Transmission of Hepatitis E Virus With Plasma Exchange in Kidney Transplant Recipients: A Retrospective Cohort Study

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Background. After observing a case of plasma exchange-mediated hepatitis E virus (HEV) infection in a kidney transplant recipient, we investigated the relationship between plasma exchange and HEV infection after kidney transplantation. **Methods.** A cohort of 263 patients who underwent kidney transplantation from January 1, 2011, through December 31, 2012, was screened for HEV markers, including anti-HEV IgG and IgM antibodies and HEV ribonucleic acid (RNA), on 3 consecutive blood samples: 1 before, 1 with a mean (standard deviation) of 9.5 (9) months, and 1 with a mean (standard deviation) of 18.2 (6.6) months after transplantation, respectively. Transfusional investigation was performed in patients with detectable HEV RNA. We explored the relationships between plasma exchange, posttransplantation transaminase elevation and HEV markers acquisition. **Results.** Overall, 24 (9.1%) patients had acquired HEV markers on the first posttransplantation sample, including 2 patients with detectable HEV RNA, and 7 (2.3%) patients had long-term persistent HEV markers on the second posttransplantation sample, including 3 patients with detectable HEV RNA without detectable anti-HEV antibodies. Plasma exchange was an independent risk factor for the acquisition of posttransplantation and long-term persistent HEV markers. Pathogen-reduced plasma-borne transmission of HEV was demonstrated. Plasma exchange and long-term persistent HEV markers were risk factors of posttransplantation transaminase elevation. **Conclusions.** Plasma exchange, including with pathogen-reduced plasma, is a risk factor for posttransplantation HEV infection and transaminase elevation. Screening for HEV RNA should be carried out in kidney transplant recipients treated with plasma exchange.

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Hepatitis E virus (HEV), the causative agent of hepatitis E, is a small, nonenveloped, single-stranded ribonucleic acid (RNA) virus endemic worldwide, including in high-income countries.[1] The virus usually causes an acute, self-limited illness with symptoms typical of other hepatitis viruses; however, acute liver failure is possible and chronic infection that

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can progress to cirrhosis, end-stage liver disease, primary liver cancer, and extra-hepatic diseases can occur in immunosuppressed persons, including kidney transplant recipients.[2-4]

There are 4 major HEV genotypes (HEV1-4) that can infect humans. HEV1 and HEV2 are prevalent in developing world and are generally transmitted via the enteric route with feces-contaminated water. HEV3 and HEV4 are zoonotic strains and are predominant in high-income countries. HEV3 and HEV4 are transmitted to humans through consumption of insufficiently cooked contaminated food products, including pork and game, or consumption of shellfish, fruits, or vegetables that have been contaminated by pig effluent.

Transmission of HEV with blood components is reported in low-income[5,6] and high-income countries, including in Japan,[7-9] France,[10,11] the United Kingdom,[12] Germany,[13] and Spain.[14] The risk of transfusion-transmitted HEV is associated with the level of HEV endemicity, HEV viral load, and anti-HEV antibody level in blood donations; it is also associated with the volume of plasma transfused with the blood component.[12] Reported prevalences of HEV RNA among blood donors, including the United States, England, China, Germany, and France, range from 1:600 in the Netherlands[15] to 1:15075 in Japan.[16]

Quarantine (secured) and pathogen-reduced (PR) plasma are currently available worldwide as a means to reduce the risk of transfusion-transmitted infections.[17] Current PR methods include solvent detergent, methylene blue (MB) plus visible light, amotosalen plus UVA (INTERCEPT), riboflavin plus UV, and UVC.[17] Blood products is not universally recommended for HEV and PR is poorly effective against non-enveloped virus, including HEV. Transmission of HEV has been reported with secured plasma,[18] solvent detergent plasma pools[19] and INTERCEPT-treated plasma.[20] There are, to date, no reports of HEV transmission with plasma-derived products, including IVIg.

Kidney transplant recipients may undergo plasma exchange to remove donor-specific anti-HLA antibodies before and after transplantation or to treat recurrences of the underlying kidney disease.[21-24] We observed in 2010 a case of HEV transmission to a kidney transplant recipient with plasma exchange.[18] After this observation, we designed a retrospective cohort study to evaluate the possibility of HEV transmission with kidney transplantation and plasma exchange.

MATERIALS AND METHODS

Sample

From January 1, 2011, through December 31, 2012, 306 patients underwent kidney transplantation in a tertiary kidney transplant center (Assistance Publique-Hôpitaux de Paris, Centre Hospitalier Necker Enfants Malades, Paris, France). Baseline (drawn on the day of transplantation) and follow-up serum samples were stored frozen at −80°C as part of our standard protocol were available for 263 (86.0%) patients (Figure 1). The local institutional review board (Comité de Protection des Personnes Ile de France 2) approved this study, and all patients gave informed consent.

Patient Characteristics and Immunosuppressive Protocol

Baseline characteristics of patients are depicted in Table 1. More than half of the patients were at high immunologic risk with donor specific anti-HLA antibodies against their graft. The induction treatment consisted of antithymocyte globulin (Thymoglobulin; Lyon, France; 1.5 mg/kg per day for 5 days) or basiliximab (Simulect; Novartis, Switzerland; 20 mg on days 0 and 4). Corticosteroid treatment was initiated on day 0, with 500 mg of methylprednisolone, followed by rapid tapering to 10 mg/d oral prednisone plus calcineurin

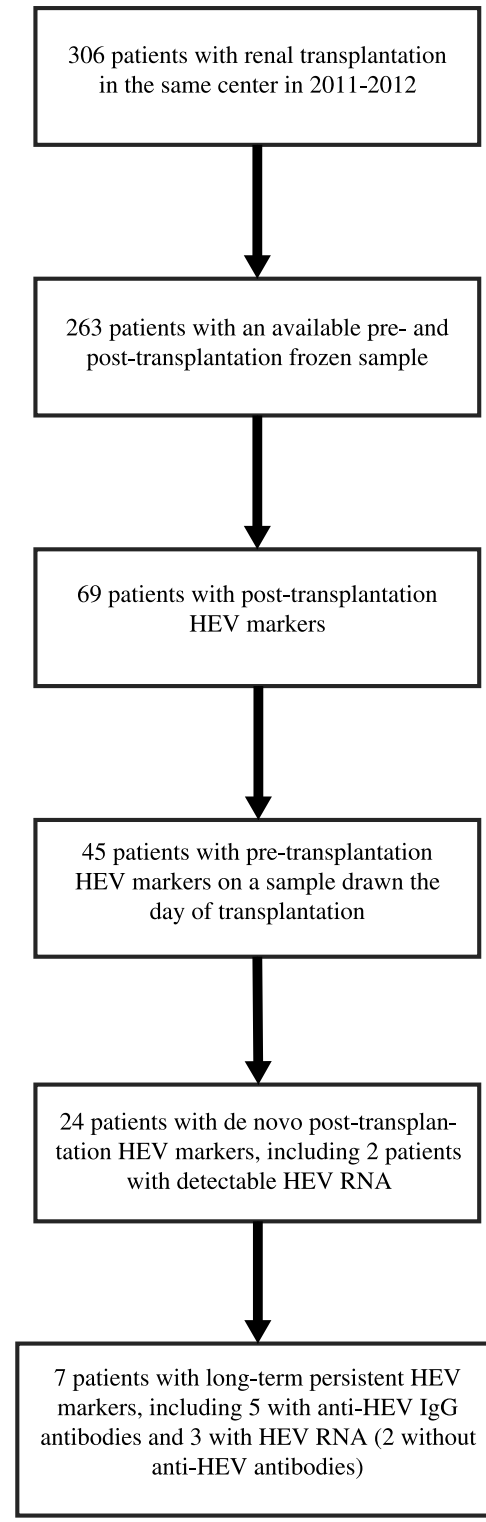

FIGURE 1. Flowchart.

TABLE 1.

Characteristics of patients

Characteristics	All patients, N = 263	With posttransplantation[a] HEV marker seroconversion (n = 24)	Without posttransplantation[a] HEV marker seroconversion (n = 239)	*P*
Mean (SD) age, y	51.9 (15.0)	49.1 (13.3)	52.1 (15.1)	0.289
Male, n (%)	157 (59.7)	13 (54.2)	144 (60.3)	0.66
Initial nephropathy, n (%)				0.92
Glomerular	101 (38.4)	8 (33.3)	93 (39.1)	
Interstitial	76 (28.9)	8 (33.3)	68 (28.6)	
Vascular	25 (25)	3 (12.5)	22 (9.2)	
Other[b]	5 (1.7)	0 (0)	5 (2.1)	
Unknown	55 (20.9)	5 (20.8)	50 (21.0)	
Mean (SD) duration of pretransplant dialysis, y	3.7 (4.4)	4.1 (4.1)	3.6 (4.4)	0.722
Previous kidney transplants, n (%), missing in 2				0.109
0	226 (85.9)	18 (75)	208 (87.8)	
> 1	35 (13.3)	6 (25.0)	29 (12.1)	
Living kidney donor, n (%)	62 (23.6)	5 (20.8)	57 (23.8)	1.0
Donor-specific anti-HLA antibodies on day 0 of transplantation, n (%)	150 (57.0)	18 (75.0)	132 (55.2)	0.083
Donor-specific antibodies score of 6 or 8 on day 0 of transplantation, n (%)	18 (6.0); missing in 2	6 (25.0)	12 (5.0)	0.003
Immunosuppression, n (%)[c]				
Antithymocyte globulin	141 (53.6)	12 (50)	129 (54)	0.83
Anti-interleukin-2 receptor antibodies	104 (39.5)	11 (45.8)	93 (38.9)	0.52
Rituximab	26 (9.9)	4 (16.7)	22 (9.2)	0.27
IVIg	140 (53.2)	13 (54.2)	127 (53.1)	1.0
Cyclosporin	63 (24.0)	8 (33.3)	55 (23.0)	0.31
Tacrolimus	202 (76.8)	17 (70.8)	185 (77.4)	0.45
Acute rejection, n (%)	42 (17.7)	9 (37.5)	33 (14.0)[d]	0.007
Plasma exchange, n (%)	42 (16.0)	9 (37.5)	36 (13.8)	0.006
Highest ALT (times the upper limit of normal range; mean [SD])	1.5 (1.9)	1.7 (1.4)	1.5 (2.0)	0.597
Red blood cell transfusion (units; mean [SD])	3.5 (5.9)	4.3 (4.3)	3.4 (6.1)	0.161
Plasma transfusion (units; mean [SD])	5.5 (18.4)	12.3 (32.9)	4.9 (16.3)	0.008
Secured plasma transfusion (units; mean [SD])	0.9 (5.3)	3.0 (8.5)	0.7 (4.8)	0.001
Solvent/detergent-treated plasma transfusion (units; mean [SD])	1.6 (11.0)	6.3 (26.1)	1.2 (8.1)	0.216
MB-treated plasma transfusion (units; mean [SD])	2.6 (10.5)	1.8 (5.4)	2.7 (10.9)	0.489
INTERCEPT-treated plasma transfusion (units; mean [SD])	0.4 (2.7)	0.3 (2.4)	0.3 (2.4)	0.034
Platelet transfusion (units; mean [SD])	0.0 (0.0)	0.1 (0.4)	0.0 (0.2)	0.712

[a] Samples drawn a mean (SD) of 9.5 (9) months after transplantation.
[b] Includes 1 case of Prune Belly syndrome, 1 case of Bourneville Pringle syndrome, and 3 uropathies.
[c] All patients were treated with mycophenolate mofetil and corticosteroids.
[d] Information missing in 3 patients.
ULN, upper limit of the normal range.

inhibitors and mycophenolic acid. Some sensitized patients (with donor-specific anti-HLA antibodies) also received prophylaxis to prevent acute antibody-mediated rejection. The prophylactic treatments administered included intravenous immunoglobulin (4 doses of 2 g/kg at 3-week intervals) and/or anti-CD20 antibodies (rituximab) at a dose of 375 mg/m^2 and/or 5 plasma exchanges.

Plasma Exchange

Overall, 42 (16.0%) patients were treated with plasma exchange for the following indications: acute antibody-mediated rejection (n = 13 [31.0%]), desensitization of highly sensitized recipients of kidney transplants from living donors (n = 11 [26.2%]), high titers of donor-specific antibodies on the day of transplantation (n = 10 [23.8%]), recurrence of focal segmentary glomerular hyalinosis or thrombotic microangiopathy (n = 8 [19.1%]).

Cross-sectional and Longitudinal Study

We first screened the cohort for posttransplantation HEV markers, including anti-HEV IgG and IgM antibodies and HEV RNA. We then checked whether HEV markers were present before transplantation, by testing serum samples collected on the day of renal transplantation. Patients with HEV markers after transplantation, but not in their baseline samples, were retested with a third sample drawn more than a year after transfusion of the last blood component.

The medical records were reviewed to collect demographic and clinical data, laboratory tests results and information about complications and outcome. The French Blood Transfusion Service (Etablissement Français du Sang Ile de France, Ivry sur Seine, France) identified all the blood products transfused. Frozen serum samples obtained at the time of donation were retrieved, for all blood products, and tested for HEV

RNA, in cases in which HEV RNA was detected in a transplant recipient.

Testing for HEV

Anti-HEV IgG and IgM antibodies were detected with an IgG and IgM capture enzyme-linked immunosorbent assay (Wantai, Beijing, People's Republic of China). Hepatitis E virus RNA was detected by quantitative, real-time, reverse transcription-polymerase chain reaction (Ceeram, La Chapelle sur Erdre, France). The polymerase chain reaction assay targeted open reading frame (ORF)-2/3, facilitating the accurate detection of all genotypes/subtypes. This assay uses the World Health Organization standard, and the lower limit of the 95% confidence interval for detection has been reported to be 86.8 (68.9-124.7) IU/mL.[25]

Genome Sequencing and Phylogenetic Analysis

Hepatitis E virus genotype was determined by the phylogenetic analysis of 2 different genomic regions, ORF-1 (RNA-dependent RNA polymerase) and ORF-2, as previously described.[11] Phylogenetic analyses were performed with MEGA6 software.[26]

Case Definition

We considered patients with long-term persistent (more than 1 year after the transfusion of the last blood component) anti-HEV seroconversion or with detectable HEV RNA in the serum to have conclusively developed HEV infection after renal transplantation. For the confirmation of transfusion-transmitted HEV infection, evidence was required of infection in the recipient due to a component from a donor with confirmed viremia, and nucleotide sequence identity between the viruses present in the recipient and the donor.

Statistical Analysis

Continuous values are presented as medians and interquartile ranges, and categorical variables are presented as counts and proportions. Proportions were compared in χ^2 tests or Fisher exact tests. Factors associated with the presence of posttransplantation and long-term persistent HEV markers were identified by univariate and multivariate binary logistic regression analyses. All statistical tests were 2-tailed, with a type I error of 5%. All statistical analyses were performed with SPSS software version 20 (SPSS, Chicago, IL).

RESULTS

Cross-sectional Study

We first screened the cohort for posttransplantation HEV markers, including anti-HEV antibodies and HEV RNA, a mean (standard deviation [SD]) of 9.5 (9) months after transplantation. Anti-HEV IgG and IgM antibodies, and HEV RNA were detected in 68 (25.9%), 1 (0.4%) and 2 (0.8%) patients, respectively. One patient with detectable HEV RNA had no detectable anti-HEV antibodies.

We then checked the cohort for HEV markers before renal transplantation. Anti-HEV IgG antibodies were detected in 45 (17.1 %) patients, and none had detectable anti-HEV IgM antibodies or HEV RNA. There was no statistical difference between characteristics of patients with and without anti-HEV IgG antibodies before renal transplantation. Therefore, 24 (9.1%) patients had acquired HEV markers posttransplantation (Figure 1 and Table 1).

Overall, patients with posttransplantation HEV markers had being more frequently treated with plasma exchange and had received more plasma, including secured, and INTERCEPT-treated plasma. Other factors associated with posttransplantation HEV markers were related to plasma exchange, including high levels of donor-specific antibodies and acute rejection. There was no evidence of a temporal relationship between HEV infection and acute rejection.

Plasma exchange was the sole factor associated with the presence of HEV markers in a multivariate logistic regression model adjusted on plasma, platelet, and red blood cell transfusions, with an adjusted odds ratio of 7.0 (95% confidence interval, 1.6-31.1).

The median (range) alanine aminotransferase (ALT) level was 0.9 (0.2-9.3) and 1.5 (0.3-22.2) the upper limit of normal range among patients treated without or with plasma exchange, respectively ($P = 0.025$). The presence of posttransplantation HEV markers was not associated with a flare in ALT level or an increase in posttransplantation ALT values.

Longitudinal Study

Patients with posttransplantation HEV markers were retested a mean (SD) of 18.2 (6.6) months after transplantation and 14.4 (6.7) months after transfusion of the last blood components: 7 (2.3%) patients had long-term persistent HEV markers, including 5 with anti-HEV IgG antibodies and 3 with HEV RNA. Factors independently associated with the presence of long-term persistent HEV markers were plasma exchange, plasma transfusion, including secured plasma, solvent detergent–treated and INTERCEPT treated-plasma. The presence of high levels of donor-specific antibodies before transplantation was associated with long-term persistent HEV markers. The median (range) ALT level was 1.6 (0.2-22.2) and 2.4 (1.0-4.0) the upper limit of normal range among patients without or with long-term persistent HEV markers, respectively ($P = 0.008$).

Transfusional Investigation

All blood components used for transfusion in the 3 patients with chronic posttransplantation HEV infection were identified. Stored frozen plasma from blood donors obtained at the time of donation were retrieved and tested for HEV RNA. For the first patient infected with a genotype 3f HEV strain (GenBank accession number KJ 650502), a single INTERCEPT-treated plasma used for plasma exchange 14 days after transplantation tested positive for the same HEV strain (Figure 2).[20] For the second patient (Figure 3), also infected with a genotype 3f HEV strain (GenBank accession number KR185382), with a viral load of 5.53 log IU/mL, 146 blood components had been used. Three batches of solvent/detergent-treated plasma used as part of the same minipool for transfusion during plasma exchange 6, 7, and 8 days after the graft were found to be HEV RNA-positive for a genotype 3f strain (GenBank accession number KR185381), which was present at a concentration of 304 IU/mL. An analysis of partial sequences from ORF-1 or ORF-2 regions showed strict identity between the sequences from the donor and the recipient (Figure 4). For the third patient, 9 blood components had been used for transfusion and all tested negative for HEV RNA. The plasma donor tested negative for anti-HEV antibodies and

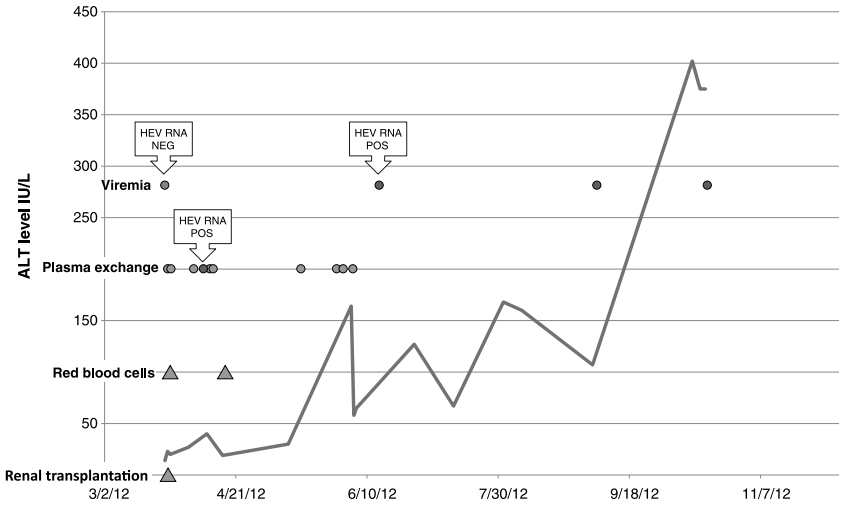

FIGURE 2. Transmission of HEV to a kidney transplant recipient with INTERCEPT-treated plasma during plasma exchange.

HEV RNA. The batches of nonviremic patients were not tested.

Outcome of Viremic Patients

The 3 patients with chronic HEV infection were treated with ribavirin monotherapy (10 mg/kg for 12 weeks), with no change to the immunosuppressive regimen. Sustained virological response was achieved in all patients.

DISCUSSION

In a cohort of patients with renal transplantation in France in 2011 to 2012, plasma exchange was an independent risk factor for posttransplantation acute and chronic hepatitis and for acquiring posttransplantation and long-term persistent HEV markers. Overall, 7 (2.3%) patients had long-term persistent HEV markers and were therefore conclusively infected with HEV after renal transplantation, including 3 (43.6%) HEV RNA-positive patients. Plasma-borne transmission of HEV with plasma exchange was demonstrated with phylogenetic analysis in 2 of 3 viremic patients. The plasma of the renal graft donor and all transfused blood products tested negative for HEV RNA for the third HEV viremic patient. Transmission of HEV was not associated with plasma exchange or blood transfusion in 3 (42.9%) patients with long-term persistent HEV markers.

The observed incidence of HEV infection in our cohort is consistent with previous reports.[27] Plasma-mediated transmission of HEV to solid-organ transplant recipients has been reported[12,28] and discussed in case-control studies.[29] However, none identified plasma exchange as a possible vector for HEV. We report that a single round of plasma exchange increases the risk of acquiring HEV infection by a factor of 10. The use of plasma pools (solvent detergent-treated plasma) for reinjection may multiply this risk, the degree of risk amplification depending on the size of the pool.[19,30] The widespread use of plasma exchange in solid-organ transplant recipients at high risk of acute humoral rejection, including heart transplant recipients with transplantation across the ABO barrier, probably accounts, as in our cohort, for the more frequent reporting of HEV infection in patients at high immunological risk of rejection.[29] As a matter of fact, there was a relationship between acute rejection and acquisition of HEV markers in our cohort. We did not observe any temporal relationship between HEV infection and acute

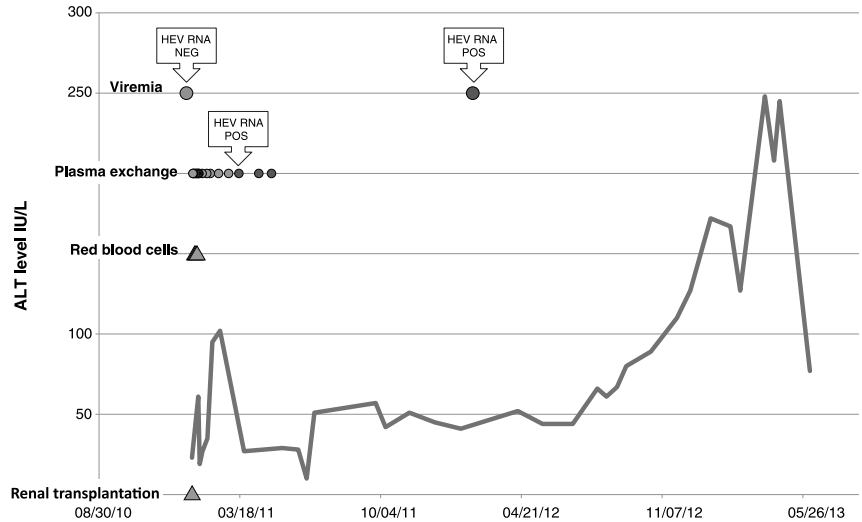

FIGURE 3. Transmission of HEV to a kidney transplant recipient with solvent/detergent-treated plasma during plasma exchange.

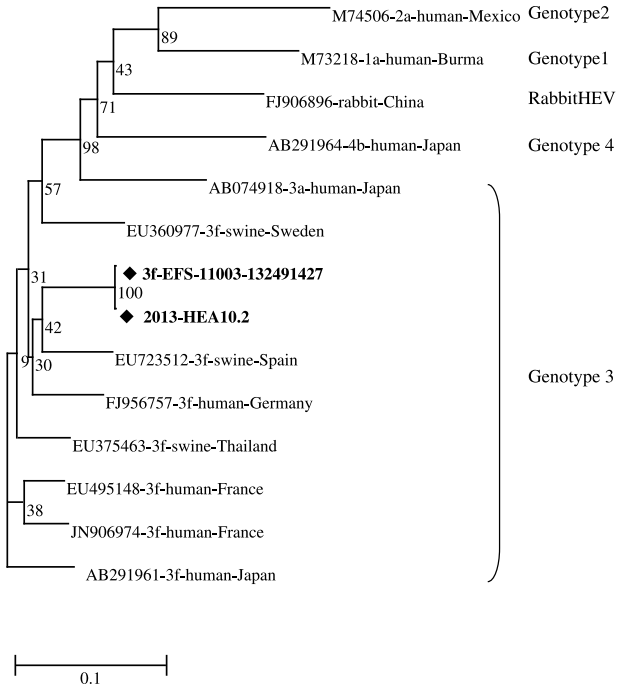

FIGURE 4. Phylogenetic tree based on partial ORF-2 sequences (318 nt). Phylogenetic analyses were performed in MEGA6, with the neighbor-joining method, using a Kimura 2-parameter distance matrix based on the partial nucleotide sequences of ORF-2. ♦ Identifies case of plasma exchange-mediated HEV transmission.

rejection. The risk of acquiring HEV with plasma exchange is probably not the same worldwide because HEV RNA prevalence in the general population and among blood donors varies between and within countries worldwide.[31,32] The observation of 3 patients with undeniable HEV infection after renal transplantation without blood product exposure is consistent with previous retrospective cohorts of HEV-infected patients without clearly identified risk factors and suggests environmental exposure to the antigen.[33-36] The patient with posttransplantation anti-HEV IgG seroconversion without HEV RNA and long-term seroreversion with detectable HEV RNA (Table 2, patient 7) had an unexplained mode of transmission. The plasma donor tested negative for HEV RNA.[37] Nosocomial transmission of HEV or HEV replication under the limit of detection could be explanations.[38,39]

The acquisition of long-term persistent HEV markers after renal transplantation, including HEV RNA and anti-HEV antibodies, corresponded conclusively to HEV infection. There was probably also a passive transmission of anti-HEV antibodies with blood product transfusions. The absence of relationship between posttransplantation elevated transaminases and posttransplantation HEV markers is in favor of this mechanism. We cannot rule out the possibility of HEV infections in some patients in whom anti-HEV IgG antibodies were transiently detected: a gradual loss of detectable anti-HEV IgG is observed in immunocompetent individuals (28% at 2 years),[40] and this loss would be expected to occur more rapidly in immunocompromised hosts.

Our study confirms that some pathogen-reduction technologies are ineffective against nonenveloped viruses like parvovirus B19 or HEV.[19,41] Since the observations of plasma exchange-associated transmission of HEV,[18,20] French regulations are providing HEV-RNA negative fresh-frozen plasma for organ-transplant recipients. In our cohort, the risk of HEV marker transmission and of posttransplantation hepatitis was not associated with MB-treated plasma transfusion. Methylene blue–treated plasma is the most adapted PR method for single plasma units worldwide. The use of MB-treated plasma has been stopped in France since 2012. Our findings suggest future researches to explore the relationship between MB-treated plasma and the risk of HEV transmission.

The main limit of the study is its retrospective nature. A complete analysis of all transfusions and of all grafts would have resulted in a better appreciation of the risk of HEV infection associated with blood product transfusion and renal transplantation.[37] It would also have identified factors associated with chronic HEV infection, including inoculum, time

TABLE 2.

Characteristics of patients with long-term persistent de novo HEV markers after a mean period of 18.2 and 14.4 months after kidney transplantation or transfusion of the last blood component, respectively

Patients	1	2	3	4	5	6	7
First blood sampling, mo	13	5	6	2	10	11	2
Anti-HEV IgG antibodies	+	−	+	+	+	+	+
Anti-HEV IgM antibodies	+	−	−	−	−	−	−
HEV RNA	+	+	−	−	−	−	−
Second blood sampling, mo	32	NA	16	11	30	22	19
Anti-HEV IgG antibodies	+	−	+	+	+	+	−
HEV RNA	+	+	−	−	−	−	+
Highest alanine aminotransferase (times the upper limit of normal range)	4.1	2.5	2.9	1.9	1.0	2.5	1.9
Plasma exchange	Yes	Yes	Yes	Yes	No	No	No
Red blood cell transfusion (units)	6	7	5	7	0	0	9
Plasma transfusion (units)	140	59	13	59	0	0	0
Secured plasma transfusion (units)	0	36	11	39	0	0	0
Solvent/detergent-treated plasma transfusion (units)	117	3	0	20	0	0	0
MB-treated plasma transfusion (units)	23	0	0	0	0	0	0
INTERCEPT-treated plasma transfusion (units)	0	20	2	0	0	0	0
Platelet transfusion (units)	0	2	0	0	0	0	0

since transplantation, degree of host immune suppression and infectivity of batches of plasma.[12,42,43] The study would have been be stronger if the entire cohort would have been tested for HEV RNA a second time as some patients could have acquired HEV during follow-up.

Hepatitis E virus infection is often overlooked and mistaken for drug-induced liver injury or other causes of elevated transaminases. Although there may be an increasing awareness of locally acquired HEV infections, there is still concern that within parts of the clinical community, HEV is not considered as a possible cause of hepatitis unless there is a recent history of travel. Screening for HEV RNA and, not for anti-HEV antibodies, should be carried out in all immunocompromised hosts with acute or chronic hepatitis, including those treated with plasma exchange. Hepatitis E virus is endemic worldwide and the frequency of HEV markers increases with age.[36] Finally, an anti-HEV vaccine is available.[44] Further studies should investigate the performance of this vaccine for preventing transmission of HEV after renal transplantation.

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