Primary biliary cholangitis associated with drug-induced liver injury and alcoholic liver fibrosis

A case report

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Abstract

Rationale: Primary biliary cholangitis (PBC) is a liver autoimmune disease. If this disease is associated with other liver injury factors, both misdiagnosis and missed diagnosis will easily occur. Therefore, detailed disease history collection and related laboratory examination should be performed on patients with liver injury for unidentified causes. When necessary, liver biopsy should be performed to confirm the histopathological diagnosis.

Patient concerns: The subject patient was a 63-year-old Chinese male with chronic liver injury who had a drinking history of about 30 years and drank 500 g daily on average and began to take health products and dietary supplements (multivitamins) since June 2014.

Diagnoses: Drug-induced liver injury (DILI) and alcoholic fatty liver disease (AFLD) were initially considered because the patient had a history of using health products (HP) and dietary supplements (DS) and drinking alcohol. However, he was subsequently considered with PBC based on the findings of anti-mitochondrial antibody positivity and elevated immunoglobulin level. Obstructive jaundice and space-occupying lesion in the liver were excluded by imaging examinations. Liver biopsy was performed to confirm the reasons for liver injury. Histopathological examination was conducted, and the patient was diagnosed with PBC associated with DILI and alcoholic liver fibrosis.

Interventions: Ursodeoxycholic acid, glycyrrhizic acid, and methylprednisolone (small dose) were used to treat the patient.

Outcomes: After 2 months, the serum levels of ALT, AST, AKP, GGT, and globulin returned to normal. After 4 months, the patient showed liver injury once again (an increase in ALT, AST, AKP, GGT and GLB) caused by repaglinide administration due to hyperglycemia. Ursodeoxycholic acid and methylprednisolone replaced the repaglinide administration. After 3 weeks, the levels of ALT, AST, AKP, GGT, and GLB returned to normal again.

Lessons: The correct knowledge on PBC and early-stage recognition and diagnosis should be emphasized. When other causes of the liver injury cannot be excluded, liver biopsy is suggested. Histopathological change can be used to further clarify the reasons for liver injury and the principal contradiction as well as to guide the therapeutic regimen.

Abbreviations: AFLD = alcoholic fatty liver disease, AMA = anti-mitochondrial antibody, DILI = drug-induced liver injury, DS = dietary supplement, HDS = herb and dietary supplement, HP = health product, NM = natural medicine, PBC = Primary biliary cholangitis, TCM = traditional Chinese medicine.

Keywords: alcoholic liver fibrosis, drug-induced liver injury (DILI), primary biliary cholangitis (PBC)

1. Introduction

Primary biliary cholangitis (earlier named primary biliary cirrhosis, PBC) is a liver autoimmune disease.\cite{1} It is a chronic cholestatic disease caused by chronic progressive nonsuppurative inflammation in medium-sized and small bile ducts in the liver. PBC is worldwide distributed among all races and ethnic origins. The disease easily occurs in young and middle-aged females. The incidence is 0.33/100,000–5.8/100,000 and significantly different among different countries and regions.\cite{2,3} Clinical epidemiological studies have indicated a few PBC-related case reports and clinical epidemiological investigations in China. The possible reason is that doctors from non-liver disease division do not have adequate knowledge of PBC. Therefore, they cannot analyze serum anti-mitochondrial antibody (AMA)-M2 in time, and patients with PBC cannot obtain timely diagnosis and therapy. If this disease is associated with such liver injury factors as DILI, both misdiagnosis and missed diagnosis will easily occur. Therefore, detailed disease history collection and related laboratory examinations should be performed on patients with liver injury with unidentified causes. When necessary, liver biopsy...
This study aimed to report the case of 1 male patient diagnosed with PBC associated with DILI and alcoholic liver disease. He was treated with glycyrrhizic acid to protect liver function (the detailed dosage and course of treatment were not clear). His liver function was repeatedly abnormal in the following 6 months. The patient underwent a second liver function examination on April 15, 2015; the results are shown in Table 1. Serum biological information of the patient 0.5 year before and after admission.

Table 1

| Liver function index | October 21, 2014 | December 19, 2014 | April 15, 2015 | Normal range |
|----------------------|------------------|-------------------|---------------|--------------|
| ALT, IU/L            | 609              | 314               | 342.3         | 5.0–40.0     |
| AST, IU/L            | 247              | 259               | 115.0         | 8.0–40.0     |
| TBL, μmol/L          | 123.0            | 36.8              | 30.7          | 5.0–21.0     |
| DBIL, μmol/L         | 82.8             | 20.9              | 28.3          | 0.0–3.4      |
| AKP, IU/L            | 130              | 92                | 202.0         | 30.0–120.0   |
| GGT, IU/L            | 320              | 329               | 273.0         | 8.0–57.0     |
| ALB, g/L             | 40.6             | 39.1              | 31.8          | 35.0–52.0    |
| GLB, g/L             | 36.7             | 36.7              | 43.3          | 20.0–35.0    |
| TBA, μmol/L          | 75.50            | 33.06             | 31.43         | 0.1–19.0     |
| GLU, mmol/L          | –                | –                 | 5.24          | 3.90–6.10    |
| TG, mmol/L           | –                | –                 | 1.08          | 0.10–1.70    |
| CHOL, mmol/L         | 2.86             | –                 | 3.00–5.70     |             |

Serum biological information of the patient 0.5 year before and after admission.

Table 2

| Virus markers | Detection result | Normal range |
|---------------|------------------|--------------|
| Anti-HAV-IgM antibody | (–) | (–) |
| HBs antigen | (–) | (–) |
| Anti-HBc-IgM antibody | (–) | (–) |
| HBV DNA by PCR | (–) | (–) |
| Anti-HCV antibody | (–) | (–) |
| HGV RNA by RT-PCR | (–) | (–) |
| Anti-HEV-IgM antibody | (–) | (–) |
| EBV IgM antibody | (–) | (–) |
| CMV IgM antibody | (–) | (–) |
| IgG, g/L | 24.5 | 8.00–16.00 |
| IgA, g/L | 4.47 | 0.70–3.30 |
| IgM, g/L | 2.53 | 0.50–2.20 |
| AMA | (–) | (–) |
| AMA-M2 | (+) | (++) |
| AMA-M2-3E | (+++) | (++) |
| Anti-tp120 | (+++) | (++) |
| ASMA | (–) | (–) |
| LKM-1 | (–) | (–) |

Serological data on admission of the patient.

Because the patient had health products, dietary supplements, and drinking history, DILI and AFLD were highly possible. Meanwhile, positive serum AMA, AMA-M2, and gp120 suggested PBC. An ultrasound-guided liver biopsy was performed on April 24, 2015 to clarify the main reasons for chronic liver injury. The histopathological images revealed collapse and wide necrosis in the liver parenchyma (Fig. 3B), and a few residual lymphocytes. A lymphocyte-dense focus was observed in the mesenchyme in the two portal areas, and residual bile duct composition was also observed (Fig. 3B), complying with the change in PBC. More hyperplastic gall capillaries were found near the portal area (Fig. 3A), accompanied by mixed inflammatory cell infiltration; and at the same time, more plasma cells were observed. Reticulin staining showed fibroplasia around the portal vein (Fig. 3C). As a result, the patient was diagnosed with PBC, DILI, and alcoholic liver fibrosis. The patient was asked to quit drinking and stop administration of all the drugs that could cause liver injury and was given glycyrrhizic acid (150 mg/day) and ursodeoxycholic acid (1000 mg/day) for 6 weeks. The reexamination results of liver function suggested that the levels of ALT, AST, and TBIL returned to normal, but the levels of GGT, AKP, and GLB were still higher than normal. Besides, the level of immune globulin still significantly increased. Based on the histopathological observation and the elevated level of immune globulin, as well as minidose of methylprednisolone (8 mg/day) and continuous administration of ursodeoxycholic acid (1000 mg/day), the reexamination results of liver function after 1 month indicated that the levels of ALT, AST, TBIL, GGT, AKP, and GLB were normal, and the level of immune globulin gradually decreased. Afterward, the dose of methylprednisolone should be performed to confirm the histopathological diagnosis.

2. Case presentation

Standard care is performed, so ethical approval is not applicable in this study. Written informed consent for publication was obtained from the patient. The subject patient was a 63-year-old Chinese male, who claimed to be in good health. Further inquiry found that he was strongly alcoholic, with a drinking history of about 30 years and that he drank 500g daily on average. He did not undergo regular physical examination, denied viral hepatitis and transfusion history, and had no family and occupational exposure history. He began to take health products and dietary supplements (multivitamins) since June 2014. Four months after administration, he felt general weakness and discomfort in the right upper abdomen. The liver function examinations in his local hospital found an increase in serum aminotransferase and bilirubin levels, and the patient was considered to have the alcoholic liver disease. He was treated with glycyrrhizic acid to protect liver function (the detailed dosage and course of treatment were not clear). His liver function was repeatedly abnormal in the following 6 months. The patient underwent a second liver function examination on April 15, 2015; the results are shown in Table 1. Virus markers associated with hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, Epstein-Barr virus, and cytomegalovirus were all negative (Table 2). AMA, antibody against M2 and M2-3E fraction of mitochondrial antigen, and gp210 antibody were all positive. The levels of immune globulins including immunoglobulin G (IgG) (24.5 g/L), IgA (4.47 g/L), and IgM (2.53 g/L) increased (Table 2). The blood routine examination and routine coagulation testing were both normal, so were tumor markers AFP and CA19-9. Large bile duct lesion, obstructive jaundice, and space-occupying lesion in the liver were excluded by imaging examinations (abdominal magnetic resonance cholangiopancreatography and liver magnetic resonance imaging enhancement) (Figs. 1 and 2).

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was decreased to 4 mg/day, and ursodeoxycholic acid was still administered (1000 mg/day) to continue therapy. One and a half months later, repaglinide was administered orally as instructed by his local hospital (3 mg/day) due to elevated blood glucose (fasting blood glucose 7.52 mmol/L), and methylprednisolone was discontinued. After 2 weeks, the reexamination results of liver function indicated that the levels of ALT, AST, GGT, and AKP increased again. Therefore, DILI caused by repaglinide was considered. The patient was asked to stop repaglinide administration, and continue to take ursodeoxycholic acid (1000 mg/day) and methylprednisolone (4 mg/day) orally. After 3 weeks, the levels of ALT, AST, TBIL, GGT, AKP, and GLB returned to normal. During this period, the patient actively controlled diet and performed more exercise. Fasting blood glucose was found to be 7.0 mmol/L. The therapeutic protocol is shown in Figures 4 and 5.

3. Discussion
Primary biliary cholangitis (earlier named primary biliary cirrhosis, PBC) is a chronic cholestatic disease caused by chronic progressive nonsuppurative inflammation in medium-sized and small bile ducts in the liver. The typical histopathological change is chronic, nonpyogenic, and necrotic cholangitis. AMA is a specific autoantibody important in diagnosing PBC. The antibody against M2 fraction of mitochondrial antigen could be detected in 90% to 95% of the patients with PBC. The titer >1:100 was confirmed positive, which had specificity for PBC diagnosis. It could be used in early-stage diagnosis to guide the therapy for patients without typical clinical manifestations, delaying the further development of the disease.[1,2] The antinuclear antibody has a close correlation with PBC diagnosis. For example, the sensitivity of karyolemma type to gp210 in PBC diagnosis is 10% to 42% (25% on average), while its specificity is relatively high (up to >99%). Thus, the antibody has a diagnostic value in PBC (especially that with negative AMA) and can be used as an evaluation index for PBC prognosis. Current evidence proved a correlation of anti-gp210 antibody with PBC diagnosis. The positive anti-gp210 antibody suggested bad prognosis.[3] Case reports and clinical epidemiological reports on PBC, especially on male patients, in China are a few. The main reason is that clinic doctors in China either do not have adequate knowledge on PBC, or do not pay much attention to the clinical manifestations of PBC, or do not timely analyze the serum AMA-M2 antibody, thus delaying its diagnosis and therapy.

Drug-induced liver injury (DILI) is the most common and severe adverse reaction. Its morbidity is increasing year by year because neither medical staff from non-liver disease division nor the public have adequate knowledge on DILI. A combination of traditional Chinese medicine (TCM)–natural medicine (NM)–health product (HP)–dietary supplement (DS) or herb and dietary supplement (HDS) has been taken seriously worldwide.[4,5] Still,
no specific indices in clinical and laboratory examination are available for the diagnosis of DILI, but specific histopathological characteristics exist. The histopathological investigation of liver biopsy helps in definitive diagnosis and exclusion of other liver lesions. Besides, it can classify and grade the DILI severity, and also determine prognosis to a certain extent. Some drugs (including non-steroid anti-inflammatory drugs, antibiotics, hypotensive drugs, hypoglycemic drugs, lipid-lowering drugs, and so on) have the bile duct epithelium as the injury target and further induce drug-induced vanishing bile duct syndrome. Desmet classified chronic cholestasis into 2 clinical forms. The major one is clinically manifested as persistent or even aggravated jaundice, pruritus caused by acute bile salt accumulation, and rapid appearance of xanthoma with a rapid increase in amount and size. Some cases may show hepatosplenomegaly and corresponding absorbing barrier. Abnormal biological indices include high serum levels of AKP, GGT, total bilirubin, bile acid, and cholesterol, and a light or a moderate increase in ALT and AST levels, but AMA is negative. The minor form is clinically manifested as the fast disappearance of moderate jaundice and pruritus, or no jaundice; however, high levels of AKP and GGT persistently exist. The other abnormal biochemical indices gradually decrease and become completely normal.

The patient in the present case study was a middle-aged man with negative hepatotropic virus results. Thus, liver injury caused by a hepatotropic virus could be excluded. Serum AKP and GGT levels increased in multiple tests, and serum levels of AMA-M2 and gp210 were positive. The level of immune globulin IgM increased in multiple tests, and histopathological examination showed a dense lymphocyte focus in the mesenchyme of the portal area. Besides, a residual small bile duct component could be observed, complying with PBC manifestation. PBC is mainly shown as bile duct injury, and hepatic cell injury is not significant. However, the patient had a repeated increase in serum ALT and AST levels 0.5 months before admission (115–609 IU/L). Given the administration of health care products and dietary supplements and long-term drinking history, DILI and alcoholic liver disease could not be excluded. Histopathological results indicated wide necrosis and collapse in liver parenchyma, a few residual hepatic cells around the portal area, more hyperplastic gall capillaries, inflammatory cellular infiltration, and more plasmocytes. A lesion was severe lobular hepatitis associated with regeneration, complying with DILI. Some of the reticulin staining showed fibroplasia around the central vein, suggesting alcohol-induced fibrosis. Two months after the patient’s taking health supplements and dietary supplements,
abnormal liver function occurred and he did not stop administration until the admission. The changes in his liver function were consistent with the histological changes. After admission, the patient was asked to quit drinking and stop administration of all the drugs that could cause liver injury. After therapy, the indices of liver function and the level of immune globulin gradually returned to normal (Figs. 4 and 5). The patient was followed up until January 12, 2017. His general status was good, and his liver function and the level of immune globulin in reexamination were normal. Thus, the final diagnosis for the patient was as follows: PBC (because the patient also had other liver injuries and histopathology was not graded); DILI; and alcoholic liver fibrosis. The diagnosis, treatment and follow-up indicated that this abnormality of liver function was mainly caused by DILI.

An early-stage diagnosis and therapy were delayed due to lack of adequate knowledge on PBC. Meanwhile, long-term administration of health products and dietary supplements easily aggravated liver injury based on the original chronic liver diseases. Liver biopsy proved that PBC, DILI, and alcoholic fatty liver disease existed simultaneously. The patient received timely and effective therapy because histopathological examination
indicated correct use of minidose of glucocorticoids inhibited inflammatory responses based on the long-term administration of ursodeoxycholic acid.

Correct knowledge on PBC and early-stage recognition and diagnosis should be firstly emphasized. Serum AMA-M2 and gp210 antibodies are the specific antibodies for PBC diagnosis. Therefore, history-taking is recommended for patients with PBC, especially those with significantly high levels of GGT and AKP associated with significantly higher levels of ALT and AST. The diagnosis and treatment process, drug administration history, and drinking history should be comprehensively inquired to exclude the possibility other liver injuries (including chronic virus infection, alcohol- and drug-induced injury, incomplete biliary obstruction, primary liver cancer, and so on). When liver injuries caused by other factors cannot be excluded, liver biopsy is suggested. The histopathological change in the liver can be used to further clarify the reason for liver injury and the principal contradiction.

Additionally, it is noteworthy that the patient’s liver function effectively improved, and the level of immune globulin significantly decreased after receiving treatment with a minidose of glucocorticoids based on the histopathological change and the level of immune globulin. Glucocorticoid is a double-edged sword for DILI. It can induce or aggravate DILI, and it is also a treatment method for DILI. Therefore, indications should be strictly mastered. If the patient has supersensitivity or significant autoimmune phenomena, or hepatic biochemical indices do not significantly improve or even deteriorate after discontinuing liver-damaging drugs, the advantages and disadvantages of glucocorticoids should be weighed before making a decision.\(^6\) In the EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease (2012), corticosteroids were suggested to improve EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease (2012), corticosteroids were suggested to improve the disease condition, prognosis, and survival rate of patients with severe alcoholic hepatitis.\(^7\) However, no precise clinical and experimental evidence is available for the effects of glucocorticoids on PBC therapy.

The patient in the present case study has never undergone any general physical examination in the past. Hence, previous liver biological information could not be followed up. Also, whether long-term drinking would cause liver biological change was not confirmed, and the possible time of occurrence of liver biological abnormality caused by PBC could not be determined. Therefore, careful inquisition of medical history, and detailed knowledge of medication history as well as drinking history are the first critical step in the clinical diagnosis of the unidentified liver injury. Understanding dynamic changes in the liver biological indicators of patients is important for identifying diagnosis and analyzing disease course. Compared with other examination methods, actively carrying-out liver biopsy has an irreplaceable role in the diagnosis, differential diagnosis, staging and grading, and prognosis judgment of unidentified liver injury. Further follow-up and one more liver biopsy are recommended to confirm the prognosis.

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References
[1] Beuers U, Gershwin ME, Gish RG, et al. Changing nomenclature for PBC: from ‘cirrhosis’ to ‘cholangitis’. Gut 2015;64:1671–2.
[2] European Association for the Study of the LiverEuropean Association for the Study of the Liver. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67:145–72.
[3] Jinhui Yang ZZ. Automobile Liver Diseases Clinical and Pathology. People’s Medical Publishing House Co., LTD, Peking:2011.
[4] Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014;109:910–66.
[5] hepatology DldGoCSoInterpretation of CSH clinical guideline: the diagnosis and management of drug-induced liver injury. Shanghai Scientific & Technical Publishers, Shanghai:2015.
[6] Ye LH, Wang CK, Zhang HC, et al. Clinicopathologic features of drug-induced vanishing bile duct syndrome. Zhonghau Gan Zang Bing Za Zhi 2017;45:117–20.
[7] Desmet VJ. Vanishing bile duct syndrome in drug-induced liver disease. J Hepatol 1997;26(Suppl 1):31–5.
[8] European Association for the Study of LEASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol 2012; 57:399–420.