

# A case of hepatitis E that developed during chemotherapy for malignant lymphoma and responded to ribavirin

Seiya Hashimoto<sup>1</sup>, Hirofumi Fukuda<sup>1</sup>, Kohei Takeda<sup>1</sup>, Keiichi Uchida<sup>1</sup>, Fumiaki Sanuki<sup>1</sup>, Takashi Akiyama<sup>1</sup>, Eisei Kondo<sup>1</sup>, and Hideho Wada<sup>1</sup>

<sup>1</sup>Kawasaki Ika Daigaku

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## Abstract

The main differentials in cases of sudden elevation of hepatic enzyme levels during immunochemotherapy are reactivation of hepatitis B virus or drug-induced liver injury. Here, we report a case of acute liver injury caused by hepatitis E virus (HEV) during chemotherapy for malignant lymphoma, wherein the patient was successfully treated and completed chemotherapy. A 57-year-old woman visited her local doctor because she felt light and tired. The patient underwent lower gastrointestinal endoscopy and was diagnosed with a malignant lymphoma of the small intestine (diffuse large B-cell lymphoma). The patient had a history of oral consumption of undercooked pork liver to improve anemia and was diagnosed with acute hepatitis E. Since the patient responded to chemotherapy, she was treated with single-agent ribavirin while continuing chemotherapy, resulting in a sustained virological response. Even during treatment with immunosuppressive drugs, if appropriate treatment for hepatitis E can be administered, the patient can be fully treated without interruption. The patient was able to complete chemotherapy adequately without interruption of treatment, which was a clinically beneficial result.

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*Department of Hematology, Kawasaki Medical School, Kurashiki, Japan*

*Department of Pathology, Kawasaki Medical School, Kurashiki, Japan*

\*Corresponding author E-mail address: fukuda7@med.kawasaki-m.ac.jp (H. Fukuda).

## Novelty Statement

In this paper, Hepatitis E that developed while on immunosuppressive therapy could be safely treated with ribavirin and continued chemotherapy. This study provides clinicians with new information and suggestions for improving the clinical outcome of patients with HEV infection.

## Abstract

The main differentials in cases of sudden elevation of hepatic enzyme levels during immunochemotherapy are reactivation of hepatitis B virus or drug-induced liver injury. Here, we report a case of acute liver injury caused by hepatitis E virus (HEV) during chemotherapy for malignant lymphoma, wherein the patient was successfully treated and completed chemotherapy.

A 57-year-old woman visited her local doctor because she felt light and tired. The patient underwent lower gastrointestinal endoscopy and was diagnosed with a malignant lymphoma of the small intestine (diffuse large B-cell lymphoma). The patient had a history of oral consumption of undercooked pork liver to improve anemia and was diagnosed with acute hepatitis E. Since the patient responded to chemotherapy, she was treated with single-agent ribavirin while continuing chemotherapy, resulting in a sustained virological response.

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Keywords: Chemotherapy, Hepatitis E virus, Ribavirin

### Case report

A 57-year-old woman was diagnosed with malignant lymphoma in July 2000 after a positive stool occult blood test during a physical examination, and rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) chemotherapy was administered. During the two courses of chemotherapy, blood tests confirmed abnormal liver enzyme levels. The patient was asymptomatic, no new medications were started, and there was no significant medical history. Laboratory tests revealed no signs of chronic liver hepatitis. The results of liver function tests were as follows; aspartate aminotransferase, 395 (10-42 U/L), alanine aminotransferase, 235 (13-30 U/L), alkaline phosphatase, 169 (38-113 U/L), and total bilirubin, less than 0.2 (0.4-1.5<mg/dl). Hepatic synthetic function was normal. Ultrasonography of the liver was normal, and contrast-enhanced computed tomography (CT) revealed no organic abnormalities in the liver. Prior to referral to our hospital, the patient had been suffering from anemia due to gastrointestinal bleeding. She had received RBC transfusion at another hospital; it was therefore surmised that her symptoms may be due to a transfusion-transmitted infection. The patient was screened for hepatitis A, B, and C virus, human immunodeficiency virus, herpes virus, and cytomegalovirus. The results of all the screening tests were negative. In addition, although the patient was of an age at which autoimmune diseases are common, liver autoantibody test results were normal. Therefore, autoimmune diseases such as primary biliary cirrhosis and autoimmune hepatitis were ruled out. Since the patient had a history of eating undercooked pork, we considered the possibility of hepatitis E and measured HEV-RNA, which was positive at  $1.63 \times 10^2$  IU/mL. A liver biopsy was performed to confirm the diagnosis, which revealed inflammatory cell infiltration including lymphocytes and histiocytes mainly in zone 1, bile stagnation including the portal vein area, and coagulation necrosis including the appearance of eosinophils, consistent with the findings of hepatitis E. Several reports have reported the initiation dose of ribavirin for hepatitis E, with a dose adjusted on the basis of the estimated glomerular filtration rate or weight-adjusted dose (1)

The patient was started on ribavirin 400 mg with a weight-adjusted dose, and blood tests showed no apparent drug-related adverse events. After the start of treatment, the HEV-RNA became almost undetectable (Figure 1); therefore, R-CHOP therapy was resumed. Positron emission tomography/CT confirmed complete remission after six course of the chemotherapy (Figure 2).

### Discussion

Differential diagnosis in patient with elevated aminotransferase undergoing chemotherapy requires the consideration of various causes. The diagnosis of HEV infection is often difficult, especially because drug toxicity-related causes must be excluded, and symptoms vary considerably from patient to patient. In the present case, a detailed interview led us to conclude that the pigs were likely reservoirs.

Because of the great diversity in the immune status of patients undergoing chemotherapy, as in this case, serodiagnosis alone may not accurately detect HEV infections. Therefore, it should be performed that the HEV polymerase chain reaction simultaneously with HEV serodiagnosis if HEV infection is suspected in immunosuppressed patients under special conditions.

In general, treatment of acute HEV infection is often supportive; however, some patients may require dis-

continuation of immunosuppressive drugs or ribavirin treatment. This includes cases in which prednisolone is being administered, as in the present case (2).

Previous reports have shown that ribavirin used either alone or in combination with peginterferon has been effective in the treatment of chronic HEV in patients with hematologic diseases (3). However, there are no data on the recommended duration of these treatments, especially the use of ribavirin. It has been shown in the past that ribavirin therapy may be necessary for high-risk patients, such as those undergoing chemotherapy for gynecologic cancer (3, 4)

Several reports have shown that immunosuppressed patients are at a high risk of HEV infection, which may have serious clinical consequences owing to prolonged HEV autoprofitation. The patient was treated with anti-CD20 antibodies and cyclophosphamide for the hematologic tumor. The chronic course of HEV infection may have been precipitated by immunosuppression. The first step in the treatment of patients with chronic infections is the reduction or cessation of immunosuppressive drugs (5) In this case, the patient was started on ribavirin therapy after adjusting the dosage of chemotherapy drugs. The patient was able to safely complete the treatment, and complete remission was achieved.

In conclusion, patients with unexplained acute or chronic hepatitis during immunosuppression should be considered for possible HEV infection and should be tested for infection. In addition, patients receiving immunosuppressive therapy should be carefully monitored for a chronic course of HEV.

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## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## Conflicts of Interest

All authors declare no conflicts of interest.

## Author Contribution Statement

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## Ethics Approval Statement

N/A

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