Chapter 6
Acute Presentation of Autoimmune Hepatitis

Masanori Abe and Morikazu Onji

Abstract Autoimmune hepatitis (AIH) can present as acute hepatitis in its onset of symptoms and features, progressing to severe hepatitis and acute liver failure. In a recent national survey in Japan, 10.9 % of the patients with AIH were diagnosed with acute hepatitis. Some patients with acute presentation of AIH lack the typical features of AIH, such as increased serum immunoglobulin G levels and high autoantibody titers. For accurate diagnosis, it is essential to exclude the other possible causes that can lead to acute hepatitis, and liver biopsy should be performed early if appropriate. Centrilobular necrosis without interface hepatitis or fibrosis is considered to be the histological characteristic in the acute hepatitis phase of AIH. Interface hepatitis is a hallmark characteristic of AIH; therefore, its absence in acute hepatitis phase can lead to missed diagnosis of AIH. Most patients with an acute presentation of AIH respond well to corticosteroid therapy; however, the prognosis of AIH patients worsens with progression to acute liver failure. Liver transplantation is a possible treatment option for patients with acute liver failure who do not respond to corticosteroid therapy.

Keywords Acute hepatitis • Acute liver failure • Autoimmune hepatitis

6.1 Introduction

Autoimmune hepatitis (AIH) is a persistent inflammatory liver disorder from unknown causes that is histologically characterized by lobular hepatitis, interface hepatitis, and mononuclear cell infiltration predominantly consisting of plasma

M. Abe (✉)
Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Shitsukawa, To-on, Ehime 791-0295, Japan
e-mail: masaben@m.ehime-u.ac.jp

M. Onji
Imabari Saiseikai Medical-Welfare Center, Ehime, Japan

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cells; the serological characteristics of AIH include the presence of autoantibodies, hypergammaglobulinemia, and elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels [1, 2]. As the diagnostic techniques for detecting hepatitis viruses have been improved, the clinical entry criteria of AIH have been more clearly established. The diagnostic criteria of AIH, based on clinicopathological features, were proposed by the International AIH Group (IAIHG) [3, 4]; these criteria have been widely accepted and used as useful diagnostic tools in clinical practice. Recently, a diagnostic guide for AIH was proposed by the Intractable Hepatobiliary Disease Study Group in Japan [5].

Most patients with AIH present with chronic hepatitis with or without specific symptoms or are observed to have liver dysfunction during routine medical examination. However, since Lefkowitch et al. first reported a case in 1984 [6], the numbers of patients with acute presentation of AIH have increased in Japan [7–13]. The acute presentation of AIH comprises clinical features of acute hepatitis with histological evidence of chronic hepatitis (acute exacerbation) or those of acute hepatitis (acute hepatitis phase); in these patients, histopathological assessment of the liver is necessary for accurate discrimination and diagnosis [14–16] (Box 1). In addition, some patients with AIH progress to acute liver failure, including fulminant hepatitis or late-onset liver failure (LOHF) [17–21].

The clinical features of Japanese AIH differ from those of Caucasian patients. In this chapter, we have mainly focused on the clinical features of Japanese AIH patients with acute presentation.

Box 1. Proposal of Autoimmune Hepatitis Presenting with Acute Hepatitis, Severe Hepatitis, and Acute Liver Failure [14]

Sometimes autoimmune hepatitis (AIH) may present in patients with no previous history of liver disease as acute hepatitis, severe hepatitis, or acute liver failure (fulminant hepatitis and late-onset liver failure [LOHF]). The disease is characterized by the presence of autoantibodies, such as antinuclear and anti-smooth muscle antibodies, and elevated serum bilirubin, transaminases, and immunoglobulin (Ig)G. However, atypical presentation may also occur. In such cases, it is necessary to exclude the possibilities of diagnosis of acute viral hepatitis and drug-induced liver injury.

There are two types of AIH presentation, for which assessment of liver biopsy specimens is necessary for an accurate discrimination:

(1) Acute exacerbation phase in which patients show clinical features of acute hepatitis with histological evidence of chronic hepatitis, such as the presence of fibrosis and moderate to severe inflammatory cell infiltrations in the portal tracts.
(2) Acute hepatitis phase in which patients exhibit histological features of acute hepatitis, such as centrilobular necrosis, without or with minimal

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periportal hepatitis. These patients sometimes show lower serum levels of IgG and/or the absence or low titers of serum autoantibodies. Some patients may exhibit histological features of transition to chronicity.

Patients with AIH usually respond well to corticosteroid treatment. For AIH patients in the acute hepatitis phase, however, diagnosis is sometimes difficult and the start of therapy is delayed. Patients progressing to acute liver failure (fulminant hepatitis and LOHF) become resistant to corticosteroid treatment, and their prognoses become poor. Consequently, liver transplantation is also considered as a therapeutic option in such patients.

Appendix

1. There are some cases with two types of presentation and a clear classification of these is difficult.
2. Some cases might be considered as non-A–E acute hepatitis.
3. Response to immunosuppressive therapy is sometimes better in young AIH patients with acute liver failure.
4. Further studies are necessary to clarify the relationship between the severity of hepatitis and the response to corticosteroid treatment.

6.2 Prevalence of the Acute Presentation of AIH

Most epidemiology data concerning the acute presentation of AIH in Japan is obtained from single-center studies (mainly tertiary referral hospitals) [8–12]. The reported prevalence has varied widely probably due to selection bias, rarity of the disease, and lack of uniformity in the diagnostic criteria used to identify cases. In a Japanese nationwide survey study conducted in 1991, 5.6 % of patients with AIH were found to have a feature of acute hepatitis upon histological examination [7]. The most recent Japanese survey was performed in 2009, which enrolled 1,056 patients with AIH from 153 hospitals and clinics throughout Japan [13]. Histological assessment results were available for 871 patients, and 95 patients (10.9 %) were diagnosed with acute hepatitis.

Few descriptive epidemiology studies are available concerning the prevalence of AIH in Japanese patients presenting with acute hepatitis. In 2006, Fukumoto et al. [22] surveyed the etiology of acute hepatitis in 1,815 patients from 15 hospitals in the Chugoku area; the prevalence of AIH was 1.3 %. In 2011, a nationwide survey of acute hepatitis was conducted in Japan [23]. The etiology of 2,547 patients with acute hepatitis from 103 hospitals throughout Japan was analyzed. The most prevalent cause was hepatitis B virus (31.8 %), followed by AIH (14.0 %). These results cannot be directly compared since the criteria used in these studies were different; however, these data suggest that the number of patients with acute presentation of AIH has increased recently.

The definition, classifications, and diagnostic criteria for acute liver failure differ between Japan and European countries and the United States. In 2011, the Intractable Hepatobiliary Disease Study Group in Japan established novel diagnostic criteria for acute liver failure, including the disease entity of fulminant hepatitis [24]. A nationwide survey of patients with acute liver failure in 2010 using this criteria showed that AIH was found in 16 of 220 patients (7.2 %) with acute liver failure and LOHF, including 9 of 96 patients (9.3 %) with acute liver failure without hepatic coma, 4 of 54 patients (7.4 %) with the subacute type of fulminant hepatitis, and 3 of 9 patients (33.3 %) with LOHF [25]. Very recently, the classification of the etiologies of acute liver failure was proposed by the same group [26]. In this classification, patients satisfying the diagnostic guide for AIH [5], or those positive for antinuclear antibody (ANA) or serum immunoglobulin G (IgG) concentrations 1.1 times the upper limit of normal range or greater, are diagnosed with acute liver failure due to AIH. Further studies using this classification are considered necessary.

6.3 Pathogenesis of the Acute Presentation of AIH

The causes of the acute presentation of AIH—either as acute hepatitis or as acute exacerbation—are unknown. As in other autoimmune diseases, it is believed that AIH develops in individuals with genetic predisposition under the influence of environmental factors. Most genetic data for AIH is derived from studies of HLA genes. Several studies indicate that HLA may influence the clinical phenotype of AIH [27]. HLA-DR4 is the major susceptibility factor for AIH in Japan [28, 29]; however, a difference in HLA for the acute presentation of AIH has not been indicated. Genetic polymorphisms of non-HLA genes, such as *cytotoxic T lymphocyte antigen 4* and *tumor necrosis factor alpha*, may also influence the clinical phenotypes of AIH [30]. To identify the genes influencing the susceptibility and clinical profile of AIH, genome-wide association studies are underway in a Japanese cohort.

It is very difficult to obtain information regarding the immunological reactions responsible for the initiation of AIH. The use of animal models might improve our understanding of the pathophysiology of this disease. Several models of experimental AIH have been reported by Japanese researchers (described in detail in Chap. 2); most of these models show acute hepatitis rather than chronic hepatitis. Recently, Kido et al. [31] reported a mouse model of spontaneous acute presentation of AIH model by inducing concurrent loss of $FoxP3^{+}$ regulatory T cells and PD-1-mediated signaling. $PD\text{-}1^{-/-}$ mice develop AIH characterized by T cell infiltration and increased ANA titers, indicating a role of autoreactive and regulatory T cells in the pathogenesis of acute presentation of AIH.

Defects in liver regeneration have been implicated as a factor contributing to the acute presentation of AIH. Fujiwara et al. [32] reported the immunohistochemical evaluation of liver tissue with cytokeratin 7 in patients with acute presentation of

AIH and demonstrated the presence of intermediate hepatocytes and intralobular progenitor cells in patients with severe acute presentation of AIH. These findings were less common in patients with non-severe presentation, indicating that impairment in the liver's regenerative response may contribute to the development or progression to acute liver failure.

6.4 Diagnostic Features of the Acute Presentation of AIH

Acute presentations of AIH are recognized in both adults and children. Fujisawa et al. [33] reported that 5 out of 12 Japanese children with AIH showed acute presentation. The clinical features of AIH in Japanese children are described in detail in Chap. 9; therefore, we have mainly focused on the acute presentation of AIH in Japanese adults in this chapter.

Most reports have demonstrated that the acute presentation of AIH typically affects middle-aged women, and their profiles are indistinguishable from those with chronic presentation in terms of age and gender [8–11]. However, Miyake et al. [12] showed that the age at diagnosis of acute hepatitis phase was younger than that of chronic hepatitis.

6.4.1 Laboratory Features

Blood biochemistry tests have shown that the acute presentation of AIH is associated with higher serum levels of AST, ALT, and total bilirubin and with lower prothrombin time (PT) activity as compared with chronic presentation [8–12]. In contrast, serum levels of γ-globulin or IgG have been reported to be lower in the acute presentation of AIH [8, 9, 11, 12]. In addition, some patients with acute presentation of AIH showed the absence or low titers of serum autoantibodies, particularly ANA. There are several differences in laboratory data among studies concerning the acute presentation of AIH, with many possible reasons for these discrepancies. First, the time points at which laboratory data were obtained may be different for each patient since all the studies were conducted retrospectively. The duration between the initial onset of symptoms and the time of diagnosis of AIH was variable, and liver injury was already in progress at the time of admission in some patients. In fact, several groups have reported IgG levels to be higher in patients with severe hepatitis or acute liver failure than those in non-severe patients [18, 19]. Second, some studies have analyzed the "acute hepatitis phase" (histologically proven acute hepatitis) as acute presentation [7, 8, 11, 12], while others have included both "acute hepatitis phase" and "acute exacerbation phase" in the definition [9, 10, 12]. Further studies with larger cohort using a well-defined classification may be necessary to clarify the clinical features of the acute presentation of AIH.

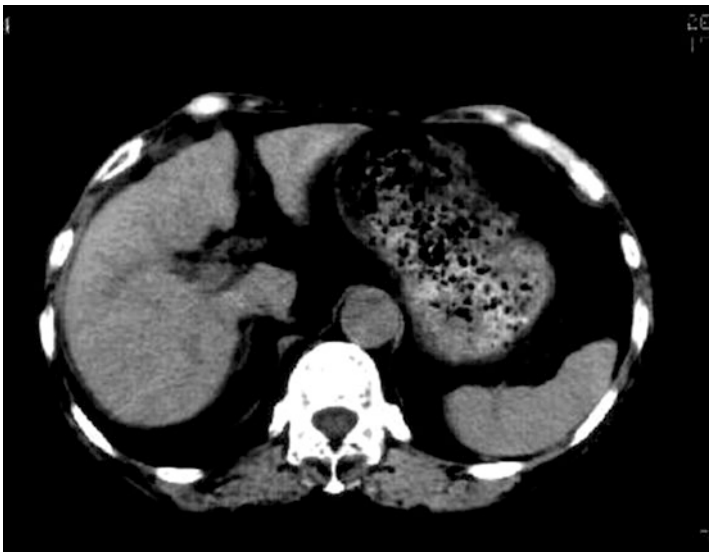

Fig. 6.1 Computed tomography image of a patient with fulminant hepatitis resulting from AIH. In addition to the liver atrophy (estimated liver volume, 440 g), an area of heterogeneous hypoattenuation was present

6.4.2 Imaging Study Findings

As described later, histological examination is useful for diagnosing patients with acute presentation of AIH. However, it is sometimes difficult to perform liver biopsy in such patients due to the presence of complicated coagulopathy and/or ascites. Yasui et al. [34] reported the usefulness of computed tomography (CT) in the diagnosis of acute liver failure due to AIH (Fig. 6.1). They showed that the heterogeneous area of hypoattenuation in the liver, which may reflect massive necrosis and preserved parenchyma, was present in 65 % of the patients with acute liver failure due to AIH.

6.4.3 Histological Features

Histological examination of liver tissue is essential in order to confirm the diagnosis of AIH and evaluate the severity of the disease. The typical histological pattern of AIH comprises interface hepatitis with portal and periportal plasma cells, hepatocyte rosettes, and in severe cases bridging necrosis or acinar collapse [1, 2]. In addition, histological evaluation is necessary to discriminate between acute hepatitis phase and acute exacerbation in patients with acute presentation of AIH [14–16].

In acute presentation, centrilobular necrosis (zone 3 necrosis), including submassive and massive necrosis—rarely seen in patients with chronic

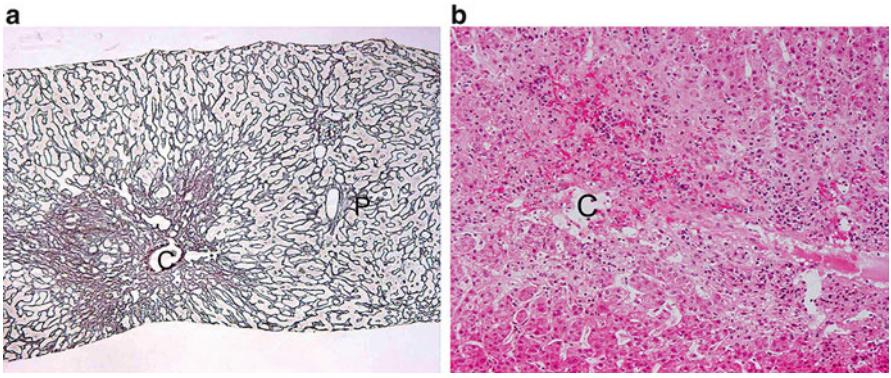

Fig. 6.2 Liver histology of a patient in the acute hepatitis phase of AIH. Hepatocellular zonal necrosis was present in the centrilobular area (C). Portal tracts (P) are preserved without evident inflammatory changes (**a**, reticulin staining; **b**, H&E staining)

presentation—has been observed frequently (Fig. 6.2) [8–12, 18, 19, 35–38], although it is a nonspecific histological finding also observed in other liver diseases, such as acute viral hepatitis or drug-induced liver injury. In particular, centrilobular necrosis with minimal to mild portal inflammation and without interface hepatitis or fibrosis is considered to be the characteristic histological feature of the acute hepatitis phase of AIH [14–16]. According to the studies that performed follow-up biopsy at the time of recurrence of AIH, some patients progressed to the typical histological features of AIH, indicating that centrilobular necrosis may reflect early lesion preceding portal involvement; in contrast, other patients showed recurrent episodes of centrilobular necrosis. These data suggest that centrilobular necrosis with acute presentation of AIH may not be a single disease entity [36], and further studies are necessary in this regard. Further, plasma cell enrichment has also been demonstrated to be characteristic of the acute presentation of AIH [18, 39].

The Acute Liver Failure Study Group in the United States analyzed the histological characteristics of acute liver failure due to AIH [39]. Massive hepatic necrosis with centrilobular hemorrhagic necrosis or classical interface hepatitis was frequently observed in patients with AIH. In addition, they also proposed that the presence of central venulitis, plasma cell enrichment, and lymphoid aggregates represent histological features of acute liver failure due to AIH.

6.4.4 Diagnostic Scoring System

The revised scoring system proposed by IAIHG [4] has been widely accepted and incorporated into clinical practice. However, the acute presentation of AIH often lacks the typical features of AIH, such as high immunoglobulin levels and autoantibody titers, as described above. These features sometimes make the diagnosis of the acute presentation of AIH difficult according to this diagnostic scoring system [8, 9, 11, 12, 14–16].

In 2008, the simplified diagnostic criteria for the diagnosis of AIH were proposed by IAIHG [40]. Miyake et al. [41] reported that 77 % of patients with acute presentation and 50 % of those presenting with the acute hepatitis phase of AIH fulfilled the diagnostic requirements of the simplified criteria. In addition, Fujiwara et al. [42] reported that only 28 % of patients presenting with the acute hepatitis phase met the diagnostic criteria of the simplified system, although the frequency was 91 % for the revised scoring system. The superiority of the revised system for the diagnosis of the acute presentation of AIH probably reflects its comprehensive nature and the frequency at which serum immunoglobulin levels and autoantibody titers are low in such patients. However, it is important to make the diagnosis based on the scoring systems as well as using the comprehensive assessments.

6.5 Treatment of the Acute Presentation of AIH

The severity of the disease should be judged based on the diagnostic guide for AIH in Japan (Table 6.1) [5] when the diagnosis is made. According to the severity, the referral to an expert hepatologist should be also considered.

In Japan, the majority of the patients with acute presentation of AIH are treated with corticosteroid (CS) therapy as the initial medical treatment. In the most cases, the medication can be given as an oral dose; however, in severe cases, intravenous therapy, including pulse steroid treatment, may be necessary. In general, patients with acute presentation as well as chronic presentation respond well to CS therapy. However, patients with acute presentation tend to require a higher dose of initial CS than those with chronic presentation. In the Japanese treatment guide for AIH published in 2013 [5], it is recommended that predonisolone (PSL) should be administered at an initial daily dose of $\geq$0.6 mg/kg. However, a higher dose ($\geq$0.8 mg/kg) of PSL is necessary for more severe cases of AIH [43]. Some patients may require pulse steroid treatment for the rapid improvement of intrahepatic inflammation.

However, some reports have shown that the acute presentation of AIH is more refractory to CS therapy than chronic presentation. In our experience [18], patients with acute presentation of AIH without severe jaundice (total bilirubin $<$10 mg/dL) exhibited a very good response to CS treatment, whereas more than 50 % of the patients with severe jaundice did not respond to CS. However, our AIH patients without severe jaundice showed lower ANA titers, making the diagnosis of AIH considerably difficult. These findings indicate that the response to CS therapy may reflect the promptness of diagnosis and treatment.

The efficacy of steroid pulse treatment in AIH has been uncertain. Recently, Yamamoto et al. [21] reported that pulse steroid treatment showed favorable outcomes in AIH patients with PT activity of $>$40 % or PT-INR $<$1.5, but poorer prognosis in those with PT activity of $\leq$40 % or PT-INR $\geq$1.5. A prospective validation study is thus necessary to prove the efficacy of steroid pulse treatment for AIH.

Table 6.1 Severity of autoimmune hepatitis [5]

Clinical signs	Clinical laboratory tests	Imaging tests
① Hepatic encephalopathy ② Reduction or disappearance of hepatic dullness	① AST/ALT > 200 U/L ② Bilirubin > 5 mg/dL ③ Prothrombin time < 60 %	① Hepatic atrophy ② Heterogenous liver parenchyma pattern
Severe: should fulfill at least one of these three findings: 1. Clinical signs: ① or ② 2. Clinical laboratory tests: both ① and ③ or both ② and ③ 3. Imaging tests: ① or ②		
Moderate: should fulfill these findings: Clinical laboratory tests: one of the criteria (①, ②, or ③) or both ① and ②, without clinical signs (neither ① nor ②), and imaging tests (neither ① nor ②)		
Mild: none of the above criteria are observed		

Notes:

1. When patients are judged in to have severe disease, they should be referred to a hepatologist immediately
2. The scoring system for predicting mortality in patients with acute liver failure or late-onset liver failure, as established by the Intractable Hepatobiliary Diseases Study Group in Japan and the model for end-stage liver disease (MELD) score, should also be evaluated and considered in patients with severe disease
3. When patients show prothrombin time of <60 %, or in cases where intense jaundice is present, referral to a hepatologist should be considered, even if the patient has moderate disease

6.6 Treatment and Outcomes of Acute Liver Failure Due to AIH

In a Japanese nationwide survey involving patients with fulminant hepatitis and LOHF between 2004 and 2009 [44], the survival rate without liver transplantation was 32.4 % in AIH patients. Despite new therapeutic approaches and intensive care, the prognosis of such patients remains poor without liver transplantation.

Although there are certain controversies regarding this point [45, 46], CS therapy is considered the first treatment choice for patients with acute liver failure due to AIH [17–21, 47, 48]. However, not all patients respond to CS therapy. Protracted therapy with CS can be complicated with the risk of serious infections with a subsequent inability to undergo liver transplantation. Therefore, the decision whether to continue CS therapy or abandon it for liver transplantation is very important to a successful outcome. Miyake et al. [17] showed that serum bilirubin levels are an important prognostic factor, with worsening levels observed during days 8–15 after the diagnosis in non-survivors. Yasui et al. [19] showed that lower PT activity at the start of CS treatment and insufficient improvement in PT activity during the first 2 weeks after the initiation of CS treatment was associated with poor outcomes. These findings indicate that the treatment response to CS can be determined at 2 weeks after initiating treatment; further, alternative treatments should be considered in patients not showing improvement. Close monitoring for the

occurrence of infectious diseases, such as viral and/or fungal infections, is also required during CS therapy.

Liver transplantation is a possible treatment choice for acute liver failure due to AIH. In Japan, the indication for liver transplantation has been determined thus far based on the guideline proposed by the Intractable Hepatobiliary Disease Study Group of Japan in 1996 [49], and new guidelines have been recently proposed by the same group [50]. The survival of patients with acute liver failure due to AIH following transplantation was 68.8 % at 5 years in Japan; this outcome was similar to that for patients undergoing liver transplantation for acute liver failure due to other etiologies [51].

6.7 Summary

AIH can present with symptoms and features of acute hepatitis and develop into severe hepatitis and acute liver failure. Patients with acute presentation of AIH do not always show increased serum IgG levels and/or autoantibody positivity; the lack of such markers makes the diagnosis of AIH difficult in these cases. For accurate diagnosis, it is essential to exclude other possible causes of acute hepatitis, and early liver biopsy should be performed if appropriate. Most patients with acute presentation of AIH respond well to CS therapy; however, when the disease progresses to acute liver failure, the response of the patient to CS treatment as well as prognosis is poor. Although the acute presentation of AIH is associated with several unsolved problems, it is clinically important that AIH be considered in the differential diagnoses for patients with unexplained acute hepatitis or acute liver failure. Early diagnosis and treatment may improve the prognosis of these patients.

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