Case Report

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Transfusion-transmitted hepatitis E in a misleading context of autoimmunity and drug-induced toxicity

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Abstract

Hepatitis E is currently diagnosed after all other causes of hepatitis have been excluded. Moreover, HEV testing is not performed to prevent blood transmission in developed countries. We report here on the case of a patient with acute hepatitis while receiving potentially hepatotoxic medications for autoimmune disorders, with low-level autoimmune markers and negative "standard" viral markers; it was finally determined that he was suffering from transfusion-transmitted hepatitis E.

Introduction

In Western countries, hepatitis E (HEV) testing is not currently performed as part of the first-line diagnosis for acute hepatitis, mainly because HEV is still believed to be rare in developed countries unless the patient has recently travelled to an endemic area where HEV-contaminated drinking water is the main source of infection. However, indigenous cases of acute hepatitis E are being increasingly reported, and most are caused by zoonotic genotype 3 and 4 strains of HEV. The risk factors for these sporadic cases include shellfish, contaminated animal meats (swine, boar, deer), and direct contact with infected animals [1]. In addition, HEV prevalence in some industrialized countries is much higher than might be expected: for example, in some French regions, up to 52% of normal blood donors have serologic evidence of past HEV infection [2].

We report here on the challenging clinical scenario of a patient who presented with acute hepatitis while receiving potentially hepatotoxic medications for autoimmune disorders, with low-level autoimmune markers and negative "standard" viral markers; it was finally determined that he was suffering from transfusion-transmitted hepatitis E.

Case report

An 81-year-old man presenting with ischemic heart disease, chronic autoimmune thrombocytopenia and anemia was hospitalized in June 2011 for a worsening of his haematological disease. At admission, his liver enzymes were normal. He was given corticosteroids (40 mg/day) and was then switched to cyclosporine (75 mg twice daily) on June 22, 2011. In July 2011, he presented with jaundice, elevated alanine aminotransferases (ALT, 192 IU/L) and cholestasis (γGT, 144 and PAL, 65 IU/L). The abdominal ultrasound and CT-scan were normal. Persistent cytolysis led to the discontinuation of cyclosporine on August 30, under the hypothesis of a drug-induced liver injury. However, his aminotransferase levels did not improve, and meanwhile the platelet count fell to 23,000/mm^3. Eltrombopag (200 mg three times daily) was then introduced on September 6. Three weeks later, the patient's cytolysis worsened (ALT 398 IU/L and AST 673 IU/ml) (Fig. 1), requiring the discontinuation of eltrombopag on September 27. Although the hepatic toxicity of eltrombopag is well known, an initial etiological assessment of the cytolysis was prescribed, including viral and autoimmune markers. The markers of ongoing hepatitis A, B, and C were negative, and viremia of Epstein–Barr virus, cytomegalovirus, herpes simplex viruses 1 and 2, varicella zoster virus and parvovirus B19 was undetectable. However, anti-smooth muscle (1/160) and antinuclear antibodies (1/80, with speckled aspect) were found to be weakly reactive, which prompted the reintroduction of corticosteroids (20 mg/day) under the hypothesis of autoimmune hepatitis. On September 30, hepatitis E infection was diagnosed with positive IgG and IgM (Adaltis®, Milan, Italy) and detectable HEV RNA (Ceeram®, La Chapelle sur Erdre, France) with a 3f genotype. As immunosuppression could promote HEV persistence, the corticosteroids were withdrawn. Liver enzyme levels returned to normal on October 17 and HEV RNA was cleared in November. Nevertheless, the patient's anemia and thrombocytopenia worsened, leading to decompensation of his cardiac disease with a fatal outcome. A case review was then performed to elucidate the origin of HEV transmission.

Analyses performed on stored sera revealed positive HEV RNA and serology since June 30. The previous sample dated May 3 was negative. We, therefore, estimated that contamination could have occurred between early April and late June 2011. A zoonotic

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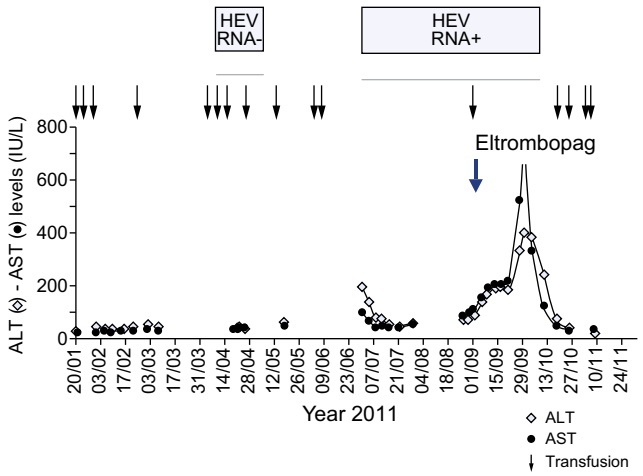

Fig. 1. Evolution of transaminase levels according to time. Multiple transfusions and eltrombopag administration are represented as black arrows and a dark blue arrow, respectively. HEV RNA presence is indicated on the graph.

transmission via infected meat was unlikely since the patient did not eat pork for religious reasons. In addition, no animal or environmental exposure was recorded. Iatrogenic transmission was then hypothesized because the patient had been hospitalized several times since January 2011, and had received several transfusions. Specifically, he received nine platelet concentrates and four red blood cell units during the potential contamination period. This blood-transmission hypothesis was explored by testing the blood donors involved in these transfusions. Twenty-eight sera stored by the *French* Blood Agency (EFS) were tested for HEV RNA. A single sample was positive with an estimated viral load of 17,000 IU/ml (4.2 log IU/ml). This blood donation, together with four others, were part of the platelet concentrate given to the patient on April 19, ten weeks before the onset of hepatitis. The donor's HEV serology was negative; HEV sequencing based on open reading frame two [3] and one [4] regions, identified a genotype 3f strain (Fig. 2) presenting strict homology with the patient's strain. The donor was a 53-year-old woman, living in a rural part of the Ile-de-France region (around Paris) and working as a secretary. As a regular donor, she was tested 6 months later and presented with undetectable HEV RNA and serologic evidence of past HEV infection. On examination, she reported no symptoms, no travel, no contact with animals or other environmental risk factors, but a habitual consumption of cured pork products.

Discussion

Transfusion-transmitted HEV infection was evidenced on the basis of a strict sequence homology between the donor's and patient's strain. Cyclosporine has occasionally been reported to cause hepatitis, nevertheless, the first ALT peak, initially attributed to drug toxicity, was certainly due to acute HEV infection. The second ALT peak occurred during the administration of a drug well-known to be hepatotoxic. However, the persistent HEV viremia observed in this immunocompromised patient might have played a role. In line with this observation, a recent report has shown that autochthonous hepatitis E might be misdiagnosed as drug-induced liver injury [5]. In this case, the low-level detection of autoimmune markers was even more misleading. Drug-induced liver injury and autoimmune hepatitis are two challenging diagnoses that are reliant on excluding other causes, including HEV. More generally, HEV infection should be ruled out in all cases of acute hepatitis, even when no recent travel to endemic areas is reported; indeed, autochthonous HEV infections are increasingly being reported [6] although the transmission modes remain elusive in most cases. In our patient, blood-borne transmission was hypothesized since the patient had received multiple transfusions. And indeed, because it cannot be inactivated in fresh blood products, hepatitis E virus poses a risk to transfusion safety. Studies from endemic areas have shown a higher prevalence of HEV markers in transfusion recipients [7], and although such an association is not reported in non-endemic areas, a few cases of transfusion-transmitted hepatitis E have been reported in Europe and Japan [8–10]. Severe clinical forms of HEV infection can occur in immunocompromised patients or those with underlying liver disease [11]. Nevertheless, in most cases, the infection may be subclinical, as suggested by the unexpectedly high seroprevalence in some parts of Western countries [2]. In South-West France, seroprevalence increases with age, reaching 70% in people over the age of 58 years. The reasons for this extremely high rate are not clearly understood, but may partly be related to dietary habits, which include eating pork. This risk factor was not shared by our patient, thus explaining the development of acute HEV at an advanced age. The subclinical nature of most HEV infections has also been highlighted by the detection of HEV viremia in a significant proportion of healthy blood donors with elevated ALT in Japan [12–15]. In France, blood donors are not tested for ALT, HEV antibodies or HEV RNA. Of note, in both the present case and that reported by Colson *et al.* [9], only HEV RNA was detectable in the blood donation. The present report underlines the need to improve our knowledge of HEV epidemiology in order to guide transfusion safety policies in developed countries, and highlights the need for HEV testing in the context of the first-line diagnosis of all cases of acute hepatitis.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

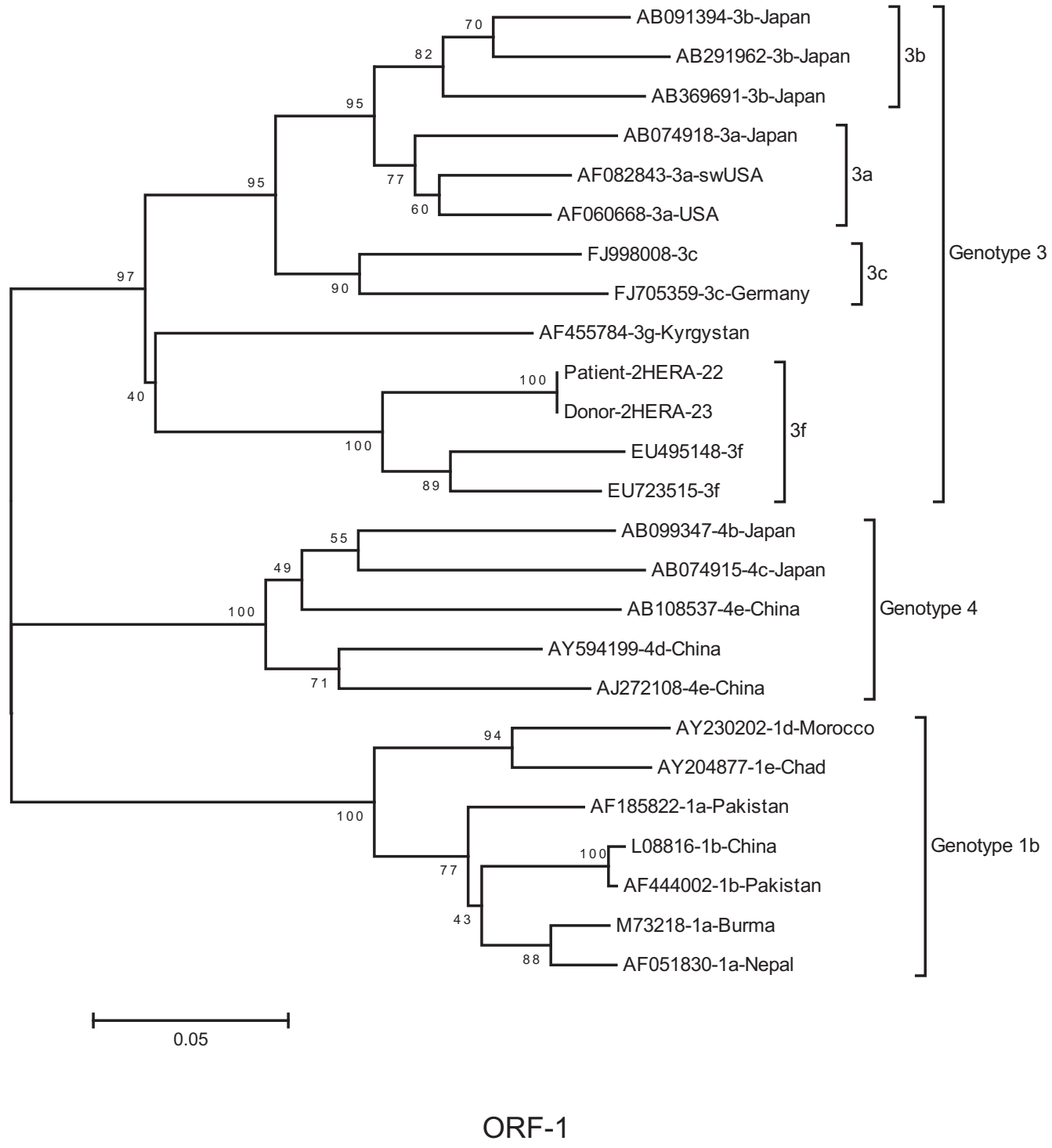

Fig. 2. Phylogenetic analysis of partial ORF2 and ORF1 regions. Phylogenetic trees were constructed on the MEGA4 software using the Neighbor-Joining method from a Kimura 2-parameter distance matrix based on partial nucleotide sequences of ORF1 encoding for RdRp (323 nt) and ORF2 (315 nt). Bootstrap values obtained from 500 resamplings are shown. A 100% sequence homology is observed between blood donor and the recipient sequences. Genbank reference sequences are indicated by their accession number.

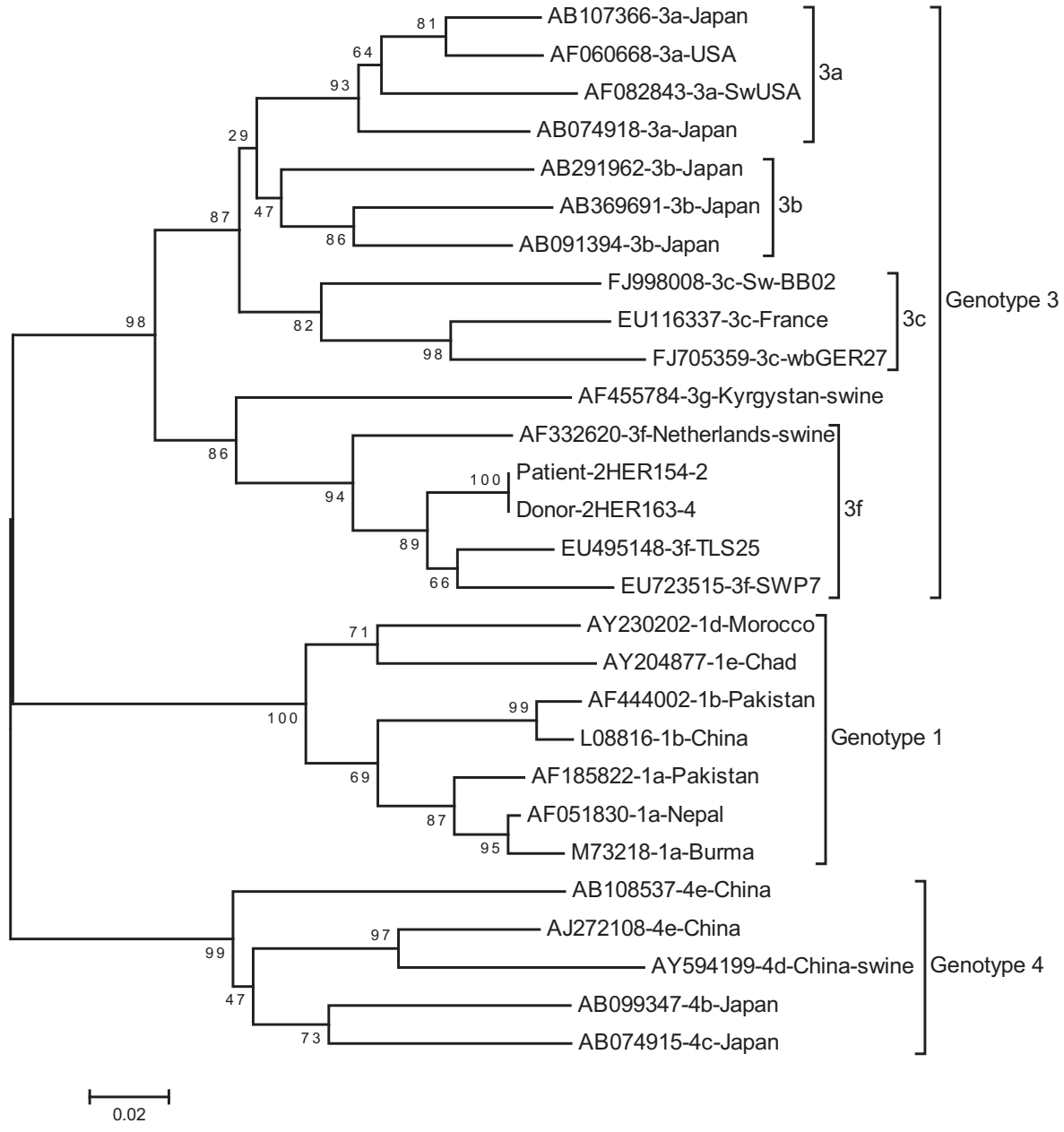

Fig. 2. (*continued*)

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