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Case Report

Autoimmune hepatitis mimicking drug-induced liver injury: a case report and review of the literature

Wei Jiang[1*], Dongbo Wu[1*], Siyu Fu[1], Shaoyu Ran[2], Taoyou Zhou[1]

[1]Center of Infectious Diseases, West China Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China; [2]Darent Valley Hospital, Dartford, Kent, UK. [*]Equal contributors and co-first authors.

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Abstract: Autoimmune hepatitis (AIH) is an unresolved progressive liver disease with an unknown etiology that leads to the loss of tolerance to hepatocyte-specific autoantigens, and it is characterized by immune dysfunction and autoimmune attack in genetically susceptible individuals, which ultimately results in chronic persistent inflammation of the liver surface parenchyma. However, AIH is often misdiagnosed as drug-induced liver injury (DILI) in the clinical setting. A 50-year-old woman was admitted to our hospital thrice for repeated abnormal liver function test results. However, after multiple etiological examinations and expectant treatments, the diagnosis remained unclear, and her liver function was repeatedly abnormal. After three admissions and many follow-ups, based on her liver histological characteristics, she was eventually diagnosed with AIH. When a patient has unexplained abnormal liver function, while evaluating the clinical data and previous medical history, clinicians should consider the possibility of AIH and actively perform a liver biopsy.

Keywords: Autoimmune hepatitis, drug-induced liver injury, liver biopsy

Introduction

Autoimmune hepatitis (AIH) is a chronic self-perpetuating inflammatory disease with a relatively high misdiagnosis rate [1]. The reported incidence of AIH was 1.68 per 100,000 people per year between 1994 and 2012 in Denmark [2]. Usually, starting with an episode of acute hepatitis, the clinical manifestation of AIH may progress to liver cirrhosis and liver cancer if there is no early detection and appropriate treatment. Because of the lack of specificity, most patients with AIH are characterized by an insidious onset, with an increase in immunoglobulin G (IgG) levels, alanine aminotransferase (ALT) levels, and aminotransferase (AST) levels, accompanied by elevated alkaline phosphatase (ALP) levels and serum bilirubin levels, with or without a positive result for autoimmune antibodies [3].

On the other hand, because of the overuse and misuse of over-the-counter drugs and herbal medicines, the incidence of drug-induced liver injury (DILI) increased between 2004 and 2012, according to a United States Drug-Induced Liver Injury Network (DILIN) study [4]. DILI can be divided into the following two types: acute hepatitis and autoimmune inflammation. AIH is often misdiagnosed as DILI in the clinical setting [4, 5]. It is important to distinguish between DILI and AIH in the early stages of liver disease, as prompt and accurate diagnosis and treatment can improve patient outcomes [6]. Here, we report an unusual case of AIH that was initially identified as DILI.

Case report

A 50-year-old woman visited our hospital for treatment of liver dysfunction. Six months previously, her physical examination revealed abnormal liver function, and she took traditional Chinese medicine prescribed by a local hospital. Subsequently, her liver function gradually returned to normal. However, five months previously, she began to experience a change in urine color and showed increasing icterus of the sclera and skin. Her liver function became abnormal, and laboratory tests showed a total

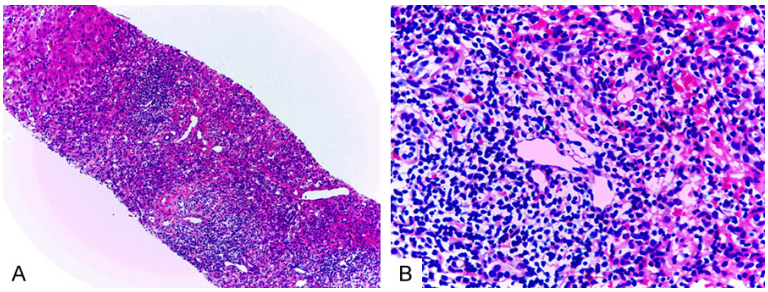

Figure 1. Histopathological findings of the liver biopsy. A. The specimen shows central zonal necrosis. The limbic part of the hepatic tissue presented few normal hepatic lobules, in which hepatocytes showed hydropic degeneration (×40). B. The limiting plate is disrupted by many lymphoplasmacytic, monocytic, and eosinophilic infiltrates affecting the interface, with rosette formation and hepatocyte necrosis (×400).

bilirubin (TB) level of 82.8 μmol/L (reference range, 5.0-28 μmol/L), ALT level of 1335 IU/L (reference, < 40 IU/L), and AST level of 1358 IU/L (reference, < 35 IU/L). She was treated in a local hospital (the specific treatment is unknown). During admission, the cause of her abnormal liver function test results was not identified. Two months previously, her liver function became abnormal again, with elevations of the ALT and AST levels, and she was then referred to our hospital for further evaluation. Her laboratory tests showed a TB level of 90.8 μmol/L, a direct bilirubin (DB) level of 86.1 μmol/L (reference, < 8.8 μmol/L), an ALT level of 856 IU/L, and an AST level of 997 IU/L. There was no history of viral hepatitis (A, B, C, D, and E), alcohol consumption, transfusion, drug abuse, or drug allergy. Furthermore, human immunodeficiency virus (HIV), Epstein-Barr virus (EB), cytomegalovirus (CMV), and autoimmune hepatitis antibodies (antinuclear antibody, smooth muscle antibody, liver/kidney microsome type 1, liver cytosol type 1, soluble liver antigen, and antineutrophil cytoplasmic antibody) were all negative. Her immunoglobulin G (IgG) level was 19.8 g/L (reference range, 8.0-15.5 g/L), serum complement C3 level was 0.6370 g/L (reference range, 0.785-0.520 g/L), and serum complement C4 level was 0.1420 g/L (reference range, 0.145-0.360 g/L). Abdominal ultrasound and upper abdominal magnetic resonance imaging (MRI) showed liver fibrotic changes and biliary obstruction. There was no abnormality on physical examination. On further assessment, she reported the use of hair dye for 20 years with about 10 applications per year and mentioned that the dye was applied twice before hospitalization (one month before and two months before the first hospitalization). Owing to her frequent hair dye use, we suspected that she might have DILI, as reported previously [7, 8]. She was informed to stop using hair dye, and she was treated with polyene phosphatidylcholine capsules, compound glycyrrhizin, and vitamin K1. Gradually, her liver function returned to normal. One month previously, she was referred to our hospital after complaining of increasing icterus of the sclera and skin. Her blood tests showed a TB level of 45.5 μmol/L, DB level of 38.2 μmol/L, ALT level of 528 IU/L, AST level of 967 IU/L, IgG level of 19.3 g/L, and antinuclear antibody (ANA) (±). As the liver pathology was still unknown, a liver biopsy was urgently needed to identify the cause of the disease. After obtaining consent from the patient, a liver biopsy was performed under ultrasound guidance. The histology revealed a predominance of necroinflammatory lesions characterized by typical interface hepatitis with a hydropic change of involved hepatocytes, lymphocytes, eosinophils, and plasma cells showing emperipolesis in the cytoplasm. Within the affected area, occasional rosette formation and hepatocyte fibrillation were noted. Masson's trichrome staining showed central necrosis of the hepatic lobule and liver fiber hyperplasia. Immunohistochemical staining showed HBsAg (-) and HBcAg (-). The presentation of the liver histopathology was consistent with a diagnosis of AIH (**Figure 1**). According to the simplified scoring system for AIH [3, 9], the score of our patient was six (two points for IgG > 1.1 times the upper normal limit, two points for liver histology, and two points for the absence of viral hepatitis). Considering the above results, she was finally diagnosed with AIH, and she was administered prednisone (50 mg/day) and azathioprine (100 mg/day). After immunosuppressive treatment for three weeks, her liver function gradually returned to normal (**Table 1**) and her liver fibrosis improved (**Figure 2**). She was followed up until May 2017, and remission was maintained through low-dose prednisone (5 mg/day) and azathioprine (100 mg/day). During

Table 1. Clinical parameters of the patients at hospital admission

Time	10/01/2014	11/09/2014	12/10/2014	02/05/2015
Item	Admission 1	Discharge 1	Admission 1	Discharge 2
TB (μmol/L)	90.8	45.9	45.5	25.6
DB (μmol/L)	86.1	44.7	38.2	17.8
ALT (IU/L)	856	296	528	26
AST (IU/L)	997	581	967	26
ALP (IU/L)	163	175	164	118
IgG (g/L)	19.8	NA	18.7	NA
AMON (μmol/L)	77	NA	49	17

Abbreviations: AMON, blood ammonia; TB, total bilirubin; DB, direct bilirubin; AST, aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; IgG, immunoglobulin G; NA, not apply.

this time, her liver function remained normal (**Figure 2**).

Discussion

AIH is a relatively rare liver disease; however, its incidence has risen steadily recently, and its morbidity has been reported to range from 16 to 18 cases per 100,000 people in Europe [10]. The prevalence rates in Alaska natives and individuals from New Zealand have been reported to be 42.9 cases per 100,000 people and 24.5 cases per 100,000 people, respectively [11, 12]. AIH shows an effect over a wide range of ages from infants to those in their 80 s, with a peak at the age of 40 years [13]. The present case was a 50-year-old woman whose liver function had been continuously abnormal for six months. The cause was elusive until a liver biopsy aided the diagnosis of AIH.

AIH is an uncommon progressive liver disease that mainly affects adult women, and it is characterized by increased IgG levels, autoimmune antibody positivity, typical interface hepatitis, and response to immunosuppressive treatment [3]. AIH is classified into the following three main types according to the latest guidelines: type 1 (AIH-1), positive for anti-nuclear (ANA) and/or anti-smooth muscle (SMA) antibodies or soluble liver antigen/liver pancreas antibodies (anti-SLA/LP); type 2 (AIH-2), positive for anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-LKM3, and/or anti-liver cytosol type 1 antibody (anti-LC1); type 3 (AIH-3), positive for anti-SLA/LP and often positive for anti-Ro52 [3, 14]. The diagnostic criteria of AIH are simple and explicit; however, in some cases, the serum IgG level may not be higher than the upper limit and ANA may be negative at the first screening. Thus, early differential diagnosis remains difficult [15]. It has been reported that 10% of AIH patients may present with acute inflammation in a nationwide survey conducted in Japan [16], and most cases present with chronic or irregular (or intermittent) progress [17].

In addition, it is worth noting that the use of some drugs can induce acute or chronic hepatitis (DILI) [18, 19]. It is complex and difficult to distinguish AIH from DILI. A comparable analysis revealed that there were differences in biochemistry and immunology between DILI and AIH, and liver histopathology was especially different, with more serious interface inflammation, greater portal inflammation, a higher fibrosis degree, and lower proportions of wax-like deposition and iron deposition in AIH patients than in DILI patients [20, 21]. The pathologist's evaluation of a liver biopsy could differentiate DILI from AIH, and it may provide important information on the pattern and severity of liver injury [22]. However, DILI patients have their own specific characteristics. Most cases of DILI involve a mild and self-limited injury that can reverse completely after discontinuation of the causative drugs or compounds [23]. The recurrence rate of AIH has been reported to be almost 80% after treatment withdrawal [24], while DILI patients showed almost no relapse [25].

The diagnosis of AIH is mostly based on a simple scoring system and descriptive criteria developed in 1993 by the International Autoimmune Hepatitis Group (IAIHG) [26]. In fact, liver biopsy is the gold standard or a prerequisite to diagnosing liver disease, as it has been suggested by the diagnostic criteria [3, 26, 27]. Once the diagnosis of AIH is confirmed, immunosuppressive treatment can achieve early remission and prevent the progress of liver fibrosis, ultimately leading to prolonged survival time and improved quality of life of the patient [15, 28].

In summary, when a patient has unexplained liver injury, clinicians should consider the pos-

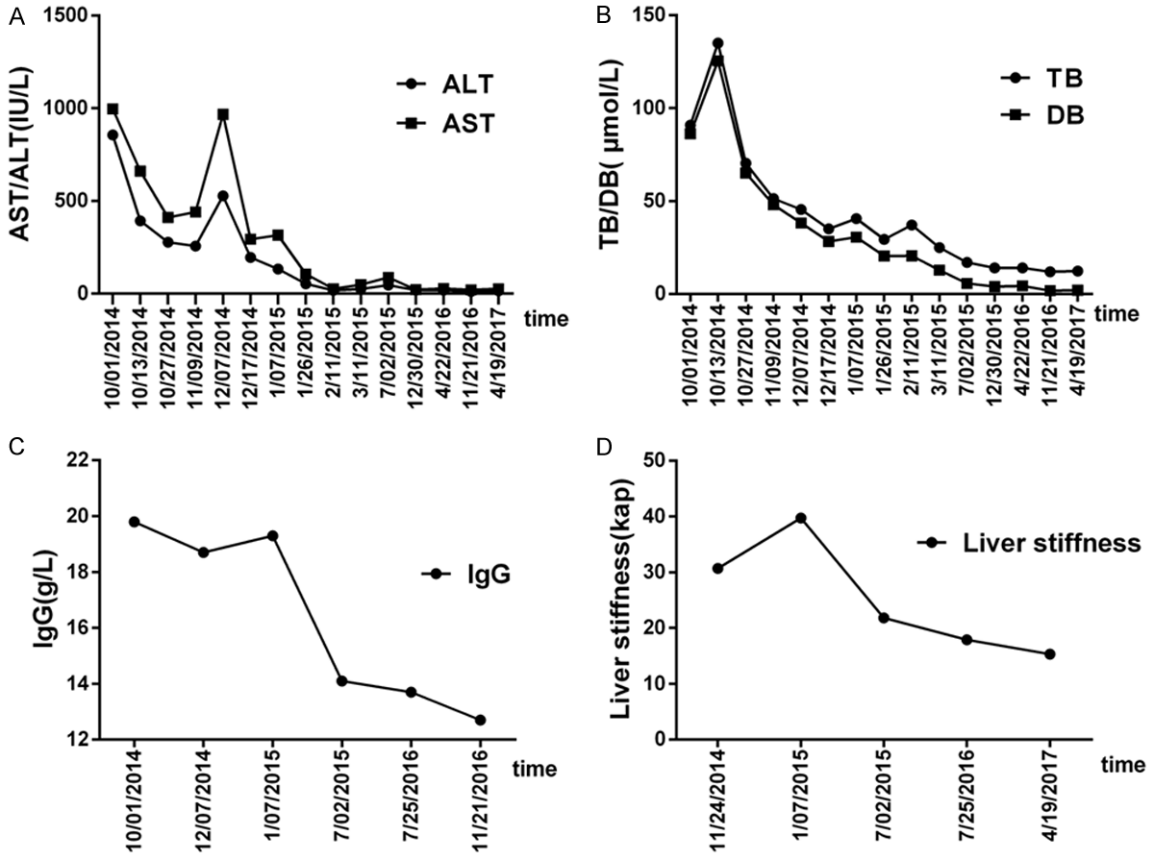

Figure 2. Changes in liver function parameters and liver stiffness. A, B. ALT, AST, TB, and DB levels almost recover in February 2015 after immunosuppressive treatment for one month. C. FibroScan shows that the liver stiffness might decrease and that it might be difficult to return to normal. D. The previous three IgG levels were greater than 1.1 times the upper limit and the last level shows a return to normal after immunosuppressive treatment. Note: TB, total bilirubin; DB, direct bilirubin; AST, aminotransferase; ALT, alanine aminotransferase; IgG, immunoglobulin G.

sibility of AIH. The diagnosis of AIH generally relies on the clinical history, biochemical indicators, autoimmune hepatitis-related antibodies, and liver histology; however, it is sometimes difficult to distinguish AIH from DILI. Clinicians are often faced with atypical clinical presentations and negative indexes of serum biochemistry. In these circumstances, a liver biopsy may play a vital role as an effective diagnostic method, especially for differentiating AIH from DILI.

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Disclosure of conflict of interest

None.

Address correspondence to: Taoyou Zhou, Center of Infectious Diseases, West China Hospital, Sichuan University, Chengdu 610000, Sichuan Province, People's Republic of China. Tel: +86-28-8542-2650; Fax: +86-28-8542-3052; E-mail: marshelztyhx@163.com

References

[1] Dyson JK, Webb G, Hirschfield GM, Lohse A, Beuers U, Lindor K and Jones DE. Unmet clinical need in autoimmune liver diseases. J Hepatol 2015; 62: 208-218.

[2] Gronbaek L, Vilstrup H and Jepsen P. Autoimmune hepatitis in denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatol 2014; 60: 612-617.

[3] Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR,

McFarlane I, Dienes HP and Lohse AW; International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008; 48: 169-176.
[4] Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM and Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014; 109: 950-966.
[5] Castiella A, Zapata E, Lucena MI and Andrade RJ. Drug-induced autoimmune liver disease: a diagnostic dilemma of an increasingly reported disease. World J Hepatol 2014; 6: 160-168.
[6] Bjornsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, Neuhauser M and Lindor K. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology 2010; 51: 2040-2048.
[7] Hou FQ, Lin XH, Yu YY, Wang TL and Wang GQ. Severe liver injury induced by repeated use of hair dye. Chin Med J (Engl) 2009; 122: 875-877.
[8] Tokumoto Y, Horiike N, Onji M, Ueda T, Kumagi T, Abe M and Michitaka K. Drug-induced hepatitis due to repeated use of hair dye. Intern Med 2003; 42: 1104-1106.
[9] Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D and Vierling JM; American Association for the Study of Liver Diseases. Diagnosis and management of autoimmune hepatitis. Hepatology 2010; 51: 2193-2213.
[10] Feld JJ and Heathcote EJ. Epidemiology of autoimmune liver disease. J Gastroenterol Hepatol 2003; 18: 1118-1128.
[11] Ferucci ED, Choromanski TL, Hurlburt KJ, Livingston S, Plotnik J, Manns MP, McMahon BJ and James JA. Autoimmune hepatitis in the alaska native population: autoantibody profile and HLA associations. Liver Int 2014; 34: 1241-1249.
[12] Ngu JH, Bechly K, Chapman BA, Burt MJ, Barclay ML, Gearry RB and Stedman CA. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol 2010; 25: 1681-1686.
[13] Zhu JY and Han Y. Autoimmune hepatitis: unveiling faces. J Dig Dis 2015; 16: 483-488.
[14] Gatselis NK, Zachou K, Koukoulis GK and Dalekos GN. Autoimmune hepatitis, one disease with many faces: etiopathogenetic, clinico-laboratory and histological characteristics. World J Gastroenterol 2015; 21: 60-83.
[15] Stravitz RT, Lefkowitch JH, Fontana RJ, Gershwin ME, Leung PS, Sterling RK, Manns MP, Norman GL and Lee WM; Acute Liver Failure Study Group. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology 2011; 53: 517-526.
[16] Abe M, Mashiba T, Zeniya M, Yamamoto K, Onji M and Tsubouchi H; Autoimmune Hepatitis Study Group-Subgroup of the Intractable Hepato-Biliary Disease Study Group in Japan. Present status of autoimmune hepatitis in Japan: a nationwide survey. J Gastroenterol 2011; 46: 1136-1141.
[17] Kumagai J, Kanda T, Yasui S, Haga Y, Sasaki R, Nakamura M, Wu S, Nakamoto S, Arai M, Iino Y and Yokosuka O. Autoimmune hepatitis following drug-induced liver injury in an elderly patient. Clin J Gastroenterol 2016; 9: 156-159.
[18] Beaune P, Dansette PM, Mansuy D, Kiffel L, Finck M, Amar C, Leroux JP and Homberg JC. Human anti-endoplasmic reticulum autoantibodies appearing in a drug-induced hepatitis are directed against a human liver cytochrome P-450 that hydroxylates the drug. Proc Natl Acad Sci U S A 1987; 84: 551-555.
[19] Wang MT, Lee WJ, Huang TY, Chu CL and Hsieh CH. Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: a population-based cohort study. Br J Clin Pharmacol 2014; 78: 619-629.
[20] Tsutsui A, Harada K, Tsuneyama K, Senoh T, Nagano T, Takaguchi K, Ando M, Nakamura S, Mizobuchi K and Kudo M. Clinicopathological study of autoimmune hepatitis cases that were difficult to differentiate from drug-induced liver injury. Dig Dis 2017; 35: 506-514.
[21] Jiang ZL, Li P, Wang JL, Yang QH, Liu YG, Shi RF and Mi YQ. Serological and pathological features of drug-induced liver injury and autoimmune hepatitis. Zhonghua Gan Zang Bing Za Zhi 2016; 24: 810-816.
[22] Kleiner DE. The histopathological evaluation of drug-induced liver injury. Histopathology 2017; 70: 81-93.
[23] Hisamochi A, Kage M, Arinaga T, Ide T, Miyajima I, Ogata K, Kuwahara R, Koga Y, Kumashiro R and Sata M. Drug-induced liver injury associated with agaricus blazei murill which is very similar to autoimmune hepatitis. Clin J Gastroenterol 2013; 6: 139-144.
[24] Terziroli Beretta-Piccoli B, Mieli-Vergani G and Vergani D. Autoimmune hepatitis: standard treatment and systematic review of alternative treatments. World J Gastroenterol 2017; 23: 6030-6048.
[25] Hisamochi A, Kage M, Ide T, Arinaga-Hino T, Amano K, Kuwahara R, Ogata K, Miyajima I, Kumashiro R, Sata M and Torimura T. An analysis of drug-induced liver injury, which showed histological findings similar to autoimmune hepatitis. J Gastroenterol 2016; 51: 597-607.
[26] Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooks-

ley WG, Czaja AJ, Desmet VJ, Donaldson PT, Eddleston AL, Fainboim L, Heathcote J, Homberg JC, Hoofnagle JH, Kakumu S, Krawitt EL, Mackay IR, MacSween RN, Maddrey WC, Manns MP, McFarlane IG, Meyer zum Büschenfelde KH, Zeniya M, et al. International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 929-938.

[27] Papamichalis PA, Zachou K, Koukoulis GK, Veloni A, Karacosta EG, Kypri L, Mamaloudis I, Gabeta S, Rigopoulou EI, Lohse AW and Dalekos GN. The revised international autoimmune hepatitis score in chronic liver diseases including autoimmune hepatitis/overlap syndromes and autoimmune hepatitis with concurrent other liver disorders. J Autoimmune Dis 2007; 4: 3.

[28] Lamers MM, van Oijen MG, Pronk M and Drenth JP. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. J Hepatol 2010; 53: 191-198.