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Locally Acquired Chronic Hepatitis E Followed by Epstein-Barr Virus Reactivation and Burkitt Lymphoma as a Suspected Extrahepatic Manifestation in a Liver Transplant Recipient

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 62
Final Diagnosis: Chronic hepatitis E • Burkitt's limphoma
Symptoms: Elevated liver enzymes
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course

Background: Hepatitis E virus (HEV) is a common cause of acute hepatitis in developing regions. In high-income countries, hepatitis E is an emergent zoonotic disease of increasing concern. Clinically, the infection is usually acute and self-limited in immunocompetent individuals, although rare chronic cases in immunocompromised patients have been reported. Both acute and chronic infections have been recently associated with several extrahepatic manifestations, including neurological and hematological disorders.

Case Report: A case of autochthonous chronic HEV infection in a liver-transplanted man from a non-endemic country is presented. Phylogenetic analysis revealed a swine origin of the HEV human infection. Chronic hepatitis E was treated with a 9-week course of ribavirin, after which viral clearance was achieved. Subsequently, the patient developed a post-transplant lymphoproliferative disorder (PTLD) in the form of Burkitt lymphoma. At the time of lymphoma diagnosis, the patient had shown a strong reactivation of Epstein-Barr virus (EBV) infection. After additional antiviral ganciclovir therapy and chemotherapy, the patient had a complete recovery with no sequelae.

Conclusions: The differential diagnosis of persistently elevated transaminases in transplanted and/or immunocompromised patients should include testing for HEV by appropriate nucleic acid techniques (NATs). Cases of HEV infection with an atypical clinical outcome, such as the one presented herein, highlights the need for increased awareness of chronic hepatitis E and its association with a wide range of extrahepatic manifestations.

MeSH Keywords: Hepatitis, Chronic • Liver Transplantation • Lymphoproliferative Disorders • Epstein-Barr Virus Infection

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Background

Hepatitis E virus (HEV), which belongs to the *Orthohepevirus* genus within the *Hepeviridae* family, is the etiological agent of acute hepatitis E, an emerging disease of increasing concern in public health [1]. Globally, 20 million infections with HEV occur per year, with 3.3 million symptomatic cases [1]. Four main genotypes are able to infect humans (HEV-1 to HEV-4). HEV-1 and HEV-2 (in Asia, North Africa, and a few Latin American countries) are regarded as anthroponotic with no other animal reservoir, whereas HEV-3 (in Europe, the Americas, and Asia) and HEV-4 (mainly in Asia) were found to infect several animal species [1,2]. In industrialized and non-endemic countries, HEV infection occurs as sporadic autochthonous cases and moderate to elevated rates of anti-HEV antibodies and RNA detection have been reported [3]. Commonly, the source of HEV infection in this epidemiological setting is undetermined, but increasing evidence supports the hypothesis of zoonotic transmission of infection from pigs and wild boars [4], serving as the main reservoir for human infections. In immunocompetent individuals, HEV typically causes an acute and self-limiting disease [5]. Unknown effects of HEV infection have been recently reported in non-endemic and high-income countries, such as clinical presentation with a wide range of extrahepatic manifestations, and the possibility of the disease to become chronic in immunocompromised individuals and transplanted patients [5].

The ability of HEV, mainly HEV-3, to progress to a chronic state is of major concern in solid organ transplant recipients [6]. This group is thought to be the main population at risk, which is well documented among liver and kidney transplant recipients [7,8]. Furthermore, chronic HEV-3 infection has been shown to occur in patients with other conditions associated with immunosuppression, such as lymphoma, leukemia, and HIV infection [9]. Overall, the prevalence of acquired HEV in the post-liver transplantation population is about 1% [7].

Herein, we present a case of autochthonous chronic HEV infection in a liver-transplanted man who afterwards showed a reactivation of Epstein-Barr virus (EBV) infection with subsequent development of a post-transplant lymphoproliferative disorder (PTLD) in the form of Burkitt lymphoblastic leukemia, 3 years after liver transplant.

The study was approved by the Ethics Committee of the Central Hospital of the Armed Forces and the patient gave written consent prior to inclusion in this study.

Case Report

In May 2014, a 62-year-old man underwent orthotopic liver transplantation (LT) for non-alcoholic steatohepatitis and cirrhosis. He had an isolated hepatitis B virus (HBV) core antibody (anti-HBc)-positive, and received a hepatitis B surface antigen (HBs Ag) and anti-HBc-negative, hepatitis B surface antibody (anti-HBs)-positive graft. The serological status donor/receptor for EBV was +/– and for cytomegalovirus (CMV) it was +/+.

As prophylactic therapy of HBV reactivation, the patient received lamivudine. Initial immunosuppression was performed with tacrolimus (2 mg 2×/day), mycophenolate mofetil (MMF) (500 mg 2×/day), and steroids (methylprednisolone 500 mg in the induction, with subsequent tapering). In the first week after LT, he presented an acute rejection, with good immune response to steroid pulse of 3 g of methylprednisolone, with histological resolution and normalizing of liver parameters at 40 days after surgery.

At the second month after transplant, the patient presented a CMV reactivation without alteration of liver enzymes, which was successfully treated with valganciclovir. Therefore, progressive reduction of immunosuppression was performed in the follow-up, with suspension of steroid and MMF. Tacrolimus therapy was continued.

In January 2016 (1 year and 6 months after LT) the patient presented asymptomatic elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), and alkaline phosphatase (AP) (Figure 1). HBV infection and CMV reactivation, as common causes of liver disease, were ruled out by PCR. Liver biopsy evidenced dense lobular inflammatory infiltrate composed mainly of neutrophils, and mixed minimal inflammatory infiltrate portal, ruling out rejection and hepatotoxicity (Figure 2A). Liver enzymes diminished spontaneously, but did not achieve normal values. In March 2016, a recurrent elevation was observed, and steroid therapy was reinitiated (prednisone 10 mg/day) with no response (Figure 1). A new liver biopsy showed expanded portal tracts with inflammatory infiltrate composed of lymphocytes, plasma cells, and neutrophils. Minimum bile duct damage with leukocyte permeation and piecemeal necrosis was noted. At the lobule, a mixed inflammatory infiltrate and endothelialitis compatible with acute rejection of low entity was found. A pulse of steroids was performed (methylprednisolone 2 g, followed by prednisone 20 mg/day) with a subsequent reintroduction of MMF (500 mg 2×/day). During the next 3 months the patient exhibited oscillation of enzymes levels, and a new liver biopsy showed portal infiltrate composed mainly of lymphocytes with piecemeal necrosis (Figure 2B). Pursuing viral etiologies as causative of the biochemical and histological features, additional PCR tests for HBV, Hepatitis C virus (HCV), and CMV were performed, with negative results. Herpes Simplex virus was also rule out by PCR. PCR for EBV showed a weak positive result, with a viral DNA copy number of 75 copies/mL (24 UI/mL) (slightly higher than

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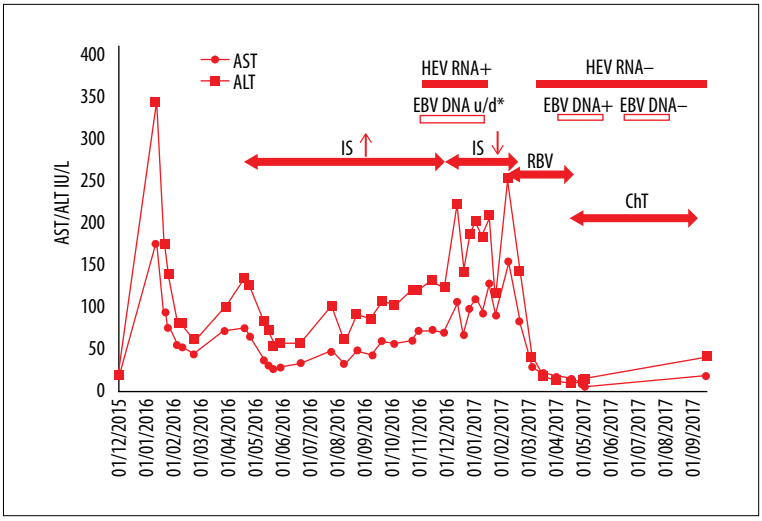
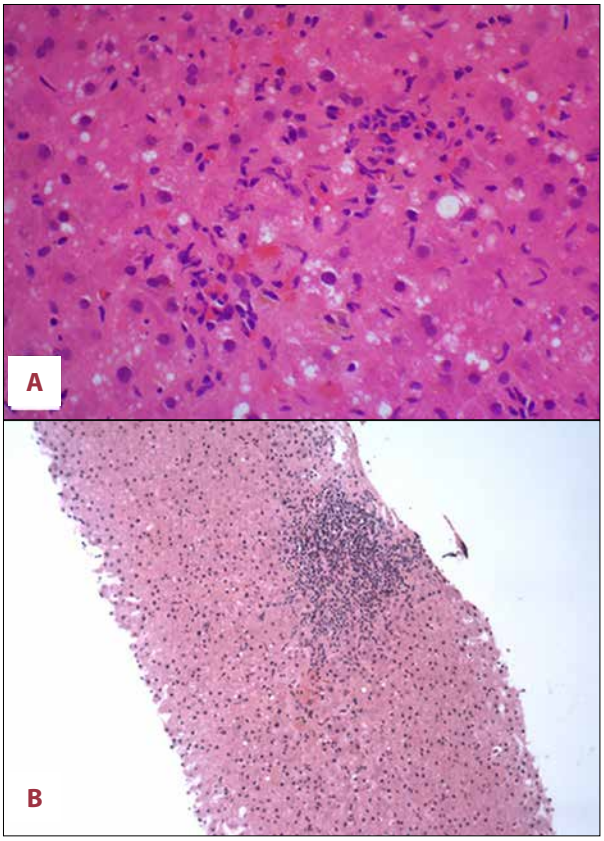


Figure 1. Paraclinical data and therapeutic interventions in the 21-month follow-up of the 62-year-old LT patient. Oscillation of liver enzymes levels are graphed. Hepatitis E Virus (HEV) and Epstein-Barr (EBV) PCR results are shown. Periods of increasing and decreasing immunosuppression (IS) are indicated. RBV – ribavirin therapy; ChT – chemotherapy; AST – aspartate aminotransferase; ALT – alanine aminotransferase; RNA – ribonucleic acid; * u/d – undetectable (DNA copies/mL slightly higher than the cut-off value). See text for detailed information.



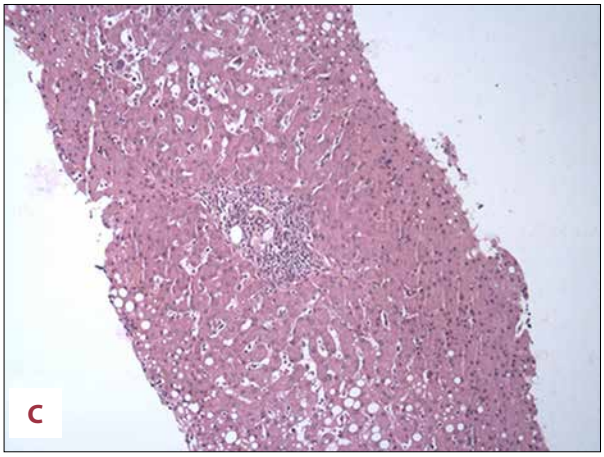


Figure 2. Histologic changes in the liver biopsies from the 62-year-old LT patient. Main histological findings observed throughout the study are shown. Hematoxylin-eosin stain. (**A**) Lobular inflammatory infiltrate composed mainly of neutrophils, compatible with acute hepatitis, observed at 1 year and 6 months after LT (original magnification 40×). (**B**) Dense portal inflammatory infiltrate composed mainly of lymphocytes with piecemeal necrosis, compatible with chronic hepatitis observed concomitantly with the detection of HEV RNA (10×). (**C**) Sinusoidal dilatation with megakaryocytes compatible with extramedullary hematopoiesis (20×).

the cut-off value, according to manufacturer`s product datasheet) (LightCycler® EBV Quantitative Kit, Roche, Switzerland). The classical form of EBV, infectious mononucleosis, is frequently associated (in almost half of the patients) with hepatitis and transient liver enzyme elevations. Serological testing for HEV showed specific IgG and IgM antibodies (recomWell HEV IgG/IgM, Mikrogen, Germany), and HEV RNA was detected by reverse transcription – nested PCR (RTnPCR) of a 287-bp region within the viral ORF2 in serum and stool samples [10]. Real-time PCR assay showed the HEV viral load in serum was 8×10^5 RNA copies/mL [10]. Sequencing and phylogenetic analysis clustered the isolate within HEV-3, very closely related to swine and human strains from Uruguay (Figure 3). Consequently, an attempt to reduce immunosuppressive therapy was undertaken, with diminished doses of tacrolimus (0.5 mg 2×/day) and suspension of steroids. The MMF dose was maintained. From then on, oscillation of the level of liver enzymes was observed, with a sharp peak in January 2017. A new liver biopsy ruled out acute

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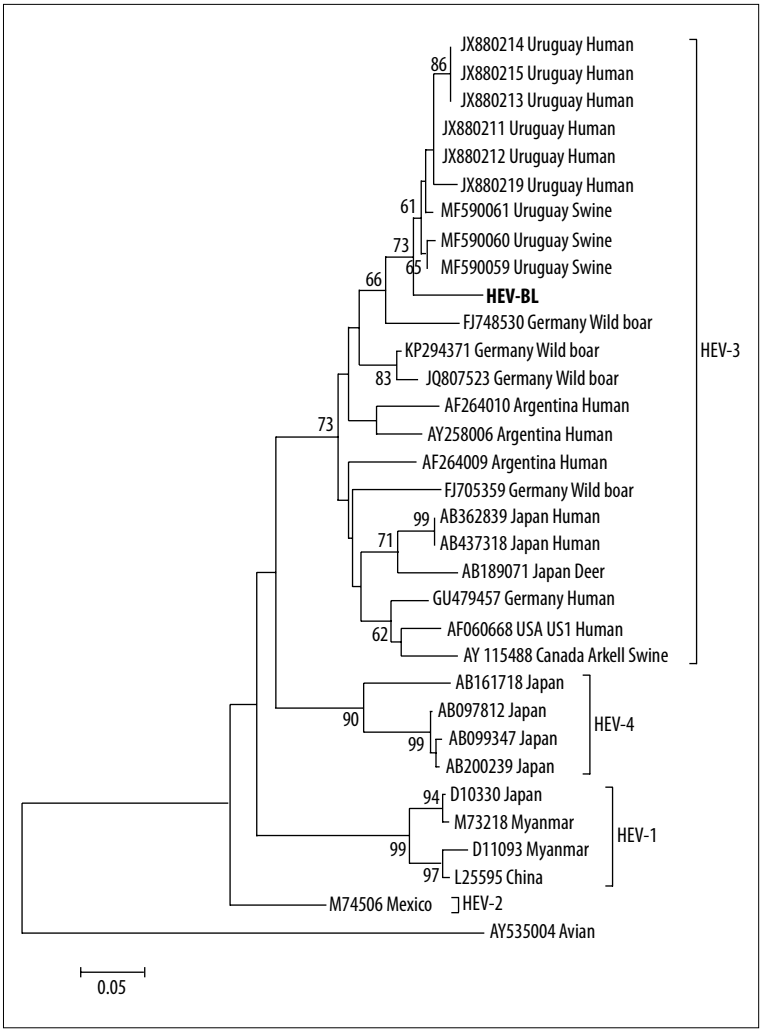

Figure 3. Phylogenetic tree based on the partial 287-nt region within the ORF1. The tree was generated using the neighbor-joining algorithm, using Tamura-Nei as the best substitution model as tested by ModelTest v3.7 tool. The robustness of the trees was determined by bootstrap for 1000 replicates. Only values ≥60% are shown. HEV-3 strain isolated form the patient, named HEV-BL (GenBank accession number MG182431) is shown in bold.

rejection, while it maintained characteristics of hepatic lesion consistent with hepatitis E (Figure 2B). In February 2017, based on an altered liver enzymogram (Figure 1), HEV viremia, and histologic evidence of HEV infection, chronic hepatitis E was suspected as per definition [11], and treatment with ribavirin (1200 mg/day) was initiated (the patient weighed 102 pounds). After 1 week of treatment, a decrease in liver enzymes levels was detected, reaching normal levels after 3 weeks (Figure 1). Four weeks after the initiation of ribavirin treatment, HEV RNA was undetectable in serum. Unfortunately, no fecal specimen was available for testing HEV shedding in stool. Shortly thereafter, the patient presented fever and rhinorrhea, so a course of antibiotic (amoxicillin-clavulanic 500–125 mg 3×/day for 10 days) was indicated. As he remained febrile, a sinus facial, thorax, and abdominal scan was performed, which showed images compatible with microabscess in the liver (data not shown). Liver enzymes, on the other hand, were constantly normal, and as HEV remained undetectable and hemoglobin level diminished progressively, ribavirin was suspended after 9 weeks of treatment. A subsequent liver biopsy showed sinusoidal dilatation with megakaryocytes, compatible with extramedullary hematopoiesis (Figure 2C). Myelogram and cytogenetic analysis (data not shown) confirmed acute lymphoblastic leukemia L3/Burkitt. PCR for EBV was positive, with a viral load of $1\times10^{4.66}$ DNA copies/mL (45 800 UI/mL) and intravenous ganciclovir therapy was initiated. The patient received 8 courses of chemotherapy based on rituximab, hyper-CVAD (hyper-fractionated-cyclophosphamide, sodium mercaptoethanesulfonate, vincristine, doxorubicin, and dexamethasone), methotrexate and Ara-C for treatment of leukemia, with a complete recovery. Clearance of EBV was also found. Throughout the 24-week follow-up after ending ribavirin therapy, liver enzyme levels remained normal and the patient had a sustained virologic response (SVR) with undetectable levels of HEV RNA in serum and stool samples (Figure 1).

Discussion

Zoonotic transmission of HEV-3 and HEV-4 from swine has been proven [1,2]. Phylogenetic analyses strongly suggest that this

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is the most likely route of infection in humans in non-endemic areas and high-income countries [2,4].

In immunocompetent individuals, HEV infection is commonly asymptomatic, but in patients with underlying chronic liver disease, acute fulminant hepatitis can occur. Furthermore, HEV-3 infection may lead to chronic infection in immunocompromised patients, such as solid organ transplant recipients under immunosuppressive therapy. Additionally, several extrahepatic manifestations have been associated with both acute and chronic hepatitis E [8]. Clinical diagnosis of chronic hepatitis E infection is challenging. Such infections are largely asymptomatic and can be misdiagnosed as drug-induced liver injury or rejection, since histological appearance on liver biopsy may not clearly distinguish lesions associated with viral replication.

Chronic hepatitis E has been reported in patients with several hematological disorders, which is attributable to their diminished immune response [12,13]. Persistent infection with HEV has been also diagnosed concomitantly with the onset or even before the development of several different types of hematologic malignancies [14,15]. However, despite several published case reports, convincing data on the association between HEV and such extrahepatic manifestations of the disease is lacking [16].

At 18 and 20 months after LT, our patient showed 2 marked unexplained liver enzyme peaks. No histological evidences of acute rejection or hepatotoxicity were observed in the first biopsy, and retrospectively it showed elements compatible with acute hepatitis E. HEV infection was diagnosed by serological testing and by nucleic acid techniques (NATs), and viral RNA could be steadily detected in the patient during at least 3 months (November to February 2016). Surprisingly, HEV clearance was successfully achieved after only 9 weeks of ribavirin therapy, when severe anemia caused treatment suspension. However, previous studies suggest that complete clearance of HEV can be accomplished with at least a 3-month course of ribavirin [14]. A shorter therapy also eliminated the virus, thus reducing the risk of liver fibrosis and cirrhosis. In addition, it reduces the probability of emergence of ribavirin-resistant mutants, which might hinder the achievement of SVR in patients [17]. Viral clearance was accompanied by a sharp reduction and subsequent normalization of liver enzymes levels, which strongly suggested that HEV was playing a crucial role in the development of the liver disease. On the other hand, HEV RNA levels stayed undetectable in serum and stool during the 24-week follow-up after therapy.

During ribavirin treatment, a liver biopsy provided evidence of a lymphoproliferative disorder. Myelogram and cytogenetic results were compatible with Burkitt's lymphoblastic leukemia. The rapid progression of the disease observed in this case was also suggestive of this type of lymphoma, which is etiologically linked to EBV [18]. Although EBV DNA levels were almost undetectable a few months before the development of the hematologic malignancy, at the time of the diagnosis, the patient showed a strong reactivation of EBV infection, as shown by real-time PCR. EBV serological status donor/receptor +/– is a major risk factor for development of PTLD, since this virus has a primordial pathogenic role in these syndromes. Nevertheless, the risk is thought to be higher in the first year after transplant, when T cell function is most suppressed. Interestingly a link between hepatitis E and reactivation of EBV in an immunosuppressed patient with rheumatoid arthritis has been previously documented. In Schultze et al. [19], both viral infections presented together and resolved after suspension of immunosuppression therapy. Conversely, in the present case, the reactivation of Epstein-Barr (EBV) infection occurred after chronic hepatitis E, under ribavirin treatment, and, most importantly, under minimal immunosuppressive therapy. However, EBV did not reactivate when the patient was most immunosuppressed and without antiviral therapy. Alternatively, a superinfection, instead of reactivation, could explain the EBV viremia at that time, suggesting that ribavirin is probably ineffective for the treatment of EBV infection. Finally, after antiviral treatment of EBV infection and following chemotherapy, the patient had a complete recovery with no sequelae.

The detailed analysis of the case presented here demonstrates the difficulty of suspecting and diagnosing HEV infection in transplanted patients and immunocompromised individuals, and the need to include this agent in the differential diagnosis in cases of unexplained elevation of liver enzymes levels. However, the results of the biopsies clearly reinforce the importance of histological documentation of clinical conditions of uncertain significance, in this case, a PTLD.

To the best of our knowledge, this is the first published case of chronic autochthonous hepatitis E in a transplanted patient followed by a strong reactivation of EBV infection and subsequent development of a PTLD. The potential role of HEV infection in this scenario needs to be further investigated in light of the recent findings of the UK Clinical Practice Research Datalink (CPRD). In that report, extensive data analysis associated infectious hepatitis with elevated risk of Burkitt lymphoma among those 60+ years old [20]. In general, the causative relationship between HEV infection and hematological disorders is difficult to establish, and less severe cases have remained unnoticed and underreported [21]. Particularly, in this patient, whether HEV infection could have contributed to the progression of PTLD through reactivation of EBV infection remains to be elucidated, and our results should thus be cautiously interpreted. Alternatively, the effect of long-term immunosuppression is a plausible explanation for the development and progression of the malignancy.

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Molecular analysis showed that the HEV strain detected in our patient was closely related to previously documented human and swine isolates from Uruguay [10]. Furthermore, the patient, who had never traveled to endemic areas, and did not report travels outside of the country in the last 3 months, reported frequent consumption of undercooked pork, suggesting an autochthonous zoonotic route for HEV infection in this case.

Conclusions

The differential diagnosis of persistently elevated transaminases in transplanted and/or immunocompromised patients should include testing for HEV by use of appropriate NATs. Cases of HEV infection with atypical clinical outcome, such as the one presented herein, highlights the need for increased awareness of chronic hepatitis E and its association with a wide range of extrahepatic manifestations.

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Conflict of interests

None.

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