Chronic hepatitis E virus infection in a cirrhotic patient

A case report

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Abstract

Rationale: Acute hepatitis E virus (HEV) infections are usually self-limiting in immunocompetent patients. HEV persistence has been described only in immunosuppressed patients such as solid-organ transplant recipients, patients with hematological diseases, or patients with human immunodeficiency virus (HIV) infection.

Patient concerns: A 61-year-old patient was admitted in hospital for jaundice and asthenia.

Diagnoses: The patient had underlying cirrhosis and developed a chronic HEV infection.

Intervention: Ribavirin therapy was initiated.

Outcomes: Ribavirin therapy for 12 months allowed the clearance of the virus and HEV viral load remained undetectable thereafter.

Lessons: Other studies are now needed to identify the population with a chronic evolution of HEV infection despite no apparent immunodepression.

Keywords: chronic infection, cirrhosis, hepatitis E virus

1. Introduction

Hepatitis E virus (HEV) has 4 major genotypes that infect humans worldwide. Genotype 3 is frequently found in industrialized countries and is zoonotically transmitted. Acute HEV infections are generally asymptomatic and spontaneously resolve in immunocompetent (IC) patients.[1] Liver failure associated with HEV infections can occur in patients with underlying liver disease. Chronic HEV genotype 3 infections, in which a detectable virus load persists for >3 months,[2] can occur in immunocompromised such as solid-organ transplant (SOT) recipients.[3] Those with hematological diseases,[1] or human immunodeficiency virus (HIV) infections whose CD4+ T cell count is below 200 mm−3.[4] Untreated chronic hepatitis can rapidly lead to liver fibrosis and cirrhosis.[1] The immunological factors implicated in virus clearance are still poorly understood but the cellular response appears essential for HEV eradication. Several studies have shown that SOT patients chronically infected with genotype 3 have poorer anti-HEV immune responses than patients with a resolved infection.[5,6] Recent data indicate that ribavirin therapy efficiently cures 78% of chronically infected SOT patients.[7] This report describes the case of a cirrhotic patient suffering from an acute HEV infection that evolved toward chronicity. We examined the patient’s specific anti-HEV immune response by quantifying his specific interferon-γ (IFN-γ) producing T cells.

2. Methods

2.1. Patients

We collected peripheral blood mononuclear cells (PBMC) from this cirrhotic patient 5 months after virus clearance by ribavirin therapy. Because he did not belong to a population known to
suffer from chronic HEV infection, we investigated not only his specific anti-HEV immune responses, but also those of other HEV-infected patients. We also studied PBMC samples collected at the acute phase of infection from 21 patients: 7 IC patients (median age: 64), 3 SOT patients who spontaneously cleared the virus (median age: 43), and 9 SOT patients who evolved toward a chronic infection previously described[61] (median age: 43). The study was approved by the institutional review board at Toulouse University hospital and all patients gave their written consent.

2.2. ELISpot assay
Specific anti-HEV responses were analyzed by enzyme-linked immunospot (ELISpot) and IFN-γ producing cells were quantified after antigen stimulation in vitro as previously described.[66] Briefly, PBMC samples were incubated with a pool of 76 HEV genotype 3 (Genbank accession number EU495148) open reading frame-2/3 peptides (15-mers, 5 amino-acid overlaps, Genscript, Piscataway, NJ) or with anti-CD3 and anti-CD28 antibodies (clones HT3a and 28.2, respectively, BD Biosciences, 0.5 μg/mL each) at 37°C for 36 hours (duplicates wells, final volume 60μL). The IFN-γ ELISpot assays were performed following manufacturer protocol (Diaclone kit); average number of IFN-γ producing cells for duplicate wells were calculated. Anti-HEV and anti-CD3/CD28 IFN-γ responses were calculated after subtracting nonspecific responses from background wells. The Mann-Whitney U test was used for statistical analysis, calculations were performed using GraphPad Prism software.

3. Case report
A 61-year-old man was hospitalized on July 21, 2012 for jaundice and asthenia. He was suffering from obesity (body mass index = 30), type 2 diabetes, hypercholesteremia, and a stable stented ischemic cardiopathy. He was treated with acetylsalicylic acid, clopidogrel, enalapril, metformin, insulin, pravastatin, rabeprazole, and celiprolol. He did not report any alcohol consumption or travel. Blood analysis showed elevated alanine aminotransferase, HEV RNA (HEV RNA) in a chronically infected cirrhotic patient treated with ribavirin. ALAT = alanine aminotransferase, HEV = hepatitis E virus, RNA = ribonucleic acid.

Figure 1. Trend of liver transaminases (ALAT) and hepatitis E virus viremia (HEV RNA) in a chronically infected cirrhotic patient treated with ribavirin. ALAT = alanine aminotransferase, HEV = hepatitis E virus, RNA = ribonucleic acid.

4. Discussion
The key feature of this unusual case of chronic HEV infection is that he had a low IFN-γ specific response to HEV peptides. Nevertheless, his overall T cells responses were apparently functional as anti-CD3/CD28 stimulation was marked by a robust IFN-γ response. The response of this patient was close to that of SOT patients who evolved toward a chronic hepatitis E. We identified no indication of immunosuppression other than a mild lymphopenia in our patient. HEV can evolve toward a chronic infection (mean: 9.9 sfc/10⁶ cells, Fig. 2B). It was lower than that of acutely HEV-infected IC patients (mean: 149.6 sfc/10⁶ cells) or SOT patients who spontaneously cleared the virus (mean: 54.2 sfc/10⁶ cells; Fig. 2B). Thus, this patient’s chronic HEV infection may be linked to an altered specific IFN-γ T cells response.

[8] Because of the absence of patient’s...
blood sample before ribavirin treatment, we were unable to assess if he was transiently immunosuppressed when acute HEV infection occurred. Similar chronic HEV infections are rarely reported in the literature. An HIV-negative patient, who was not given any immunosuppressive therapy, was found to have an undefined CD4+ T-cell defect associated with a chronic HEV infection[9] and a study described a cohort of chronic genotype 4 HEV infection in assumed IC patients[10] but no cell count data were provided. Grewal et al described the case of an IC patient suffering from chronic hepatitis E. He had a history of autoimmune disease and had previously been given immunosuppressive therapy (he had been treated with hydroxychloroquine and steroids nearly 40 years before the hepatitis episode).[11] An undiagnosed immune defect or lymphopenia could also be linked to the chronic evolution in our cirrhotic patient or it could be a diabetes-associated immune dysfunction. This patient probably had underlying NASH cirrhosis although no liver biopsy was performed. The patient cleared the virus with an increased dosage of 800mg ribavirin; absence of response under 600mg could be explained by a lack of observance or by a subtherapeutic dosage.

Previous in vitro studies on chronic and resolving SOT patients explained by a lack of observance or by a subtherapeutic dosage. The patient cleared the virus with an increased dosage and may also be critical for HEV clearance. Although for the present patient, we have investigated the patient T-cell specific response 5 months after virus clearance, in the other groups of patients tested (IC and SOT), the specific responses were measured during the acute phase. However, Brown et al showed that IC. HEV-exposed patients had IFN-γ responses still detectable 12 months after the acute phase of infection.[12] In the present case, ribavirin was initiated because he was unable to clear the virus. Ribavirin therapy is now recommended for immunocompromised patients to cure chronic infections.[3] In HEV-infected IC patients, ribavirin could be proposed in specific cases such as patients with severe extrahepatic manifestations[13] or who are unable to spontaneously clear the infection. Other studies are now needed to identify those patients that may evolve toward a chronic infection despite no apparent immunodepression.

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