Late Onset Post-Transfusion Hepatitis E Developing during Chemotherapy for Acute Promyelocytic Leukemia

Kyoko Fuse¹, Yuichi Matsuyama², Masato Moriyama¹, Shukuko Miyakoshi¹, Yasuhiko Shibasaki¹, Jun Takizawa¹, Tatsuo Furukawa³, Ichiro Fuse⁴, Hiro Matsumura², Shigeharu Uchida², Yoshifumi Takahashi¹, Kenya Kamimura³, Hiroyuki Abe⁵, Takeshi Suda¹, Yutaka Aoyagi⁵, Hirohito Sone¹ and Masayoshi Masuko³

Abstract

We herein report the case of a leukemia patient who developed hepatitis E seven months after undergoing a transfusion with contaminated blood products. The latency period in this case was significantly longer than that of typical hepatitis E. Recently, chronic infection with hepatitis E virus (HEV) genotype 3 has been reported in immunocompromised patients. There is a possibility that our patient was unable to eliminate the virus due to immunosuppression following chemotherapy and the administration of steroids. The prevalence of HEV in healthy Japanese individuals is relatively high and constitutes a critical source of infection via transfusion. Hepatitis E is an important post-transfusion infection, and immunocompromised patients may exhibit a long latency period before developing the disease.

Key words: acute promyelocytic leukemia, hepatitis E virus, hepatitis associated with transfusion therapy

(DOI: 10.2169/internalmedicine.54.2332)

Introduction

Blood transfusions are an essential supportive therapy for chemotherapy in patients with hematological malignancies. Post-transfusion infection, particularly that with viral hepatitis, is a major complication of blood transfusions; however, hepatitis E virus (HEV) infection associated with blood transfusions is rare, with only 12 cases, including ours, previously reported in Japan prior to 2013 based on the official announcement of the Japanese Red Cross Society (1-4). The Nucleic acid Amplification Test (NAT) for HEV in blood products used for screening is performed in only some regions in Japan, and the clinical significance of this test has not been established (3).

HEV belongs to the genus Hepevirus in the Hepeviridae family and is grouped into four genotypes. HEV of genotype 1 or 2 causes sporadic and endemic outbreaks in developing countries and cases of travelers’ hepatitis, which show the typical clinical features of acute hepatitis. In contrast, HEV of genotype 3 or 4 causes sporadic or asymptomatic cases of hepatitis in industrialized countries (5, 6). Over the past few years, chronic infections with HEV genotype 3 have been reported among patients with a history of solid organ transplantation, steroid therapy, human immunodeficiency virus infection or hematological malignancy (7-10). In this report, we describe the case of a leukemia patient who developed late-onset post-transfusion hepatitis E seven months after receiving a blood transfusion during chemotherapy.

Case Report

A-27-year-old Japanese woman was admitted to our hospital due to a bleeding tendency and thrombocytopenia with...
leukocytosis in October 2011. She was subsequently diagnosed with acute promyelocytic leukemia (APL) with a variable (V)-form type of PML-RARα mRNA fusion transcript complicated by severe disseminated intravascular coagulation syndrome (DIC). The initial white blood cell count (WBC) was 17,830/μL (APL cells: 98%), with a hemoglobin (Hb) level of 10.2 g/dL and platelet count (Plt) of 3.5×10⁵/μL. Laboratory findings for coagulation parameters showed a fibrinogen level of 34 mg/dL, FDP level of 191.0 μg/mL and D-dimer level of 77.4 μg/mL. Therefore, treatment with all-trans retinoic acid (ATRA; 45 mg/m²) monotherapy combined with protease inhibitors and massive fresh frozen plasma (FFP) transfusion (10-20 units per day) was started. In cases involving a high WBC count, combination treatment consisting of ATRA and chemotherapy is recommended to prevent differentiation syndrome (DS). However, the current patient had already displayed overt genital bleeding and a low fibrinogen level (<100 mg/dL), suggesting a high risk that chemotherapy may induce tumor lysis syndrome and lethal bleeding events. Therefore, we planned to administer combination chemotherapy after controlling the severe DIC with initial ATRA treatment. On day 4, DS and alveolar and intestinal hemorrhage developed, without improvements in the DIC. The patient was treated with steroid pulse therapy (methylprednisolone, 1 g/day for three days), the dose of which was gradually tapered, and ventilator management in the intensive care unit was subsequently required due to respiratory failure. The ATRA treatment was then discontinued, and combination chemotherapy consisting of cytarabine and daunorubicin was initiated. Following the administration of induction chemotherapy, the DIC and DS improved, with a decrease in the number of APL cells. The patient was withdrawn from transfusion therapy and the ventilator and ultimately achieved hematological complete remission. During the induction chemotherapy, she received a transfusion of 232 units of FFP, 26 units of red cell concentrates (RCC) and 190 units of platelet concentrates (PC).

In December 2011, the patient received the first cycle of consolidation chemotherapy consisting of mitoxantrone at a dose of 7.0 mg/m² on days 1-3 and cytarabine at a dose of 200 mg/m² on days 1-5, with a typical blood recovery (neutrophil count over 500/μL on day 25 from the initiation of therapy). In January 2012, she received the second cycle of consolidation chemotherapy consisting of daunorubicin at a dose of 50 mg/m² on days 1-3 and cytarabine at a dose of 200 mg/m² on days 1-5. Subsequently, the third cycle of consolidation chemotherapy with idarubicin at a dose of 12 mg/m² on days 1-3 and cytarabine at a dose of 200 mg/m² on days 1-5 was started in March 2012 (Figure).

In April, during the nadir after the third cycle of consolidation therapy, the patient developed sepsis caused by coagulase-negative staphylococci. Therefore, antibiotics were administered; however, she developed liver dysfunction. Although the antibiotic therapy was discontinued, the transaminase levels continued to increase without symptoms. A peak in the transaminase elevation (AST 697 IU/L, ALT 972 IU/L) was observed on 35 day, after which the levels gradually improved without treatment. We conducted a serum viral examination in order to diagnose the liver injury and found DNA for the hepatitis B virus, Cytomegalovirus,
Table 1. Patients who Received Transfusion from the Same Donor

<table>
<thead>
<tr>
<th></th>
<th>this case</th>
<th>another recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary diagnosis</td>
<td>APL, severe DIC, bleeding</td>
<td>bleeding at surgical operation</td>
</tr>
<tr>
<td>age</td>
<td>27 y.o.</td>
<td>40’s y.o.</td>
</tr>
<tr>
<td>type of HEV</td>
<td>FFP</td>
<td>RCC</td>
</tr>
<tr>
<td>contaminated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>blood product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive drug</td>
<td>Chemotherapy, steroid puls</td>
<td>(-)</td>
</tr>
<tr>
<td>Serological test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-transfusion</td>
<td>HEV-RNA negative</td>
<td>negative</td>
</tr>
<tr>
<td>anti-HEV IgG</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>Post-transfusion</td>
<td>HEV-RNA Positive</td>
<td>negative</td>
</tr>
<tr>
<td>anti-HEV IgM</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>anti-HEV IgG</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>Onset of hepatitis E</td>
<td>(+)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

Epstein-Barr virus, human herpes virus 6, Herpes simplex virus, varicella zoster virus and Parovu B19 virus and RNA for the hepatitis C virus to be negative, whereas HEV-RNA alone was positive (3.1 log copies/mL). Therefore, we considered the patient’s liver injury to be caused by acute hepatitis E. A serological examination of HEV was subsequently performed using the patient’s monthly stored serum obtained after admission; however, no HEV-RNA was found in the serum samples stored between October 2011 and January 2012. The HEV-RNA titer in the serum ultimately turned positive in February 2012, while the levels of anti-HEV IgM and IgG antibodies remained negative. The HEV-RNA titer then turned negative in July 2012, whereas anti-HEV IgG antibodies were positive in the serum. Therefore, we inferred that HEV had been removed from the patient’s serum between June and July. Meanwhile, anti-HEV IgM antibodies remained negative in all serum samples collected during the patient’s entire clinical course.

Importantly, there was no clinical history of infection with HEV, as the patient had been hospitalized during this period. Therefore, in order to examine whether the HEV-RNA had been transmitted by a blood product, the samples of all blood products (232 units of FFP, 50 units of RCC and 525 units of PC from 177 donors during her hospital stay) received by the patient were tested for HEV-RNA retrospectively. Consequently, HEV-RNA was detected in one donated FFP sample transfused in late October 2011. An HEV-RNA sequence analysis of the HEV isolated from the donor and the sample showed only a one-nucleotide difference in open reading frames 1 and 2, demonstrating that the viruses were the same and of genotype 3. Taken together, we concluded that the patient’s HEV viremia had developed three months after the transfusion and was sustained over the next four months without the elimination of HEV or improvements in the hepatitis. In addition, we found that another recipient had been transfused with HEV-contaminated RCC from the same donor. The recipient was a middle-aged woman who had undergone gynecological surgery. We subsequently tested her serum and found anti-HEV IgG antibodies to be positive prior to the transfusion, whereas no HEV-RNA was detected in her serum after the transfusion. This recipient did not develop hepatitis E during follow-up (Table 1).

After the current patient’s transaminase levels normalized, she was discharged from the hospital in late June 2012. She is currently under maintenance therapy with ATRA (45 mg/m²) on an outpatient basis and remains in molecular complete remission. There is no evidence of HEV reactivation.

Discussion

According to a nationwide survey, the rate of HEV-RNA-positive blood donors is 0.7% in London (11) and 0.07% in China (12). In Japan, the rate of positive anti-HEV IgG antibodies among healthy volunteers is 5.3%, compared to 0.2% for anti-IgM antibodies and 0.01-0.2% for HEV-RNA (13-15). It is estimated that HEV infection occurs in approximately 150,000 people each year, almost all of whom are asymptomatic. Because the rate of infection in the general population is relatively high, HEV is a critical source of infection in blood products. Twelve cases, including ours, in Japan and nine cases in several other countries of post-transfusion hepatitis E have been reported as of 2013. Six of the 21 patients, including our patient, were under treatment for hematological malignancy, while two patients had undergone solid-organ transplantation (16-20) (Table 2).

The clinical significance of the current case is that the latency period was significantly longer than that of typical hepatitis E, and another recipient who received the same HEV-contaminated blood product did not develop hepatitis E infection. The usual latency period is two to six weeks (5). However, it took seven months for our patient to develop hepatitis after receiving the blood transfusion. In addition, viremia appeared three months after HEV transmission and lasted for at least the next four months. HEV geno-
type 3 is reported to cause chronic infection and liver cirrhosis in immunocompromised hosts (7-10), and hepatitis E virus excretion can be prolonged in patients with hematological malignancies (21).

It is also well known that forms of viral hepatitis, such as hepatitis B infection, are caused by immune responses, with T lymphocytes playing a major role in the immunopathogenesis. T lymphocytes eliminate hepatocytes infected with the virus and control viral replication (22, 23). Among pediatric HBV carriers infected due to maternal infection, infants may display chronic HBV infection before developing their own immunity. Such patients exhibit exacerbation of hepatitis in late childhood or adolescence after their immunity matures (24). In the present case, it was possible that the patient was unable to eliminate the virus due to immunosuppression resulting from the administration of chemotherapy and steroids for DS, which permitted the HEV to remain latent in her body without symptoms. She may therefore develop hepatitis E infection after her immunity returns to normal following the completion of the consolidation therapy.

In summary, the probability that HEV may contaminate blood products is not low. This case suggests that hepatitis E is an important post-transfusion infection, especially among leukemia patients, who are immunocompromised and require frequent transfusions. In addition, physicians should keep in mind that immunocompromised patients may exhibit a long phase of latency before developing hepatitis E infection.

The authors state that they have no Conflict of Interest (COI).

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

References