Chronic Hepatitis E Virus Infection in a Pediatric Female Liver Transplant Recipient

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We describe a case of chronic hepatitis E virus (HEV) infection in a 13-year-old female liver transplant recipient with recurrent increased aminotransferase levels and acute cellular rejection. This finding demonstrates that chronic HEV infection can occur and should be further investigated in immunocompromised patients in Latin America.

CASE REPORT

A 4-year-old girl who had undergone orthotopic liver transplantation in 2003 presented with increased aminotransferase levels and biopsy-confirmed acute cellular rejection in 2006. Liver enzyme levels were normalized after 3 days of methylprednisolone pulse therapy and increased tacrolimus dosage. In 2009, the alanine aminotransferase concentration reached 715 IU per liter and thereafter plateaued at nearly 2.5 times the upper limit of the normal range. Acute cellular rejection was additionally confirmed by biopsy. Results of serology and molecular testing for hepatitis A virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, and Epstein-Barr virus were negative. Results of molecular testing for cytomegalovirus and Epstein-Barr virus in liver tissue and testing for autoantibodies and antinuclear antibodies were also negative. Serum transaminase levels remained elevated, and in 2011, histological examination showed prominent inflammatory activity and fibrosis compatible with viral infection. Hepatitis E was diagnosed in February 2012 on the basis of positive results for anti-hepatitis E virus (HEV) IgG and IgM antibody testing (Mikrogen, Germany) and, later, in May 2013, HEV RNA detection (genotype 3b, Brazil h4; GenBank accession number [KF152884](#)), with a load of 4.5 log₁₀ copies per ml. The patient did not report any recent travel, and no potential route of HEV transmission other than consumption of pork was identified. The living organ donor tested negative for anti-HEV antibodies. No prior serum samples were available. However, retrospective examination of viral RNA extracted from paraffin-embedded formalin-fixed liver tissue (RNeasy FFPE kit; Qiagen, Germany) from 2009 showed the presence of HEV with >99% homology to the sequence found in the serum sample from 2013, thus characterizing chronic hepatitis E infection (Brazil h4.1; GenBank accession number [KM502569](#)). At the time of HEV RNA detection, the alanine aminotransferase concentration was 120 IU per liter. The patient received ribavirin treatment (500 mg/day) for 10 months, and her HEV RNA load became undetectable (<100 copies per liter) in August 2013.

Infections caused by HEV can become chronic, with persistently elevated aminotransferase levels and persistent viremia in immunocompromised adults and children; certain chronic cases have been described in pediatric patients with HIV or hematolog-

ical malignancies and in pediatric patients who have received solid-organ transplants (1–4).

Increased levels of aminotransferases are frequently observed after solid-organ transplantation (5). In certain patients, after ruling out viral and alcohol-, toxin-, and drug-related causes, no etiology is established. In the case presented here, the living organ donor tested negative for anti-HEV antibodies, and no potential route of HEV transmission other than consumption of pork was identified. Kamar et al. stated that although the route of infection is uncertain in most patients, it is recommended that transplant patients avoid consuming this type of meat (6).

The diagnosis of HEV infection can be especially difficult in immunosuppressed patients, as results of tests for anti-HEV antibodies are frequently negative. Furthermore, HEV is not commonly investigated in Brazil, even with the occurrence of unexplained elevation of levels of liver enzyme or acute hepatitis, and currently, only few laboratories perform anti-HEV tests. In the present case, initial HEV infection diagnosis was performed by detection of anti-HEV antibodies 7 years after the patient first presented with increased aminotransferase levels and acute cellular rejection.

Once hepatitis E was diagnosed through serology, HEV RNA was detected, and a phylogenetic analysis characterized the strain as genotype 3b. The HEV isolate (Brazil h4; GenBank accession number [KF152884](#)) shared 87% to 93% homology with sequences of human HEV previously characterized by our group in renal transplant recipients in Brazil (7) and 83% to 97% homology with sequences of swine HEV from Brazil (8–10). Among all HEV sequences compared, the highest homology (95% to 97%) was to swine sequences recently isolated in southern Brazil (10). The results from the phylogenetic analysis are shown in Fig. 1. The strain isolated from the retrospectively analyzed paraffin-embedded formalin-fixed liver tissue showed >99% homology to the sequence

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FIG 1 Phylogenetic tree reconstructed by the neighbor-joining method with common 304-nucleotide (nt) ORF2 sequences from 46 isolates, including 13 porcine isolates from Brazil, 2 human isolates from Brazil, and the 2 human isolates described in this study, Brazilh4 and Brazilh4.1 (highlighted in red). The GenBank accession number in parentheses, name of the country of origin, species from which it was isolated, and genotype/subtype of the isolate identify each viral strain. Bootstrap values of >50 are indicated for the major nodes as a percentage of the data obtained from 1,000 replicates (bar, 0.02 substitutions per site). Major branches indicate genotypes. Avian HEV is the outgroup.

found in the serum sample, thus classifying the infection as chronic hepatitis E.

To our knowledge, this is the first report of chronic and/or pediatric HEV infection in Latin America. These findings demonstrate that chronic HEV infection can occur in immunocompromised patients in Brazil. Additionally, the results suggest that HEV infection should be further investigated and incorporated into the differential diagnosis of hepatitis and acute cellular rejection among liver transplant recipients in this setting, including pediatric patients.

Nucleotide sequence accession numbers. Nucleotide sequence data for the HEV isolate determined in this study are available in GenBank under accession no. [KF152884](#) and [KM502569](#).

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