Hepatitis E virus re-infection accelerates hepatocellular carcinoma development and relapse in a patient with liver cirrhosis: A case report and review of literature

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Abstract

BACKGROUND
Hepatitis E virus (HEV) superinfection is a suspected promoting factor for hepatocellular carcinoma (HCC) in patients with chronic hepatitis and cirrhosis. However, to date, very few cases of HEV-related HCC have been reported. Nevertheless, the role of HEV re-infection in cirrhotic liver without other chronic hepatitis infections has rarely been explored.

CASE SUMMARY
A 53-year-old male farmer was diagnosed with liver cirrhosis and splenomegaly in August 2016, accompanied with negative HEV-IgM and positive HEV-IgG. No evidence of hepatitis B virus or hepatitis C virus infection was found. Since then the patient was evaluated for liver function and viral parameters every 3 mo. In June 2017, the patient presented severe fatigue with whole body itching and was diagnosed with HCC. Afterwards this patient experienced quick HCC development, progression, relapse, and metastasis in the following 8 mo, and presented persistent dual positivity of HEV-IgM and HEV-IgG. This patient had a long history of smoking and alcohol consumption.

CONCLUSION
This unique case invokes the importance of HEV surveillance and treatment...
A 53-year-old male farmer presented himself to the clinic of general surgery in June 2016 because of severe fatigue with whole body itching for 10 mo.

**History of present illness**

In August 2016, the patient was admitted to the hospital due to hematemesis and melena. He had been diagnosed with liver cirrhosis, confirmed by ultrasonography and computed tomography (CT), complicated with esophagogastric varices by gastroscopy and splenomegaly by ultrasonography and CT. This patient had splenectomy in September 2016 and blood transfusion during surgery. The pathological result suggested a chronic congestive splenomegaly. At that moment, the serum test determined that he was anti-HEV IgM negative and IgG positive.

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History of past illness
He had no hypertension, diabetes, or other chronic diseases.

Personal and family history
The patient had a history of alcohol use with 200 mL daily intake and smoking 20 cigarettes a day for 20 years. Since June 2017 when HCC was diagnosed, the patient had quit alcohol drinking and smoking. Moreover, he had no family history of cancer.

Physical examination
Initial physical examination demonstrated pale skin with normal blood pressure (85/122 mmHg) and normal heart rate (80/min). No jaundice was observed in the skin and abdominal palpation elicited no pain.

Laboratory examinations
Serum anti-HEV IgG and IgM detection performed by enzyme-linked immunosorbent assay revealed that this patient was HEV-IgM and HEV-IgG double positive at admission in June 2017, and no evidence of hepatitis A virus (HAV), HBV, or hepatitis C virus (HCV) infection was detected (Table 1).

The biochemical test at admission showed normal alanine aminotransferase (ALT, < 40 U/L), slightly elevated aspartate aminotransferase (AST, 39-60 U/L) and alkaline phosphatase (ALP, 121-147 U/L), and highly elevated gamma glutamyl transferase (GGT, 154-186 U/L) and total bile acid (TBA, 27-34 µmol/L) (Figure 1, Table 1, and Supplementary Material).

Imaging examinations
At admission in June 2017, the CT and magnetic resonance imaging (MRI) examinations detected multi-site liver masses (S5, S8), cirrhosis, portal hypertension, and esophageal and fundus varices (Supplementary Material).

FINAL DIAGNOSIS
The patient was diagnosed with HCC based on CT and MRI results[8], accompanied with double positivity for HEV-IgM and HEV-IgG.

TREATMENT
In July 2017, the patient was classified with Barcelona Clinical Liver Cancer (BCLC) stage B, and transarterial chemoembolization (TACE) was conducted at S5 and S8 according to the international guidelines[9,10].

OUTCOME AND FOLLOW-UP
The patient was then regularly followed every 3 mo upon discharge in August 2017. Since then, serum sample tests were persistently positive for HEV-IgM and HEV-IgG till April 2018, but HEV RNA was not detectable by quantitative real-time PCR.

During the follow-up period till April 2018, the patient presented significantly increased blood levels of GGT, type IV pro-collagen, and hyaluronidase. There was an obvious peak of ALT (135-139) and AST (67-167) in November 2017 during hepatectomy. Except for this perioperative elevation, ALT and AST remained normal or slightly increased (Figure 1). A normal range of alpha fetoprotein (AFP) was also observed during the whole admission period (Figure 2). Serum HEV RNA result was negative by quantitative real-time PCR (Supplementary Material).

One month after the discharge, CT examination suggested enhanced areas in S8 again. Then the patient was treated with radiofrequency ablation (RFA), which was commonly applied among patients with old age and/or accompanied by other diseases such as liver cirrhosis[11], or used to shrink the tumor and reduce the surgical trauma probably caused by succeeding partial hepatectomy. Afterward, progressive HCC was evidenced by strengthened CT signal at the previously diagnosed site (S8) as well as a new site (S3) after 2 mo, in November 2017. A partial hepatectomy was...
| Time of admission (d) | 1st    | 2nd    | 3rd    | 4th    | 5th    | 6th    | 7th    |
|----------------------|--------|--------|--------|--------|--------|--------|--------|
| Date of admission   | 2016-08-19 | 2017-06-20 | 2017-09-26 | 2017-11-20 | 2018-02-07 | 2018-02-23 | 2018-04-16 |
| Diagnosis            | Cirrhosis | HCC | HCC | HCC | HCC | HCC | HCC |
| Treatment            | Splenectomy | TACE | RFA | Partial hepatectomy | MWA | TACE and MWA | MWA |
| HEV IgM              | Negative | Positive | Positive | Positive | Positive | Positive | Positive |
| HEV IgG              | Positive | Positive | Positive | Positive | Positive | Positive | Positive |
| GLU (mmol/L)         | 7.81 | 4.49 | 5.82 | 5.04 | 5.44 | 5.31 | 4.67 |
| BUN (mmol/L)         | 13.1 | 3.1 | 3.54 | 4.35 | 4.3 | 4.2 | 3.7 |
| CO2_CP (mmol/L)      | 23.7 | 21.2 | 22.3 | 24 | 25.4 | 25.9 | 23.5 |
| UA (umol/L)          | 334 | 271 | 312 | 293 | 282 | 289 | 300 |
| CREA (umol/L)        | 65.5 | 58.4 | 72.8 | 65.25 | 65.7 | 61.1 | 62 |
| ALT (U/L)            | 27 | 24 | 40 | 45 | 20 | 20 | 43 |
| GGT (U/L)            | 166 | 154 | 224 | 232 | 67 | 65 | 195 |
| ALP (U/L)            | 59 | 121 | 119 | 132 | 114 | 104 | 151 |
| CHE (U/L)            | 3405 | 3926 | 4545 | 4393 | 3834 | 3515 | 3966 |
| TP (g/L)             | 56.5 | 63.8 | 63.8 | 63.8 | 67.6 | 63.2 | 70.7 |
| ALB (g/L)            | 27.2 | 29.3 | 30.8 | 31.3 | 30.6 | 29.2 | 32.5 |
| TB (umol/L)          | 30.9 | 33.7 | 26.6 | 36.1 | 29.8 | 33.5 | 30.8 |
| DB (umol/L)          | 8 | 7.7 | 5.4 | 7.7 | 7.7 | 7 | 7.8 |
| TBA (umol/L)         | 2 | 27 | 46 | 22 | 76 | 41 | 32 |
| Na (mmol/L)          | 141.6 | 141.2 | 140.7 | 141.9 | 139.3 | 141.4 | 139.9 |
| K (mmol/L)           | 3.96 | 3.95 | 3.94 | 4.15 | 4.06 | 3.9 | 4.04 |
| Cl (mmol/L)          | 109.6 | 109 | 107.1 | 108 | 109.9 | 109.3 | 107.7 |
| Ca (mmol/L)          | 2 | 2 | 2.1 | 2.1 | 2.19 | 2.13 | 2.06 |
| PHOS (mmol/L)        | 1.22 | 1.28 | 1.21 | 1.27 | 1.2 | 1.26 | 1.23 |
| Mg (mmol/L)          | 0.81 | 0.7 | 0.81 | 0.82 | 0.83 | 0.81 | 0.84 |
| AST (U/L)            | 38 | 39 | 49 | 67 | 38 | 37 | 55 |
| CIV (ng/mL)          | 151.98 | 169.96 | 162.28 | 82.65 | 60.27 | 17.33 | 15.82 |
| LN (ng/mL)           | 32.25 | 592.83 | 553.67 | 199 | 178 | 159 | 140 |
| PIIIP (ng/mL)        | 10.9 | 17.33 | 15.82 | 17.33 | 15.82 | 15.82 | 15.82 |
| HA (ng/mL)           | 841.13 | 592.83 | 553.67 | 199 | 178 | 159 | 140 |
| HBsAg (E) (COI)      | 0.48 | 0.478 | 0.452 | 0.575 | 0.386 | 309.7 | 308.1 | 353.5 |
| Anti-HBs (E) (IU/L)  | 494.2 | 309.7 | 308.1 | 353.5 | 309.7 | 308.1 | 353.5 |
| HBeAg (E) (COI)      | 0.102 | 0.087 | 0.097 | 0.1 | 0.087 | 0.097 | 0.1 |
| Anti-HBe (E) (COI)   | 1.27 | 1.12 | 1.15 | 1.23 | 1.12 | 1.15 | 1.23 |
| Anti-HBc (E) (COI)   | 0.008 | 0.009 | 0.01 | 0.011 | 0.009 | 0.01 | 0.011 |
| HBV-DNA (FQ-PCR) (IU/mL) | 10 | 10 | 10 | < 500 | 10 | 10 | < 500 |
| HAV IgM              | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| Anti-HCV (COI)       | 0.03 | 0.04 | 0.04 | 0.03 | 0.04 | 0.04 | 0.04 |
| HIV COM (COI)        | 0.21 | 0.22 | 0.24 | 0.21 | 0.22 | 0.24 | 0.24 |
Syphilis (COI) 0.08 0.07 0.08
AFP (A) (ng/mL) 4.12 3.6 4.57 8.59 2.7 3.79 3.58
CEA (A) (ng/ml) 4.86 4.32 5.47 4.71 5.89 5.65
PSA (A) (ng/mL) 0.1

HCC: Hepatocellular carcinoma; TACE: Transcatheater arterial chemoembolization; RFA: Radiofrequency ablation; MWA: Microwave ablation; HEV: Hepatitis E virus; IgM: Immunoglobulin M; IgG: Immunoglobulin G; GLU: Glucose; BUN: Blood urea nitrogen; CO2_CP: Carbon dioxide combining power; UA: Uric acid; CREA: Creatinine; ALT: Alanine aminotransferase; GGT: Gamma glutamyl transferase; ALP: Alkaline phosphatase; ChE: Cholinesterase; TP: Total protein; ALB: Albumin; TB: Total bilirubin; DB: Direct bilirubin; TBA: Total bile acids; AST: Aspartate aminotransferase; CIV: collagen IV; LN: Laminin; PIIIPI: Pre collagen type III peptidease; HA: Hyaluronate; HBsAg: Hepatitis B surface antigen; Anti-HBs: Hepatitis B surface antibody; HBeAg: Hepatitis B e Antigen; Anti-HBe: Hepatitis B e antibody; Anti-HBc: Hepatitis B core antibody; Anti-HCV: Hepatitis C virus antibody; HIV COM: Combination of HIV antibody; AFP: Alpha fetoprotein; CEA: Carcino-embryonic antigen; PSA: Prostate specific antigen; PHOS: Phosphorus; COI: Cut off index.

Figure 1
Biological measurements of liver function of the patient from August 2016 to April 2018. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma glutamyl transferase; ALP: Alkaline phosphatase; TBA: Total bile acid; HCC: Hepatocellular carcinoma; HEV: Hepatitis E virus.

Conducted to remove the relapsed tumors at the previous treatment site (S8) and the new site (S3). The histological examination of surgically resected tissue confirmed cirrhosis and multi-site HCC grading from I to II, with sizes ranging from 0.6 cm to 0.9 cm. The histopathological examination revealed that tumors were CD10, CD34, CEA, and Glypican III positive (Figure 3, Supplementary Material).

In the following 2 mo, a newly developed liver tumor was identified by CT at S2 and a suspected right upper zone lung metastasis was also indicated. Microwave ablation (MWA) treatment was applied at S2 for HCC relapse. In April 2018, suspected tumor nodes at S8 were detected by CT again, followed by TACE and MWA treatment at S8 (Supplementary Material).
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Figure 2 Alpha fetoprotein test results of the patient between August 2016 and April 2018. AFP: Alpha fetoprotein; HEV: Hepatitis E virus.

Figure 3 Histopathologic characterization of hepatocellular carcinoma. A and B: Haematoxylin and eosin staining of the patient’s pathological tissue.

This patient was treated with MWAs in July 2018 and December 2018 due to newly identified HCC relapses.
During the whole process, no anti-viral medications including interferon-based therapeutics were prescribed to the patient. And, no further HEV infection examination was performed after April 2018.
DISCUSSION

At the first presentation to the clinic, this patient suffered from chronic HEV infection, evidenced by positive HEV-IgG and negative HEV-IgM, and cirrhosis simultaneously, but no chronic HBV or HCV infection. In the following 20 mo, this patient was suspected with repeated HEV infection, supported by persistent dual positivity for HEV-IgM and HEV-IgG. More importantly, in the following 20 mo, the patient experienced rapid HCC development, progression, multiple times of relapse, and metastasis.

The patient is speculated to have initial infection of HEV in his farm where farm animals are a suspected source of HEV infection[22]. A previous study has defined farmers as a high risk group of HEV infection due to the potential dissemination of HEV infection in Chinese farms[23]. However, the presumed cause of HEV re-infection is blood transfusion during splenectomy. Previous studies have indicated that the likelihood of developing clinically relevant HEV infection after transfusion of a HEV positive blood product can be as high as approximately 50%[14-19]. And in immunosuppressed patients, receiving HEV-RNA positive blood products might lead to or prompt the development of fatal acute-on-chronic liver failure[18-20]. Regarding to this, the blood authorities in Europe have advocated to implement HEV screening among blood donors[21]. Unfortunately, currently in China HEV is not tested on blood donations, which therefore lets the patients on the risk of HEV infection from blood transfusion. In this specific case, pre-existing liver cirrhosis predisposes the patient to HEV reinfection, as well as subsequent HCC development. Additionally, the persistent HEV re-infection might also be a result of the lack of anti-viral treatment for HEV chronic infection, especially after the patient has developed HCC and during the progression of HCC. In consequence, a small amount of virus in the liver is able to repeatedly reactivate or cause infection, and invoke weak immune response which is deficient to eliminate the viruses regardless of the production of a small amount of anti-HEV antibodies.

The patient had the history of alcohol drinking and smoking, which might be the underlying causes of cirrhosis[22-26]. And the functional decompensated liver predisposes the patient to HEV re-infection and rapid HCC development, progression, relapse, and metastasis[22-24]. It was reported that long-term tobacco exposure would increase the levels of hepatic cancer stem cell-like markers and variate the expression of inflammatory factors IL-33[25]. Similarly, chronic and acute HEV infection would increase the levels of some inflammatory factors and compromise liver function. On the other hand, alcohol intake would lead to chromosomal loss, DNA methylation aberration, genetic susceptibility, oxidative stress, and retinoic acid level decrease in the liver[26]. Previous investigations revealed that excess alcohol consumption was associated with high seroprevalence of HEV in cirrhosis cases, indicating that the alcohol-decompensated liver would be more susceptible to HEV infection[22,27]. All abovementioned risk factors are exhibited in this patient. Thus, we have rationale to speculate a synergic effect evolved from proinflammatory state, genetic instability, and hepatic decompensation leading to accelerated malignant progression in an HEV-infected and re-infected cirrhotic liver. Nevertheless, the definite association between these factors and liver carcinogenesis remains to be further investigated.

Our study has several limitations. First, HEV genotype was not determined because the test is not routinely performed for patients infected with HEV in clinical practice in China. It has been well documented that in China genotype 4 is the most dominant type in human chronic HEV infection, and the cases infected with other genotypes have been reported but remain sporadic in China[26-29]. Nevertheless, in future a routine diagnosis of HEV genotype should be implemented in both clinical and research settings to acquire a deep insight into the association between chronic HEV infection and development of HCC. Second, other potential HCC serum biomarkers such as PIVKA were not screened. This case presented a normal range of AFP during the whole admission period, which warned us the importance of utilizing other biomarkers to assist in early detection of HCC, especially for cases with an uncommon etiology. Further studies should set effort to develop a set of multiple biomarkers, complementary with AFP, for clinical diagnosis of HCC.

Recent studies have suggested that immunocompromised patients are predisposed to HEV infection[10,20], and HEV might promote the progression of HCC in patients with chronic HBV infection and/or cirrhosis[10,20]. However, the role of HEV re-infection in patients with hepatic decompensation with or without chronic HBV infection has not yet been explored, to our knowledge. Our observation in this unique case has indicated that, regardless of chronic HBV infection, in patients with liver cirrhosis HEV superinfection might promote not only HCC development and
progression, but also relapse and metastasis. Our report provides new knowledge to HEV-related carcinogenesis and clinical management of HEV-associated liver pathologies. Future studies should emphasize on the mechanisms underlying HEV re-infection accelerated malignant transformation of cirrhotic liver in the presence or absence of chronic HBV infection. The potentially distinct effect on HCC progression exposed by unique sequential acquisition of HEV infection and cirrhosis is an important question to address in future study as well.

CONCLUSION

This unique case highlights an urgent need to investigate the effect of HEV re-infection on rapid HCC development and progression in cirrhotic liver, despite the presence of chronic HBV infection. Our report also reveals the importance of routine screening on rapid HCC development and progression in cirrhotic liver, despite the presence of absence of chronic HBV infection. The potentially distinct effect on HCC progression but also relapse and metastasis. Our report provides new knowledge to HEV-related carcinogenesis and clinical management of HEV-associated liver pathologies. Future studies should emphasize on the mechanisms underlying HEV re-infection accelerated malignant transformation of cirrhotic liver in the presence or absence of chronic HBV infection. The potentially distinct effect on HCC progression exposed by unique sequential acquisition of HEV infection and cirrhosis is an important question to address in future study as well.

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