Case Report

A Drug-induced Hepatitis Patient with a Manifestation of Liver Occupying Lesions on Ultrasound B: Case Report and Literature Review

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Drug-induced liver injury (DILI) is defined as injury to the liver caused by exposure to a drug or some drugs. The number of cases suffering from DILI has been increasing. There are few clinical features specifically associated with DILI. The recognition and diagnosis of DILI is difficult. In this report, we described a DILI case caused by herbal remedies.

Key words: Drug-induced liver injury; Diagnosis; Liver occupying lesions; Ultrasound B

Drug-induced liver injury (DILI) is referred to liver injury caused by exposure to a drug or some drugs. In this paper, we report one case of DILI in Beijing Ditan Hospital, Capital Medical University and review the papers related to DILI in the literature.

CASE REPORT

The patient, female, 31 years old, was admitted to our hospital with a history of fatigue, poor appetite and jaundice for 4 months. The patient was treated once with patent herbal medicine because of pelvic inflammatory disease in August 2009, and then she felt fatigue, poor appetite and jaundice. In her local hospital, she was diagnosed as “drug-induced liver injury, cirrhosis” according to the negative serologic markers of viral hepatitis. With the combined treatment of liver-protecting and artificial liver support system, the elevation of serum bilirubin was well controlled. Then she was discharged from hospital. However, the serum bilirubin elevated again after she took some traditional Chinese medicine. So she was admitted to our hospital.

The patient was healthy before, with no history of infectious diseases and no allergy history of food and drugs.

Physical examination: T: 36.5°C, P: 80/min, BR: 20/min, BP: 100/60 mm Hg. She was conscious and with jaundice. No spider angioma or liver palm. Her breath

sound was clear, without bubble and wheezing sound in both lung fields. The cardiac rhythm was regular and no murmur at any valve auscultation field was heard. Her abdomen was flat and soft, with no tenderness or rebounding tenderness. And her liver and spleen was untouched, without shifting dullness. And her limbs had no pitting edema.

Laboratory examination: complete blood count, WBC $5.61 \times 10^9/L$, NE 55.58%, E 4.34%, Hb 120.9 g/L, PLT $86 \times 10^9/L$, ESR 4 mm/h, PT 20.1 s, PTA 41%. Liver function: ALT 78.5 U/L, AST 357.6 U/L, TBil 180.9 $\mu\text{mol/L}$, DBil 138.1 $\mu\text{mol/L}$, ALB 27.9 g/L, GLO 33 g/L, A/G 0.8, LDH 248.4 U/L, γ -GT 335.4 U/L, ALP 397.8 U/L, CHE 3513 U/L, AFP 84.5 ng/ml. The serologic markers of hepatitis viruses (HBVAg, HCVAb, HAVAb) and immunological antibodies (IgA, IgG, IgM, ANA, AMA) were all negative. The detection result of CA-125 was 136.5 U/ml and CRP was 0.2 mg/L.

Diagnostic examination: the results of X-ray and ECG were normal, while cirrhosis and a solid space-occupying lesion in the right lobe of liver were observed under abdominal ultrasound (Figure 1). Hence, she was suspected to be diagnosed as hepatocellular carcinoma.

Cirrhosis with inhomogeneous density was observed in CT, and the low density area was obviously enhanced after contrast administration (Figure 2). Hence, the inflammation was suspected.

A liver biopsy was performed, and histology exhibited dropsy, degeneration necrosis, obvious lobular inflammation, confluent necrosis and inflammatory

Figure 1. Multiple high level echo masses in the right lobe of liver with unclear boundary observed under abdominal ultrasound.

Figure 2. Cirrhosis with abnormal low density observed in CT, which had inhomogeneous enhancement after injection of contrast medium in portal vein and balance phase.

Figure 3. The lesions of hepatitis, degeneration necrosis, reactive hyperplasia of fibrous tissue and inflammatory cell infiltration observed in the pathological feature of the liver tissues (Hematoxylin-Eosin staining, 100 $\times$).

cell infiltration in portal triad. Immunohistochemistry showed: CK19 (+), pre-S1 (-), HCV (-), HBsAg (-), CMV (-), HBcAg (-), EBV (-). Pathological diagnosis was considered as subacute hepatic necrosis, with suspicion of drug-induced hepatitis (Figure 3).

For this case, drug-induced hepatitis diagnosis was considered according to the following criteria: occurrence of hepatic damage directly related to drug administration, exclusion of other causes of hepatitis, and the results of liver histology.

Symptomatic and supportive treatment such as liver-protecting and albumin replenishing were applied after admission. But the patients' serum bilirubin elevated gradually. Then she had a high fever, headache, sore throat with increasing percentage of neutrophils. And she was diagnosed as respiratory infection and antibiotics were given. But the outcomes of medication was not very well and she left hospital due to economy reason voluntarily.

DISCUSSION

Drug-induced liver injury is a serious health problem

that impacts patients, physicians, the pharmaceutical industry and government regulators.¹⁻³ The report indicated that the number of cases suffering from DILI has been increasing.⁴ DILI is the most common causes of acute liver failure in the United States, accounting for approximately 13% of cases.⁵ It's found that there were over 1 100 kinds of medicine which has the potential to induce hepatotoxicity.⁶ DILI is the most common cause for the drugs withdrawal from the pharmaceutical market.⁷

Studies showed that acetaminophen, antiretroviral therapy, antibiotics, lipid-lowering drugs and anticonvulsants were responsible for DILI.⁸⁻¹¹ Although traditional Chinese medicine was always considered to be safety with no side effects. It was notable that the incidence of DILI caused by herbal remedies or traditional medicine have been increasing over the last decade.^{12,13}

Age, gender, pregnancy, and alcohol intake were estimated as risk factors for patients, and if combined with liver injury, they are considered to be related to acute cytolytic hepatitis.¹⁴ Moreover, genetic factors for drug metabolism, such as polymorphisms of cytochrome P (CYP) 450 or deficiency of N-acetyltransferase, have been reported to contribute to DILI.¹⁵

The diagnosis of DILI is often challenging because there are no specific biomarkers for it, and the clinical features are nonspecific. In essence, the diagnosis requires exclusion of a wide array of other causes of liver injury, including viral and autoimmune hepatitis, bile duct obstruction, sepsis, hepatic ischemia, and metabolic disorders. In patients with abnormalities in liver function without an obvious cause, a careful history, including not only medications in hospital, but also herbal remedies or supplements, should be taken

into consideration. Some clinical scales are available for the diagnosis of DILI.¹⁶⁻¹⁹ However, it is impractical to apply these diagnostic scales for each patient with liver injury who are taking medications.

The causes of misdiagnosis as hepatocellular carcinoma by ultrasound for this case were as follows: (1) the ultrasonography of residual liver diffuse lesions and the “tissue island in liver” was similar to that of hepatocellular carcinoma.²⁰ (2) reverberation influenced by irregular nodules of regenerating liver tissue. (3) the interference of flatulence and covering with the lower lobe of lung. (4) the relatively limited scope of ultrasonic examination. Hence, it's very important to combine ultrasonography with multiple imaging methods, which can complement each other to improve the diagnostic accuracy.

In most cases with DILI, liver injury will improve after discontinuation of the drug suspected to be responsible. DILI cases with severe hepatitis showing elevation of serum bilirubin higher than $3 \times \text{ULN}$ (upper limit of normal) may lead to liver failure, and should be treated carefully with referral to the hepatologist after discontinuing all suspected drugs. Corticosteroid therapy may be applied in DILI cases with evident hypersensitivity, but it does not have proven benefits.²¹ Corticosteroid treatment might do more harm than good in this patient due to her respiratory infection. Artificial liver support system and liver transplantation are useful therapy for severe liver failure.²² Although the patient had a severe hepatic failure, she still had a good chance of recovering with active treatment according to the increasing of her serum alpha-fetoprotein which indicated the compensatory growth of hepatocytes. However, she gave up the treatment for economic reason.

Many drugs can cause abnormalities in liver function detection without any symptoms of liver disease. Preplanned liver function tests should be performed whenever treatment with a new drug is stated. In the meantime, attention should be paid to elders, children and those with dysfunction of liver and kidneys. In addition, we should try to avoid using the same medicine or others with a similar chemical substance.²³

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