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Hepatitis E Virus Infection in a Liver Transplant Recipient in the United States: A Case Report

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ABSTRACT

Background. Chronic infection with hepatitis E virus (HEV) has recently been recognized in immunocompromised or immunosuppressed individuals.

Case Report. We report a case of concurrent HEV and human herpes virus-6 (HHV-6) infection, documented by serum HEV RNA and HHV-6 DNA, in an orthotopic liver transplant (OLT) recipient in the United States, where HEV genotype 3 infection, although prevalent, is considered to be self-limited and almost always asymptomatic. The coinfection was accompanied by elevated serum aminotransaminases, liver biopsies demonstrating chronic hepatitis, and the presence of HEV RNA in the tissue. After lowering of immunosuppressive therapy and 2 courses of valganciclovir, sequential clearance of the viruses and normalization of the serum aminotransaminases were observed.

Conclusions. HEV infection can lead to chronic hepatitis in OLT recipients, and evaluation of this virus should be considered in immunosuppressed individuals with unexplained liver test abnormalities.

IN THE UNITED STATES, acute hepatitis E virus (HEV) genotype 1 is typically diagnosed in travelers returning from developing countries as a self-limited illness. Rarely, it progresses to liver failure, particularly among pregnant women or patients with underlying liver disease. Whereas travel-related HEV infection has been associated with waterborne HEV genotypes 1 and 2 from developing countries, autochthonous HEV infection in industrialized countries have been associated with zoonotic transmission of genotypes 3 and 4.[1]

The first case of possible chronicity was described in a patient with T-cell lymphoma, where HEV infection was observed over a course of 6 months.[2] More recently, chronic hepatitis E from HEV genotype 3 has been reported in a patient infected with HIV infection[3] and in liver, kidney and pancreas transplant recipients in The Netherlands, France, and Germany.[4–7]

We report a case of concurrent HEV and human herpes virus (HHV)-6 infection in a liver transplant recipient in the United States, and their sequential clearance from the serum after treatment with 2 courses of valganciclovir.

CASE REPORT

A 60-year-old man of Indian origin underwent orthotopic liver transplantation (OLT) on January 13, 2005, for hepatitis B virus (HBV)-related cirrhosis and hepatocellular carcinoma. At the time of OLT, he was on treatment with lamivudine, and HBV DNA was not detectable in his serum. After OLT, he received hepatitis B immunoglobulin perioperatively and remained on lamivudine to prevent HBV recurrence. All follow-up serum specimens were negative for HBV DNA. Immunosuppression consisted of tacrolimus and sirolimus. The patient recovered well, and liver function tests were normal by 2 months posttransplantation.

Four months after OLT, the patient had elevated liver enzymes with serum aspartate aminotransferase (AST) 121 IU/mL and alanine aminotransferase (ALT) 195 IU/mL (Fig 1) accompanied by fatigue and malaise. Serum HBV DNA, hepatitis C virus (HCV) RNA, cytomegalovirus (CMV) DNA, and antinuclear antibody were all negative. The enzyme elevations persisted, and a liver biopsy obtained at 24 months after OLT revealed chronic hepatitis (grade 2, stage 0) but of unknown etiology. The portal tracts were expanded by mononuclear cell infiltrates composed primarily of

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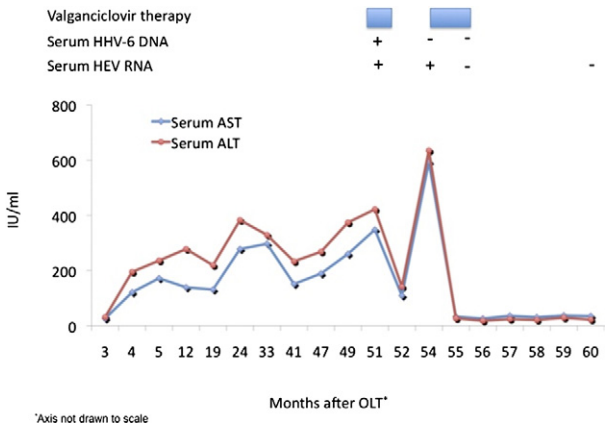

Fig 1. Course of serum AST, ALT, and viral serologies in relation to valganciclovir therapy.

lymphocytes, with rare scattered admixed eosinophils and macrophages. There were also rare scattered lymphocytes within the lobules, and a few acidophil bodies were identified. Plasma cells were not evident, and there was mild interface activity. Bile ducts were unremarkable. Minimal macrovesicular steatosis, involving <5% of the hepatocytes, was present. No ground glass hepatocytes were identified and immunohistologic stains utilizing hepatitis B surface antigen and hepatitis B core antigen were both negative. No viral intranuclear inclusions were identified.

At 50 months after OLT (March 2009), the patient's liver function tests remained elevated with serum AST 241 IU/mL, ALT 369 IU/mL, and alkaline phosphatase 158 IU/mL, although the total bilirubin remained normal at 0.7 mg/dL; he continued to experience fatigue and malaise, but also complained of dizziness and abdominal bloating.

He came to our institution for further management. Additional evaluation included a repeat serum HBV DNA, hepatitis D antibody, HCV RNA, Epstein-Barr virus immunoglobulin (Ig)M, herpes simplex virus IgM, and HIV antibody, which were all negative. However, the serum HHV-6 DNA and anti-HEV IgG were positive, and anti-HEV IgM was negative. Serology for hepatitis E was repeated on a subsequent serum sample collected 3 months later at the Division of Viral Hepatitis Laboratory, US Centers for Disease Control and Prevention. The sample tested positive for both IgM and IgG anti-HEV. Furthermore, HEV RNA was detected in the serum and sequencing studies showed it belonged to HEV genotype 3. A repeat liver biopsy showed similar findings as the first, mild chronic hepatitis (grade 2, stage 0) of unknown etiology (Fig 2). Polymerase chain reaction (PCR) detection of HEV RNA was performed on the second liver biopsy and was positive. The liver tissue was scratched from the block, homogenized, RNA extracted and subjected to PCR as described previously.[8] The patient's last travel to India was 18 months before his visit to our institution, and he denied consuming any raw meat products, or known exposure to live animals or known cases of viral hepatitis.

Immunosuppression was reduced with discontinuation of sirolimus, but tacrolimus was continued (serum trough level, 5.8 mg/dL). He was treated with valganciclovir at 900 mg PO BID for 3 weeks for the HHV-6 viremia, which led to eradication of his HHV-6 DNA and improvement in his liver function tests to serum AST 109 IU/mL and ALT 141 IU/mL (Fig 1). After completing the course of valganciclovir, however, the liver function tests were further elevated to serum AST 593 IU/mL and ALT 635 IU/mL, despite a negative repeat serum HHV-6 DNA titer. The serum HEV RNA remained positive. The patient was then retreated with 8 weeks of valganciclovir 900 mg PO BID. One month later, his liver enzymes normalized, IgM anti-HEV became negative, and HEV RNA at the end of treatment was undetectable. At 6 months' follow-up, his liver function tests remain normal and his symptoms have resolved. In addition, the HEV RNA and serum IgM anti-HEV remained negative; IgG anti-HEV remained positive.

DISCUSSION

Chronic HEV infection has been recently reported in immunosuppressed or immunocompromised patients, occasionally leading to significant hepatic injury or advanced fibrosis and cirrhosis.[5,6,9,10] Anti-HEV prevalence of 4%–14% has been reported in liver or other solid-organ trans-

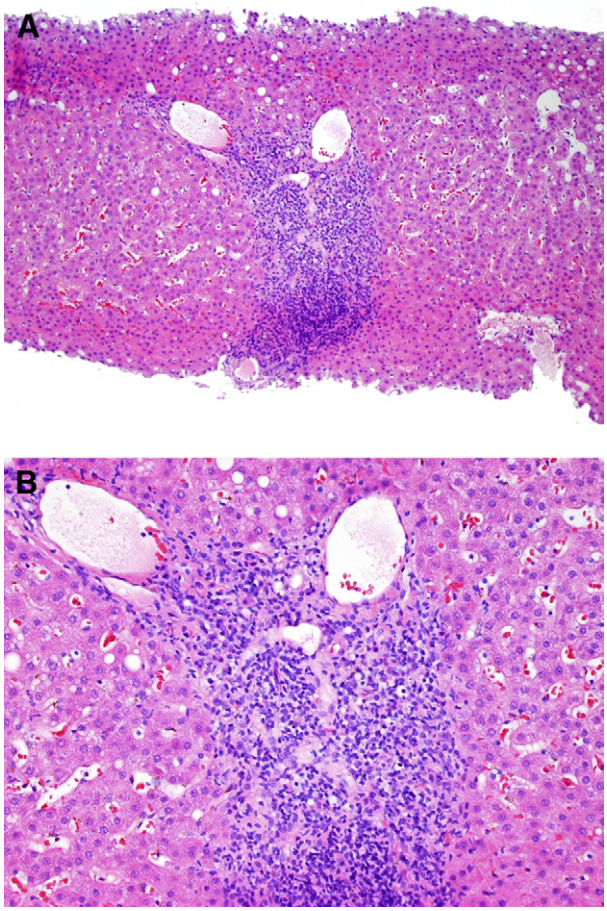

Fig 2. Histologic findings on liver biopsy, at medium **(A)** and high power views **(B)**. The portal tracts were expanded by mononuclear cell infiltrates composed primarily of lymphocytes, with rare scattered admixed eosinophils and macrophages. There were also rare scattered lymphocytes within the lobules, and a few acidophil bodies were identified. Plasma cells were not evident, and there was mild interface activity. Bile ducts were unremarkable. Minimal macrovesicular steatosis, involving <5% of the hepatocytes, was present. There was no fibrosis.