Immunoserological and histological differences between autoimmune hepatitis with acute presentation and chronic autoimmune hepatitis

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Aim: The histological features of clinically chronic autoimmune hepatitis (AIH) have been well established, with interface hepatitis and plasma cell infiltration as hallmark lesions, however, the immunoserological and histological features of recent-onset and acute AIH remain undefined. The goal of this study was to define the immunoserological and histological differences between AIH with acute presentation and chronic AIH.

Methods: Thirty-two consecutive patients with well-characterized AIH who had undergone a liver biopsy were identified at our institution. These patients were divided into two groups. Sixteen patients whose liver dysfunction had persisted for at least 12 months were defined as chronic AIH (C-AIH) patients, and 16 patients whose liver dysfunction had been within normal limits for >12 months previously, and had only recently been found to have abnormal function for the first time, were defined as AIH with acute presentation (AIH-a) patients. Various biological and histological characteristics were compared between these two patient groups.

Results: No significant differences were found between the groups for age, body mass index, serum levels of total bilirubin, transaminase, alkaline phosphatase, prothrombin activity, immunoglobulin, titers of antinuclear antibody, or diagnostic scores between the groups. Histologically, there was no significant difference in the degree of interface hepatitis, plasma cell infiltration, or centrilobular necrosis between AIH-a and C-AIH patients. However, histological active findings such as activity, lobular inflammation, rosette formation, spotty necrosis, seroid-laden macrophages, and single cell necrosis were significantly more frequent in AIH-a patients, whereas portal fibrosis was significantly more frequent in C-AIH patients. Only one case among the 16 AIH-a patients was confirmed as acute AIH, showing massive centrilobular necrosis with a mild degree of portal inflammation and interface hepatitis. All patients with AIH-a and C-AIH responded well to corticosteroid or ursodeoxycholic acid treatment.

Conclusions: Patients with AIH-a could not be distinguished from C-AIH patients clinically or immunoserologically. Based on the histopathological findings of the liver, almost all cases of AIH-a might be exacerbations of non-symptomatic pre-existing C-AIH.

Key words: acute onset, autoimmune hepatitis, fulminant, liver histology

INTRODUCTION

The histological findings in chronic autoimmune hepatitis (C-AIH) have been well described, with hallmark lesions such as portal inflammation, interface hepatitis, rosette formations of hepatocytes, prominent plasma cell infiltration, and lymphocytic piecemeal necrosis with variable activity.1-5 In contrast, relatively little is known about the histopathology of clinically acute AIH (AIH-a). The confirmation of portal inflammatory cell infiltration in AIH-a cases has suggested the possibility of pre-existing chronic diseases.6 Mouse model studies have suggested that AIH-a results in lobular hepatitis, but the applicability of these findings to humans has not been confirmed.

Hofer et al. reported that centrilobular necrosis sparing of portal lymphoplasmacytic infiltration is associated with

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an acute clinical presentation of AIH.7 Burgart et al. found that in 26 recent-onset AIH cases, only one showed lobular hepatitis with confluent hepatocyte necrosis that was compatible with acute AIH.8 They therefore concluded that most recent-onset AIH cases have a lobular “flare” in disease activity.8 Okano et al. reviewed 29 Japanese patients with acute presentation of AIH and reported that many had acute exacerbations of chronic AIH.9 However, the differences between AIH-a and C-AIH immunoserological features are unclear.

The goal of this study was to define the differences between AIH-a and C-AIH in immunoserological characteristics and to reconfirm the histological findings of both types of AIH.

METHODS

Patients

From January 2008 to January 2016, we consecutively recruited 32 AIH patients. A diagnosis of AIH was made based on the presence of anti-nuclear antibodies as well as the criteria defined by the International Autoimmune Hepatitis Group (IAIHG) for probable or definite AIH.10 Autoimmune hepatitis with acute presentation was defined as a patient having normal liver function for >12 months previously and only recently found to have abnormal function for the first time. Sixteen patients with AIH-a were referred to our hospital from clinics. At the time of presentation, eight patients complained of slight general fatigue or appetite loss, and jaundice was observed in three patients. The other eight patients were incidentally diagnosed with liver dysfunction without any symptoms. Although these patients had biannual or annual health checks, or had been examined for common symptoms such as fever, cough, or anorexia between two and 10 times (median, 3 times) at other clinics, for time periods ranging from 1 to 6 years (median, 3 years) before being referred to our hospital, the levels of serum aspartate transaminase (AST) or alanine aminotransferase (ALT) were less than 31 IU/L or 33 IU/L, respectively. Their platelet counts were normal (more than 150 000 μL). However, immunoglobulin G (IgG) and antinuclear antibody (ANA) levels were not examined. Chronic AIH was defined as liver dysfunction persisting for >12 months. Sixteen patients with C-AIH were also referred to our hospital from clinics. These patients were only followed up without medication at the clinics, but were advised to avoid alcohol or supplements, and to maintain their body weight. These 16 C-AIH patients reported no symptoms. Four patients who had not been previously evaluated for liver function were excluded. Therefore, 16 patients each with AIH-a and C-AIH were enrolled in this study. Each patient had a liver biopsy carried out at the time of evaluation. All patients denied i.v. drug abuse, exposure to hepatotoxic medications or chemicals, and receipt of a blood transfusion within 3 years of onset of illness. This study was undertaken in accordance with the ethical guidelines of the Declaration of Helsinki, and the study protocol was approved by the Chihaya Hospital Ethics Committee (Fukuoka, Japan).

Methods

The subjects had their histories taken and underwent a physical examination at admission. Laboratory tests for liver biochemical parameters, lipids, uric acid, serum creatinine, serum IgG and IgM levels, ANA, and a complete blood cell count were carried out at admission. The diagnostic scores from the revised original system of the IAIHG10 were used. Treatment responses were classified according to the criteria of the IAIHG.10

Histological assessment

Liver biopsies were undertaken within 7 days of admission. For all biopsies, the degree of activity, portal fibrosis, portal inflammation, lobular inflammation, interface hepatitis, rosette formation, spotty necrosis, plasma cell infiltration, neutrophil infiltration, centrilobular necrosis, serum-laden macrophages, single cell necrosis, collapse of hepatocytes, clear cell changes in hepatocytes, biliary duct injury, ductular reaction of hepatocytes, and cholestasis were recorded. The results of hematoxylin–eosin and Masson trichrome stains were available in all cases.

Statistical analyses

All values are expressed as mean ± standard deviation. The analyses were carried out using the T-square test and χ²-test, as appropriate. A P-value <0.05 was considered to be statistically significant.

RESULTS

Clinical and immunoserological features

The clinical features of the patients are summarized in Table 1. The 16 patients with AIH-a included 1 man and 15 women, and the 16 patients with C-AIH included 3 men and 13 women. All patients were negative serologically for hepatitis B, hepatitis C, Epstein–Barr virus, and cytomegalovirus. There were no significant differences between the AIH-a and C-AIH patients in terms of age (56.9 ± 14.6 vs. 63.0 ± 11.9 years), body mass index (22.0 ± 3.1 vs. 22.9 ± 2.3 kg/m²), levels of

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total bilirubin (TB) (3.7 ± 5.0 vs. 2.0 ± 2.2 mg/dL), AST (982 ± 196 vs. 262 ± 175 IU/L), serum alkaline phosphatase (520 ± 211 vs. 599 ± 238 IU/L), albumin (3.8 ± 0.5 vs. 3.5 ± 0.5 g/dL), prothrombin activity (70.9% ± 23.5% vs. 75.2% ± 15.8%), or IgG (2213 ± 1507 vs. 2107 ± 889 mg/dL). Twelve AIH-a (75%) and 13 C-AIH (81%) patients had serum ANA titers ≥1:40. The ANA titers showed no significant differences between the groups.

The serum level of ALT (934 ± 133 vs. 298 ± 235 IU/l) was higher in the AIH-a patients than in the C-AIH patients; however, the difference was not significant.

International Autoimmune Hepatitis Group scoring system

Based on the revised IAIHG scoring system,10 the score for definite AIH (aggregate score >17) was 16.1 ± 2.1 for AIH-a patients and 16.1 ± 3.7 for C-AIH patients, and the difference was not significant (Table 1).

Histological findings of liver biopsies

The observed histological patterns of disease varied widely among these 32 patients (Table 2). All 32 cases showed at least mild portal inflammation. No significant differences in the rate of interface hepatitis or plasma cell infiltration, which are considered hallmark findings of chronic AIH, were found between the groups. Only one patient showed massive lobular necrosis with a mild degree of portal inflammation and interface hepatitis. This case was confirmed as AIH-a, described as follows.

Table 1 Characteristics of patients with autoimmune hepatitis (AIH) with acute presentation or chronic AIH

| Factors                  | AIH with acute presentation | Chronic AIH | P-value |
|--------------------------|-----------------------------|-------------|---------|
|                          | Sex, male: female           | 1:15        | 3:13    | 0.600 |
|                          | Age, years                  | 56.9 ± 14.6 | 63.0 ± 11.9 | 0.220 |
|                          | BMI, kg/m²                  | 22.0 ± 3.1  | 22.9 ± 2.3 | 0.390 |
|                          | Total bilirubin, mg/dL      | 3.7 ± 5.0   | 2.0 ± 2.2 | 0.258 |
|                          | AST, IU/L                   | 982 ± 196   | 262 ± 175 | 0.177 |
|                          | ALT, IU/L                   | 934 ± 133   | 298 ± 235 | 0.088 |
|                          | ALP, IU/L                   | 520 ± 211   | 599 ± 238 | 0.344 |
|                          | Albumin, g/dL               | 3.8 ± 0.5   | 3.5 ± 0.5 | 0.185 |
|                          | PT, %                       | 70.9 ± 23.5 | 75.2 ± 15.8 | 0.559 |
|                          | IgG, mg/dL                  | 2213 ± 1507 | 2107 ± 889 | 0.816 |
|                          | ANA, ≥40-fold, <40-fold     | 12:4        | 13:3     | 1.000 |
|                          | IAIHG scoring system        | 16.1 ± 2.1  | 16.1 ± 3.7 | 0.115 |

Table 2 Histopathological findings in patients with autoimmune hepatitis (AIH) with acute presentation or chronic AIH

| Pathological findings | AIH with acute presentation | Chronic AIH | P-value |
|-----------------------|-----------------------------|-------------|---------|
|                       | No. of cases                |             |         |
| Activity              | None | Mild | Moderate | Severe | None | Mild | Moderate | Severe |             |         |
| Portal fibrosis       | 6    | 10   | 0        | 0      | 2    | 9    | 3        | 2      | 0.012 |
| Portal inflammation   | 6    | 7    | 3        | 3      | 10   | 4    | 1        | 3      | 4.51 |
| Lobular inflammation  | 0    | 7    | 9        | 9      | 6    | 5    | 5        | 5      | 0.019 |
| Interface hepatitis   | 1    | 8    | 1        | 6      | 3    | 10   | 3        | 1      | 0.478 |
| Rosette formation     | 4    | 7    | 2        | 3      | 9    | 6    | 1        | 0      | 0.023 |
| Spotty necrosis       | 2    | 2    | 5        | 7      | 6    | 2    | 6        | 2      | 0.045 |
| Plasma cell infiltration | 10  | 2    | 4        | 4      | 6    | 4    | 4        | 4      | 0.451 |
| Neutrophils infiltration | 1   | 11   | 3        | 1      | 2    | 10   | 4        | 0      | 0.628 |
| Centrilobular necrosis | 10  | 2    | 3        | 1      | 6    | 6    | 3        | 1      | 0.473 |
| Seroid-laden macrophages | 5   | 2    | 1        | 8      | 12   | 2    | 1        | 1      | 0.003 |
| Single-cell necrosis  | 0    | 4    | 0        | 12     | 2    | 8    | 2        | 4      | 0.006 |
| Collapse of hepatocytes | 10  | 2    | 2        | 2      | 10   | 2    | 2        | 2      | 1.000 |
| Clear cell changes in hepatocytes | 2   | 9    | 2        | 3      | 2    | 8    | 4        | 2      | 0.890 |
| Biliary duct injury   | 13   | 1    | 0        | 2      | 9    | 6    | 1        | 0      | 0.838 |
|DUCTURAL reaction of hepatocytes | 12  | 2    | 0        | 2      | 4    | 8    | 3        | 1      | 0.104 |
| Cholestasis           | 14   | 1    | 0        | 1      | 16   | 0    | 0        | 0      | 0.910 |

Activity, portal inflammation, lobular inflammation, and plasma cell infiltration were categorized into three groups (mild, moderate, and severe). Other findings were categorized into four groups (none, mild, moderate, and severe).
A 75-year-old woman complaining of general fatigue was referred to our hospital (Fig. 1). She had never been found to have abnormal liver function at her routine 6-monthly examination. The TB, AST, ALT, IgG, and ANA levels, and the percent prolongation of prothrombin time (PT) were 1.9 mg/dL, 580 IU/L, 629 IU/L, 1462 mg/dL, <1:40, and 80.0%, respectively, on admission. Unenhanced computed tomography showed hepatomegaly with homogenous structures, although heterogeneous hypoattenuated areas within the liver are

Figure 1 Clinical course of a 75-year-old woman with acute-onset autoimmune hepatitis. ALT, alanine aminotransferase; PSL, prednisolone; PT, prothrombin time; TB, total bilirubin. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 2 Histopathology of a 75-year-old woman with acute-onset autoimmune hepatitis, showing massive centrilobular necrosis with a mild degree of portal inflammation and interface hepatitis. [Color figure can be viewed at wileyonlinelibrary.com]

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often present in acute or severe AIH. Liver histology obtained from this AIH-a patient showed massive centrilobular necrosis with a mild degree of portal inflammation and interface hepatitis (Fig. 2). These findings are compatible with AIH-a.

In contrast to this case, we also report a typical sudden onset case with severe liver dysfunction showing acute exacerbation of C-AIH detected histologically. A 57-year-old man complaining of general fatigue and appetite loss with elevated serum levels of TB, AST, ALT, and prolongation of prothrombin activity was referred to our hospital (Fig. 3). The TB, AST, ALT, IgG, and ANA levels, and the percent prolongation of PT were 3.4 mg/dL, 8497 IU/L, 5954 IU/L, 1387 mg/dL, 1:80, and 18.0%, respectively, on admission. Unenhanced computed tomography showed hepatomegaly with homogenous structures (Fig. 4). Liver histology obtained from this AIH-a patient with severe disease on day 7 after admission showed portal inflammation and rosette formations without submassive lobular necrosis (Fig. 5). The patient was treated with steroid pulse therapy and responded well. The values of AST and ALT were maintained within normal limits with ursodeoxycholic acid following steroid pulse therapy.

These findings support the view that AIH is a priority chronic disease. There were no marked between-group differences in the rates of portal inflammation, interface hepatitis, plasma cell infiltration, neutrophil infiltration, centrilobular necrosis, collapse of hepatocytes, clear cell changes in hepatocytes, biliary duct injury, ductular reactions of hepatocytes, or cholestasis. The degree of activity, lobular inflammation, rosette formation, spotty necrosis, seroid-laden macrophages, and single cell necrosis were more severe in AIH-a patients, whereas the degree of fibrosis was more severe in C-AIH patients.
Treatment

One of the AIH-a patients was treated with corticosteroid pulse therapy (1000 mg/day for 4 days). Two of the C-AIH patients responded well to ursodeoxycholic acid only. The other 29 patients responded well to corticosteroid therapy (0.5–0.8 mg/kg/day).

DISCUSSION

Some researchers have defined AIH-a as sudden onset of jaundice, anorexia, nausea, and fatigue, in addition to ALT levels >300 IU/mL. In our study, patients with AIH-a were defined as those whose ALT levels had been within normal limits for >12 months previously and had only recently been found to have abnormal ALT levels for the first time.

It has been reported that ANA antibodies are absent or weakly positive (titers less or 1:40) in 29–39% of patients, and serum IgG levels are normal in 25–39% of patients, with acute and fulminant AIH. In our study, ANA antibodies (titers 1:40 or higher) were present in 75% (12/16) of AIH-a patients and 81% (13/16) of C-AIH patients, with no marked difference between the groups. Increased serum levels of IgG (≥1 time the upper limit of normal) were found in 8 of 12 (75%) AIH-a patients and 10 of 12 (83%) C-AIH patients. No significant difference in serum IgG levels was evident between the groups.

The diagnostic scores assigned by the revised original system of the IAIHG were 16.1 ± 2.1 in the AIH-a patients and 16.1 ± 3.7 in the C-AIH patients, which also were not significantly different. These results show that the basal immunological reactions are similar between AIH-a and C-AIH patients. Our findings seem to be consistent with the notion that both recent- and acute-onset AIH occur against a background of subclinical chronic AIH. In addition, the sex, age, body mass index, serum levels of TB, AST, ALT, albumin, PT, IgG, and ANA, and IAIHG scores showed no significant differences between the AIH-a and C-AIH patients, although the serum levels of ALT in the AIH-a patients tended to be higher than those in the C-AIH patients. Therefore, it is difficult to distinguish AIH-a patients from C-AIH patients based on clinicolaboratory data alone.

Lobular hepatitis and centrilobular necrosis, including submassive and massive necrosis, were characteristically within the histological spectrum, especially in AIH patients with acute presentation. Centrilobular necrosis might reflect an early lesion in AIH-a preceding portal involvement. However, nowadays, the concept of AIH-a is assumed to include patients with C-AIH that has exacerbated spontaneously.

The common feature of all acute presentations is the presence of liver inflammation manifested by marked

Figure 5 Histopathology of a 57-year-old man with acute-onset autoimmune hepatitis, showing interface hepatitis with lymphoplasmacytic inflammatory infiltrate and rosette formation (arrow). [Color figure can be viewed at wileyonlinelibrary.com]
serum ALT elevation and histological changes. The features of centrilobular necrosis without portal inflammation typify acute onset disease.

Therefore, we anticipated that the liver biopsies taken from AIH-a patients would show an acute hepatitis-like pattern, that is, lobular hepatitis with confluent necrosis but no portal inflammation; such pure acute hepatitis was found in only one case among the 16 patients with AIH-a. However, this case showed a mild degree of portal inflammation and interface hepatitis. In contrast, one case that occurred fulminantly showed a flare of a pre-existing condition histologically. Therefore, the use of clinical terms such as acute, unresolved, and chronic disease is inappropriate because, from our histological findings, clinically occult, long-standing chronic disease appears to be quite common in these patients.

In our study of 16 AIH-a and 16 C-AIH patients, activity, lobular inflammation, rosette formation, spotty necrosis, seroid-laden macrophages, and single-cell necrosis, which are recognized in the acute stage, were found more frequently in AIH-a patients. Regarding the histological signature of classical autoimmune hepatitis, the presence of interface hepatitis and rosette formation has been addressed. We noted no marked difference in the rates of histological findings such as interface hepatitis and plasma cell infiltration between the groups in our study, suggesting that AIH-a occurs against a background of chronic AIH. Although a diagnosis of acute or fulminant autoimmune hepatitis cannot be established by histological findings alone, our findings reconfirmed that most AIH-a cases have a lobular “flare” in disease activity. Only portal fibrosis was more frequent in C-AIH patients than in AIH-a patients. Moderate or severe degrees of fibrosis were not found in AIH-a patients, while moderate or severe degrees of fibrosis were found in 5 C-AIH patients; the difference was statistically significant (P = 0.012). Portal fibrosis might be a potential marker for C-AIH.

Acute AIH responds as well to conventional corticosteroid therapy as does AIH with a chronic presentation. In our study, one patient with AIH-a who showed prothrombin activity of 18% was treated with steroid pulse therapy and responded well. The other 11 patients with AIH-a responded well to corticosteroids. Two patients with C-AIH responded well to ursodeoxycholic acid, and the other 10 patients with C-AIH responded well to corticosteroids. Although standard therapy with corticosteroids was effective in most cases in both groups, non-standard drugs such as steroid pulse therapy should be considered in severe cases of both AIH-a and C-AIH.

In conclusion, the existence of a genuine acute form of AIH characterized by the presence of massive central necrosis, no or mild inflammatory infiltration in the portal area, and no portal fibrosis could not be denied. However, given the similarities in the clinicolaboratory features and common histological findings such as interface hepatitis and plasma cell infiltrations between the two groups, most cases of AIH-a might be attributed to an exacerbation of pre-existing subclinical C-AIH.

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