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RESEARCH NOTE

Hepatitis E virus as a newly identified cause of acute viral hepatitis during human immunodeficiency virus infection

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ABSTRACT

The recent description of chronic hepatitis E in organ transplant recipients deserves increased awareness in the context of hepatitis E virus (HEV) infection in immunocompromised individuals. Reported here is what is apparently the first PCR-documented case of acute hepatitis E in a human immunodeficiency virus (HIV)-1-infected patient. The CD4^{+} T-lymphocyte count was $246/mm^3$. The IgM anti-HEV antibody and HEV RNA tests results from serum were positive. Hepatitis was benign, and chronic HEV infection was ruled out. The HEV genotype was 3f. The patient did not report recent travel abroad. HEV should be tested in HIV-infected individuals presenting with acute hepatitis. HEV RNA detection is useful in diagnosing HEV infection and in monitoring recovery.

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Hepatitis E virus (HEV) is the leading, or the second leading, cause of acute hepatitis in adults in many parts of the developing world, where it is principally waterborne. However, seroprevalence data suggest that HEV might be endemic in industrialized countries as well [1]. Moreover, an increasing number of sporadic autochthonous cases of hepatitis E have been recently reported in these geographical areas, and some of them were fatal [1,2]. Although HEV epidemiology remains poorly understood in developed countries, there is increasing evidence that hepatitis E is a zoonosis with a swine reservoir, which might be a source of contamination for humans [1].

Recently, very unexpected clinical features of hepatitis E have been highlighted in immunosuppressed individuals. Indeed, chronic hepatitis E, and even rapidly progressing hepatitis E-associated cirrhosis, have been described in organ transplant recipients [3–5]. Hence, these data deserve increased attention in the context of hepatitis E in immunocompromised individuals. Reported here is apparently the first PCR-documented case of acute HEV infection in a patient infected with the human immunodeficiency virus (HIV).

A 49-year-old male with sexually-acquired HIV-1 infection presented in September 2007 with fever, asthaenia and hepatomegaly. The alanine aminotransferase (ALT) level was 813 IU/L, bilirubinaemia was 31 μmol/L, and the prothrombin index was 100% (Table 1). The CD4$^+$ T-lymphocyte count was 246/mm^3, and the plasma HIV-1 RNA level was 2.9 $\log_{10}$ copies/mL under treatment with tenofovir, abacavir, atazanavir and ritonavir. The patient reported chronic excessive alcohol consumption, and he reported having multiple sexual partners. Hepatitis E was diagnosed on the basis of positive results after IgM anti-HEV antibody testing (EIAGen kit, Adaltis; optical density ratios for IgG and IgM anti-HEV antibodies were 0.79 and 10.1, respectively) and HEV RNA detection and sequencing from serum [6]. Other aetiologies for acute hepatitis were excluded, including hepatitis A virus, hepatitis B virus and hepatitis C virus infection. Neither HEV RNA nor anti-HEV antibodies were detected 2 months prior to the onset of hepatitis. Clinical symptoms spontaneously regressed during the following month, and in January 2008 the ALT level was 10 IU/L. At that time, IgG anti-HEV antibody seroconversion had occurred, IgM anti-HEV antibodies still persisted, and HEV RNA was no longer detected in serum.

The patient did not report recent travel abroad, contacts with travellers, or consumption of wild boar meat or shellfish. Nevertheless, he reported eating barbecued pork 2 weeks before onset of hepatitis. The HEV RNA ORF-2 sequence clustered into genotype 3f, which is found in cases of autochthonous hepatitis E and in swine in Europe

Table 1. Evolution of biochemical, haematological and virological markers

Marker	Date				
	6 June 2007	18 June 2007	6 July 2007	17 September 2007	22 January 2008
Alanine aminotransferase (IU/L)	29	15	10	813	10
Aspartate aminotransferase (IU/L)	22	19	17	714	22
γ- Glutamyl transferase (IU/L)	73	43	34	778	26
Bilirubinaemia (μmol/L)	11	6	11	31	60
Alkaline phosphatase (IU/L)	90	82	51	204	71
Prothrombin index (%)	100	100	100	100	–
Platelet count (per mm^3)	181	304	258	212	–
Lymphocyte T-CD4 cell count (per mm^3)	462	248	231	246	–
HEV RNA in serum[a]	Negative	–	–	Positive	Negative
Anti-HEV IgG antibodies[a]	Negative	–	Negative	Negative	Positive
Optical density ratio[b]	<0.9	–	<0.9	<0.9	3.6
Anti-HEV IgM antibodies[a]	Negative	–	Negative	Positive	Positive
Optical density ratio[b]	<0.9	–	<0.9	10.0	7.7
HBV serology	–	–	–	Negative	–
HBV DNA in serum (IU/mL)	–	–	–	Negative	–
Anti-HCV antibodies	–	–	–	Negative	–
HCV RNA in serum (IU/mL)	–	–	–	Negative	–
HIV-1 RNA in serum (copies/mL)	<40	87 366	489 543	829	<40
Antiretroviral therapy	Interruption of treatment that included ABC, TDF, fosAPV, and RTV[c]	None	Re-introduction of treatment that included ABC, TDF, ATV, and RTV	ABC, TDF, ATV, RTV	ABC, TDF, ATV, RTV

–, Not available; HEV, hepatitis E virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ABC, abacavir; TDF, tenofovir; fosAPV, fosamprenavir; RTV, ritonavir; ATV, atazanavir.
[a]Retrospective analysis of serum samples could be performed due to their availability for routine laboratory examinations in the context of HIV infection.
[b]Positivity corresponds to an optical density ratio >1.
[c]Interruption of antiviral therapy was motivated by severe lipodystrophia.
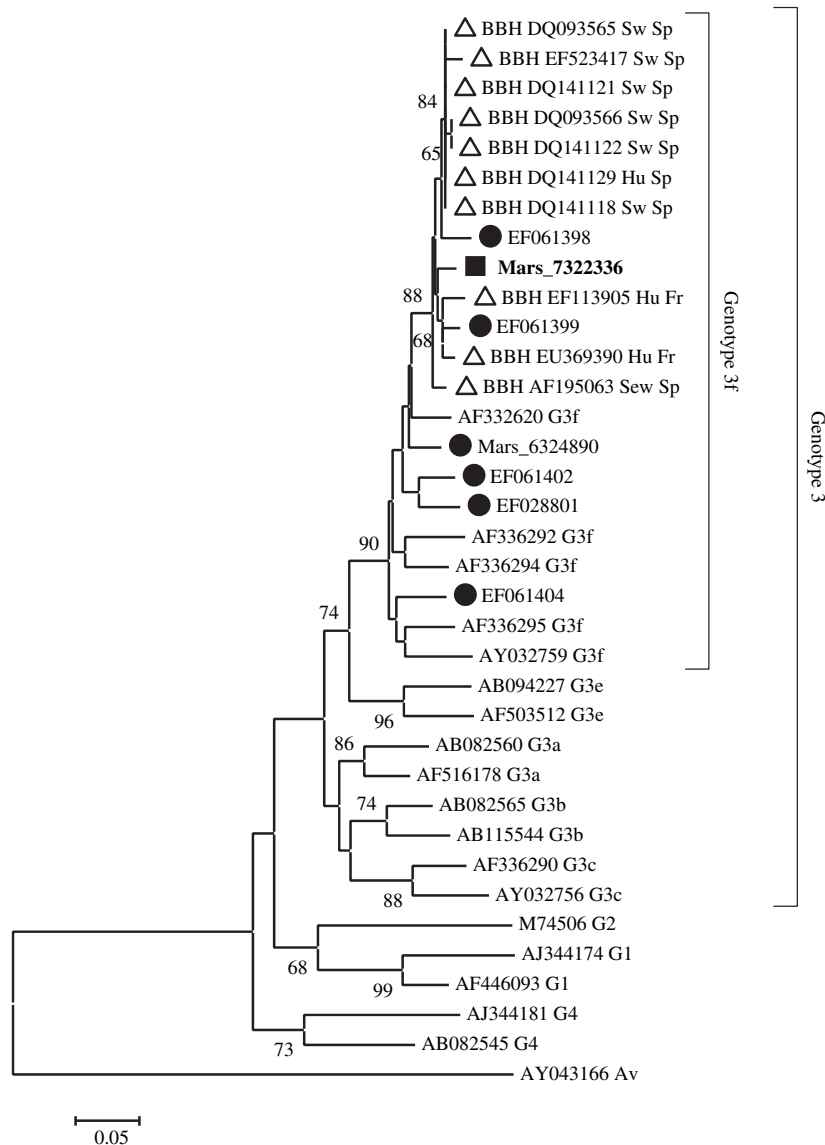
Fig. 1. Phylogenetic tree based on partial nucleotide sequence of the open reading frame 2 (ORF2) region of the hepatitis E virus (HEV) genome obtained from the patient whose case is reported herein together with HEV sequences: (i) from human cases diagnosed in the Timone Virology laboratory of Marseille; (ii) of previously determined genotypes and subtypes [7]; and (iii) from GenBank and corresponding to the ten highest-score BLAST hits with the sequence from the present case (http://www.ncbi.nlm.nih.gov/BLAST/). The phylogenetic tree was constructed by the neighbour-joining method based on the partial nucleotide sequences of the 5'-ORF2 region of HEV genome (230 bp). The HEV sequence from the case reported here is in bold and is indicated by a black square. HEV sequences from human cases diagnosed in the Timone Virology laboratory of Marseille are indicated by black circles. The HEV sequences corresponding to the ten BLAST hits obtained with the sequences from the case reported here are indicated by white triangles. They are labelled as follows: GenBank accession no., source and country of origin. Bootstrap values are indicated when they were >60% (percentage obtained from 1000 resamplings of the data). Avian HEV sequence GenBank accession no. AY043166 was used as an outgroup. The scale bar indicates the number of nucleotide substitutions per site. BBH, best BLAST hits; Av, Avian; Hu, Human; Sew, Sewage; Sw, Swine; Fr, France; Mars, Marseille (France); Sp, Spain.

[7,8] (Fig. 1). Thus, the HEV sequences corresponding to the ten BLAST hits with the highest scores with respect to the sequence from the case reported here were from French and Spanish humans or swine (http://www.ncbi.nlm.nih.gov/BLAST/).

Hepatitis E might represent an important clinical problem in HIV-seropositive individuals.

First, recent reports from India and Europe indicate that hepatitis E could aggravate prior chronic viral hepatitis and that it carries a poor prognosis in the context of chronic liver disease [2,9,10]. This might be critical in HIV-infected patients with high rates of chronic co-infections with hepatitis B virus and/or hepatitis C virus, especially those with a history of injecting drug use [11]. Second, it has been very recently suggested that HEV infection might result in chronic hepatitis, and even cirrhosis in the setting of severe immunosuppression, in organ transplant recipients [3–5].

To date, the clinical presentation and outcome of hepatitis E in HIV-seropositive individuals are unknown. Indeed, the association between HEV and HIV infections has been debated mostly on the basis of IgG anti-HEV antibody seroprevalence data from developed countries, and this debate revealed controversial results [12–17]. In these studies, acute hepatitis E was not described. Moreover, discordance between the results of IgG anti-HEV antibody detection assays has been previously reported, and this discordance complicates the interpretation of HEV seroprevalence studies [18]. In another seroprevalence study from Malaysia, IgM anti-HEV antibodies were found in 4% of HIV-1-infected patients, in the absence of IgG anti-HEV antibodies in all cases [19]. However, their clinical significance was difficult to assess, as no individual complained of symptoms of acute hepatitis. Very recently, hepatitis E was reported in an HIV-positive pregnant Nigerian woman living in Germany, whose CD4$^+$ T-lymphocyte count was >200/mm^3 [20]. HEV infection was diagnosed at week 27 of pregnancy only on the basis of positive results according to IgG anti-HEV antibody testing, with HEV RNA not being tested. The ALT level was 1683 IU/L, and the beginning of liver failure was noted. Nevertheless, the clinical outcome was favourable.

In the case described here, hepatitis E was benign, and the clinical outcome was also favourable. These outcomes may have been due to the absence of underlying chronic hepatitis B and C [20]. In addition, in the present case, the PI before acute hepatitis was 100%. Furthermore, chronic HEV infection was ruled out, as assessed by longitudinal HEV RNA testing. The resolution of HEV infection may be explained by the patient's moderate level of immunosuppression, as indicated by a CD4$^+$ T-lymphocyte count >200/mm^3. Indeed, in the study by Kamar et al. [4], total lymphocyte and CD4$^+$ T-cell counts were significantly lower in organ transplant recipients in whom chronic hepatitis E developed than in those in whom hepatitis E resolved.

Finally, in the case described here, and in contrast to the case reported by Thoden et al. [20], hepatitis E was diagnosed on the basis of positive results according to IgM anti-HEV antibody and HEV RNA testing, whereas IgG anti-HEV antibodies were detected only 4 months after hepatitis onset. In the study by Kamar et al. [4], IgG anti-HEV antibodies were detected in only one of 14 organ transplant recipients at the time of diagnosis of hepatitis E. Furthermore, persistently negative results of IgG anti-HEV antibody testing have previously been observed in PCR-documented HEV infections in immunosuppressed individuals [3–5, 21]. These data make apparent the need for systematic testing for HEV RNA and IgM anti-HEV antibodies in such patients, to diagnose HEV infection.

In conclusion, HEV testing should be included in diagnostic investigations of acute hepatitis in HIV-infected individuals. HEV RNA should be assayed for reliable diagnosis of hepatitis E, and its negativation should be monitored to verify the complete recovery from HEV disease.

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RESEARCH NOTE

Panton–Valentine leukocidin is expressed at toxic levels in human skin abscesses

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ABSTRACT

Pus samples were prospectively collected from patients with *Staphylococcus aureus* skin infections and tested for Panton–Valentine leukocidin (PVL). PVL was detected at concentrations that were toxic for rabbit skin in all specimens from patients infected with strains harbouring PVL genes.

Keywords ELISA, Panton–Valentine leukocidin, quantification, skin infection, *Staphylococcus aureus*

Staphylococcus aureus is an important human pathogen that expresses a variety of exoproteins, including Panton–Valentine leukocidin (PVL) [1]. PVL genes are carried by community-acquired methicillin-resistant *S. aureus* (CA-MRSA) clones that are spreading throughout the world [2,3].

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