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Case Report

Autoimmune hepatitis showing spontaneous remission and acute exacerbation

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Abstract

Autoimmune hepatitis (AIH) represents a chronic liver disease with a progressive nature. Cortocosteroid therapy is routinely used to control this pathological condition. Herein, we describe a case of AIH with spontaneous remission and exacerbation. A previously healthy young Japanese woman presented with features of acute hepatitis. The patient was not acutely infected with hepatotrophic viruses and the possibility of drug-induced AIH was also excluded. A diagnosis of AIH was made from subjective symptoms and laboratory data, which showed increased levels of liver enzymes, total bilirubin, IgG and positive titers of antinuclear antibody. Finally, liver biopsy revealed an expansion of portal tracts and infiltration of mononuclear cells, including plasma cells. This patient experienced a total of three episodes of acute exacerbation of AIH during the past 5 years, two of which subsided spontaneously. An immunosuppressive drug was used to control the last episode of acute exacerbation of AIH, which was very similar to acute hepatitis. The immunosuppressive drug was withdrawn 7 months after the last epoisode of acute exacerbation of AIH and the patient is now passing an uneventful course. There are cases of spontaneous remission and acute exacerbation of AIH, although the underlying mechanism of this pathological process is yet to be determined. Liver biopsy is needed to diagnose these cases. Periodic follow up of these patients is required for proper management.

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Introduction

Autoimmune hepatitis (AIH) represents a type of chronic liver disease with an autoimmune etiology that is characterized by female predominance, hypergammaglobulinemia and the presence of auto-antibodies in the sera.[1–3] Diagnosis of AIH is based on clinical, biochemical and histopathological findings. Exclusion of identifiable viruses, drugs, primary biliary cirrhosis, Wilson's disease and hemochromatosis is essential to diagnose AIH. The presence of plasma cells in the liver is helpful to make a histological diagnosis. Most patients with AIH show very good responses to immunosuppressive therapy.[4] The disease usually runs a progressive courses, although an acute pattern of AIH has been described recently.[5,6] In both chronic and acute patterns of AIH, immunosuppressive drugs are routinely used to bring about a remission. Spontaneous remission of AIH is an unusual phenomenon and only a few such cases have been reported.[7] Herein, we report on a patient with AIH who had three episodes of acute exacerbation and subsequent remission of AIH; two of these remissions were achieved without any immunosuppressive drugs.

Clinical summary

The patient was a 29-year-old woman. Her family history was non-contributing to her present illness and the patient was free from history of allergic diseases and had never had a blood transfusion. She was not even a habitual smoker or a social drinker. On 14 September 1998, the patient was referred to Ehime University Hospital from a nearby hospital for evaluation of her liver function test.

The patient's past history showed that she was admitted into the local hospital on 10 December 1996 with a complaint of general fatigue, jaundice, fever, itching, upper abdominal discomfort and arthalgia of the left hip joint. She was not using any medication prior to her admission at that time. The clinical course of this patient is summarized in Fig. 1. Biochemical tests revealed that she had very high levels of serum bilirubin (5.48 mg/dL), asparate aminotransferase (AST; 1334 IU/L), alanine aminotransferase (ALT; 1652 IU/L), γ-glutamyltranspeptidase (γ-GTP; 122 IU/L) and alkaline phosphatase (ALP; 277 IU/L). Although the peripheral blood cell counts and the levels of hemoglobin were within the normal range, urinary bilirubin was detected during urinalysis. The patient was negative for all viral markers and had a normal thyroid function test. The lupus erythromatosus phenomenon was negative and the titer of antinuclear antibodies (ANA) was 1 : 80 with a homogeneous and speckled type of staining. The only abnormal finding on abdominal ultrasonography was the thickness of the gall-bladder. Abdominal ultrasongraphy, computed tomography and magnetic resonance cholangiography revealed that there was no dilatation of the common bile duct or swelling of the gall-bladder. The patient was diagnosed as acute hepatitis and was given intravenous Stronger Neo Minophagen C (SNMC;

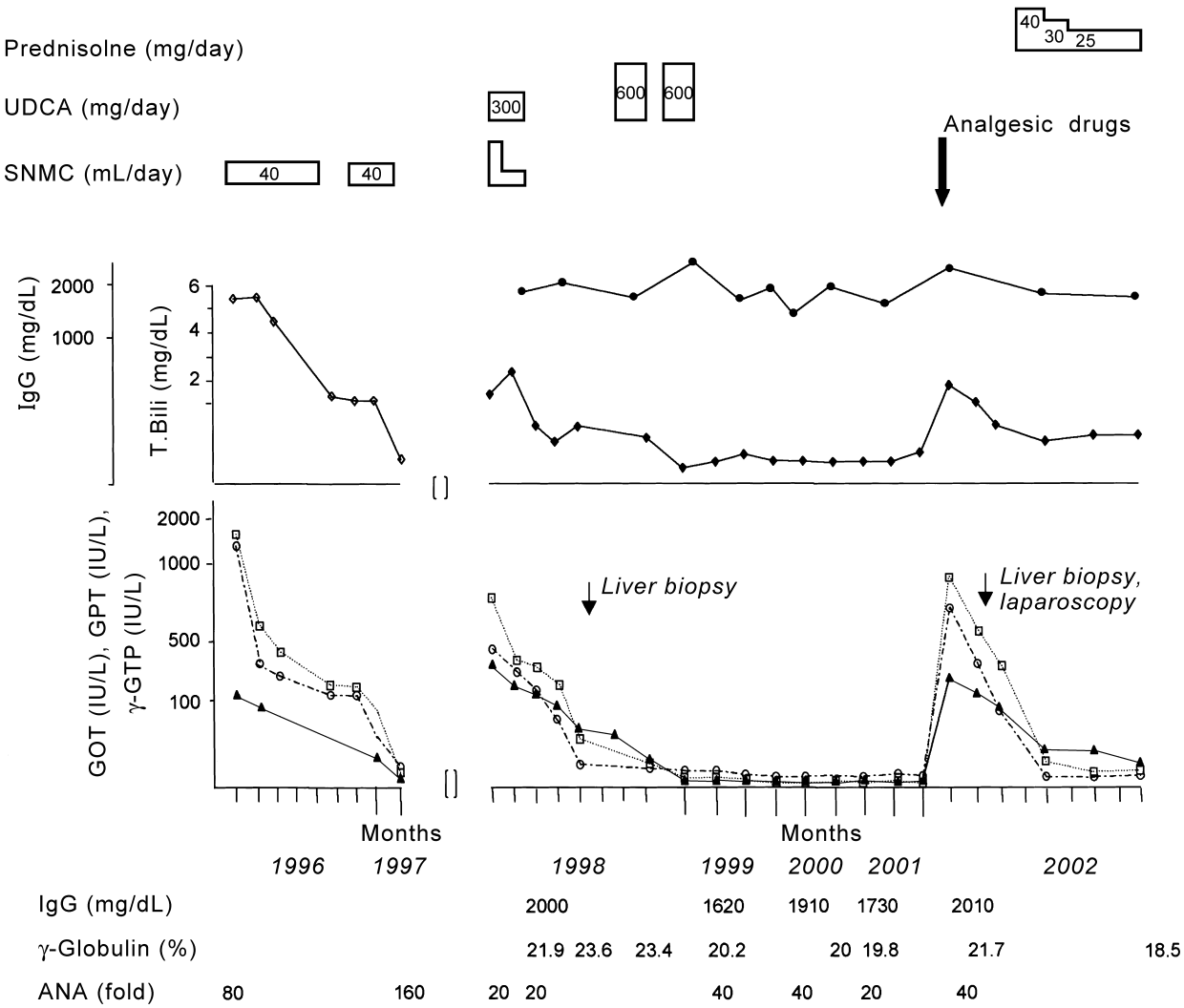

Fig. 1 Clinical course of the patient with autoimmune hepatitis (AIH). (a) The drugs used. (b) Levels of total bilirubin (TBil; ●) and IgG (◆). (c) Levels of alanine aminotransferase (ALT; □), aspartate aminotransferase (AST; ○) and γ-glutamyl transpeptidase (g-GTP; ▲). Liver biopsy was performed twice, once on 1 October 1998 and then on 23 October 2001. UDCA, ursodeoxycholic acid; SNMC, Stronger Neo Minophagen C (Minophagen Pharmaceutical, Tokyo, Japan); ANA, antinuclear antibodies.

Minophagen Pharmaceutical, Tokyo, Japan) at a dose of 40 mL/day, which was discontinued on 24 December 1996 due to marked improvement of the patient's liver function test.

On 24 August 1998, approximately 20 months after her first attack, the patient was readmitted to the local hospital with an abnormal liver function test and was given SNMC along with a daily dose of 300 mg ursodeoxycholic acid (UDCA). Being referred from that nearby hospital, she was admitted to our hospital for the first time on 14 September 1998. On admission, the patient was alert with normal body temperature. Vital signs were normal and she had a good appetite. Physical examination did not reveal anemia, hepatomegaly, splenomegaly or ascites. The laboratory data on admission to our hospital are given in Table 1. The patient had normal levels of serum total bilirubin (0.5 mg/dL), but the levels of liver enzymes in the sera were moderately elevated (AST 77 IU/L; ALT 193 IU/L; γ-GTP 99 IU/L; ALP 172 IU/L). Serum IgG was 2000 mg/dL and the titers of autoantibodies were not markedly elevated. Major histocompatibility complex (MHC) typing indicated that she had HLA-DR1 and HLA-DR2. She was negative for markers of hepatitis viruses, except for transfusion-transmitted virus DNA. No abnormality was found on abdominal ultrasonography and upper gastrointestinal endoscopy. The size of the liver, spleen and pancreas was normal. Thirty-seven days after onset of this episode, a liver biopsy was obtained under ultrasonography, which revealed expansion of portal areas with an infiltration of mononuclear cells containing approximately 5% plasma cells (Fig. 2a). Focal necrosis (one to three per lobule) and interface hepatitis were also detected in the liver specimen. According to a modified histologic activity index (HAI) score, the histological diagnosis was chronic hepatitis with moderate activity and mild fibrosis. The patient scored 11 points according to the scoring system recommended by the International Autoimmune Hepatitis Group and she was diagnosed as 'probable AIH'. She was given 600 mg/day UDCA and her liver function tests soon improved. The patient was discharged and was followed up at our out-patient department.

After approximately 3 years, on 10 October 2001, the patient developed high fever (39°C), chilliness and nasal obstruction. Although she became afebrile the following day, general fatigue, abdominal discomfort and symptoms suggestive of a common cold continued. This led her to take analgesic drugs, such as acetoaminophen, isopropamide and diclofenac sodium. On 14 October 2001, the patient noticed itching and dark urine and was admitted to our hospital on 17 October 2001 (Fig. 1).

On admission, the patient complained of poor appetite and jaundice, but no abdominal pains. On examination, the liver was found to be enlarged and palpable (two to three fingers in breadth below the right costal margin). As shown in Table 1, increased levels of total bilirubin and liver enzymes were detected at this time. The ANA titer was elevated (1 : 40). The drug-induced lymphocyte stimulating test was negative for acetoaminophen, isopropamide and diclofenac sodium. Two stones were detected in the gall-bladder by abdominal ultrasonography. Two days later, upper gastrointestinal

Table 1 Laboratory data

	September 1998	October 2001
Total bilirubin (0.2–0.8 mg/dL)	0.5 mg/dL	2.2 mg/dL
Alanine aminotransferase (3–49 IU/L)	193 IU/L	874 IU/L
Asparate aminotransferase (9–37 IU/L)	77 IU/L	600 IU/L
γ-Glutamyl transpeptidase (6–71 IU/L)	99 IU/L	198 IU/L
γ-Globulin (8.6–20%)	21.9%	21.9%
IgG (870–1700 mg/dL)	2000 mg/dL	2010 mg/dL
IgM (35–220 mg/dL)	116 mg/dL	114 mg/dL
Antinuclear antibody (< 1 : 20)	1 : 20	1 : 40
Antismooth muscle antibody (< 1 : 20)	1 : 20	1 : 20
Antimitochondrial antibody (1 : 20)	1 : 20	< 1 : 20
Anti-M2 antibody (< 20 U/mL)	< 4 U/mL	< 4 U/mL
Anti-liver kidney microsomal antibody (< 17 U)	< 1 U	< 5 U
C-Reactive protein (< 0.25 mg/dL)	< 0.25 mg/dL	ND
Rheumatoid arthritis factor	< 11 IU/mL	ND
Lupus erythromatous phenomenon	Negative	ND

Figures in parentheses indicate the normal range.

ND, not done.

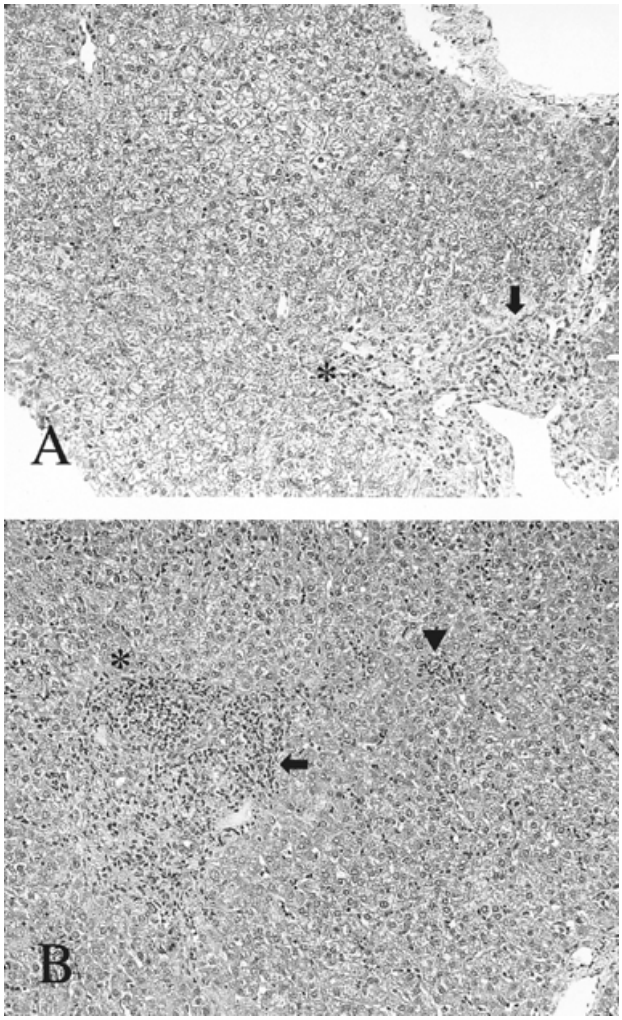

Fig. 2 Microscopic pictures of liver biopsy specimens taken on 1 October 1998 during the patient's second admission (a) and on 23 October 2001 during her third admission (b) to Ehime University Hospital. Expansion of the portal area (arrows), destruction of limiting plates (asterisk) and infiltration of mononuclear cells (arrowheads) are seen. Infiltration of mononuclear cells is also expanding into the hepatic parenchyma and liver sinusoids in (b). (Hematoxylin eosin staining.)

endoscopy showed erosive gastritis with antral atrophy and gastric ulcer. No abnormality was detected by magnetic resonance cholangiopancreatography.

A liver biopsy was performed on 23 October 2001 (7th admission day) under laparoscopy. This revealed an expansion of portal areas with portal–portal and portal–central bridging fibrosis. A moderate degree of lymphocyte infiltration into the portal tracts was observed and there were five to six focal necroses per lobule (Fig. 1). However, laparoscopic findings showed no evidence of reddish or whitish markings and depressions on the surface of the liver. The score for the diagnosis of AIH remained as before. Itching and skin rashes subsided. From 14th day of admission (30 October 2001), 40 mg/day prednisolone was prescribed, which was tapered subsequently. Due to an improvement of the patient's general condition and liver function tests, prednisolone was discontinued from 1 June 2002 and she was given UDCA (600 mg/day). The patient is currently under supervision at our out-patient department.

Discussion

Autoimmune hepatitis is a chronic liver disease with an autoimmune etiology, which takes a variable course and usually responds well to immunosuppressive therapy.[1–4] Herein, we report on a case of AIH showing acute exacerbation and subsequent spontaneous remission.

Although the patient experienced three attacks of acute hepatitis within the past 5 years, spontaneous remission of AIH was achieved in the first two episodes, whereas prednisolone therapy was required for the management of her last and most recent attack.

The diagnosis of this patient is important. The first attack of acute hepatitis, which she experienced in 1996 in a nearby hospital, was characterized by marked elevation of direct bilirubin and liver enzymes. Infection with hepatitis virus and drug-induced hepatitis were ruled out. Increased titers of ANA supported a clinical diagnosis of AIH; however, a histological diagnosis of AIH could not be made at that time due to a lack of a liver biopsy specimen.

The second attack of acute hepatitis, which was comparatively milder than the first, was characterized by increased levels of IgG in addition to elevated levels of liver enzymes. Moreover, a histological diagnosis of AIH was suggested from the presence of plasma cells in the portal areas.

The role of UDCA in bringing about a remission of AIH is controversal. Nakamura *et al*. have suggested a favorable effect of UDCA in AIH after using UDCA for 1 year;[8] however, Czaja *et al*. did not find any therapeutic role for UDCA in AIH.[9] In the present case, remission of AIH continued even after the cessation of UDCA, indicating that the contribution of UDCA, if any, would be insignificant for the remission of AIH.

Although drug-induced hepatitis due to diclofenac sodium may underlie the third and most recent attack of

hepatitis, this possibility was completely discarded on the basis of the clinical history, laboratory investigations and histological findings. The patient took the drug on 12 October 2001 and was admitted with frank jaundice to our hospital on 17 October 2001. Hepatic injury due to diclofenac sodium may develop 1–44 weeks after the intake of this drug.[8] In exceptional cases, the minimum period between the intake of this drug and a fatal attack of acute hepatitis has been reported to be 4 days.[10] Our patient took this drug only once and it is evident that she already had liver injury before taking the drug. Moreover, peripheral eosinophilia with rash, only eosinophilia or only rash are characteristic features of diclofenac-induced hepatitis; none of these features was present in our patient. The drug lymphocyte stimulation test was also negative for diclofenac sodium.

A diagnosis of AIH was also supported by rising titers of ANA (which was 1 : 80 during the first attack and elevated to 1 : 160 during the first remission), although this was not very high, and elevated serum levels of IgG. The pattern of ANA (homogeneous and speckled) also sugested a diagnosis of AIH.[1–4] The patient's MHC typing also indicated a possible diagnosis of AIH. Obermayer *et al*. have reported that there is a significant association between HLA-DR2 and Japanese patients with AIH.[3]

Patients with AIH are characterized by relapses and remissions, although this is mostly achieved by immunosuppressive drugs and few cases with spontaneous remission have been reported.[7] The point that we would like to emphasise is the course of illness in our patient. Although her transaminase levels reached as high as 10-fold the upper limit of normal, she had a spontaneous remission without immnuosuppressive drugs. Although the present case mimics acute AIH[5,6] from the viewpoint of acute exacerbation and spontaneous remission, histological features showed expansion of the portal tracts, destruction of the limiting plates and the presence of fibrosis (i.e. features of AIH). The future clinical course of this patient may provide an insight into the transition of acute AIH to chronicity or remission.

It is not known why this patient has had three attacks of acute exacerbation during the past 5 years. Hepatitis A virus and drugs are known to trigger AIH[11] and Lohse *et al*.[7] have reported the spontaneous remission of AIH. The present patient was not infected with hepatitis A virus and a role of drugs in the induction of AIH could not be documented. The immunoreactivity of the host to its own autoantigens may be altered with the progression of disease or a protracted prodormal period may be necessary before a clinical attack is observed.

Immunosuppressive therapy has been withdrawn from this patient from 1 June 2002. She is now under follow up at our out-patient department and it will be interesting to evaluate how long the quality of life of this patient can be maintained without immunosuppressive therapy.

REFERENCES

1 Manns MP, Strassburg CP. Autoimmune hepatitis: Clinical challenges. *Gastroenterology* 2001; **120**: 1502–17.
2 Czaja AJ. Natural history, clinical features, and treatment of autoimmune hepatitis. *Semin. Liver Dis.* 1984; **4**: 1–12.
3 Obermayer-Straub P, Strassburg CP, Manns MP. Autoimmune hepatitis. *J. Hepatol.* 2000; **32**: 181–97.
4 Alvarez F, Berg PA, Bianchi FB *et al*. International Autoimmune Hepatitis Group Report: Review of criteria for diagnosis of autoimmune hepatitis. *J. Hepatol.* 1999; **31**: 929–38.
5 Abe M, Hiasa Y, Masumoto T *et al*. Clinical charactersitics of autoimmune hepatitis with histological features of acute hepatitis. *Hepatol. Res.* 2001; **21**: 213–9.
6 Nikias GA, Batts KP, Czaja AJ. The nature and prognostic implication of autoimmune hepatitis with an acute presentation. *J. Hepatol.* 1994; **21**: 866–71.
7 Lohse AW, Kogel M, Meyerzum Buschenfelde KH. Evidence for spontaneous immunosuppression in autoimmune hepatitis. *Hepatology* 1995; **22**: 381–8.
8 Nakamura K, Yoneda M, Yokohama S *et al*. Efficacy of ursodeoxycholic acid in Japanese patients with type 1 autoimmune hepatitis. *J. Gastroenterol. Hepatol.* 1998; **13**: 490–5.
9 Czaja AJ, Carpenter HA, Lindor KD. Ursodeoxycholic acid as adjuvant herapy for problematic type 1 autoimmune hepatitis: A randomized control treatment trail. *Hepatology* 1999; **30**: 1381–6.
10 Banks AT, Zimmerman HJ, Ishak KG, Harter JG. Diclofenac-associated hepatotoxicity. Analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology* 1995; **22**: 82–7.
11 Rahaman SM, Chira P, Koff RS. Idiopathic autoimmune chronic hepatitis triggered by hepatitis A. *Am. J. Gastroenterol.* 1994; **89**: 106–8.