Received: 8 May 2017 | Revised: 18 June 2017 | Accepted: 19 June 2017

DOI: 10.1111/tid.12784

CASE REPORT

WILEY

Transfusion-acquired hepatitis E infection misdiagnosed as severe critical illness polyneuromyopathy in a heart transplant patient

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Abstract

This is the case of a 56-year-old man who underwent heart transplantation. Within the first postoperative days, his respiratory and limb muscles weakened, which was attributed to critical illness polyneuromyopathy (CIPM). At day 70 post transplantation, he had increased liver enzyme levels and acute hepatitis E virus (HEV) infection was diagnosed. HEV RNA was found in the serum, stools, and cerebrospinal fluid. Results of further investigations suggested a possible HEV-related polyradiculoneuropathy. At transplantation, the patient was negative for immunoglobulin (Ig)G, IgM, and HEV RNA. A trace-back procedure identified the source of infection and concluded that HEV infection was contracted from blood transfusion 12 days prior to transplantation from an HEV RNA-positive donor. Tests of the organ donor for HEV were negative. Phylogenetic analysis revealed sequence homology between the HEV-3 strain of the patient and the HEV-3 strain of the blood donor. Despite ribavirin treatment, the patient died on day 153 post transplantation from multiorgan failure. In conclusion, patients with hepatitis or neuropathic illness who have received blood products should be screened for HEV.

KEYWORDS

blood transfusion, heart recipient, hepatitis E, HEV RNA screening, polyradiculoneuropathy

1 | INTRODUCTION

Genotype-3 hepatitis E virus (HEV-3) infection can cause hepatic and extra-hepatic manifestations.[1] In immunocompetent patients, it can cause hepatitis and fulminant hepatitis in patients with an underlying liver disease.[2] In immunosuppressed patients, it can lead to cirrhosis.[3] Neurological symptoms, such as Guillain–Barré syndrome (GBS), neuralgic amyotrophy, and kidney injuries are the main extra-hepatic manifestations.[2]

HEV-3 is a zoonosis that is mainly transmitted via an oral-fecal route.[2] However, it has been recently reported and confirmed that HEV infection can be also transmitted through the transfusion of blood products.[4-7] Nevertheless, very few cases of transfusion-acquired HEV infection have been reported in immunosuppressed patients.[7,8] Actually, only a few European countries have implemented HEV RNA screening of blood donations (Ireland, UK, Netherlands). In France, only the fraction of plasma collected that is intended for use in high-risk patients is screened for HEV RNA. Systematic screening of all

Abbreviations: CIPM, critical illness polyneuromyopathy; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; HEV, hepatitis E virus; Ig, immunoglobulin; POD, postoperative day; RBC, red blood cell.

blood donations is under consideration.[9] Consequently, HEV infection can still be underdiagnosed.

Herein, we report a case of HEV infection with possible HEV-associated neurological symptoms that developed immediately after heart transplantation, and that was caused by a pre-transplant red blood cell (RBC) transfusion, raising the prospect of screening blood donors in France.

2 | CASE PRESENTATION

A 56-year-old man underwent heart transplantation for Emery-Dreifuss laminopathy. He had been admitted for severe heart failure 3 months before transplantation and had required peripheral veno-arterial extracorporeal membrane oxygenation during the 22 days before transplantation. After transplantation, he was given basiliximab as induction therapy, followed by a triple immunosuppression therapy that consisted of tacrolimus, mycophenolate mofetil, and steroids.

He experienced a severe pulmonary infection rapidly after transplantation, caused by *Pseudomonas aeruginosa* and *Candida krusei*, which was treated by meropenem, vancomycin, amikacin, and micafungin. He required prolonged mechanical ventilation and a tracheostomy (postoperative day [POD] 24). He also developed acute kidney failure that required continuous veno-venous hemodiafiltration, started on POD 17. Within the first 15 PODs, he developed respiratory and limb muscle weakness, which was attributed to critical illness polyneuromyopathy (CIPM). The proximal and distal motor power of his upper and lower extremities were 0 and 1/5 respectively. His muscle tone was reduced symmetrically. At POD 70, mild rises in liver function tests prompted evaluation (Figure 1). Anti-HEV immunoglobulin (Ig)G and IgM (Wantai Biologic Pharmacy Enterprise, Beijing, China), and HEV RNA in the serum and stools were positive (6.95 copies/mL in the serum, genotype-3),[10,11] confirming a diagnosis of acute HEV infection. Hepatitis B, hepatitis C, and cytomegalovirus infections were ruled out.

A lumbar puncture was performed and analysis of cerebrospinal fluid (CSF) showed increased protein levels (protein 0.54 g/L [ref: 0.15-0.45 g/L], glucose 3.10 mmol/L [ref: 2.22-3.89 mmol/L], white blood cells 20/mm^3, red blood cells 0.4/mm^3). HEV RNA was positive in the CSF (300 copies/mL). Nerve-conduction studies showed a demyelinating neuropathy with conduction block and trigemino-facial involvement on blink reflex (bilateral prolongation of R1 latency) that are atypical for CIPM. Needle electromyography did not show any chronic denervation, showing an even myogenic pattern (Table S1). The diagnosis was compatible with HEV-related acute inflammatory polyradiculoneuropathy. He was given oral ribavirin therapy on POD 93 at the initial daily dose of 200 mg. On POD 116, the daily dose was increased to 400 mg. As the infection was diagnosed in the early phase after transplantation, we were unable to decrease immunosuppression. Tacrolimus trough level was around 7 ng/mL, and the mycophenolate mofetil and methylprednisolone daily doses were 1 g and 10 mg respectively. Unfortunately, he failed to achieve HEV clearance. HEV RNA was still positive 4.10 copies/mL in the serum at POD 136. He died at POD 153 from multiorgan failure: ie, hemodynamic instability, encysted pleural effusion, dialysis dependency, multidrug-resistant bacteria, and persistent tetraparesis.

Possible routes of HEV infection were investigated. The patient was hospitalized for a long period before heart transplantation and had no contact with animals. No additional cases of HEV infection were suspected at the intensive care unit during his stay. Serum from

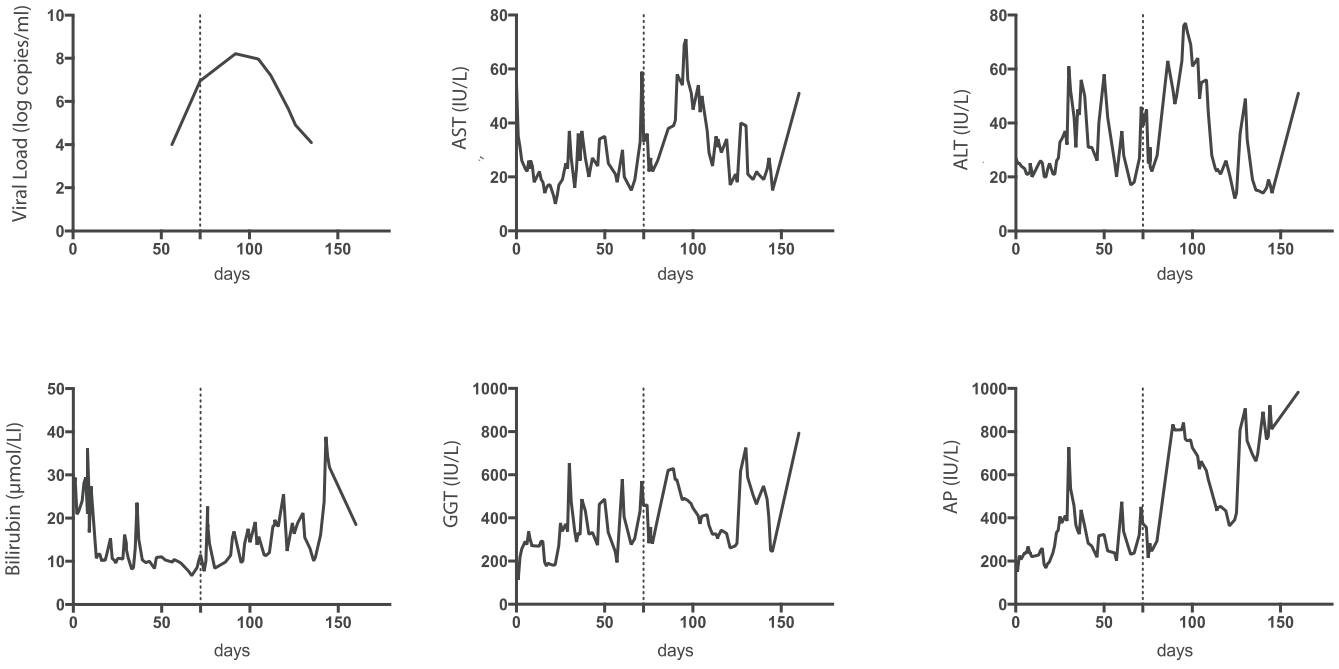

FIGURE 1 Evolution of hepatitis E virus (HEV) viral load (log copies/mL) and liver parameters after transplantation. Vertical line indicates date of diagnosis. AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase; AP, alkaline phosphatase

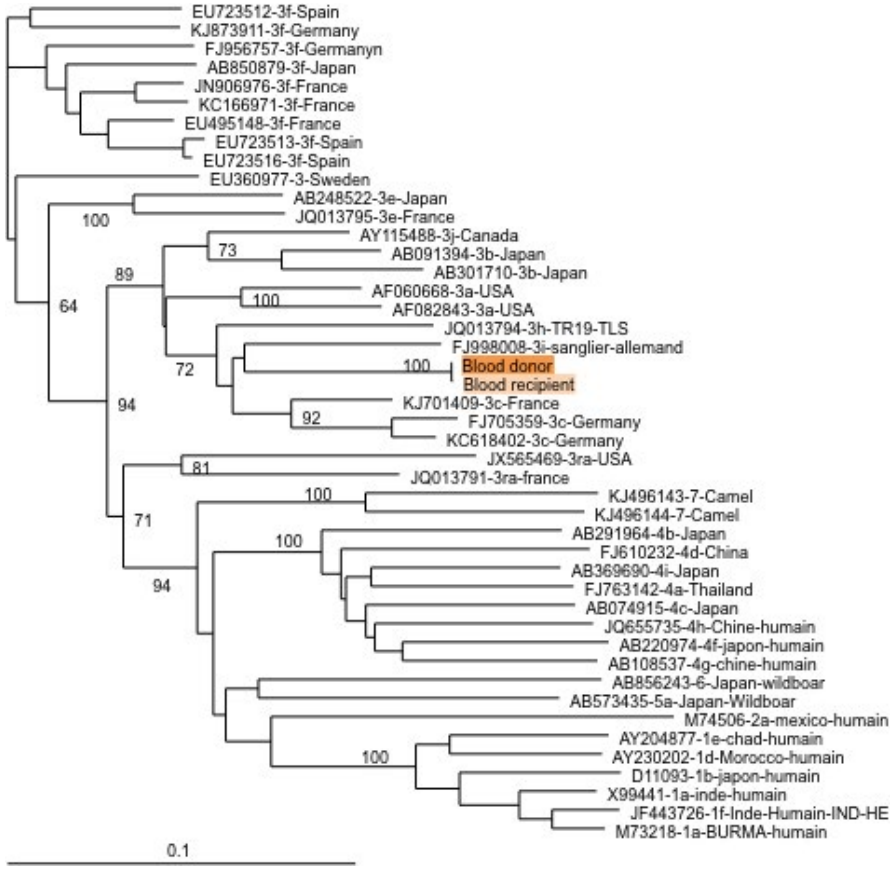

FIGURE 2 Phylogenetic tree constructed using 345-nt-length partial sequences within ORF2. Genetic distances were calculated using the Kimura two parameters method, phylogenetic trees were plotted by the neighbor joining method. Bootstrap values acquired after 100 replications are shown (branch lengths measured in the number of substitutions per site). Patients sequences highlighted in gray were compared to reference sequences of subtypes 3 proposed by Smith et al in 2016. Accession numbers, genotype, and country of origin of collection are listed

the heart donor was retrospectively investigated and found negative for HEV RNA, anti-HEV IgG, and anti-HEV IgM.

At transplantation, the patient's serum tested negative for IgG, IgM, and HEV RNA. Before surgery, and during and shortly after extracorporeal membrane oxygenation, the patient received considerable quantities of blood-derived products, including RBCs, thrombocytes, clotting factors, and plasma (n = 43 transfusions). A trace-back procedure was carried out on all the blood products, and one of the archived RBC samples tested positive for HEV RNA with an estimated viral load of 1430 copies/mL but negative serology (IgG and IgM). The patient had received the HEV-positive RBC product 12 days before transplantation. We retrospectively tested an available serum corresponding to POD 56 and found HEV at 4 log copies/mL. Unfortunately, we were not able to test for HEV RNA between transplantation and the clinical manifestations. Hence, we were not able to determine the length of incubation.

Phylogenetic analysis was performed to compare the ORF2 sequences in the virus obtained from our patient and that from the blood donor with HEV reference sequences (GenBank and local bank of the Virology Laboratory in University Hospital, Toulouse, France). The neighbor-joining two-parameter Kimura algorithm was applied. As shown in Figure 2, phylogenetic analysis revealed sequence homology between the HEV-3 strain in our patient and the HEV-3 strain in the blood donor. This genetic link was confirmed in several constructions. Robustness of the phylogenetic tree was estimated, with a bootstrap method, to be 100% on the tested panels.

TABLE 1 Cases of blood or organ hepatitis E virus (HEV) transmission in transplant recipients

HEV transmission	Recipient	Author (Reference)
Kidney donor	Kidney recipient	Pourbaix et al[22]
Liver donor	Liver recipient	Schlosser et al[28]
Blood donor	Liver recipient	Coilly et al[7]
Suspected blood donor	Heart recipient	Waldenström et al[29]
Identified blood donor	Heart recipient	Belliere et al (Present case)

3 | DISCUSSION

In immunocompromised patients, HEV-3 and -4 infections can lead to chronic hepatitis and cirrhosis.[2] In addition to liver injuries, it can cause extra-hepatic manifestations, mainly neurological disorders.[12] Recent studies have suggested a strong correlation between HEV infection and GBS[13,14] or neuralgic amyotrophy.[15] In a Dutch case-controlled study, markers of acute HEV infection were observed in 5% of patients presenting with GBS compared to 0.5% of matched healthy controls.[13] More recently, Stevens et al[14] found that 6 of 73 patients presenting with GBS or a GBS variant had a concomitant HEV infection. HEV RNA has been detected in the CSF of patients with a

HEV infection. Analysis of clonal HEV sequences in the serum and CSF, obtained at the same time, have shown quasispecies compartmentalization, suggesting that neurological symptoms could be linked to neurotropic variants.[16] In addition, recent in vitro data indicate that HEV could potentially complete its full viral life-cycle in neuronal-derived tissues, which would explain the HEV-associated neurological symptoms.[17]

In the present case, the patient had undergone heart transplantation after a long period of hospitalization and then presented with several complications post transplantation. Severe respiratory and peripheral muscle weakness was attributed to CIPM. However, critical illness neuropathies are characterized by their axonal involvement. Conduction blocks that were observed in our patient represent an exclusion criterion.[18] Chronic inflammatory demyelinating neuropathies have been described after solid organ transplantation secondary to immunosuppressive therapies or direct tacrolimus toxicity.[19,20] Herein, a diagnosis of HEV infection and the presence of HEV RNA in the CSF suggested the participation of the HEV infection, at least in part, in the neurological symptoms. Ribavirin has been found to be efficient at achieving a sustained virological response.[21] However, in the present case, ribavirin was not given at an adequate dose because of the patient's poor hematological tolerance owing to the severe post-transplant complications and impaired kidney function.

HEV-3 infection is mainly transmitted via an oral-fecal route.[2] Only a very few cases of HEV transmission via an organ allograft have been reported.[22] In the present case, serum HEV RNA and HEV serology were negative in the heart donor.

The prevalence of pre-transplant HEV IgG is 11.4% for heart transplant candidates according to recent data from Arizona.[23] Current estimations of positive HEV RNA in blood donations are as follows: one in 1240 donations in Germany,[24] one in 1761 donations in the Netherlands,[25] one in 2218 in France,[26] and one in 1430 in China.[27] For instance, in a very large English study, one of 2848 (0.04%) blood donors was HEV viremic.[4] That study also observed that transfusion-transmitted infections led to persistent infections in immunosuppressed patients.[4] A few cases of transfusion-transmitted HEV infection have been reported after liver or kidney transplantation, leading, in some cases, to chronic hepatitis.[5,7,8] In other patients, the transplanted organ transmitted HEV infection. Table 1 summarizes literature reports of blood or organ-transmitted HEV infection in transplant patients.[7,22,28,29]

Owing to the relatively high prevalence of HEV RNA among blood donors, medical authorities could discuss a systematic HEV RNA screening, at least in countries with high HEV prevalence. Patients awaiting or undergoing a solid organ transplantation (liver, heart, lung) may receive a large quantity of blood products before, during, and after transplantation. Hence, the risk of transfusion-acquired HEV infection can be significantly increased. In the present case, the patient was given HEV-positive RBCs at 12 days before transplantation. The HEV RNA and HEV serology were negative on the day of transplantation, but were found to be positive on POD 70 when the patient had increased liver enzyme levels.

However, no data regarding incubation times for transfusion-acquired HEV infection are available. Hence, our case report highlights that patients who have received large quantities of blood products and then develop hepatitis should be screened for HEV infection, and the blood donors should be retrospectively screened to confirm the origin of infection. In immunocompetent patients, HEV serology can be done. In immunocompromised patients, serology may be insensitive and nucleic-acid tests should be performed.[30]

In conclusion, patients with hepatitis or neuropathic illness, who have received blood products, should be screened for HEV. HEV screening of blood and/or organ donors could be proposed as systematic procedures in the future.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Belliere J, Abravanel F, Nogier MB, et al. Transfusion-acquired hepatitis E infection misdiagnosed as severe critical illness polyneuromyopathy in a heart transplant patient. *Transpl Infect Dis*. 2017;19:e12784. https://doi.org/10.1111/tid.12784