Hepatitis E virus: An underdiagnosed cause of chronic hepatitis in renal transplant recipients

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Hepatitis E virus (HEV) is a single-stranded hepatotropic nonenveloped RNA virus that causes enterically transmitted acute hepatitis. It is endemic in several developing countries in Asia, the Middle East, Africa, and Central America, and is emerging in industrialized countries (1). Like hepatitis A virus (HAV), acute HEV infection runs a self-limited course in immunocompetent individuals and evolution to chronicity occurs only in the setting of immunodepression (2–4). In solid organ transplant recipients, acute hepatitis E can progress to chronicity in up to 60% of infected patients (5, 6). Moreover, chronic HEV infection can lead to rapidly progressive cirrhosis (7, 8). Recognizing this entity is therefore important, as initiating proper therapy can halt or reverse the disease progression.

We report a case of chronic HEV infection in a renal transplant recipient that went undiagnosed for many years, discuss the therapeutic options, and review the current available literature.
aminotransferase levels stabilized at 4 times the upper limit of normal.

Serologic testing for hepatitis B virus (HBV), hepatitis C virus (HCV), HAV, and human immunodeficiency virus (HIV), as well as HCV RNA were all negative at the time of transplantation and during follow-up. Also, no evidence was found of cytomegalovirus (CMV) or Epstein–Barr virus (EBV) infection. Antinuclear, anti-smooth muscle, antimitochondrial, anti-LKM, and antinuclear cytoplasmic antibodies were all negative. The patient did not consume alcohol. No drug toxicity was suspected and she had not travelled abroad during the last years. Liver ultrasound showed steatosis.

She refused to undergo liver biopsy until 2008, when the biopsy was performed during surgical treatment for hiatal hernia. Histological findings were compatible with chronic active viral hepatitis with Ludwig scores of P2 L2 S2 and Metavir fibrosis score of F2 (Fig. 1). HCV RNA was repeatedly negative in the serum and HBV antigen was absent in the liver biopsy.

HEV virus infection was diagnosed in April 2009 based on immunoglobulin-G (IgG) anti-HEV antibodies positivity (determined by recomWell HEV IgG Elisa Kit; Mikrogen, Neuried, Germany) and HEV RNA detection in serum by polymerase chain reaction (PCR) (qualitative homebrew real-time PCR developed by the Belgium Scientific Institute of Public Health). HEV strain belonged to genotype 3 (Fig. 2). Retrospective analysis of frozen sera revealed that HEV RNA was detectable in the patient’s serum in September 2008. Unfortunately, no earlier serum samples were available.

Methylprednisolone doses were reduced to 2 mg/day followed by a lowering of tacrolimus trough level to 4–5 ng/mL. Within 1 month, levels of ALT and AST returned to normal values (Fig. 3). Serum HEV RNA was checked 7 months after the reduction of immunosuppression and was undetectable. At that time, the total lymphocyte count and the CD2, CD3, and CD4 lymphocyte counts were normal. Transient elastography (FibroScan; Echosens, Paris, France) performed 1 year after the reduction of immunosuppression showed a median stiffness value of 5.6 KPa, with an interquartile range of 1.0, and a success rate of 91%, consistent with absent or mild fibrosis (F0–F1).

**Discussion**

Increased levels of aminotransferases are frequently encountered following renal transplantation. In some patients, after ruling out viral (HAV, HBV, HCV, EBV, CMV, HIV), alcohol, toxic- and drug-related causes, no etiology is found. In our patient, liver test levels increased 7 months after transplantation and diagnosis of HEV infection was not made until 5 years later, after the patient finally agreed to undergo a liver biopsy and was referred to the hepatologist for investigation.

The acute hepatitis episode can be asymptomatic in > 50% of patients, as in our patient, or patients can present with fatigue, jaundice, weight loss, and diffuse arthralgias or myalgias (6). Diagnosis can be difficult because anti-HEV IgG antibodies are frequently negative (6, 9). Thus, a negative HEV serology does not rule out the diagnosis, and HEV RNA must be sought by PCR in the serum or the stools. In areas or hospitals where this test might not be available, HEV infection can remain undiagnosed.

Evolution of acute HEV infection to chronicity is indicated by persistently elevated liver enzymes and detectable serum HEV RNA 6 months after the acute episode, along with histological findings of chronic hepatitis similar to that observed in patients with

**Fig. 1.** Liver biopsy. Portal fibrosis (left panel) and dense lymphocytic portal infiltrate with piecemeal necrosis (right panel).
HCV infection. Comparing patients who cleared their virus after acute hepatitis with patients who evolved to chronicity, risk factors for chronicity seemed related to heavy immunosuppression, reflected by a shorter time from transplantation to infection, lower CD2, CD3, CD4, and total lymphocyte counts, as well as being on a tacrolimus versus a cyclosporine regimen (5, 6, 10). In this context, reduction of immunosuppression was reported to clear the virus in 30% of patients with chronic HEV infection (10). Our patient showed a favorable response to tapering off steroids and tacrolimus levels, with normalization of liver enzymes and clearance of the virus. Unfortunately, HEV RNA viral load was not available, making it difficult to assess the evolution of viral replication after reduction of immunosuppressive therapy.

The F0–F1 fibrosis score on the Fibroscan elastography performed 1 year after the reduction of immunosuppression suggested a regression of fibrosis from the F2 Metavir score recorded on the initial liver biopsy. Reversibility of cirrhosis of various etiologies, including HCV and HBV, has been reported after successful treatment of the etiologic agent (11). Consequently, regression of fibrosis could be possible in chronic HEV infection after viral clearance.

For patients in whom reduction of immunosuppressive therapy does not lead to HEV clearance, pegylated α-interferon is not an option in renal transplant recipients owing to the high incidence of acute rejection and graft loss reported after its use (12). Recently, Kamar et al. (13) have reported the favorable response of 6 patients treated with a 3-month course of ribavirin monotherapy, with a sustained virological response in 4 of them. Two patients experienced relapses at 1 and 2 months after ribavirin therapy was stopped (13). Thus, ribavirin seems a promising therapy that needs further investigation to confirm its efficacy, lack of secondary effects, and to determine the optimal duration of treatment.

Fig. 2. Phylogenetic tree based on a 148-nt fragment of the capsid gene, showing that the virus (HEV 09-74) belongs to genotype 3.

Fig. 3. Normalization of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels with the decrease of tacrolimus trough level.
In conclusion, this case highlights the facts that 1) HEV should be considered in the differential diagnosis of persistently elevated liver enzymes; 2) the diagnosis requires HEV RNA detection in the serum or the feces, as serological tests can be negative despite active infection; 3) attempt to treat is mandatory as chronic HEV hepatitis can progress rapidly to cirrhosis; 4) reduction of immunosuppression can lead to viral clearance and possibly regression of fibrosis; and 5) close monitoring is required after reducing immunosuppression to avoid the risk of acute rejection.

References