Chronic Hepatitis E Virus Infection: A Red Flag for Undiagnosed Hematological Malignancy?

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Abstract

Hepatitis E virus (HEV) is known to be able to establish chronic infection in a subset of patients who are immunosuppressed. We present a case of a patient who was initially diagnosed with a chronic HEV infection which subsequently revealed a hematological malignancy. We believe this to be the first case in which the finding of chronic HEV infection has led directly to the finding of an underlying cause of immune compromise. A 66-year-old female of Northern European origin presented to gastroenterology with right upper quadrant pain and weight loss. The cause was initially unclear despite investigations. The following year she was diagnosed with chronic HEV infection. As chronic HEV is not recognized in patients without underlying immune compromise, she was thoroughly investigated for a cause and was found to have extra-nodal marginal zone lymphoma of mucosa-associated lymphoid tissue type. HEV was successfully eradicated using ribavirin. Combination chemotherapy was given for lymphoma and she made a good recovery, with resolution of her previous gastrointestinal symptoms. This reinforces the understanding that chronic HEV infection does not occur in immunocompetent patients and that a finding of chronic HEV infection in a patient without a pre-existing reason for immune compromise should be followed with a thorough search for the underlying cause.

Keywords: Hepatitis E virus; Hematological malignancy; MALT; Ribavirin

Introduction

It is recognized that hepatitis E virus (HEV) can establish chronic infection in a subset of patients who are immunosuppressed. These include patients with a solid organ transplant, bone marrow transplant, human immunodeficiency virus (HIV) and chronic hematological malignancies [1]. The treatment of such patients is reported in case series as well as in the European Association for the Study of Liver (EASL) clinical practice guideline [2]. We present the first case of a patient who was initially diagnosed with chronic HEV infection which subsequently revealed a hematological malignancy.

Case Report

A 66-year-old Northern European female was referred to the gastroenterology unit with right upper quadrant pain and weight loss. She had been diagnosed with Guillain-Barre syndrome previously. Her fecal calprotectin was 75 µg/g. A magnetic resonance imaging (MRI) of the small bowel was reported as normal and a duodenal biopsy was performed which was consistent with an enteropathy. An anti-tissue transglutaminase (anti-tTG) level was 9 U/mL but anti-endomysial antibodies and HLA-DQ2/DQ8 genotyping were negative, thus excluding celiac disease as a diagnosis. She showed no improvement in her symptoms with gluten exclusion or a trial of budesonide.

The next year, in December 2016, she was diagnosed with HEV genotype 3 infection following a liver screen undertaken because of a raised alanine aminotransferase (ALT) which was between 55 and 61 U/L (5 - 40 U/L) (Fig. 1). The patient was found to have persistent positive serum HEV RNA PCR in March 2017, 3 months after the initial positive serum sample, and a positive stool HEV RNA PCR in May 2017 (Fig. 2).

With the demonstration of evidence of continuing infection after 5 months and with 6 months of persistently abnormal liver function tests, she was commenced on treatment. She received treatment with ribavirin 400 mg twice daily which was dosed based on her weight. She did not experience any side effects from the treatment, importantly anemia and/or hyperuricemia, which can be significant adverse effects with riba-

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doi: https://doi.org/10.14740/cii108
She underwent fortnightly blood monitoring, which comprised of a full blood count, liver blood tests, urea, creatinine and electrolytes and uric acid. She also provided a monthly serum and stool sample which were tested for HEV RNA PCR. Two negative serum and stool samples taken 4 weeks apart were used to determine the end point of therapy. This was achieved after a 12-week course. Her ALT decreased back to normal over the course of the treatment. She has had a serum and stool sample checked for HEV RNA PCR 3 and 6 months after the end of treatment, all of which have been negative.

Chronic HEV infection is not recognized in healthy patients without immunocompromise or a hematological malignancy [1]. This prompted a search for an underlying cause in this lady. The patient had no previous signs of immune altera-

**Figure 1.** Change in ALT over time, relative to treatment course. ALT: alanine aminotransferase.

**Figure 2.** Change in HEV viral load in blood and stool over time. HEV: hepatitis E virus.
tion, particularly no previous recurrent or atypical infections. Her immunoglobulins were normal and she had no leukopenia, lymphopenia or neutropenia.

Further investigations were pursued based on ongoing symptoms of weight loss and the previous finding of enteropathy. A capsule endoscopy revealed loss of villi and scalloping of the mucosa of the proximal small bowel and a subsequent computed tomography (CT) (Fig. 3) shows diffusely abnormal small bowel with loco-regional adenopathy. She underwent a push enteroscopy, biopsy samples from which led to a diagnosis of extra-nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type. *Helicobacter pylori*, which can be associated with MALT lymphoma, was negative on both antibody and urease test. She entered a period of observation for her lymphoma and was commenced on combination chemotherapy due to persistent upper gastrointestinal symptoms, with a good response. She is currently maintained on rituximab monotherapy to maintain remission.

**Discussion**

We believe this to be the first reported case in which chronic HEV infection has been diagnosed in a patient prior to the recognition of a cause of immunocompromise. It is the first case in which the finding of chronic HEV infection has led to the finding of a hematological malignancy.

HEV had previously been considered to cause an acute and self-limiting infection but is now known to establish chronic infection in patients with immunocompromise and can cause progression to liver cirrhosis as well as a number of extra-hepatic manifestations. This patient’s serum was retrospectively tested and was negative for HEV RNA PCR at the time of her Guillain-Barre syndrome. Multiple cases of chronic HEV infection have been recognized in patients with hematological malignancies, particularly in those receiving chemotherapy [4], but these have all been in patients with established hematological diagnoses.

HEV infection is increasingly tested for as part of a non-invasive liver screen in the UK. It is important to recognize that a repeated finding of positive HEV RNA PCR in a patient may be representative of chronic HEV infection. Follow-up with monitoring of liver enzymes and HEV RNA PCR in stool and serum should be undertaken until the patient is proven to have cleared the infection.

**Conclusion**

In conclusion, this case reinforces the understanding that chronic HEV infection does not tend to occur in immunocompetent patients [5] and that a finding of chronic HEV infection in a patient without a pre-existing reason for immunocompromise should be followed with a thorough search for the underlying cause. This may include investigating for hematological malignancy, inherited or acquired immune deficiency and HIV.

**Acknowledgments**

The authors acknowledged Gastroenterology and Hepatology Department, North Bristol NHS Trust, and Haematology Department, North Bristol NHS Trust.

**Financial Disclosure**

None to declare.

**Conflict of Interest**

None to report for any author.

**Informed Consent**

The patient has reviewed the written case report and has provided written informed consent for her case and images to be published.

**Author Contributions**

CN: literature review, review of patient case notes, primary author of case report, compiled graphs. SP: reporting consultant radiologist during case, advised on selection of radiological images for case. RP: consultant gastroenterologist involved in management of patient, provided review of written case report. TV: consultant hepatologist involved in management of patient, identified usefulness of case for case report, provided extensive review and advice on written case report.
Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

References