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—【Case Report】— 症例報告 —

# Transfusion-associated hepatitis E in a patient with refractory malignant lymphoma

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We encountered a patient who received multiple transfusions during treatment for hematologic disease and was found to be infected with hepatitis E virus (HEV). Elevated concentrations of hepatobiliary enzyme led to the discovery of HEV infection during outpatient follow-up for Hodgkin's lymphoma. Viral hepatitis-related tests yielded positive results for anti-HEV immunoglobulin A antibody, despite negative results from stored samples collected before transfusion. We reported this case of suspected transfusion-associated HEV infection to the Japanese Red Cross Society. According to a survey by the Japanese Red Cross Society, HEV nucleotide sequences from the patient's post-transfusion specimen were identical to those of the corresponding stored donor specimen, confirming that HEV infection originated from the transfusion. His condition resolved rapidly and did not show a chronic course. While HEV is not included in infectious disease tests for blood donors, the frequency of HEV infection in transfusion recipients has increased in recent years. Indeed, we encountered another transfusion-associated hepatitis E case in the same period at our hospital. Our findings from these two cases suggest that medical institutions in the Hokkaido area, as well as the Kanto-Kohshinetsu area should be on alert regarding the high prevalence of HEV. Our findings also highlight the importance of pre-transfusion storage of patient specimens.

***Keywords:*** post-transfusion hepatitis, HEV, pre-transfusion specimen storage

## Introduction

The hepatitis E virus (HEV) causes hepatitis E, and has a mean incubation period of about six weeks[1)]. HEV is primarily transmitted via the fecal-oral route, which occurs by drinking contaminated water or consuming raw or undercooked meat such as the internal organs of pigs and wild animals. Given that viremia is present in the early stage of infection, transfusion-associated HEV infection is possible if a blood donor has a subclinical infection.

HEV is classified into at least four genotypes. Apart from cases of imported infection, genotypes 3 and 4 are detected in humans in Japan. HEV genotype 4 is reported to cause severe clinical manifestation[2)]. While most patients with this infection develop acute hepatitis, a recent report showed that patients who received an organ transplant developed chronic hepatitis after blood transfusion[3)].

Recently, we encountered a patient with transfusion-associated acute hepatitis E who received multiple transfusions during treatment for a hematologic disorder. Here, we report his clinical details. We also encountered another transfusion-associated hepatitis E in our hospital in the same period, which has been reported elsewhere[4)]. Here, we provide additional clinical information about this case, and discuss the underlying reason for the development of multiple transfusion-associated acute hepatitis E cases at the same hospital in the same period, and the importance of pre-transfusion storage of patient specimens.

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**Case report**

A 67-year-old man developed Hodgkin's lymphoma in August 201X-1. He showed resistance to doxorubicin, bleomycin vinblastine and dacarbazine (ABVD) therapy. He was then successfully treated with six courses of gemcitabine, dexthamethasone and cisplatin (GDP) therapy, from January to May, 201X. Shortly after the end of GDP therapy, he was diagnosed with liver disorder (AST 466 IU/*l*, ALT 337 IU/*l*, LDH 370 IU/*l*, γGTP 678 IU/*l*) and was subsequently admitted to our hospital for precise screening and treatment for acute hepatitis.

Transfusion records: He received a blood transfusion of 6 units (3 bags) of leucocytes reduced red blood cells, (RBC-LR) and 80 units (8 bags) of leucocytes reduced platelet concentrate, (PC-LR) between February and May, 201X.

Infection screening: Before transfusion, he was anti-hepatitis B surface (HBs) antibody positive, anti-hepatitis B core (HBc) antibody positive, and HBV DNA negative in January 201X. At admission, he was anti-HBc antibody positive, HBs antigen negative, HBV DNA negative, and anti-hepatitis C virus (HCV) antibody negative in June 201X. Additionally, he was, anti-HEV IgA antibody positive, despite the fact that his stored samples from before the transfusion in January 201X were negative.

Clinical course: He was treated with glycyrrhizin and ursodeoxycholic acid. After 15 days, he recovered and was discharged without any complications. Because he was HEV IgA antibody positive at admission and negative before transfusion, we reported this as a case of suspected transfusion-associated HEV infection to the Japanese Red Cross Society, in accordance with government regulations. A Japanese Red Cross Society survey, revealed that HEV RNA was detected in the stored specimen of 1 in 11 blood donors. All nucleotide sequences in open reading frame (ORF) 1, ORF2 and the proline-rich domain of ORF1 (V area) were consistent between the patient strain and blood donor strain, confirming that HEV had originated from transfusion. The strain was HEV genotype 3 and the concentration was $1.05\times10^5$ IU/*l*. The contaminated blood product was PC-LR. Assuming that the day the patient received PC-LR was day 0, he was HEV RNA, anti-HEV IgM antibody, and anti-HEV IgG antibody negative on day -22. He was admitted to our hospital on day 104. He was HEV RNA, anti-HEV IgM antibody, and anti-HEV IgG antibody positive on days 108 and 119. He was HEV RNA and anti-HEV IgM antibody negative and anti-HEV IgG antibody positive on day 141 (Fig. 1).

After recovery from acute hepatitis, the patient received brentuximab vedotin followed by nivolumab for resistant illness, but his liver function has not worsened.

Presently, he has been free from hepatitis E since his improvement. He was still positive for anti-HEV IgA two years after HEV infection.

**Discussion**

Although symptomatic treatment is the standard for acute hepatitis E, identification of the cause of acute hepatitis is important for predicting prognosis. With respect to post-transfusion hepatitis, it is important to consider the possibility of HEV when HCV and HBV are negative. However, according to guidelines by the Japanese Ministry of Health, Labour and Welfare, testing for the HBs antigen, HBs antibody, HBc antibody, HCV antibody, HCV core antigen, and anti-human immunodeficiency virus (HIV) antibody in recipient samples should be performed before transfusion. Recipients with possible transfusion-associated hepatitis should be tested for, HBV DNA, HCV core antigen, and anti-HIV antibody[5]. Given that HEV is not included in hepatitis tests before or after transfusion, additional screening is required to survey the presence of HEV. Currently, anti-HEV IgA antibody is the only test for HEV covered by the Japanese national health insurance scheme. To confirm that HEV infection is due to blood transfusion, it is necessary to prove that the recipient was not infected before transfusion. Showing a clear relationship between HEV infection and transfusion requires the availability of store patient specimens before transfusion. Therefore, it is essential to retain stored patient specimens collected before transfusion for testing after potential infection[6].

According to an investigation conducted by the National Institute of Infectious Diseases[7], the frequency of hepatitis E in Japan is increasing. While the rate of HEV infection was thought to be higher in Hokkaido than in other areas of Japan, the Kanto-Koshinetsu area actually demonstrates the highest proportion of hepatitis E cases (Fig. 2).

In addition to the present case, we encountered another patient with multiple myeloma infected with HEV by transfusion in April 201X, as reported else-

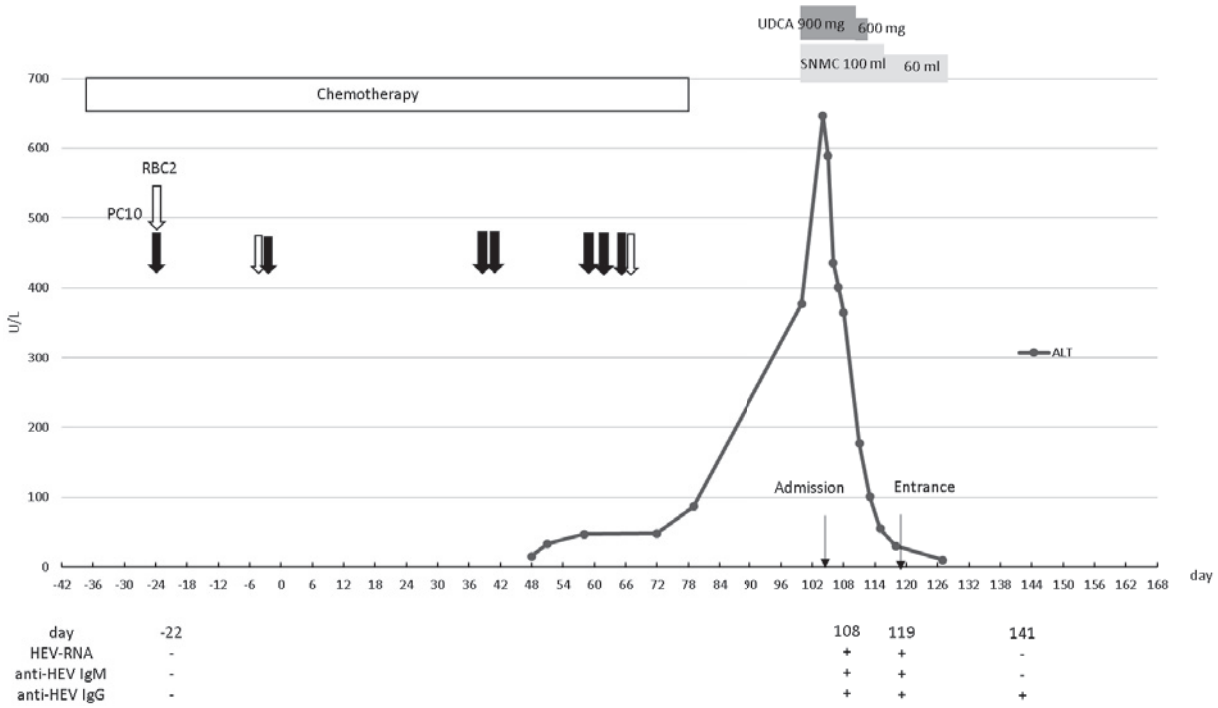


Fig. 1　Clinical course

ALT: alanin aminotransferase; RBC: red blood cells; PC: platelet concentrate; GGAC: monoammonium glycyrrhizinate, glycine, aminoacetic acid, L-cysteine hydrochloride hydrate; UDCA: ursodeoxycholic acid

where[4]. We confirmed that the HEV strain of the present case was different from that of this previous case[4], suggesting that the two strains differed from each other[8]. In our two cases, the HEV-positive blood products were drawn in Tokyo and Saitama Prefectures, where the infection rate is high. The clinical course of HEV infection is primarily transient acute hepatitis and chronicity is rare, although immunocompromised patients such as recipients of organ transplantation often progress to chronic hepatitis[8]. Although both of our patients were likely in an immunocompromised state after intensive chemotherapy, they did not progress to chronic hepatitis. Fortunately, HEV RNA disappeared on days 141 and 171 after transfusion. HEV genotype and immune status of the patient may affect clinical prognosis.

The Japanese Red Cross Society conducted a survey on actual HEV infections in Tokyo in 2016. They randomly extracted blood donor specimens from the Kanto-Koshinetsu Block Blood Center and conducted HEV nucleic acid amplification tests (NATs). Among 15,039 specimens, 11 specimens were HEV RNA-positive (positivity rate 0.073%) and all were genotype 3[9]. Assuming that the HEV positivity rate of blood donors is 0.073%, 1.3 of the 1,768 bags, of PC-LR transfused at our hospital in 201X, are expected to be HEV-positive. Moreover, considering that HEV can be transmitted by any kind of blood component, we expect that more HEV-positive blood products have been transfused[10]. Therefore, it should be noted that HEV infection can occur in the same area or even in the same facility in a very short period of time. Currently, HEV screening of blood donor specimens is conducted only in Hokkaido. It is therefore, impossible for most medical institutions across Japan to avoid HEV-positive blood products. Medical personnel must consider that similar cases can occur, especially in the Kanto-Koshinetsu area where HEV cases are prevalent.

## Conclusions

It is important to recognize that HEV is now the most probable cause of post-transfusion hepatitis. Furthermore, stored patient specimens collected before transfusion are important for identifying untested and unknown infectious agents via transfusion.

The authors state that there are no Conflicts of Interest (COI).

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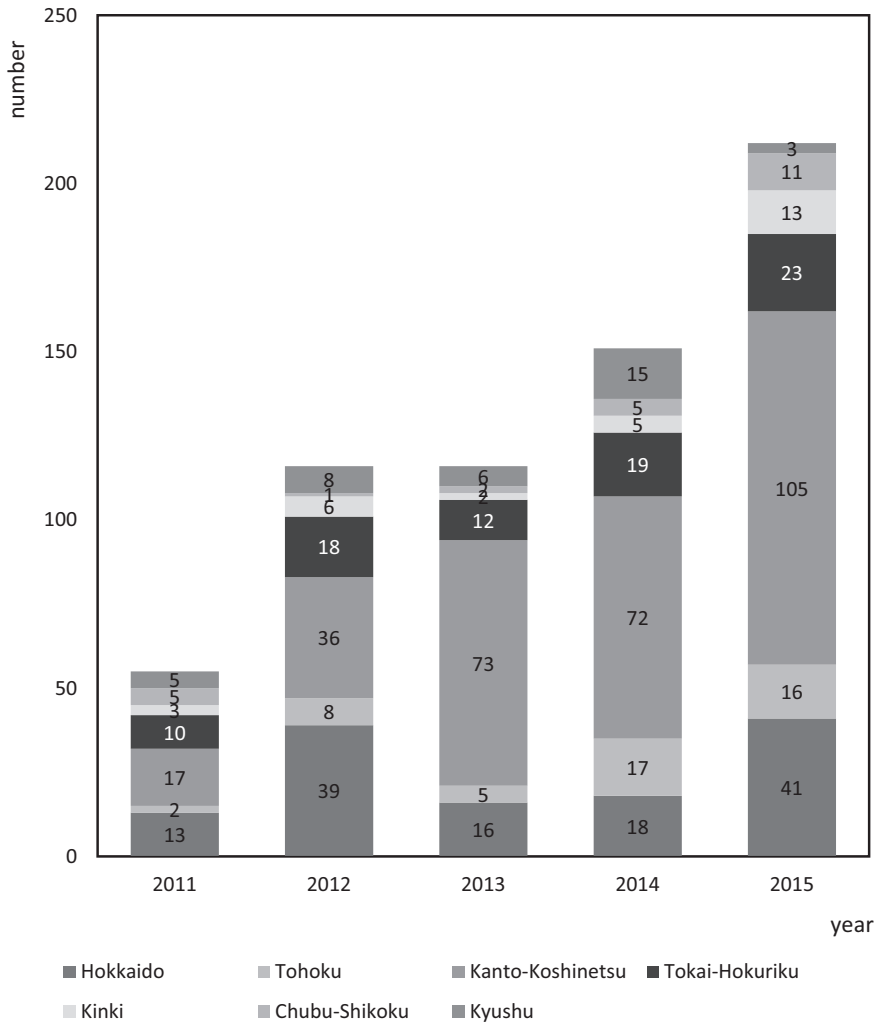


Fig. 2 Number of hepatitis E infections in Japan
Modified from the Infection Diseases Weekly Report of the National Institute of Infectious Diseases[10]

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# 難治性悪性リンパ腫患者における輸血関連E型肝炎

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**要旨：**

血液疾患治療中に輸血を複数回受けた患者がE型肝炎ウイルス（hepatitis E virus，HEV）に感染した症例を経験した. 患者はホジキンリンパ腫化学療法後の外来経過観察中に, 肝胆道系酵素の上昇が認められたことが発見の発端となった．ウイルス性肝炎関連検査の結果，HEV IgA抗体が輸血前保存検体で陰性，肝炎発症時に陽性であったため，日本赤十字社に輸血後感染症疑いの報告をした．調査の結果，患者と献血者の保管検体から検出したHEVの塩基配列が一致したため，輸血後E型肝炎であると確認された. 肝炎は早期に軽快し，慢性化は見られなかった. HEVは献血者の感染症検査項目に含まれていないが, 近年感染の報告が増加している. 多くの輸血用血液製剤を使用する施設では少なからぬHEV RNA陽性の製剤が使用されている可能性がある．当院では同時期にもう一例の輸血後E型肝炎を報告しており，HEVは輸血後肝炎の原因としてHEV感染が高頻度に見られる北海道のみならず，関東甲信越地域であっても現在もっとも考慮するべきである. また, 輸血と感染の関連を特定するために患者の輸血前検体の保管が重要である.

**キーワード：**
輸血後肝炎，HEV，輸血前検体保管


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