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

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Received January 13, 2018; Accepted December 7, 2018; Epub August 15, 2020; Published August 30, 2020

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 aspartate 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
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 emperiplois 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

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).
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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 80s, 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, 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-

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**Table 1. Clinical parameters of the patients at hospital admission**

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

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

Acknowledgements

This work was supported by the Science and Technology Support Program of Sichuan Province, People’s Republic of China (no. 0040205301D22).

Disclosure of conflict of interest

None.

References


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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.
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[26] Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooks-
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