A Case of Hepatitis E Persistence in a Patient With Myelofibrosis Under Ruxolitinib

Maria Ribeiro da Cunha, MD1, and Tiago Marques, MD1

1Department of Infectious Diseases, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

ABSTRACT

Hepatitis E virus (HEV) is a mostly enterically transmitted agent of viral, usually acute hepatitis. In recent years, however, it has been proven to establish chronicity in immunosuppressed patients. We report the first case of HEV infection in a patient with myelofibrosis under ruxolitinib, a tyrosine kinase inhibitor. Although this patient was able to mount a humoral response with specific immunoglobulin G, viral replication could not be controlled until ruxolitinib suspension. After normalization of liver enzymes and clearance of HEV, ruxolitinib was reintroduced with no disease relapse, suggesting spontaneous eradication of the virus.

INTRODUCTION

Hepatitis E virus (HEV), the sole member of family Hepeviridae, was first identified as an etiological agent of epidemic of non-A, non-B hepatitis in Kashmir, India, in 1978. It is usually enterically transmitted, although vertical and transfusion-related acquisition have been reported. Most infections are asymptomatic. However, HEV may cause acute hepatitis, which can be particularly severe during pregnancy and in those with underlying liver cirrhosis. A chronic form of HEV infection, characterized by a detectable viral load after 3–6 months from the time of HEV diagnosis, was recently identified in immunosuppressed individuals such as transplant recipients, persons infected with human immunodeficiency virus (HIV), and patients with hematological diseases. Chronic infection usually manifests as mild elevation in liver enzymes without clinical signs of overt hepatitis. Clinical progression afterward is varied, ranging from spontaneous clearance to rapid progression to cirrhosis. Many classical immunosuppressive drugs have been implicated in the establishment of hepatitis E chronicity; however, newer immunosuppressors, including monoclonal antibodies, cytokine inhibitors, and other specific signal-pathway inhibitors, are being investigated as potential risk factors. We describe the first case of HEV infection in a patient with myelofibrosis who was being treated with ruxolitinib, a tyrosine kinase inhibitor; despite developing specific immunoglobulin (Ig)G, the patient displayed continued viral replication until the suspension of ruxolitinib. This report aims to raise awareness of hepatitis E infection and its potentially atypical presentation in patients medicated with signal-pathway inhibitors.

CASE REPORT

We present the case of a 66-year-old man with a history of myelofibrosis, medicated with ruxolitinib and darbepoetin, and allopurinol since 2016, with good disease control. In July 2019, he reported to a hematology appointment, complaining of occasional night sweats, nausea, and general malaise, which had worsened in the previous week. Blood work revealed a de novo rise in liver enzymes (aspartate transaminase 366 U/L; alanine aminotransferase 680 U/L) and cholestasis parameters (gamma-glutamyl transferase 229 U/L; total bilirubin 3.28 mg/dL). There was also a decrease in fibrinogen (160 mg/dL), with normal prothrombin and activated thrombin times, as well as negative D-dimers, which was attributed to liver damage. He had last been consulted in March 2019; at the time, routine blood work was unremarkable. An abdominal ultrasound revealed no abnormalities other than a previously known splenomegaly. HIV, as well as hepatitis A, B, and C infections, was excluded. He admitted to taking occasional paracetamol and ibuprofen 3 weeks earlier, but denied any other new medications, as well as any alcohol drinking habits.
On further investigation, the patient revealed he had visited Brazil between the months of March and April of 2019. He could recall no illness during his stay and did not remember eating undercooked pork or wild game. Further serological tests were ordered, and the patient was found to be HEV IgM and IgG positive, with Epstein-Barr virus and Cytomegalovirus past immunity. HEV viral load was 1,920,000 UI/mL (Log10 6.28). No stool samples were analyzed.

To prevent further liver damage and progression to chronic hepatitis, it was decided to completely wean off ruxolitinib. Over the next 4 weeks, the patient’s liver parameters and fibrinogen gradually returned to normal. On September 9, 2019, HEV viral load was below detection level, and ruxolitinib was reinstated. HEV viral load remained undetectable 6 months later.

DISCUSSION

Recent years have seen an explosion in the number and clinical applications of monoclonal antibodies, target-specific cytokine, and cellular pathway inhibitors. However, despite their efficacy, the full consequences of their immunomodulating effects are still being investigated. The impact of Janus kinase inhibitors such as ruxolitinib in immune system function has not yet been completely understood. However, these drugs have been found to affect both innate and adaptive immunity, through the reduction in circulating natural killer and dendritic cells, as well as downregulation of secretion of inflammatory cytokines by CD4+ cells, among other effects. The overall impact of ruxolitinib on infection control has been controversial; although infection risk was initially considered to be low, more recent systematic reviews and meta-analysis have found a statistically significant increased risk of infections such as herpes zoster, bronchitis, and urinary tract infections. Furthermore, there have been several case reports of opportunistic and non-opportunistic infections in patients treated with ruxolitinib in clinical trials and postmarketing.

In this context, it seems plausible that HEV infection may undergo a more atypical and protracted course as the immune system struggles to control viral replication. Studies in transplant patients and persons with HIV suggest that T-cell inhibition seems to be a key factor in progression to chronic HEV infection; in fact, decreasing the doses of immunosuppressive drugs that are aimed at T cells (mainly calcineurin inhibitors) leads to spontaneous HEV clearance in 30% of transplant recipients and is considered the first-line therapeutic approach. Interestingly, not all immunosuppressors have the same effect on HEV-directed immunity because mycophenolate mofetil appears to suppress viral replication and may be considered as an alternative in specific cases. Innate immunity also seems to play an essential part in viral control through the production of cytokines and chemokines such as antiviral interferons. When withdrawal or switching of immunosuppressive medication is not achievable, pegylated interferon-alpha and antivirals such as ribavirin have been used to various degrees of success; although ribavirin is efficacious in controlling viral load, it is often accompanied by severe side effects.

In the case presented above, considering the evidence of continued viral replication despite the development of an antibody-specific response, it was decided to withhold treatment with ruxolitinib. Spontaneous viral clearance thereafter seems to indicate that myelofibrosis does not represent per se a risk factor for impaired immunity against HEV. This case report aims to raise awareness of HEV infection in patients treated with immunomodulating drugs, particularly in nonendemic countries, where the diagnostic delay or misinterpretation as drug-related hepatotoxicity may potentially culminate in chronic HEV infection and cirrhosis. Moreover, reports of HEV manifestations in these patients may provide clues to the mechanisms involved in pathogenesis and immune protection from similar agents.

DISCLOSURES

Author contributions: M. Ribeiro da Cunha wrote the manuscript and is the article guarantor. T. Marques edited the manuscript and approved the final manuscript.

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