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CORRESPONDENCE

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Chronic Hepatitis E in a Renal Transplant Recipient: The First Report of Genotype 4 Hepatitis E Virus Caused Chronic Infection in Organ Recipient

Dear Editors:

Chronic hepatitis E (CHE) infection in organ transplant recipients has been exclusively related to genotype 3 hepatitis E virus (HEV) infection, and mainly prevalent in Western countries.[1] However, it remains unclear whether other genotypes of HEV can also result in chronic hepatitis. Herein, we report the first case of genotype 4 (G4) HEV caused chronic infection and the clinical outcome in organ transplant recipient in China, warranting the devotion of future research to CHE in organ transplant recipients, where G4 HEV is prevalent.

A 36-year-old Chinese man underwent living-donor renal transplantation in 2008 for uremia and received tacrolimus-based immunosuppressive medication constantly. This patient recuperated well until 2012, when he felt discomfort in the upper right area of the abdomen. Serologic tests reported modest elevation of serum transaminases and negative examinations for hepatitis A, B, C and D viruses, cytomegalovirus, and autoantibodies. HEV infection was diagnosed by positive anti-HEV IgM antibody in 2013, when the transaminase increased again (Figure 1*A*). Histologic analysis revealed hydropic and ballooning hepatocytes with inflammatory cell infiltration (Figure 1*B*). Retrospective immunohistochemistry of liver biopsy in September 2013 revealed scattered expression of HEV viral protein in both cytoplasm and nucleus with anti-HEV open reading frame 2 antibody, further confirming HEV infection (Figure 1*C*). Of note, Masson staining showed fibrosis around the perisinusoidal and portal area (Figure 1*B*). Because there was no previous diagnosis of fibrosis in this patient, we suspected that the fibrosis was due to HEV infection. Rapid progression of fibrosis has been reported in the first year of HEV infection.[2]

CHE in this patient is defined by persistent positive of anti-HEV IgM antibody and the presence of the virus in the liver to date (Figure 1*A*). Liver enzymes and total bilirubin levels are not high during infection (Figure 1*A* and Supplementary Figure 1*A*), suggesting a low immune response. Liver biopsy in April 2017 revealed swollen hepatocytes and severe inflammation (Figure 1*B*). Portal tracts were infiltrated with abundant mixture of inflammatory cells and apoptotic bodies, consistent with chronic viral hepatitis. Interlobular biliary canals were integrated and no lymphocytes or eosinophils infiltration, indicating the apoptosis of hepatocytes was not due to organ rejection. Masson staining showed expanded portal tracts and proliferative fibrosis. HEV RNA was also detected in stool. Furthermore, HEV viral particles were able to be visualized in liver tissue and stool specimen (Figure 1*D*). Sequencing of the full-length genome revealed as G4a strain (GenBank accession number MF567575; Figure 1*E*, Supplementary Figure 2).

G4 HEV is mainly spread in Asia by zoonosis.[3] This patient reported no consumption of pork products, but moved to a village in 2012 just 1 month before showing an abnormal transaminase. The village lacks a secure source of water and the sanitary conditions are inadequate. He drank the water and ate seafood from the river in the village, which runs near a livestock farm. In fact, different sub-G4 HEVs have been detected in fecal matter–contaminated water in China.[4] It is reasonable to speculate that this patient got HEV infection possibly by contacting water and aquatic products contaminated with HEV.

Reduction of immunosuppressant dose and ribavirin therapy are the main treatment choices for CHE.[1] However, reduction of the tacrolimus dose had no effect on viral clearance and transaminase normalization in this patient. Ribavirin monotherapy was implemented in 2015, which normalized the liver function. There was a transient seronegative conversion, but this treatment was withdrawn after 3 months owing to anemia. The following ribavirin treatment and withdrawal with fluctuated liver enzymes led to virus relapse and persistence (Figure 1*A*). The treatment outcome of this patient seems different from most transplant patients with genotype 3 HEV, in whom HEV clearance was observed in 30% and 95% of patients with a reduction of immunosuppressants or ribavirin treatment, respectively.[2,5] Similarly, a patient with an acute G4 HEV infection after liver transplantation did not show liver function improvement or viral clearance with ribavirin treatment.[6] The antiviral activity of ribavirin against genotype 1, genotype 2, and genotype 3 strains, but not G4, of HEV have been confirmed in vitro.[7] Although G4 HEV is thought to be more pathogenic,[8] it remains obscure as to whether the outcome of our patient is associated with this genotypic specificity.

HEV is endemic in China and the predominant genotype is G4. With respect to rapidly increasing organ transplantation in China, large prospective multicenter cohort studies are essential to investigate the prevalence and clinical features of G4 HEV infection in this population.

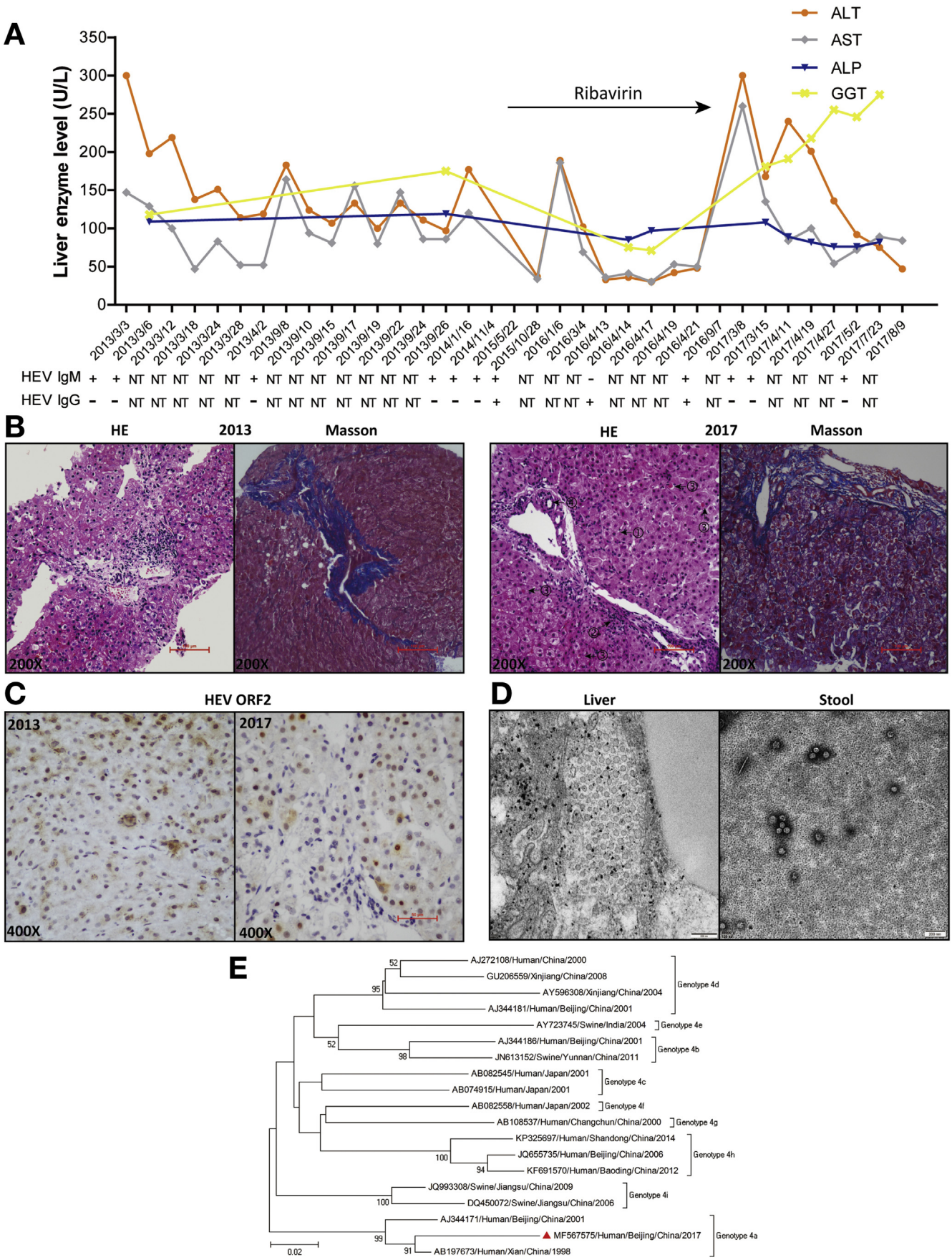

Figure 1. Serologic examination, pathologic presentation, hepatitis E virus (HEV) detection and phylogenetic analysis of HEV sequence in this patient. A histologic description is provided in the supplementary materials.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2017.12.028. Q2

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Conflicts of interest
The authors disclose no conflicts. Q1

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