 2) is presented in Fig. 4. Although her fibrosis stage was 2–3, fibers were not coarse but delicate. We suppose that 3 months of severe acute hepatitis induced newly formed fibrosis.

Many of our patients in the early 2000s showed histologically chronic hepatitis; in contrast, many of our recent patients showed histologically acute hepatitis. It is clear that the recognition of A-AIH as a differential diagnosis of acute hepatitis has made early histological examination possible. Thus, our speculation described above would be supported by change of histological findings over time.

In the present study, there are significant differences in the background between patients with histologically acute and chronic hepatitis (Table 2), although there were no significant differences in our previous reports of non-severe A-AIH [10, 19]. In our unit, we diagnose A-AIH in the early stage of clinically acute hepatitis, resulting in the proportion of histologically acute hepatitis increasing recently as described above. In contrast, long-term treatment-naïve patients were transferred to our unit from not only general clinics, but also core hospitals, for many of whom histology showed chronic hepatitis [19]. We diagnosed such patients, introduced treatment and transferred them back to former clinics or hospitals advising the strategy thereafter. As a result, we could not observe them for a long follow-up period and did not include them in the present study, which we suppose is the reason why there

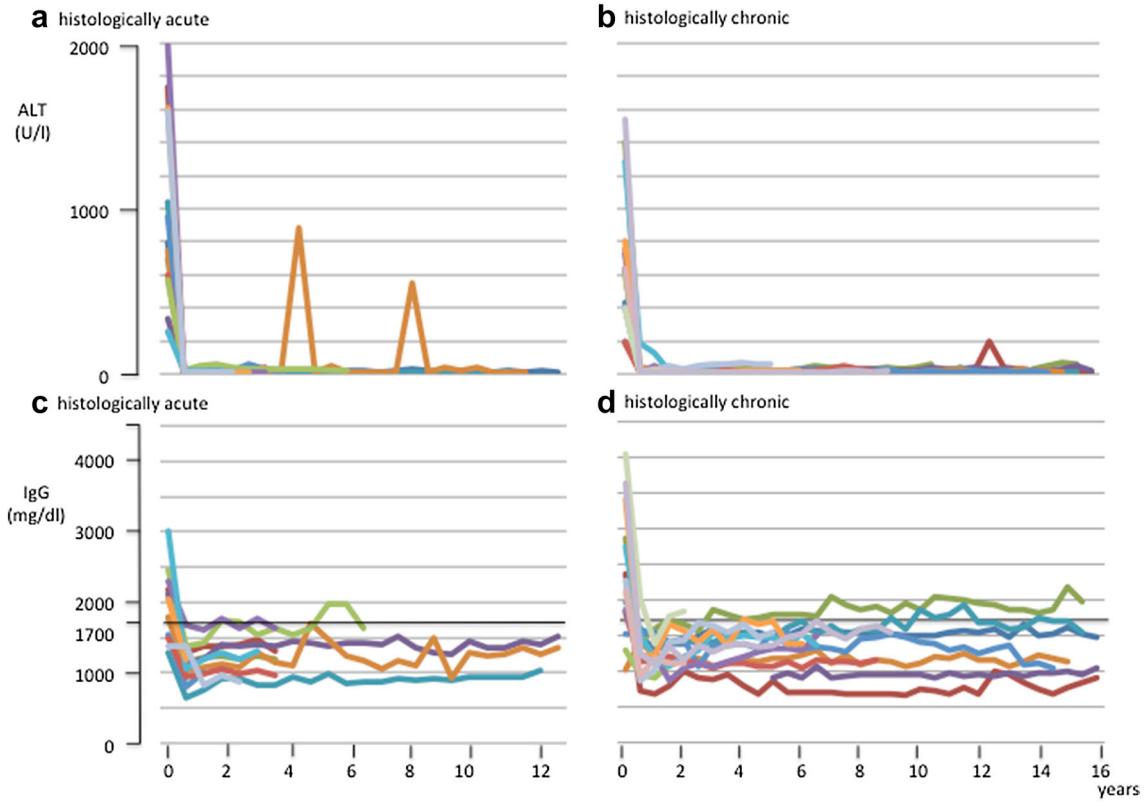

Fig. 3 Serial changes of ALT (**a**, **b**) and IgG (**c**, **d**) levels of histologically acute (**a**) and chronic (**b**) AIH patients after the start of treatment. The IgG level of the upper limit of normal is shown (1700 mg/dL) (**c**, **d**). ALT, alanine aminotransaminase; *IgG* immunoglobulin G

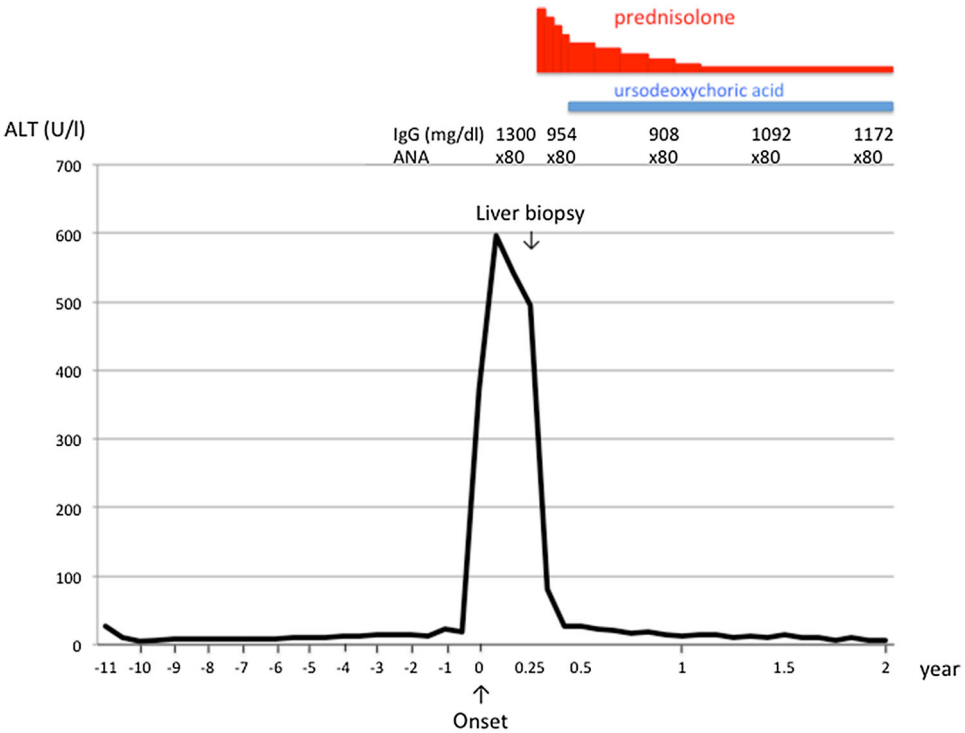

Fig. 4 Clinical course of a 33-year-old female patient. She suffered from Basedow's disease for 11 years with normal liver function tests. She showed ALT elevation with normal thyroid hormones and was transferred to our unit 3 months after clinical onset. Liver histology showed chronic hepatitis with fibrosis stage 2–3 and severe activity (Fig. 2). Corticosteroid was administered and her liver function tests improved to normal rapidly. *ALT* alanine aminotransaminase, *IgG* immunoglobulin G, *ANA* anti-nuclear antibody

are discrepancies among our three studies. Histologically acute hepatitis could progress to histologically chronic one in a few months without adequate treatment [13, 23, 24]. The mean duration from onset to histological examination was slightly longer in histologically chronic hepatitis than histologically acute one (62.3 ± 53.5 and 37.2 ± 27.7 days, respectively, $p = 0.14$) (Table 2).

Regarding treatment for AIH, two regimens are the mainstay therapies of AIH worldwide: a higher dose of PSL alone or a lower dose of PSL in combination with azathioprine. However, PSL monotherapy is the mainstay therapy in Japan, because treatment with azathioprine for AIH is not covered by the Japanese National Health Insurance. Czaja demonstrated that non-severe A-AIH responds as well to conventional immunosuppressive therapy as AIH with a chronic presentation [2], which was true in our present study.

Yoshizawa et al. reported that episode of repeated relapses was the only factor associated with a poorer long-term prognosis in Japanese AIH patients in their long-term study [25]. This was also true in the reports from the USA [26] and England [27]. In many guidelines worldwide, immunosuppressive therapy has been recommended to be withdrawn after remission was achieved, but 50–90% of patients have a relapse within 12 months of discontinuing therapy following remission [28]. In Japanese long-term study, only 6.4% of patients were successfully withdrawn from prednisolone with sustained remission [25].

In their Italian study, Muratori et al. concluded that continuous low-dose steroids are necessary to maintain remission, significantly reducing the risk of disease progression [29]. In a Japanese cohort, PSL monotherapy was continued indefinitely after remission was achieved, and sustained remission was maintained without severe side effects, suggesting that long-term or life-long therapy with a small amount of immunosuppressive agents was safe, well tolerated, and effective [25]. Based on these results, Yoshizawa et al. also emphasized the importance of sustaining remission, especially after the first relapse, by maintaining a small but sufficient doses of immunosuppressive agents for an extended period [25], which is consistent with our present study.

Regarding the occurrence of HCC, it has been reported in AIH with cirrhosis at the risks of 1.1 and 1.9% per year [30]. In our A-AIH patients without radiological chronicity, HCC was not found during the follow-up period.

Although this would be the first report of retrospective analysis of long-term prospective observation of strict acute-onset AIH without clinical and radiological chronicity, our study has some limitations. First, the sample size is limited. Secondly, our observation period was shorter than in previous reports of AIH. These results from the fact that there is yet no gold standard for the diagnosis of A-AIH, especially histologically acute AIH. The diagnosis of A-AIH came to be done somehow after the establishment of revised original criteria by IAIHG in November 1999 [6]. Accordingly, our study from 2001 includes patients with the longest follow-up period, because prospective observation became possible after November 1999.

This is a single center study conducted by one hepatologist; therefore, the diagnostic method and treatment protocol were more uniform than a multicenter study, but the way of follow-up, especially the regimens for tapering CS, was unexpectedly different among outpatient doctors. We have keenly felt the need of continuous and life-long learning and education based on the newly formed evidence. Further long-term and multicenter studies with uniform eligibility criteria and treatment protocol are necessary in the future.

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Authors contributions KF designed and performed the research, analyzed the clinical data and wrote the manuscript. KF, YF, KS, MS, SY, OY and NK contributed to the clinical aspects. KF and MN reviewed the histopathological changes. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest Keiichi Fujiwara, Yoshihiro Fukuda, Katsushi Seza, Masaya Saito, Shin Yasui, Masayuki Nakano, Osamu Yokosuka and Naoya Kato declare that they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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