Chronic Hepatitis E With Genotype 1—Masquerading as Allograft Rejection After LiverTransplantation

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Hepatitis E is one of the leading causes of acute viral hepatitis worldwide. Chronic infection with hepatitis E is less common and limited to immunosuppressed patients and is usually due to genotype 3 of the virus. Genotype 1, the most prevalent strain in the South Asian region, is seldom known to be associated with chronic hepatitis. Here we describe a case of chronic hepatitis E with genotype 1 in a post-liver transplant setting. In the index case, previously compensated cryptogenic cirrhosis was decompensated by an acute hepatitis E infection, which necessitated liver transplantation because of acute chronic liver failure. This later progressed to chronicity. This case may have significant implications in management, especially in the post-liver transplant setting. (J Clin Exp Hepatol 2021;11:400–403)

Hepatitis E is one of the leading causes of acute viral hepatitis worldwide, which is more in developing countries. A genotypic dichotomy is seen in the geographical distribution of this infection, where genotypes 1 and 2 are mainly seen in developing countries with high endemicity, often being responsible for epidemics. Genotypes 3 and 4 are predominantly seen in areas of low endemicity.[1] The classic presentation ranges from acute hepatitis with self-limiting course to acute liver failure in 1–2% cases.[1]

Rarely, an indolent, chronic hepatitis is seen with hepatitis E. This is largely restricted to those with compromised immunity such as those with HIV, post-chemotherapy, and post-transplant setting. Genotype 3 of the virus is the most common offending agent for chronic hepatitis E (CHE), and a few cases with genotypes 4 and 7 have also been reported.[2,3] Genotype 1, which is the most prevalent strain in the South Asian region, is almost never known to cause chronic hepatitis. Here we describe a case of CHE with genotype 1 in a post-liver transplant patient, who evaded the initial diagnosis masquerading as allograft rejection.

CASE REPORT

A 48-year-old man with cryptogenic cirrhosis was presented with acute-on-chronic liver failure (ACLF) as per the Asian Pacific Association for the Study of the Liver (APASL) definition. The acute decompensation was precipitated by the hepatitis E virus (HEV) related to acute hepatitis with positive IgM anti-HEV antibodies in the serum. Because of his worsening liver failure, he underwent un-eventful living-donor liver transplantation after a month of his illness and since then was on immunosuppression with prednisolone, tacrolimus, and mycophenolate mofetil.

A month after the liver transplantation, he developed a mild elevation of serum transaminases (2–3 times higher than the normal), along with an elevation of alkaline phosphatase (2 times higher than the normal). Initial magnetic resonance cholangiopancreatography showed mildly dilated intrahepatic biliary radicals, a biliary stricture was suspected and a stent was placed across the bile duct anastomosis. However, there was only a partial reduction in transaminases and alkaline phosphatase. An alternative pathology was therefore suspected.

A liver biopsy was performed, which suggested moderate acute cellular rejection (ACR; Figure 1, **biopsy 1**); however, despite the administration of 2 pulses of methylprednisolone and the histological resolution of ACR on the repeat liver biopsy (Figure 1, **biopsy 2**), his jaundice continued to increase with a maximum bilirubin of 58 mg/dl. On further work-up, he was found to be positive for IgM anti-HEV antibodies, and negative for hepatitis B surface antigen, anti–hepatitis C virus antibodies, and autoimmune markers. Markers for the cytomegalovirus, Epstein–Barr virus, and herpes simplex virus were also negative. HEV RNA was detectable both in serum and in

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Abbreviations: ACLF: acute-on-chronic liver failure; ACR: acute cellular rejection; CHE: chronic hepatitis E; HEV: hepatitis E virus; ORF: open reading frame; RdRp: RNA-dependent RNA polymerase
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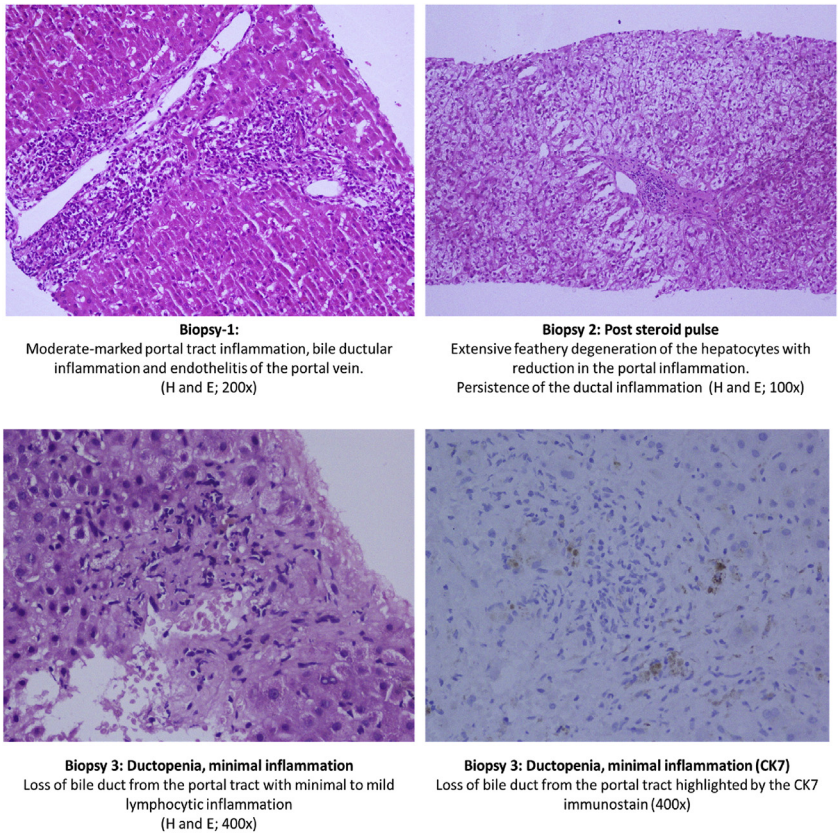

Figure 1 Photomicrographs of liver biopsies.

stool samples using nested polymerase chain reaction (nested-PCR). The sequencing of the RNA-dependent RNA polymerase (RdRp) region of HEV ORF-1 revealed that the isolate belonged to genotype 1 (Figure 2; accession numberKX670814).

Despite the supportive care, he continued to have worsening jaundice, and a third liver biopsy 2 months later showed chronic biliary ductopenia and the presence of HEV RNA in the liver tissue (Figure 1, biopsy 3). Because of renal dysfunction (serum creatinine 2.3 mg/dl), he was put on low-dose ribavirin (200 mg/day) with the reduction in immunosuppressive drugs. After 3 weeks, his serum bilirubin declined (from 62 to 45 mg/dl) and serum creatinine became normal, allowing an increase of the ribavirin dose to 400 mg/day. However, there was no further decline in bilirubin. The patient was simultaneously worked up for a re-transplantation due to severe ductopenia and persistent cholestasis. Unfortunately, he developed a soft tissue infection, which led to fulminant sepsis and multi-organ dysfunction, and he succumbed to his illness.

DISCUSSION

Hepatitis E is usually an acute, self-limiting illness. However, during the last decade, many cases of chronic infection with HEV have been published.[1–3]CHE is defined as the persistence of viral replication beyond 3 months of infection in either serum or stool. This is usually seen in patients with lowered immunity—HIV, immunosuppressive medications, or hematological malignancies. Most cases described till date belonged to genotype 3, and a few cases with genotypes 4 and 7.[2-3]The common denominator for genotypes 3, 4, and 7 is animal to human transmission. Conversely, genotype 1 is commonly transmitted from human to human.

Solid organ transplant recipients are particularly susceptible to CHE, with up to 60% of those exposed to HEV progressing to chronicity. CHE in this population may have worrisome complications, as it may lead to faster progression to cirrhosis.[4-5] Moreover, this condition requires a high degree of suspicion as it may mimic ACR histologically. In fact, among all patients with moderate to severe rejection, 4% had evidence of HEV viremia.[6] This distinction is crucial, as ACR would require pulse steroids, which may further enhance viral replication in patients with CHE.

Although genotype 3 is well known to cause CHE in post-transplant patients, genotype 1 is almost never reported in this context. This is quite important, as genotype 1 is the most prevalent genotype of South Asia, which is the most endemic region for hepatitis E worldwide. Therefore, the index of suspicion for CHE is extremely low. Here we

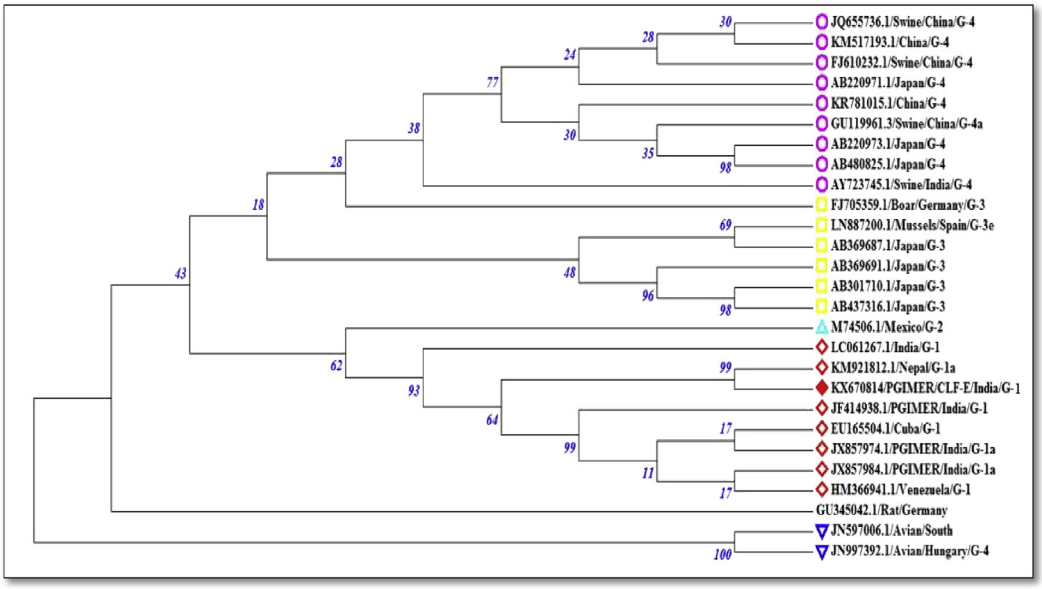

Figure 2 Phylogenetic analysis of our strain (KX670814) by constructing NJ tree for the conserved RdRp region (ORF-1) of HEV. The avian strain of HEV (JN997392.1) was included as an outlier group. Length of the branches represent distances computed using the p-distance method. Bootstrap value of 1000 replicates were used for statistical verification. Evolutionary analysis was conducted in MEGA7.

describe a case of CHE with genotype 1 in a post-liver transplant setting. In the index case, previously compensated cryptogenic cirrhosis was decompensated by an acute hepatitis E infection, which necessitated liver transplantation because of ACLF.

The graft dysfunction started early in the post-transplant period. This was initially thought to be due to biliary obstruction. However, non-improvement with biliary drainage led to suspicion of alternate pathology. Progressively worsening jaundice and elevated transaminases with periportal inflammatory mononuclear infiltrates raised the suspicion of ACR. However, the progression of jaundice despite 2 pulses of methylprednisolone and histological evidence of resolution of inflammation on biopsies promoted further investigation. The persistence of HEV IgM antibody and HEV RNA even 6 months after transplant pointed toward the diagnosis of CHE. Whether the hepatic inflammation was a consequence of rejection, viral insult, or a combination of the two, is unclear.

Ribavirin has been used in the past to treat genotype 3 CHE with reasonable success, in combination with the reduction of immunosuppression. In this patient, there was only a transient, incomplete clinical improvement in starting ribavirin. This may be due to advanced graft dysfunction at the initiation. Alternatively, a possibility of genotype 1 having a poorer response to ribavirin may also be considered. The only other reported case of genotype 1 CHE was 2 years after chemotherapy for acute lymphoblastic leukemia.[7] The patient was treated with ribavirin, but took 6 months for viral clearance, and was treated for 1 year despite not being on any immunosuppressive medication. Generally, genotype 3–associated CHE needs treatment for 3 months duration.[8]

The identification of genotype 1 as an etiologic factor for CHE has crucial clinical implications, especially in South Asia. Firstly, till date, there has been no reported case of genotype 1 CHE in a post-liver transplant setting. It is possible that many such cases may be missed in the absence of a high index of suspicion. The possibility of CHE should be considered in immunosuppressed patients with chronic hepatitis, which is not otherwise explained. Secondly, although ribavirin has been shown to be useful in CHE related to genotype 3, its efficacy in patients with genotype 1 CHE is yet unclear. Its potential benefit should therefore be considered guarded. Lastly, the implications of CHE on liver allograft dysfunction, graft rejection, and accelerated progression to cirrhosis and/or ductopenia need to be further studied.

HEV genotype 1 is widely prevalent in South Asia. Although previously not considered a cause, it may lead to CHE. A high index of suspicion is required and immunosuppressed patients with persistent unexplained hepatitis should be tested for HEV RNA in blood and/or stool. This may have significant implications in management, especially in the post-liver transplant setting. The relationship between HEV and chronic rejection is poorly understood and needs to be explored in future studies.

CREDIT AUTHOR STATEMENT

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CONFLICTS OF INTEREST

The authors have none to declare.

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