

Case Report

First report of chronic hepatitis E in renal transplant recipients in Portugal

Filipe Breda¹, Joana Cochicho¹, João Rodrigo Mesquita², Ana Bento¹, Rui Pedro Oliveira³, Emília Louro¹, Maria São José Nascimento², Jorge Leitão¹, Henrique Vieira Gomes⁴, Armando Carvalho¹

¹ Internal Medicine Department, Liver Disease Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

² Laboratory of Microbiology, Department of Biological Sciences, Faculdade de Farmácia da Universidade do Porto, Porto, Portugal

³ Anatomic Pathology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

⁴ Nephrology Department, Kidney Transplantation Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Abstract

Hepatitis E virus (HEV) infection can be responsible for chronic hepatitis in immunocompromised patients, and can rapidly evolve into fibrosis and/or hepatic cirrhosis. We present two cases of chronic hepatitis E, emphasizing the need to be aware of this entity as a growing etiology of hepatitis in transplant and immunocompromised patients.

Key words: hepatitis E virus; immunosuppression; renal transplantation; chronic hepatitis E.

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Introduction

Hepatitis E is caused by a single strain RNA virus, hepatitis E virus (HEV), which is transmitted enterically and is responsible for a significant number of cases of acute hepatitis with endemic characteristic in several developing countries in Asia, the Middle East, Africa, and Central America (genotypes 1 and 2), and is generally sporadic in the United States and developed countries in Europe (genotypes 3 and 4) [1]. In immunocompetent patients, infection is usually self-limited, evolving to chronicity only in cases of immunosuppression [1]. Such cases include transplant patients (mainly kidney and liver), today recognized as a risk group, where HEV infection has emerged in developed countries [2]. As in other non-endemic countries, there are reports of autochthonous infection Portugal [3] as well as reports of the presence of anti-HEV antibodies in healthy individuals [4].

Herein we report two cases of chronic hepatitis E in patients who had undergone kidney transplantation, were under immunosuppressive therapy, and had prolonged elevation of aminotransferases.

Case 1

The first case was a 55-year-old Caucasian male who received a kidney transplant from a deceased donor in April 2011 for chronic kidney disease (CKD) of unknown cause. He had past medical history of hypertension, depression and chronic sinusitis, and was medicated with enalapril, trazodone, and alprazolam. His body mass index (BMI) was 24.4 Kg/m². He was an active smoker and denied alcohol consumption and recent travel abroad. His immunosuppressive regimen included tacrolimus (4 mg once daily), mycophenolate mofetil (500 mg twice daily), and prednisolone (5 mg once daily). Three months after receiving the transplant, he developed an asymptomatic increase in aminotransferases, with aspartate aminotransferase (AST) two times the upper limit of normal (2x ULN), alanine aminotransferase (ALT) 3x ULN, and gamma glutamyl transferase (GGT) 3x ULN. Hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) 1 and 2, Epstein-Barr virus (EBV), herpes simplex virus (HSV) 1 and 2, and cytomegalovirus (CMV) serologies were negative. DNA HBV and RNA HCV were undetectable. Liver autoimmunity screening was negative. Abdominal ultrasound was normal. During

the following months, he maintained a fluctuating evolution of liver enzymology with AST under 1.5x ULN, ALT 2x ULN, and GGT 3x ULN. In December 2011, he was admitted for acute cellular rejection of the kidney allograft and interstitial nephritis; DNA-polyomavirus was detected by polymerase chain reaction (PCR). Due to the high plasma viral load of BKV, his immunosuppressive regimen was changed; cyclosporine (150 mg twice daily) and prednisolone (20 mg once daily) were initiated. The percutaneous liver biopsy (March 2012) found lobular hepatitis without fibrosis (Figure 1a). The patient's aminotransferases elevation (AST 4x ULN, ALT 13.5x ULN and GGT 9x ULN) continued, motivating another change in the immunosuppressive therapy to everolimus (0.75 mg + 0.25 mg once daily). Hepatitis E was diagnosed on May 2012 by the presence of serum anti-HEV antibodies, immunoglobulin M (IgM) type (determined by ELISA [EUROIMMUN, Lübeck, Germany]), with an absence of immunoglobulin G (IgG). HEV RNA was detected in May 2012 in a serum sample by nested-PCR preceded by reverse transcription selective for the conserved open reading frame (ORF) 1 of the HEV genome [5]. The same test detected identical sequences in serum samples from July 2012 and October 2012, confirming the presence

Figure 1. Liver biopsy – a) lobular inflammatory infiltrate with some acidophilic bodies (H&E, 200x); b) mild peri-portal fibrosis; interface and lobular necroinflammatory activity (H&E, 100x

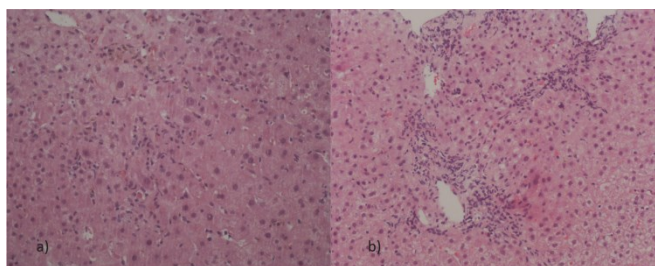
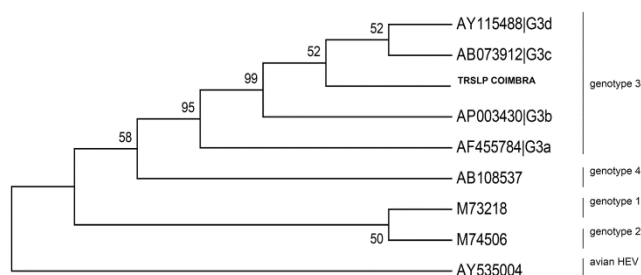


Figure 2. Phylogenetic analysis through MEGA5 software [adapted from Tamura *et al.*, 2007]. The sequence of the presented case [TRSLP COIMBRA] is in bold. There were a total of 334 positions in the final dataset.

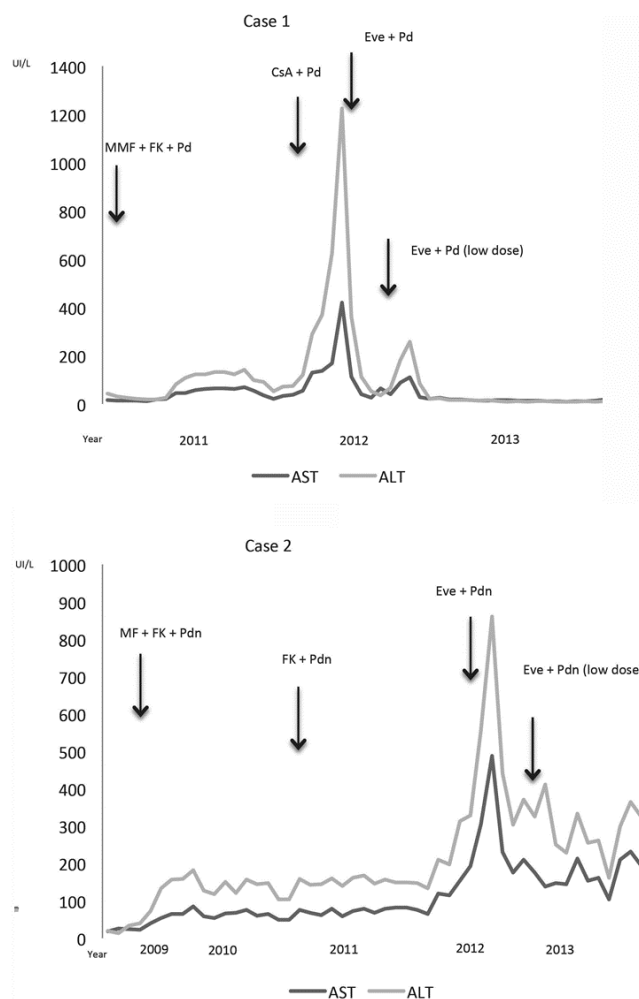


of chronic viremia. The amplified products obtained (330 bp) were sequenced and compared with sequences for ORF 1 HEV genotypes 1 to 4 deposited in GenBank through the neighbor-joining methodology based on the Jukes-Cantor model. Phylogenetic analysis demonstrated that the amplified product clustered with HEV genotype 3, sub-genotype 3c (Figure 2). The doses of everolimus were reduced to 0.5 mg twice daily with normalization of aminotransferases (Figure 3). Anti-HEV IgM and IgG remained positive on posterior control analysis.

Case 2

The second case was a 34-year-old Caucasian male who received a kidney transplant from a deceased donor in November 2009 for CKD (probable hypertensive etiology). He had poorly controlled hypertension, medicated with nifedipine LP and

Figure 3. Aminotransferase evolution and relation with immunosuppressive therapy. MMF: mycophenolate mofetil; FK: tacrolimus; Pd: prednisolone; CsA: cyclosporine; Eve: everolimus; MF mycophenolic acid



carvedilol. He denied alcohol consumption or recent travel abroad but was an active smoker. His BMI was 23.2 Kg/m². He was under immunosuppression with mycophenolic acid (720 mg twice daily), tacrolimus (12 mg once daily), and prednisolone (10 mg once daily). Two months after transplantation, he developed aminotransferase elevation, with AST 1.5x ULN, ALT 3.5x ULN, and GGT 3x ULN. He had no symptoms. Serologies for HBV, HCV, HIV 1 and 2, EBV, CMV, and HSV were all negative. Liver autoimmunity screening was negative. Abdominal ultrasound was normal. Several changes were made in immunosuppressive therapy, with reduction and posterior conversion of tacrolimus to everolimus, and resulted in persistence of abnormal liver blood tests (Figure 3). Two years after the transplant (December 2012), he underwent native kidney nephrectomy for small renal cell carcinoma, without complications. On January 2013, a liver biopsy was performed, revealing moderate chronic hepatitis with mild fibrosis (Figure 1b). Serology for HEV (March 2013) was positive (IgG and IgM), and RNA HEV was detected in this serum sample. Unfortunately, the amplified products (330 bp) did not produce sequence data for phylogenetic analysis. Immunosuppression was reduced to everolimus 0.75 mg once daily and prednisolone 2.5 mg once daily. Because he maintained elevated aminotransferases, ribavirin was introduced at 800 mg once daily, which he will continue for three months unless a contraindication develops.

Discussion

Hepatitis E is a frequent cause of acute hepatitis in developing countries and an emerging cause of hepatitis in industrialized countries. Typically, HEV causes acute, self-limited infection in immunocompetent patients, with a low mortality rate [1]. Recently, genotype 3 has been noted to be as responsible for hepatitis in patients submitted to solid organ transplant under immunosuppressive therapy, with about 60% of cases evolving to chronicity. Seroprevalence studies report the presence of the anti-HEV IgG antibody in 6% to 16% of kidney transplant patients [2,6], with particular incidence in southern France [7]. Patients infected with hematologic disturbances under chemotherapy and HIV-infected patients seem also to be at higher risk of chronic infection [8]. Transmission in developed countries is associated with the consumption of veal, pork, and boar meat that has been undercooked or cooked at low temperatures [9]. Although the mechanisms

responsible for chronic evolution are not fully understood, they are at least in part connected with the intensity of immunosuppressive therapy [10]. The importance of these situations results from the possibility of rapid evolution to fibrosis and liver cirrhosis [6,11]. There is no approved treatment for chronic hepatitis E. In the absence of spontaneous resolution, reduction of immunosuppressive therapy should be considered, which can eliminate the virus in over 30% of cases [12]. Some studies point to the efficacy of interferon and ribavirin in the treatment of HEV [8,13]. In kidney transplant recipients, because therapy with interferon is contraindicated, three months of ribavirin seem effective in the elimination of the virus [8,12].

Elevation of aminotransferases is, on the other hand, frequent in kidney transplant patients. In some of them, after exclusion of viral, toxic, and alcoholic causes, it is not possible to find any other etiology. Moreover, acute HEV infection can easily be confused with toxic hepatitis [14]. Acute presentation can, as in the presented cases, remain asymptomatic in over 50% of patients. In the remaining patients, it usually presents with jaundice, fatigue, weight loss, and diffuse myalgias or arthralgias [10]. In both of our patients, analytic changes began shortly after the transplant, with the diagnosis of hepatitis E only confirmed years later. Since they had no history of recent travel abroad, it seems likely that the infection had autochthonous origin. The high prevalence of HEV3 in domestic pigs in Portugal [15] associated with the high consumption of pork meat and derivatives in the Portuguese population leads us to believe that this was the source of transmission in our cases. Only one of the patients had histologic changes suggestive of chronic hepatitis, probably due to a longer evolution. However, evolution to chronicity is suggested in both cases by the changes in liver enzymology for more than six months, with persistence of RNA HEV in serum six months after the first detection of anti-HEV antibodies [16]. Both patients had anti-HEV IgM in successive monitorizations and were under immunosuppression with tacrolimus, which seems to be related with a higher risk of evolution to chronic hepatitis [10]. In the first case, the reduction of the immunosuppression resulted in normalization of liver enzymology, which was not accompanied with the correspondent anti-HEV IgM disappearance. In the second, the persistence of elevated aminotransferases justified, in our opinion, the need to treat with ribavirin.

Conclusions

To our knowledge, these are the first two cases of chronic hepatitis E diagnosed in Portugal. Considering the crescent prevalence of HEV infection, we believe that hepatitis E should be included in the differential diagnosis of elevated liver function tests, if it is not explained by other etiology, especially in the setting of transplant and immunosuppressed patients.

Acknowledgements

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Corresponding author

Filipe Breda
Hospitais da Universidade de Coimbra
Centro Hospitalar e Universitário de Coimbra
Av. Bissaya Barreto - Praceta Prof. Mota Pinto, 3000-075
Coimbra, Portugal
Phone: +351914736351
Email: filipebreda82@gmail.com

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