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Evidence of hepatitis E virus transmission by renal graft

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Abstract

Hepatitis E virus (HEV) can cause chronic infection among immunocompromised patients, especially solid organ transplant (SOT) recipients, and can evolve to cirrhosis. Several modes of transmission are known. Here we describe the first 2 cases, to our knowledge, of HEV infection transmitted by a kidney graft from the same infected donor that led to chronic hepatitis. Consequently, systematic screening of donors by HEV serology and HEV RNA detection by polymerase chain reaction, particularly in endemic regions, should be considered.

KEYWORDS:

chronic hepatitis E, renal graft; transmission, transplantation

1 INTRODUCTION

Hepatitis E virus (HEV) is endemic in developing countries but also in some regions of developed countries such as France. It usually causes acute hepatitis, with a clinically silent course, spontaneous recovery among immunocompetent patients and low mortality rate, <4%. [1]

HEV is an RNA virus with 4 major genotypes. Genotypes 1 and 2 are responsible for waterborne outbreaks and sporadic cases in developing countries. Genotype 3 and 4 are zoonotic and infect both humans and several other mammals, but mainly pigs. Genotype 3 is widely distributed, and genotype 4 prevails in Asia.[1] Their transmission occurs mainly by ingestion of raw or undercooked infected meat or by contact with the animal reservoir.[2]

Cases of chronic HEV infection were described several years ago in immunocompromised patients.[3] These infections are related to genotype 3 or 4 and defined by HEV RNA detection in patients' serum or stools and persistently elevated serum alanine aminotransferase (ALT) levels.[4] Among solid organ transplant (SOT) recipients, HEV infection spontaneously evolves to chronic infection in 65% to 80% of cases, [5,6] but 30% to 50% of these patients may clear HEV after reduction of immunosuppressive therapy. For the remainder, antiviral therapy may be proposed. Among chronically infected patients, progression of fibrosis to cirrhosis is rapid.[7]

Several modes of HEV transmission are known. The most frequent contamination mode is pork consumption,[10] but zoonotic transmission through direct contact with infected animals has also been reported.[11] Cases of parenteral transmission via blood transfusion have been reported,[12,13] although systematic screening among blood donors is nowadays not recommended.[14] Recently, Féray et al.[15] reported that 5 of 367 consecutive liver transplant recipients (1.4%) in France acquired chronic HEV infection through blood transfusion and developed persistent liver graft damage. A recent study in southeast England[16] revealed HEV RNA prevalence of 1 in 2848 blood donations (0.04%), and underlined that viremic donors were also frequently seronegative (71%). The overall transmission rate in recipients was 42%, and the risk is higher if the donor has a negative serology with a high viral load. These data suggest a need for systematic screening of blood donations by RNA detection, [17] but cost-effectiveness studies need to be performed.

Until now, no case of transmission via a nonhepatic graft has been described. We report here the first 2 cases, to our knowledge, of kidney transplant recipients who were infected by HEV via renal grafts from a single donor.

2 CASE REPORT

2.1 Index case

The index case is of a 66-year-old man who underwent kidney transplantation in August 2013 for hypertensive nephrosclerosis (Figure 1A). The donor was a 73-year-old-man, who died from a cerebral hemorrhage. Our patient required 2 packed red blood cell transfusions a few days after transplantation.

Nine months after transplantation, he presented with progressive hepatic cytolysis and cholestasis: aspartate aminotransferase (AST)=106 U/L, ALT=103 U/L, gamma glutamyl transferase (GGT)=1141 U/L, alkaline phosphatase (AP)=246 U/L, and bilirubin=70 µmol/L, without hepatocellular insufficiency. Abdominal ultrasonography revealed hepatosplenomegaly. The patient had no toxic or drug-related cause of abnormal liver function tests (LFT). HEV serology was negative on immunoglobulin (Ig)M and IgG enzyme-linked immunosorbent assays (Wantai, Beijing, China) with positive HEV RNA detection (6.56 log IU/mL, by quantitative reverse transcriptase real-time polymerase chain reaction (RT-PCR) (Hepatitis@ceeram Tools; Ceeram, La Chapelle-Sur-Erdre, France), and sequence analysis of the open reading frame (ORF)2 region identified genotype 3f. All other virological tests were negative, except for a low positive viral load for Epstein-Barr virus.

Retrospective analysis detected negative RNA until the day of transplantation and positive RNA from the first month after transplantation. Immunosuppressive therapy was reduced and the patient received antiviral therapy (ribavirin [RBV]). LFT normalized and serum RNA was negative 2 months after reduction of immunosuppression and 3 months from starting RBV. HEV RNA currently remains negative.

The 2 units of packed red blood cells that he received tested negative for HEV RNA. Donor's serum revealed a positive RT-PCR test for HEV (2 870 000 IU/mL, i.e., 6.46 log IU/mL) with a positive serology for IgG and IgM, and genotype 3f was identified. The donor's LFT were abnormal just before transplantation: ALT=110 U/L, AP=400 U/L. No other organ from the same donor was transplanted. In particular, the liver was unsuitable for transplanting as the biopsy showed portal vascular lesions and lobular atrophy.

2.2 Second case

The second recipient from the same donor was identified after biomonitoring (Figure 1B). He was a 65-year-old man with a history of type 2 diabetes. The transplantation was uneventful.

Eleven months after transplantation, he developed subacute cholestasis (bilirubin=44 µmol/L, GGT=771 U/L, and AP=271 U/L) and elevated transaminases (ALT=392 U/L and AST=198 U/L). Abdominal ultrasonography revealed hepatomegaly. HEV RNA detection became positive (6.78 log IU/mL) and genotyping also identified genotype 3f. Other causes of chronic liver disease have also been ruled out.

The patient was treated with RBV from November 2014 to January 2015. At this time, LFT were subnormal and hepatitis E RNA was 1.68 log IU/mL, but treatment was withdrawn because of severe anemia. HEV recurred (6.68 log IU/mL) 2 months later and RBV was prescribed. At last follow-up (December 2015), LFT were normal, HEV RNA was undetectable, and RBV could be stopped.

As shown on Figure 2, the phylogenetic analysis revealed a 100% homology of sequences between the 3 HEV strains when comparing 2 regions: ORF-2 encoding the viral capsid protein (nucleotides 5996-6343), and the ORF encoding the RNA-dependent RNA polymerase (RDRP, nucleotides 4254-4560).

3 DISCUSSION

HEV seroprevalence in kidney transplant recipients has been found to be between 19% and 43% in western endemic countries.[8,9] RNA detection has been shown to be positive in 8% of kidney transplant patients with LFT abnormalities and, of those patients with a positive RNA, 3% had a negative HEV serology.[8]

The only previous known case of nosocomial HEV transmitted via SOT is an occult HEV transmission through a liver transplant,[18] with negative donor serology and serum RNA detection; HEV RNA replication in the liver biopsy was detected before transplantation. Phylogenetic analysis revealed the same strain in the donor and in the recipient, and thus demonstrated direct transmission via the liver graft.

The cases reported herein are, to our knowledge, the first to demonstrate that HEV can be transmitted by a kidney donor presenting with high viral load, leading to chronic hepatitis. The strict homology between donor's and recipients' sequences in different genomic regions demonstrates transmission probably by the blood contained in the kidney grafts. These cases also confirm that, while RNA detection is strongly positive, seroconversion may not be observed in immunocompromised patients. It should be noted that our 2 patients presented with a cholestatic profile. This is unusual in this setting, but has already been reported in acute infection with HEV.[19]

Currently, routine HEV screening of organ donors is not recommended. These cases of HEV transmission via the renal graft should question this practice, and perhaps lead to systematic screening by RNA detection, at least for donors with abnormal LFT. However, the cost/benefit of such a policy has to be evaluated, in particular because an efficient treatment (RBV) is treatment. The other option is to rule out HEV infection in all cases of elevated aminotransferases and to treat patients with persistent infection, as was done here.

Author contributions*:*

A.P. and M.-N.P.: Drafting article; Data analysis/interpretation; N.O., P. S., and A.M.R.A.: Data analysis/interpretation; approval of article; E.R.: Concept/design; approval of article; J.P.: Concept/design; critical revision of article.

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FIGURE LEGENDS:

FIGURE 1 Evolution of liver function tests and hepatitis E virus RNA before and after treatment of hepatitis E in the index case (A), and in the second case (B). Ribavirin November 15, stopped January 17, Ribavirin March 18, stopped December 28.

FIGURE 2 Phylogenetic trees, constructed on MEGA4 software using the Neighbor-Joining method from a Kimura 2-parameter distance matrix, based on partial nucleotide sequences of the open reading frame (ORF)1 encoding RdRp (333 nt) and ORF2 (324 nt). Bootstrap values obtained from 500 resamplings are shown. A 100% sequence homology is observed in both regions between the sequence of the kidney donor and the sequences of the 2 recipients

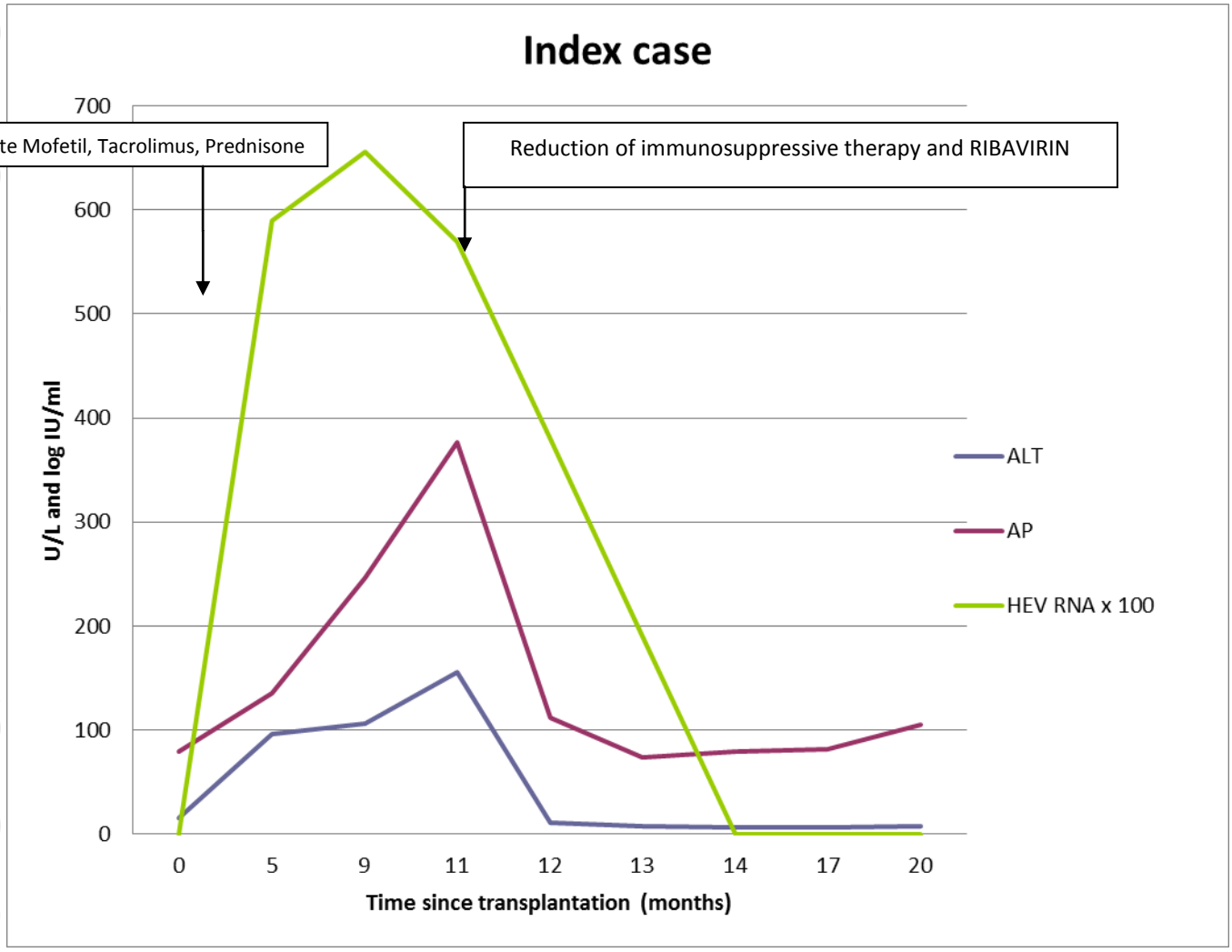

Figure 1a

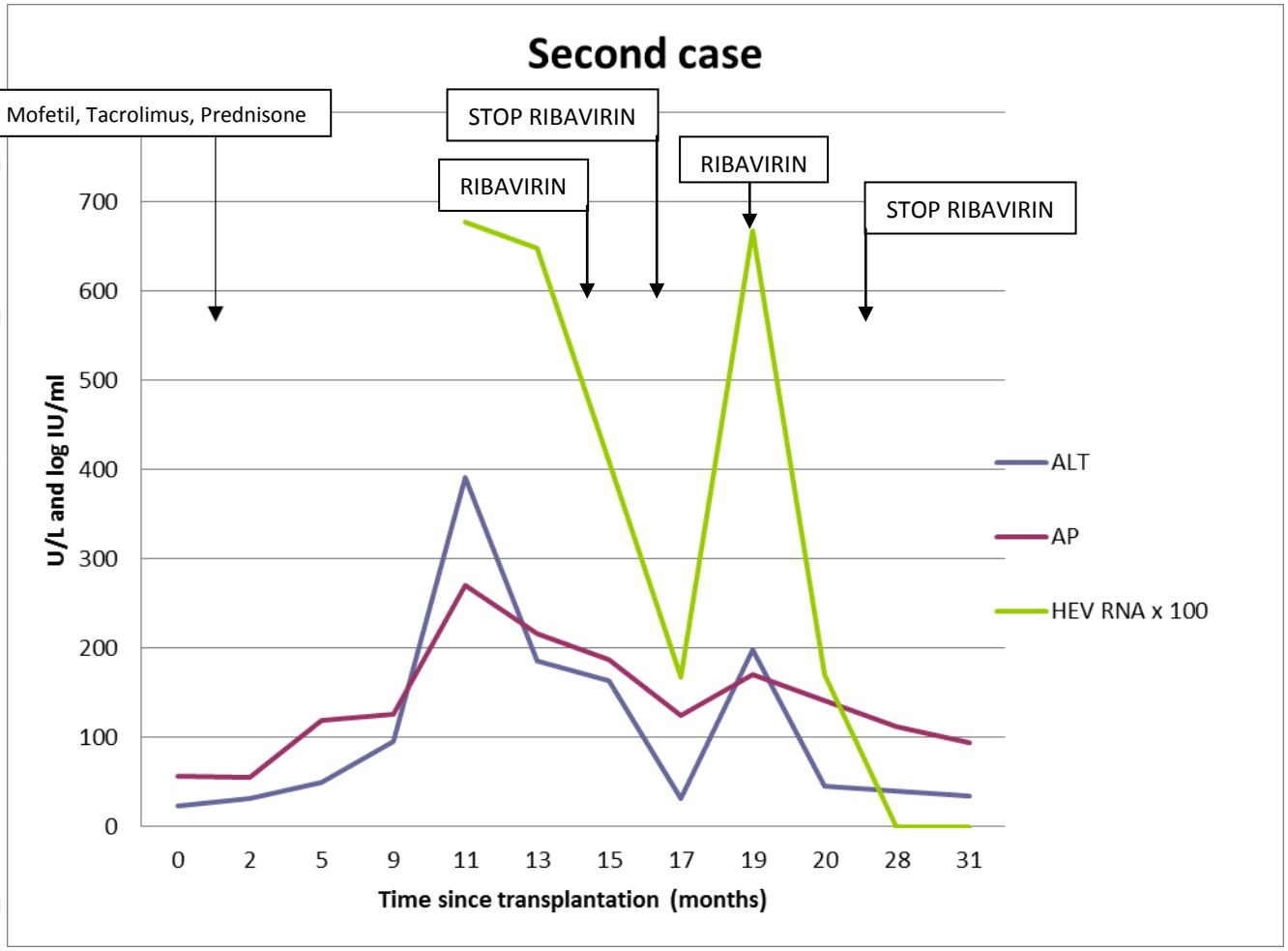

Figure 1b

Figure 2a

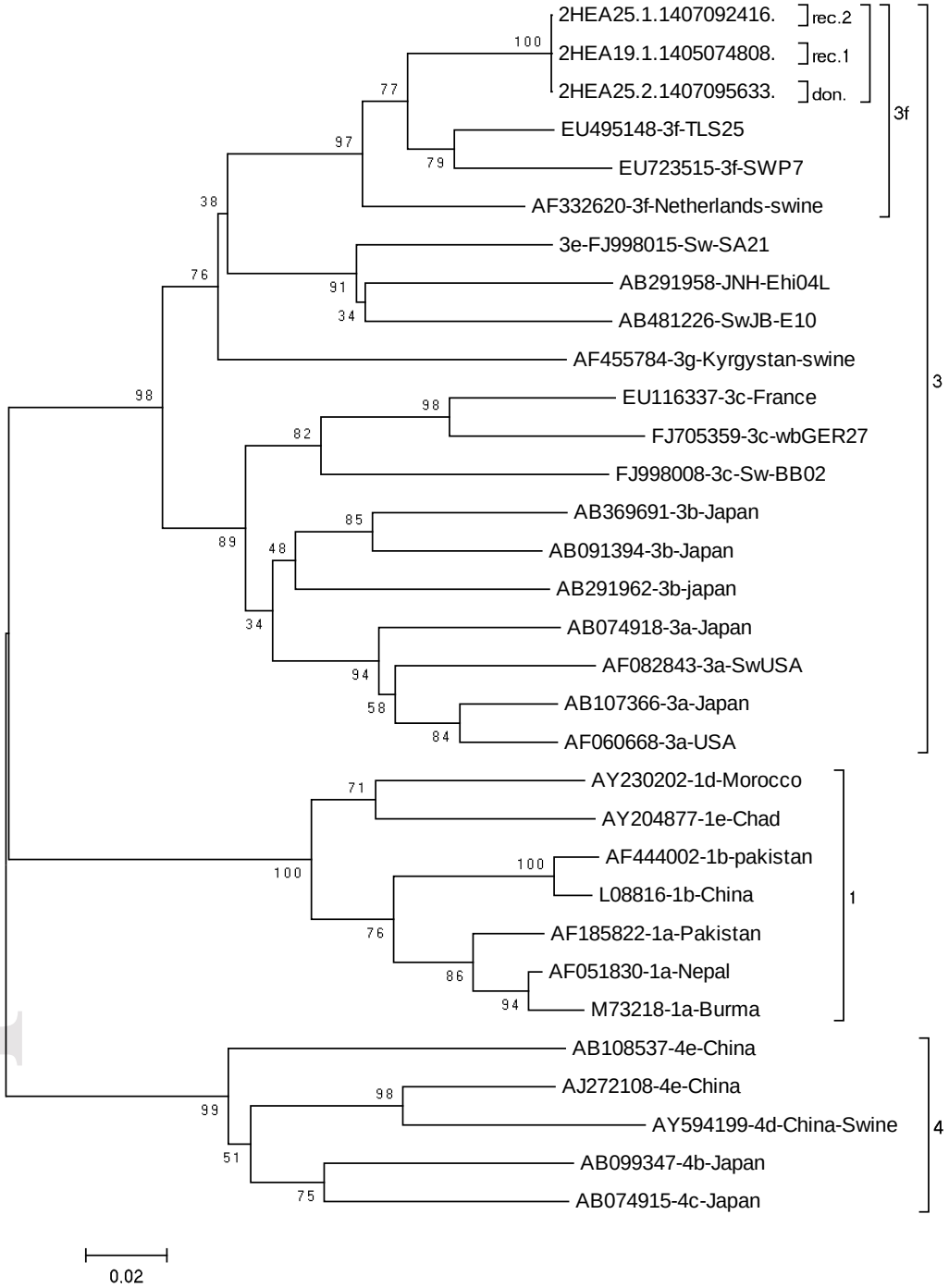

Figure 2b