Early Ultrasonographic Diagnosis and Clinical Follow-up of Hepatic Veno-Occlusive Disease after Allogeneic Bone Marrow Transplantation in a Patient with Acute Lymphoblastic Leukemia

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Abstract

Hepatic veno-occlusive disease (VOD) is a typical complication occurring soon after allogeneic hematopoietic stem cell transplantation (HST), characterized by jaundice, painful liver enlargement, and weight gain due to fluid retention. The study reported here concerns a patient with VOD after allogeneic HST. Hemodynamic evaluation using ultrasonography revealed reversed portal venous flow before elevation of serum bilirubin, in addition to gallbladder wall thickening, ascites, and hepatomegaly. Quantitative evaluation using abdominal ultrasonography showed improvement in the reversed portal venous flow before the peaking of the serum bilirubin level and coagulopathy. This analysis was useful for both early diagnosis and clinical follow-up of VOD.

Key words: ultrasonography, veno-occlusive disease, portal venous flow, bone marrow transplantation

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Introduction

Hepatic veno-occlusive disease (VOD) is a clinical syndrome characterized by jaundice, liver enlargement accompanied by pain and weight gain due to fluid retention. It is one of the lethal complications that may occur following allogeneic hematopoietic stem cell transplantation (HST) because various complications resulting from VOD include multiorgan failure showing thrombocytopenia with refractoriness to transfusions, coagulopathy, pleural effusion, renal failure and respiratory failure. Clinical criteria for diagnosis of VOD following bone marrow transplantation (BMT) have been developed by two independent groups. The criteria proposed by the Seattle group specify the occurrence of two of the following events within 20 days of transplantation: hyperbilirubinemia (total serum bilirubin >2 mg/dL), hepatomegaly or right upper quadrant pain of liver origin, and sudden weight gain (>2% of baseline body weight) because of fluid accumulation (1). The other criteria proposed by the Baltimore group specify hyperbilirubinemia peaking at 2 mg/dL or more in conjunction with at least two of three other findings: hepatomegaly, ascites, and 5% or greater weight gain within the first 3 weeks after marrow infusion (2).

Accurate and early diagnosis of VOD is clinically important because the reported fatality rate is greater than 20% (2-5). Jones et al reported that only 1 of 25 patients with VOD and a serum bilirubin level higher than 15 mg/dL survived (2), while Zager et al reported that only 14% of VOD patients who required hemodialysis survived (6). In the case of HST patients, however, differential diagnosis of VOD and

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other causes of liver dysfunction, particularly hepatic graft-versus-host disease (GVHD), may be difficult because such entities may be associated with similar biochemical abnormalities.

There are many reports on the role of ultrasonography in the diagnosis of VOD (7-13). Ultrasonography is useful in detecting morphologic and hemodynamic changes including hepatomegaly, ascites, gallbladder wall thickening and reversed portal venous flow in patients with VOD. On the other hand, only a few reports have dealt with clinical follow-up of VOD by means of ultrasonography (7, 8). The report presented here concerns a patient with acute lymphoblastic leukemia who received allogeneic BMT. For this patient, longitudinal ultrasonographic analysis of portal blood flow was found to be a useful tool for early diagnosis, decision making regarding discontinuation of cyclosporin A, and clinical follow-up since this technique allows for quantitative evaluation of VOD.

Case Report

A 22-year-old man was admitted to our hospital in July 2005 because of general malaise and dyspnea on exertion. His peripheral blood cell count findings were: hemoglobin 5.3 g/dL, platelets 24×10^3/L, white blood cell count 294×10^3/L, with 1% neutrophils, 4% lymphocytes and 95% blasts. Laboratory studies showed evidence of disseminated intravascular coagulation with a prolonged prothrombin time of 18.6 seconds, activated partial thromboplastin time of 35.1 seconds, elevated fibrin degradation products of 162.5 μg/mL and a low fibrinogen level of 144 mg/dL. The serum lactate dehydrogenase (LDH) level was elevated to 3,511 IU/L, although no other abnormal liver function test results were obtained before the chemotherapy. Bone marrow aspiration disclosed hypercellularity with 95% blast cells of various sizes featuring folded nuclei with prominent nucleoli, which were negative for myeloperoxidase (MPO). The flow-cytometric (FCM) analysis findings were positive for CD1a (91.8%), CD3 (92.2%), CD4 (74.1%), CD5 (92.4%), CD7 (99.9%), CD8 (49.2%), terminal deoxynucleotidyld transferase (TdT) (69.0%) and cytoplasmic CD3 (98.7%). Cytogenetic analysis of marrow cells using G-bandning demonstrated a normal man karyotype, 46,XY. Based on these findings, the patient was diagnosed as having acute lymphoblastic leukemia (ALL) L2 according to the FAB classification as well as precursor T lymphoblastic leukemia based on the WHO classification.

The present patient achieved complete remission (CR) with a hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone) followed by high-dose methotrexate and cytarabine administration (14). Because of one of the adverse prognostic factors, a significant increase of WBC detected at diagnosis, we performed a myeloablative BMT from a human leukocyte antigen (HLA)-matched unrelated donor during the first CR, 7 months after the diagnosis. The conditioning regimen consisted oral busulfan 4 mg/kg per day on days -7 to -4 and intravenous cyclophosphamide at 60 mg/kg per day on days -3 and -2. The total quantity of marrow nuclear cells infused was 3.42×10^8/kg recipient weight. To prevent GVHD, cyclosporin A was administered starting on day -1 at 3 mg/kg per day as a continuous intravenous infusion and intravenous methotrexate at 10 mg/m^2 on day 1 and at 7 mg/m^2 on days 3 and 6. Continuous intravenous infusion of dalteparin sodium was performed starting at 100 mg/kg per day and oral ursodeoxycholic acid at 600 mg per day on day 7 as prophylaxis agents for VOD. However, the administration had to be terminated a few days after the transplantation because of nasal hemorrhage and inability to ingest anything orally due to regimen-related nausea.

In addition to several transplantation-related complications, including VOD and acute GVHD of the skin, fever associated with isolation of Staphylococcus hominis in blood cultures started from day 10. This was followed by successful treatment with cefepime, amikacin and vancomycin in accordance with the guidelines of the Infectious Disease Society of America (15).

As for the signs of VOD, the patient weighed 62 kg at the time of transplantation and had gained 1.6 kg as well as developed right upper quadrant pain of the liver on day 14. At that time, despite a neutrophil count of up to 0.5×10^9/L, thrombocytopenia became prominent with refractoriness to transfusions. On day 18, right upper quadrant pain had increased with a weight gain of 3.4 kg, while gray-scale hepatobiliary ultrasonography showed gallbladder wall thickening (12.5 mm) (Table 1) but neither hepatomegaly nor ascites (Fig. 1). On day 21, we examined our patient with the following findings and resultant treatment. First, because of acute renal dysfunction (Cr 1.64 mg/dL) with anuria and 7.3 kg weight gain, we introduced continuous hemodiafiltration. Second, gray-scale hepatobiliary ultrasonography showed hepatomegaly, ascites and gallbladder wall thickening (16.1 mm) (Fig. 1), and quantitative pulsed Doppler ultrasonography disclosed reversed portal venous flow (~351 mL/min) (Figs. 2, 3). Although serum liver function tests indicated limited hyperbilirubinemia (1.24 mg/dL), the patient was diagnosed with VOD on the basis of these ultrasonographic findings, and administration of dalteparin sodium was resumed. Third, because of acute renal dysfunction concomitant with VOD, the administration of cyclosporin A was discontinued. Finally, laboratory studies showed coagulopathy and an elevated serum level of a fibrotic marker, the aminopeptidase of type III procollagen (PiINP) (Table 1). On day 25, the serum bilirubin level reached 11.28 mg/dL. Because we made no change of medication including antimicrobial agents at this time, and the absence of weight gain and fluid retention is usually sufficient to distinguish VOD from other forms of early liver injury with jaundice including regimen-related toxicity and infections (16), we diagnosed this severe hyperbilirubinemia as a case of VOD. Even though the serum bilirubin had not peaked yet, ultrasonography showed diminished ascites and gallbladder wall-related toxemia.
Table 1. Ultrasonographic Measurements and Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Day 18</th>
<th>Day 21</th>
<th>Day 23</th>
<th>Day 25</th>
<th>Day 28</th>
<th>Day 34</th>
<th>Day 48</th>
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<tr>
<td>Body weight gain (kg)</td>
<td>2.8</td>
<td>7.3</td>
<td>6.5</td>
<td>0.4</td>
<td>-1.3</td>
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<td>Gray-scale hepato-</td>
<td></td>
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<td>bililiary ultrasonography</td>
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<tr>
<td>Gallbladder wall thickening (mm)</td>
<td>12.5</td>
<td>16.1</td>
<td>NA</td>
<td>8.9</td>
<td>NA</td>
<td>NA</td>
<td>4.0</td>
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<tr>
<td>Hepatomegaly</td>
<td>-</td>
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<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>±</td>
</tr>
<tr>
<td>Ascites</td>
<td>-</td>
<td>+++</td>
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<td>++</td>
<td>NA</td>
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<td>+</td>
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<td>Portal venous flow (mL/min)</td>
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<td>NA</td>
<td>470</td>
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<td>Vmax of portal venous flow (cm/second)</td>
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<td>NA</td>
<td>15.1</td>
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<td>Serum bilirubin (mg/dL)</td>
<td>0.48</td>
<td>1.24</td>
<td>1.09</td>
<td>11.28</td>
<td>16.08</td>
<td>4.00</td>
<td>1.31</td>
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<td>Prothrombin time (seconds)</td>
<td>13.0*</td>
<td>17.7</td>
<td>32.0</td>
<td>19.8</td>
<td>15.7</td>
<td>14.9</td>
<td>13.3*</td>
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<td>188</td>
<td>158</td>
<td>253</td>
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<td>67*</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.0</td>
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</table>

NA: not analyzed, Vmax: maximal velocity, * Day 17, # Day 52

Figure 1. Ascites of Morison pouch and gallbladder wall thickening detected by gray-scale hepatobiliary ultrasonography.

thickening (8.9 mm) and anterograde portal venous flow (470 mL/min) (Figs. 1, 2 and 3). On day 28, the serum bilirubin level peaked to 16.08 mg/dL, after which the symptoms of VOD, including hyperbilirubinemia, acute renal failure, thrombocytopenia and abnormalities of the coagulation system, started to improve. On day 48, gray-scale hepatobiliary and pulsed Doppler ultrasonography showed further improvement in ascites and gallbladder wall thickening (4.0 mm) and an increase in the anterograde portal venous flow volume (1,106 mL/min) (Figs. 1, 2 and 3). The hepatic arterial resistive index (HARI; systolic velocity minus diastolic velocity divided by systolic velocity) was 0.57 on day 21 and increased to 0.76 on day 48 in spite of the clinical improvement of VOD (Table 1).

Stage 3 (17) acute GVHD of the skin (histological Grade II (18)) appeared on day 33, and was treated with 2 mg/kg of methylprednisolone and resumption of the administration of cyclosporin A, as a result of which GVHD improved
promptly with complete response (19). Twenty-seven months after the transplantation, our patient remains in good condition, showing continuing CR without liver dysfunction.

**Discussion**

The patient who is the subject of this report was noninvasively diagnosed as having VOD by means of gray-scale and Doppler ultrasonography at an early stage. VOD following HST is usually diagnosed based on two clinical criteria proposed by the Baltimore and Seattle groups. Our patient had typical symptoms of VOD including hyperbilirubinemia, hepatomegaly, upper quadrant pain, sudden weight gain and ascites, and fulfilled the diagnostic criteria with the exception of the occurrence time. A variety of ultrasonographic findings have been reported in patients with VOD. Gray-scale hepatobiliary ultrasonography yields relevant findings including hepatomegaly, ascites and gallbladder wall thickening in patients with VOD. Furthermore, because VOD is caused by obliteration of the terminal hepatic venules and hepatic sinusoids, hemodynamic changes occur, including decreased or reversed portal venous flow, which become detectable with pulsed Doppler ultrasonography (9, 10). Las-sau et al and Kriegshauser et al reported that the detection

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**Figure 2.** Portal venous flow detected by pulsed Doppler ultrasonography.

**Figure 3.** Longitudinal courses of portal venous flow, gallbladder wall thickening, serum bilirubin and blood concentration of cyclosporin A.
of ascites, gallbladder wall thickening, and reversed portal venous flow by ultrasonography was valid for the diagnosis of VOD (8, 10) although they were found to be not necessarily associated with VOD or were nonspecific for its diagnosis in several studies (7, 11, 12).

In the present patient, the early detection of hepatomegaly, ascites, gallbladder wall thickening and reversed portal venous flow was of diagnostic value. By using ultrasonography, these findings were detected before serum bilirubin had reached 2 mg/dL, as specified in the diagnostic criteria. Bearman reported that hepatomegaly and fluid retention was followed by hyperbilirubinemia in patients with VOD (16). Furthermore, whereas Brown et al reported that decreased or reversed portal venous flow represents one of the relatively late changes in patients with clinically evident VOD (9), Hashiguchi et al recently reported that six of nine patients did not fulfill the diagnostic criteria when the reversed portal venous flow was first detected (13). For these reasons, ultrasonographic analysis is thought to be useful to detect these early events of VOD. Because reversed portal venous flow is reportedly never found in GVHD (8), we decided to discontinue the administration of cyclosporin A.

Although ultrasonography is a noninvasive and repeatable method, there have been only a few reports of its use for monitoring the course of VOD (7, 8). In our case study, we found that gallbladder wall thickening and abnormal portal venous flow started to improve before serum bilirubin level and coagulopathy had reached a peak and that this improvement paralleled the patient’s clinical course. Ultrasonographic findings may therefore constitute useful markers for clinical follow-up of VOD.

It has been controversial whether measurement of HARI is valuable for the diagnosis and the clinical follow-up of VOD or not. Herbetko et al (11) and Lassau et al (8) reported that increased HARI (0.81 or more specified by the former and 0.75 or more by the latter) is associated with the diagnosis of VOD. On the other hand, Teevey et al reported that HARI is of no value for the diagnosis of VOD (12). Eventually, HARI proved to be not associated with the diagnosis and the clinical course of VOD of the present patient.

This report concerns a transplant patient, whose early and accurate diagnosis of VOD may have been responsible for his good clinical course. Further prospective studies will be necessary to identify and clarify the role of ultrasonography in the early diagnosis and clinical follow-up of VOD.

References