Thrombotic thrombocytopenic purpura relapse induced by acute hepatitis E transmitted by cryosupernatant plasma and successfully controlled with ribavirin

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BACKGROUND: Hepatitis E virus (HEV) can be transmitted by transfusion of any type of blood component, but there are few data on the potential risk of transmitting this virus and the associated complications. We provide evidence that HEV can be transmitted by cryosupernatant plasma, and that HEV infection can act as a trigger for thrombotic thrombocytopenic purpura (TTP).

STUDY DESIGN AND METHODS: A patient with a history of TTP treated with plasmapheresis 2 months previously developed jaundice and a TTP exacerbation with purpura, thrombocytopenia, schistocytes, and undetectable ADAMTS-13 activity. He was diagnosed with acute hepatitis E and treated with ribavirin. TTP remitted with remission of HEV infection.

RESULTS: Traceback to determine the source of the infection showed that 1 cryosupernatant plasma among the 99 different blood components used for the patient's last plasmapheresis was positive for HEV RNA, with an estimated viral load of 5000 to 10,000 IU/mL. Phylogenetic analysis proved the transfusion-transmitted route of acute hepatitis E.

CONCLUSION: In a patient with TTP, acute HEV infection transmitted by cryosupernatant plasma may trigger exacerbation of TTP, which can be controlled on remission of HEV infection with ribavirin.

Over the past decade, an increasing number of autochthonous cases of acute hepatitis E have been documented in Europe, and hepatitis E virus (HEV) is already the leading source of acute hepatitis in some countries such as Scotland.[1] HEV infection in developed countries is predominantly caused by genotype 3 and is considered a zoonotic disease. However,

ABBREVIATIONS: HEV = hepatitis E virus; TTP = thrombotic thrombocytopenic purpura.

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transfusion-transmitted HEV infection is becoming a major concern, as HEV RNA has been detected in blood components. The incidence of HEV RNA in blood donors varies between countries, with rates of 1 in 1321 donors in the Netherlands to 1 in 14,520 in Scotland.[2,3] In our setting, 1 in every 3332 donations is positive for HEV RNA, which is the equivalent of 80 viremic donations per year in Catalonia.[4]

The risk of transmitting HEV infection depends on the serologic and virologic status of the donor, the immunologic state of the recipient, and the type of blood component.[5] Fresh frozen plasma is the most highly infectious blood component. There are no data regarding the potential risk associated with cryosupernatant, that is, the supernatant plasma removed during preparation of cryoprecipitate and mainly used for plasmapheresis in patients with thrombotic thrombocytopenic purpura (TTP).[6]

Acute HEV infection can be associated with extrahepatic manifestations, mainly neurologic involvement.[7] Among the hematologic complications, there are few reported cases of thrombocytopenia,[8,9] and most are transient and self-limited. No cases of TTP triggered by HEV have been documented in Western countries. Here, we present the case of a 48-year-old man diagnosed with acute hepatitis E 2 months after receiving plasmapheresis for TTP. HEV detection in 1 of the 99 blood components used during plasmapheresis confirmed the transfusion-transmitted infection. Acute hepatitis E induced a new episode of TTP that was successfully controlled after virologic response was achieved with ribavirin.

CASE REPORT

A 48-year-old man consulted at our hospital for jaundice and malaise. His medical history included Crohn disease treated with mesalazine, choroidal melanoma under periodic follow-up, and TTP, diagnosed in 1995 by the presence of thrombocytopenia, purpura, acute kidney injury, and dysarthria. This episode was followed by four other TTP exacerbations (1995, 2009, 2016, 2017), all successfully treated with plasmapheresis. The last episode (January 2017) occurred following an influenza A infection.

Two months after the last TTP relapse, the patient was admitted to the hospital with asthenia. Physical examination showed jaundiced skin. On laboratory testing, blood count was normal, liver function tests were abnormal (aspartate aminotransferase [AST], 1515 IU/mL; alanine aminotransferase [ALT], 991 IU/mL; total bilirubin, 5.35 mg/dL), and clotting and albumin levels were within normal limits. An abdominal sonogram was normal. Hepatitis B surface antigen, antibodies against hepatitis C virus, human immunodeficiency virus, Epstein-Barr virus immunoglobulin M (IgM), and cytomegalovirus all tested negative. Anti–hepatitis E virus IgM and immunoglobulin G (IgG) and HEV RNA (7000 IU/mL) were positive, which prompted the diagnosis of acute hepatitis E.

During hospital admission, the patient remained asymptomatic, clotting was normal, and there were no signs of hepatic encephalopathy. Bilirubin and transaminase values showed gradual increases (peak AST, 3429 IU/mL; ALT, 1635 IU/mL; total bilirubin, 24.5 mg/dL), which later declined without specific therapy. Despite the improvements in liver function parameters, platelet counts progressively decreased (minimum platelet count, 39,000 × $10E^6$/L), with the development of purpura in the lower limbs, mild anemia, schistocytes in peripheral blood, elevated serum lactate dehydrogenase concentrations, and undetectable levels of both ADAMTS-13 activity and haptoglobin, findings suggestive of a new TTP relapse. As HEV RNA remained detectable (2000 IU/mL) and acute infections can trigger TTP, treatment with ribavirin was initiated at a dose of 600 mg/day. One week after starting therapy, HEV RNA was almost undetectable (40 IU/mL), platelet count increased, and the purpuric lesions faded (Fig. 1). Ribavirin therapy was administrated for 12 weeks, with no side effects. Twelve weeks after completion of this treatment, ALT levels and platelet counts were within normal range, ADAMTS-13 activity was 25% and HEV RNA remained undetectable.

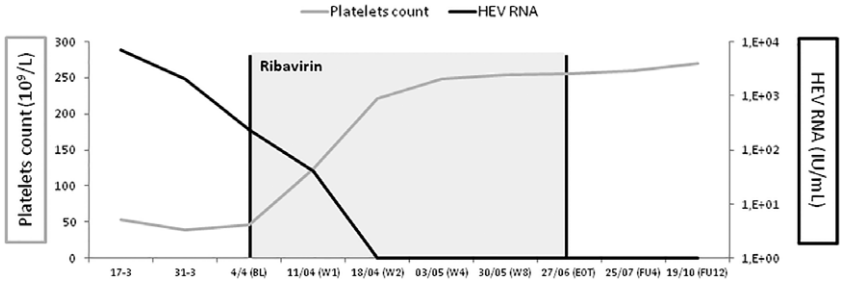

Fig. 1. Analytical follow-up. Despite improvements in liver function parameters, platelet counts progressively decreased, with the appearance of purpura in the lower limbs, mild anemia, schistocytes in peripheral blood, elevated serum lactate dehydrogenase concentration, and undetectable levels of both ADAMTS-13 activity and haptoglobin, findings suggestive of a new TTP relapse. As HEV RNA remained detectable (2000 IU/mL), ribavirin therapy was started at dose of 600 mg/day. One week later, HEV RNA was almost undetectable, and platelet count increased with fading of the purpuric lesions. Twelve weeks after completion of ribavirin, ALT levels, ADAMTS-13 activity, and platelet counts were within normal ranges, and HEV RNA remained undetectable.

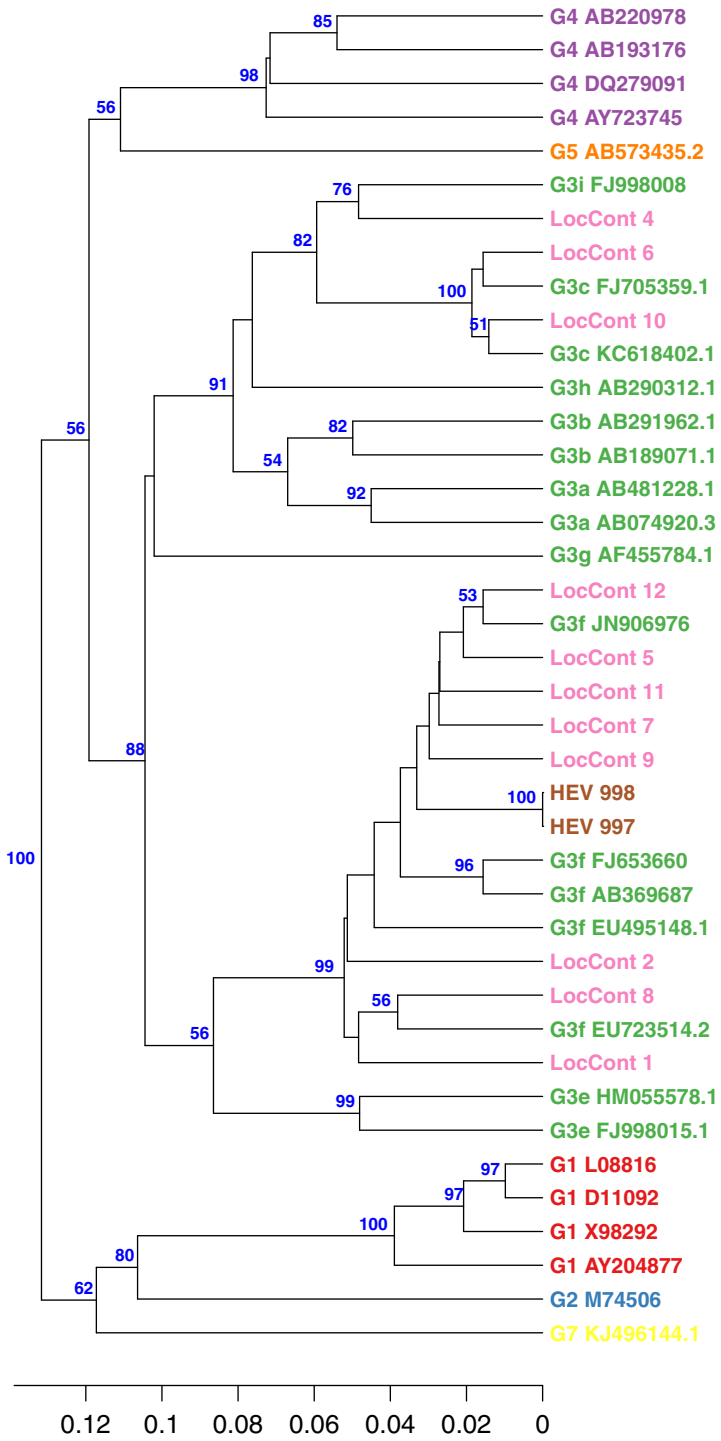

Fig. 2. Phylogenetic analysis. An Unweighted Pair Group Method with Arithmetic Mean phylogenetic tree was constructed using the two problem samples (Donor HEV 998 and Receptor HEV 997), 11 local controls in pink (LocCont) and 27 reference sequences from 7 genotypes downloaded from GenBank. Sequences were named with the genotype and the corresponding sequencing identification code and colored depending on the genotype (4 of G1 in red, 1 of G2 in blue, 16 of G3 in green, four of G4 in violet, one of G5 in orange, and 1 of G7 in yellow).

Analysis of blood components from the donor

A traceback procedure was started on the blood components the patient had received to treat TTP. From January 10 to 16, 2017, the patient received 99 different blood components (1 pooled platelet unit, 38 cryosupernatant plasmas, 12 quarantined plasma units, and 48 methylene

blue inactivated plasma units) from 101 different blood donors. All samples archived at donation were tested for the presence of HEV RNA (HEV Elite, Panther system, Grifols; analytical sensitivity, 7.9 IU/mL). One archived sample was HEV RNA reactive, with an estimated viral load of 5000–10,000 IU/mL (in-house real-time polymerase chain reaction[4]). The sample corresponded to one of the cryosupernatant plasma units, obtained from a whole blood donation taken in May 2016. The archived donation sample was negative for HEV IgG, but positive for IgM antibodies (enzyme-linked immunosorbent assay RecomWell HEV IgG/IgM, Mikrogen). The donor was a 47-year-old man who had donated on three occasions: November 2016 and January and March 2017. All follow-up samples were HEV RNA negative and HEV IgG/IgM positive. Lookback investigations were carried out on the three additional components obtained from the same HEV RNA–positive donation (an RBC concentrate, a pooled platelet unit, and the cryoprecipitate plasma unit). The three recipients were HEV IgG positive/IgM negative either before or shortly after transfusion, and they showed no evidence of active HEV infection in the posttransfusion follow-up sample.

Phylogenetic analysis

Briefly, HEV RNA was extracted from 140 μL of plasma using a QIAamp viral RNA minikit (Qiagen), and a fragment from HEV structural capsid region ORF2 (nt 5145 to nt 7127) was amplified using reverse transcriptase nested polymerase chain reaction and Sanger sequenced. Both samples were processed in different extraction days, and serum samples from local controls were included in the process to discard cross-contaminations. Phylogenetic analysis and nucleotide genetic distances showed that both sequences clustered together in 100% of the trees generated, and no nucleotide differences were found between both sequences. The closest isolate to our samples (donor HEV 998 and recipient HEV 997) were a local control (LocCont_11) and a GenBank reference sequence (G3f_JN906976) with 21 nucleotide differences. Both results revealed a very close relationship between virus sequences from the donor (HEV 998) and the acute infected patient (HEV 997) (Fig. 2).[10]

DISCUSSION

To our knowledge, this is the first report of acute HEV infection transmitted by cryosupernatant plasma used for plasmapheresis. In addition, the acute infection induced a TTP exacerbation, which was successfully controlled after sustained virologic response to ribavirin treatment.

Blood donation safety has become a major concern since the publication of data from several countries reporting the presence of HEV RNA in blood components.[3–5,11] The importance of acute hepatitis E is related to the risk of fulminant hepatitis, acute-on-chronic liver failure, and, mainly, the risk of chronic infection in immunosuppressed patients, with development of liver cirrhosis.[12,13] A retrospective study carried out in England showed that the risk of HEV transmission from blood donations differed according to the blood component transfused.[5] Although fresh frozen plasma has been described as the most infectious blood component, cryosupernatant plasma has not previously been identified as a source of acute HEV infection.

Acute hepatitis E infection has been associated with various extrahepatic manifestations, mainly neurologic in nature.[14] Concerning hematologic complications, few cases of acute thrombocytopenia have been observed, the majority mild and self-limited following resolution of the infection[8,9] or treatment with immunoglobulin[15]; to our knowledge, there are no reports of TTP associated with acute HEV infection.

TTP is a thrombotic microangiopathy that results from severe ADAMTS-13 deficiency. It is well recognized that TTP exacerbations can be triggered by acute infections.[16,17] In fact, our patient's previous TTP episode occurred after a respiratory infection due to influenza A virus. At that episode, oseltamivir therapy did not suffice to control TTP, and plasmapheresis was also needed, which resulted in the transfusion-transmitted acute hepatitis E. Some cases of TTP triggered by an infectious agent have been controlled after resolution of the infection spontaneously or following antiviral/antibiotic treatment, although fatal outcomes have also been reported. In our case, because the thrombocytopenia was mild and it was not associated with kidney, neurologic, or any other extrahematologic manifestation, and while waiting for ADAMTS-13 studies, we decided to start treatment with ribavirin to control the HEV infection without additional plasmapheresis with plasma exchange. One week after starting ribavirin treatment, HEV RNA was almost undetectable, ALT levels had returned to normal values, platelet count increased from less than 40×10^9/mL to greater than 100×10^9/mL, and the purpura progressively disappeared, suggesting that treatment of HEV infection led to control of TTP. Although HEV infection can produce mild thrombocytopenia, the undetectable ADAMTS-13 levels led us to correlate the viral infection with a TTP exacerbation, and the normalization of hematologic values and ADAMTS-13 after the antiviral therapy seems to support this hypothesis.

CONCLUSION

To our knowledge, we report the first case of cryosupernatant-transmitted acute hepatitis E complicated with a TTP exacerbation, successfully controlled after treatment with ribavirin. This report supports the importance of HEV screening of all blood components to avoid transmission of the infection. Treatment of hepatitis E may be of help in the management of extrahepatic manifestations, as was illustrated in our patient: Ribavirin therapy helped to control the TTP exacerbation.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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