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Case report

Successful recovery from acute-on-chronic liver failure due to acute hepatitis E virus superinfection in chronic hepatitis B: A case report

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ABSTRACT

Introduction: Acute hepatitis E virus (HEV) infection is a self-limiting disease, but HEV superinfection in patients with chronic hepatitis B virus (HBV) infection may lead to acute-on-chronic liver failure (ACLF) and significantly increase short-term mortality. Diagnosis and comprehensive management of these patients remain in a dilemma.
Case presentation: A 32-year-old man with chronic HBV infection for 8 years received entecavir due to abnormal liver function for 4 months. He was admitted for symptomatic hepatitis flare for nearly 2 weeks. Initial investigations did not reveal a cause other than HBV, but repeated tests showed a progressive increase in his anti-HEV IgM. His condition worsened rapidly. Mid-stage ACLF and spontaneous peritonitis were diagnosed. Entecavir and hepatoprotective drugs were continued. Ribavirin, ceftriaxone, and repeated artificial liver support system (ALSS) therapy were administered. His condition gradually improved and his liver function eventually returned to normal.
Conclusions: Repeated HEV screening is important for patients with chronic liver disease and symptomatic hepatitis flare. Negative anti-HEV IgM for the first time can easily lead clinicians to mistakenly rule out HEV infection. A progressive increase in anti-HEV IgM is one of the diagnostic criteria for HEV infection, which is not rare but deserves attention. Additionally, comprehensive management including ribavirin and ALSS would be effective therapies for patients who superinfect with HEV and develop ACLF.

Introduction

Hepatitis E virus (HEV) cause liver damage and result in different degrees of clinical manifestations, mostly asymptomatic or non-life-threatening. Hepatitis B virus (HBV) mainly cause chronic infections that can progress to cirrhosis and even hepatocellular carcinoma in the long term. As there is no cross-immunogenicity between various hepatitis viruses, patients with chronic HBV infection can still overlap with other hepatitis viruses, of which the most common are hepatitis A virus and HEV [1].

HEV superinfection may rapidly lead to acute-on-chronic liver failure (ACLF) and significantly increase mortality [2]. However, due to the immune tolerance, alanine aminotransaminase (ALT) elevation can be mild, which makes it difficult to maintain an eye on the HEV. Even with HEV screening, the diagnosis of HEV infection may be missed because of a negative test in the early stage. With the high risk of liver failure and mortality, comprehensive management of HEV superinfection in patients with chronic HBV infection remains in challenging.

The present study describes a patient with chronic hepatitis B who developed ACLF due to HEV superinfection, revealing the importance of repeated HEV screening in patients with chronic HBV infection and hepatitis flare. Progressive elevation of anti-HEV-IgM can be a diagnostic criterion of HEV infection, which is uncommon and needs to be taken seriously. In addition, timely assessment and effective comprehensive management are critical for patients who superinfect with HEV and develop ACLF.

Case presentation

A 32-year-old male was admitted to the hospital due to fatigue, loss of appetite for 13 days and yellow skin staining for 5 days. He was positive for hepatitis B surface antigen (HBsAg) for 8 years and was first

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treated with entecavir due to an elevated ALT of 95 IU/L and an HBV DNA concentration of 1.5×10^5 IU/L four months previously. He had an average daily alcohol consumption of 22–35 g for approximately 10 years until 4 months ago. Both his mother and uncle were HBsAg positive, and his uncle had compensated cirrhosis. He denied a history of blood transfusions or unclean intravenous injections. A laboratory test revealed an elevated total bilirubin (TBIL) of 32.1 μmol/L, direct bilirubin (DBIL) of 24.6 μmol/L, ALT of 2294 IU/L, and aspartate aminotransferase (AST) of 1541 IU/L 13 days before admission. His HBV markers were positive for HBsAg, antibody against hepatitis B e antigen (anti-HBe), and anti-hepatitis B core antigen (anti-HBc). The level of HBV DNA was 3.5×10^2 IU/L. Hepatoprotective drugs were added. However, the patient's condition continued to worsen, and he underwent repeated tests 5 days before admission. His TBIL and DBIL levels increased to 121.7 μmol/L and 92.3 μmol/L, and the ALT and AST levels decreased to 1354 IU/L and 892 IU/L, respectively. The international normalized ratio of prothrombin time (PT-INR) was 1.35. Alpha-fetoprotein was 78.61 ng/ml. Antibodies against hepatitis A virus (anti-HAV), hepatitis C virus (HCV), and HEV were all negative. The serum markers of toxoplasma gondii, rubella virus, cytomegalovirus, and herpes simplex virus (TORCH) were also negative. Even with hepatoprotective and anti-HBV treatment, the patient's condition continued to deteriorate.

On admission, a general physical examination revealed clear consciousness, hepatic face and mucocutaneous jaundice. No abnormalities were found in his heart or lungs. He had a full abdomen with light tenderness in the upper abdomen and slight rebound pain from the midsection to the lower abdomen. His spleen had a moderate texture and was palpable 2 cm below the costal area. A shifting dullness test was positive. No edema was found in his lower limbs.

During the first three days after admission, repeated examinations confirmed that the patient was superinfected with HEV. Laboratory tests revealed an increase in the TBIL of 287.4 μmol/L, DBIL of 249.0 μmol/L, ALT of 968 IU/L, AST of 681 IU/L, alkaline phosphatase of 154 IU/L, glutamyl transpeptidase 175 IU/L, blood ammonia of 48.6 μmol/L, blood lactate of 1.2 mmol/L, PT-INR of 1.97, and HBV DNA of 1.2×10^1 IU/L. His kidney functions were normal with serum creatinine of 71 μmol/L and eGFR of 118.01 ml/min/1.73 m^2. The markers of autoimmune liver disease, anti-HAV IgM, anti-HDV IgM, anti-TORCH IgM, cytomegalovirus DNA, Epstein-Barr virus DNA, and thyroid function were negative or normal. However, the anti-HEV IgM turned positive (1.13 S/CO; reference value: < 1.0 S/CO). Abdominal ultrasound revealed that his liver parenchymal echo was enhanced, rough, and uneven, indicating fatty liver and liver parenchymal injury (Fig. 1). Computed tomography of abdomen revealed splenomegaly and portal hypertension with open collateral circulation, indicating the possibility of cirrhosis. Parietal thickening, swelling mesentery and omentum, and minor pelvic effusion were also found, indicating peritonitis. A small inflammatory nodule about 0.5 cm was found in his middle lobe of the right lung. Gastroscopy displayed two veins visible 25 cm away from the incisor.

The primary diagnosis was early-stage ACLF caused by acute HEV superinfection in chronic hepatitis B. In addition, decompensated cirrhosis and spontaneous peritonitis were diagnosed, and alcoholic liver disease was suspected. Standard medical treatments including entecavir, ribavirin, ceftriaxone, lactulose, hepatoprotective drugs, and diuretic agents were adopted. The patient's disease continued to worsen, with an increase in TBIL to 329.6 μmol/L and PT-INR to 2.11 (Fig. 2). The primary diagnosis was revised to mid-stage ACLF. After standard medical treatment with four sessions of Artificial liver support system (ALSS) therapy (double plasma molecular adsorption system (DPMAS) plus low-volume plasma exchange (PE)), the patient's condition gradually improved and he was discharged after nearly three weeks in the hospital. During hospitalization, his anti-HEV-IgM increased from 1.13 S/CO to 5.29 S/CO in approximately one week and increased rapidly to 12.50 S/CO in the next two weeks. After discharge, his condition continued to improve. The total bilirubin, ALT, PT-INR and anti-HEV IgM returned to normal or negative during follow-up.

Discussion

Herein, we report a case of ACLF caused by acute HEV superinfection in a patient with chronic hepatitis B. Repeated HEV-IgM antibody tests led us to accurately detect the cause of his disease. Although deteriorating rapidly, he eventually recovered after a combination of medication and ALSS therapy. As an area of shortage of liver sources but with high prevalence of chronic HBV infection and HEV infection, non-liver transplantation treatment is of great significance in the treatment of

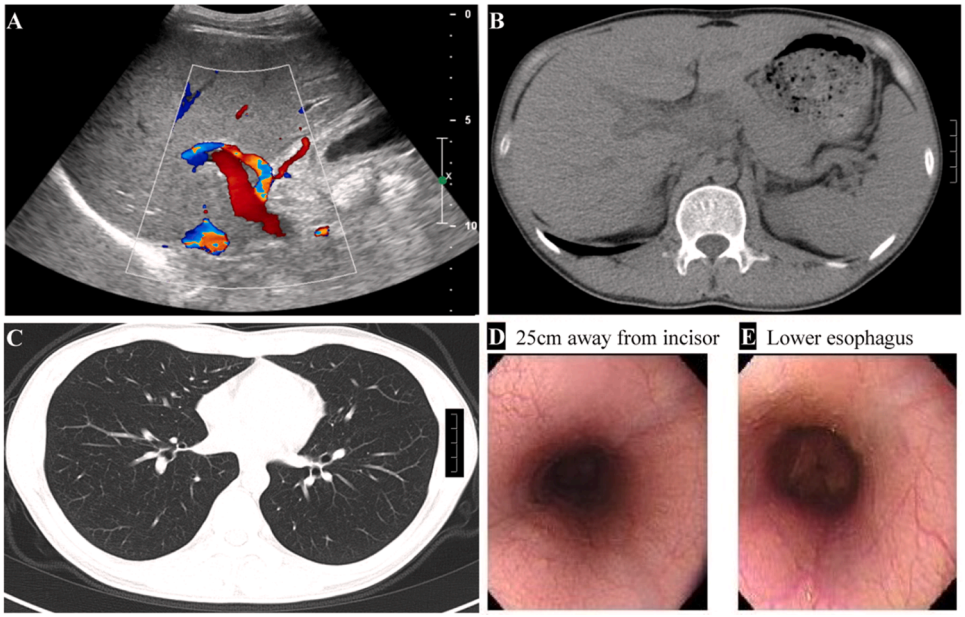

Fig. 1. Imaging manifestations. A. Abdominal ultrasound showed his liver parenchymal echo was enhanced, rough, uneven, indicating fatty liver and parenchymal injury. B. Computed tomography of abdomen showed splenomegaly, portal hypertension with open collateral circulation, possible cirrhosis. C. Computed tomography of chest showed a small nodule in the middle lobe of right lung. D and E. Gastroscopy displayed two veins visible 25 cm away from the incisor.

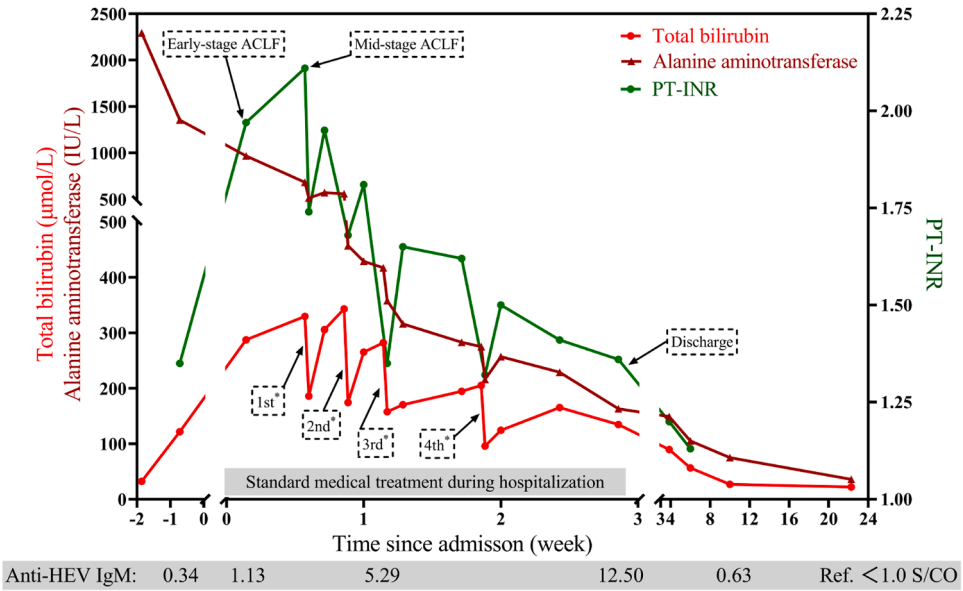

Fig. 2. Disease progression and outcome. *, four sessions of artificial liver support system therapy. Abbreviation: ACLF, acute-on-chronic liver failure; PT-INR, international normalized ratio of prothrombin time; HEV, hepatitis E virus; Ref., reference value.

liver failure in China. It could be a well-available and effective treatment or a bridge to liver transplantation for these patients.

Patients with chronic liver disease may develop liver failure when suffer from acute attacks. Our patient took entecavir regularly to treat hepatitis B due to mild abnormal liver function 4 months before admission. However, with well virological response, he still suffered acute symptomatic hepatitis and his liver function continued to deteriorate even with hepatoprotective drugs. Therefore, we considered the possible causes of acute hepatitis flare in addition to HBV. The most common causes of acute hepatitis flare include hepatotropic viruses and non-hepatotropic viruses. We repeatedly screened for common non-hepatotropic viruses, including TORCH, EBV, and CMV, all of which were negative. Among the other four common hepatotropic viruses, HCV infection often has a history of blood transfusion or unclean intravenous injection, which was denied by our patient. Besides, HCV infection is usually chronic, insidious, and asymptomatic in the early stages of infection. When screening showed negative HCV antibodies, we excluded HCV infection. Hepatitis D virus (HDV) is a defective virus. It infects chronic hepatitis B patients with the help of HBV. The co-infection rate of HBV and HDV is very low in west China. Our team has detected anti-HDV IgM in 400 patients with HBV-related liver failure, and only 2 (0.5 %) patients were found to be positive (unpublished data). We also tested the patient's anti-HDV IgM in the laboratory, and the result showed negative. Therefore, we considered that the patient did not have concomitant HDV infection. HAV and HEV are the most common hepatotropic viruses that cause acute hepatitis, and they are transmitted mainly through fecal-to-oral route. With relatively high serological prevalence of HAV and HEV, coinfection of HBV with HAV or HEV is more common. Studies from China [3] showed that the incidence rate of HBV-HAV superinfection was about 4.7 % to 16.5 %, while the incidence of HBV-HEV superinfection is about 1.7–25.1 % in 2016. Notably, HBV-HEV superinfection has more severe clinical symptoms and poorer prognosis than HBV-HAV superinfection. For our patient, his first test was negative for anti-HAV IgM and anti-HEV IgM. Considering the window period, we rechecked anti-HAV IgM and anti-HEV IgM. The results showed that anti-HAV IgM was still negative, while anti-HEV IgM turned positive this time. Based on the existing test results and his manifestation, we considered that he might have developed acute hepatitis E with chronic hepatitis B. Subsequent repeated tests showed that the titer of anti-HEV IgM increased progressively, which also confirmed our diagnosis.

HEV infection can be diagnosed by detection of anti-HEV antibodies, HEV RNA, and HEV capsid antigen. Generally, anti-HEV antibodies testing is considered first for its good performance and availability. Anti-HEV IgM turns positive after an incubation period of 2–9 weeks, reaches the peak level in two or more weeks, and turns negative in approximately 32 weeks in most patients [4]. Anti-HEV IgG presents later but it can last for years [5]. HEV RNA can be detected 3 weeks after infection, persisting about 3 weeks in the blood and 2 weeks longer in the stool[6]. HEV capsid antigen can be used to assist in the diagnosis of acute and chronic HEV infection and its detectable time is close to HEV RNA [7]. In our patient, the first test for anti-HEV IgM on the 8th day of illness was negative. On the 13th day of his illness, the repeated test for anti-HEV IgM turned positive, and only then did we diagnose him with acute HEV superinfection. The patient's anti-HEV IgM progressively increased and peaked in the fifth week after illness onset, which also confirmed our diagnosis. Therefore, HEV infection cannot be ruled out when early-stage antibody tests are negative. The progressive increasing titer (OD) of HEV IgM antibody may be an alternative diagnostic strategy for acute HEV infection in patients with abnormal liver function, especially in areas where HEV RNA and HEV Ag are inaccessible. Regrettably, we were supposed to check the HEV RNA load and HEV Ag status, but they were not routinely performed in our hospital when the patient sought medical attention, which is our limitation. With the development of pathogen biology detection technology, we have gradually expanded the application of nucleic acid testing. The detection of HEV RNA is also gradually being promoted.

HEV infection is usually asymptomatic or causes mild liver damage. In contrast, HBV-HEV superinfection may lead to severe clinical symptoms and complications. A prospective cohort study [8] showed that HBV-HEV superinfection results in severe liver function damage, deeper jaundice, and higher incidence of hepatic encephalopathy. Besides, HBV-HEV superinfection may cause damage to extrahepatic organs. Renal dysfunction, which is associated with poorer prognosis, is one of the most common extrahepatic manifestations. Other common extrahepatic manifestations caused by HEV include Guillain-Barre syndrome, acute pancreatitis, male infertility, acute arthritis, and so on. In the current case, his main manifestations were progressive deterioration of liver function. Although no significant kidney damage or other extrahepatic manifestations was observed in our patient, monitoring renal function was still necessary throughout the entire treatment period. Also, attention should be paid to the possibility of HEV coinfection when

presented with the above clinical manifestations.

A widely accepted view is that hepatitis E is an acute self-limiting disease. However, patients with chronic liver disease may have a worse prognosis after acute HEV infection. A retrospective cohort study showed that the 1-year mortality of cirrhotic patients with HEV superinfection was significantly higher than those without superinfection (30 % vs. 0 %, $p < 0.001$) [9]. Similarly, chronic hepatitis B patients with cirrhosis and HEV superinfection have a higher 1-year mortality than those without cirrhosis but with HEV superinfection (35.7 % vs. 2.4 %, $p < 0.001$) [9]. In our case, the patient had cirrhosis and deteriorated to mid-stage ACLF (APASL-ACLF Research Consortium (AARC) Grade 2) [10]. The European Association for the Study of the Liver (EASL) guidelines on HEV infection [11] recommend that ribavirin be considered in patients with severe acute hepatitis E or ACLF for its potential role in lowering liver enzymes and reducing mortality. Treatment with 400 mg po bid ribavirin may have shortened our patient's disease course and delayed further deterioration.

According to the DELPHI consensus [12], ALSS is a bridge to liver regeneration or liver transplantation in the management of patients with ACLF. A systematic review and meta-analysis of randomized trials revealed that ALSS therapy could reduce mortality (relative risk (RR) (95 % confidence interval (CI)): 0.84 (0.74–0.96); moderate certainty) and improve hepatic encephalopathy (RR (95 % CI): 0.71 (0.60–0.84); low certainty) in patients with acute liver failure and ACLF [13]. Currently, the widely used artificial liver models include models with exogenous plasma and without exogenous plasma. Models with exogenous plasma are relatively easier to operate and can remove broad-spectrum toxin, but the source of plasma is limited. Models without exogenous plasma have a wider adsorption range including inflammatory factors, whereas they are difficult to replenish plasma components and will lose albumin and coagulation factors. In our case, a combination model of DPMAS plus low-volume PE was adopted. It combines the advantages of DPMAS and PE to specifically adsorb bilirubin, remove inflammatory factors, supplement coagulation factors and albumin, and alleviate the problem of plasma shortage. Recently, a randomized trial revealed that DPMAS plus low-volume PE treatment in mid-stage HBV-related ACLF significantly improved the 12-week cumulative liver transplantation-free survival rate (52 % vs. 24 %, $p = 0.041$) [14]. In our patient, he progressed from early to mid-stage ACLF. Considering that his mortality rate may be as high as 30 %, there were indications for ALSS. The patient's bilirubin decreased after each ALSS therapy. After the first session of ALSS therapy, his bilirubin level initially decreased, indicating good absorption efficiency of ALSS. However, it subsequently rose to higher levels than ever before, implying that his disease was still progressing. Starting from the second ALSS therapy, the increase in bilirubin was lower than the previous peak. His bilirubin decreased after four sessions of ALSS therapy, with the bilirubin increasing slightly at first, and then slowly decreasing to normal under conservative medication. Reviewing the development and treatment process of the patient, comprehensive management, including ribavirin and ALSS therapies, was proven to be effective and timely.

Patients with chronic liver disease urgently need to take preventive measures against HEV. Currently, a recombinant HEV vaccine is available. Phase III clinical trials showed that the 12-month vaccine efficacy after three doses was 100.0 % (95 % CI: 72.1–100.0 %) [15]. Studies on long-term effectiveness suggested that the vaccine efficacy at 4.5 years and 10 years were 86.8 % (95 % CI: 71–94 %) [16] and 86.6 % (95 % CI: 73.0–94.1 %) [17], respectively. A randomized controlled clinical trial in 2013 showed that the vaccine had good immunogenicity and safety in HBsAg-positive adults [18]. Further research in 2019 showed that the vaccine has good immunogenicity and tolerability in people over 65 years old [19]. The patient in this case report was susceptible to HEV vaccine but he did not receive it. There is still an urgent need to widely disseminate information about the role of the HEV vaccine and increase its availability.

Conclusions

In summary, the present case highlights the importance of HEV screening among patients with chronic liver diseases and symptomatic hepatitis flares. The absence of anti-HEV IgM for the first time does not completely rule out HEV infection, and repeated examinations are necessary. A progressive increase in HEV IgM is one of the diagnostic criteria for acute HEV infection. Furthermore, comprehensive management including ribavirin and ALSS therapy could be an effective treatment for patients who superinfect with HEV and develop ACLF.

CRediT authorship contribution statement

hong tang: Writing – review & editing, Visualization, Resources, Funding acquisition, Conceptualization. **Weixiu Li:** Writing – review & editing, Writing – original draft, Formal analysis. **Yuanji Ma:** Writing – review & editing, Supervision, Software, Project administration, Formal analysis, Data curation, Conceptualization. **Lingyao Du:** Writing – review & editing, Software, Funding acquisition, Data curation, Conceptualization.

Author statement

The authors declare no competing interests.

All authors carried out final approval of the version to be published.

Ethical approval

The patient was recorded in a clinical database enrolled patients who received artificial liver support system therapy at the Center of Infectious Diseases, West China Hospital of Sichuan University. Approval for the cohort used was obtained from the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (2019-668). All study components were performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent to participate in the study has been obtained from all adult participants and all underaged participants' legal guardians.

Consent

All study components were performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent to participate in the study has been obtained from all adult participants and all underaged participants' legal guardians.

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Abbreviations

ACLF, acute-on-chronic liver failure; ALSS, artificial liver support system; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; DPMAS, double plasma molecular adsorption system; HBV, hepatitis B virus; HEV, hepatitis E virus; TBIL, total bilirubin; PE, plasma exchange; PT-INR, international normalized ratio of prothrombin time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of interest

The authors declare no competing interests.

Author contributions

MY and DL collected the case data. LW and MY conceived and designed the study and wrote the manuscript. DL, MY, and TH revised the manuscript. All authors carried out final approval of the version to be published.

Author Agreement

The authors declare no competing interests.

Data sharing statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

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