Adenovirus Fulminant Hepatic Failure: Disseminated Adenovirus Disease after Unrelated Allogeneic Stem Cell Transplantation for Acute Lymphoblastic Leukemia

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Abstract

Adenovirus is one of the major causes of non-relapse morbidity and mortality after allogeneic hematopoietic stem cell transplantation for hematological malignancy. Fulminant hepatic failure is a rare manifestation of post-transplant complication with adenovirus. Extremely high mortality and aggressiveness of the clinical course have been posing clinical challenges for the diagnosis as well as for the treatment. Here, we report a case with disseminated adenovirus disease presenting with fulminant hepatic failure after bone marrow transplantation for acute lymphoblastic leukemia.

Key words: disseminated adenovirus disease, fulminant hepatic failure, bone marrow transplantation, leukemia

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Introduction

Viral infections have been one of the major causes of non-relapse morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HCT) for hematological malignancy (1). With the development of early detection methods and preemptive therapy for viremia, and the advent of new anti-viral drugs, there has been significant progress in the management of some viral infections, such as that of herpes zoster, herpes simplex and cytomegalovirus (1, 2). At the same time, however, other viruses have had more important roles in the HCT setting, such as adenovirus (ADV), herpesviruses 6-8, community respiratory viruses, papovaviruses, parvovirus B19, enteroviruses, rotavirus and Norwalk virus (3). Among these, ADV infection is the third most virulent among HCT recipients (4-6), and it is a significant cause of morbidity and mortality in patients after HCT, although the reported mortality rate varies from five to eighty-three percent (1, 7-10). Hepatitis is not an uncommon form of ADV infection, but its fulminant type is a rare entity. In this article, we report a case of adenoviral fulminant hepatic failure with acute lymphoblastic leukemia (ALL) after unrelated allogeneic bone marrow transplantation, and present a short review of the cases with adenoviral fulminant hepatic failure after HCT.

Case Report

A 51-year-old Japanese woman was diagnosed as having precursor B-lymphoblastic leukemia with a normal karyotype in March 1999. A course of induction therapy with an anthracyclin-containing regimen was successful, and she maintained complete remission after consolidation and maintenance chemotherapies. Her disease was under control until September 2000, when her disease relapsed in the bone marrow. After reinduction therapy and reconsolidation, she went through allogeneic HCT from an unrelated HLA-matched donor in March 2004. Her laboratory data on admission for HCT is shown in Table 1. The conditioning regimen was 12

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Table 1. Laboratory Data before and after Allogeneic Bone Marrow Transplantation

<table>
<thead>
<tr>
<th></th>
<th>day -10</th>
<th>day 159</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspartate aminotransferase (U/l)</td>
<td>16</td>
<td>8,800</td>
</tr>
<tr>
<td>alanine aminotransferase (U/l)</td>
<td>16</td>
<td>5,180</td>
</tr>
<tr>
<td>alkaline phosphatase (U/l)</td>
<td>411</td>
<td>5,180</td>
</tr>
<tr>
<td>total bilirubin (mg/dl)</td>
<td>0.53</td>
<td>4</td>
</tr>
<tr>
<td>prothrombin time (%)</td>
<td>101</td>
<td>18</td>
</tr>
</tbody>
</table>

*; normal range: less than 367

cGy of total body irradiation and cyclophosphamide, and cyclosporine A and short-term methotrexate were used for acute graft-versus-host disease (aGVHD) prophylaxis. Engraftment was confirmed on day 16. Transfusion-related lung injury and diffuse alveolar hemorrhage occurred, each of which was resolved with methylprednisone administration. On day 55, she presented with persistent fever and maculopapular exanthema in the extremities. The skin biopsy showed vacuolar change in the interface with sporadic apoptotic cells, eosinophilic keratinocytes, and only minor lymphocytic infiltration. Neither ballooned keratinocytes nor inclusions were observed, making viral infection unlikely.

She was diagnosed as having grade II acute GVHD in the skin, which was treated with 1 mg/kg of methylprednisone. On the refractory exanthema, cyclosporine A was switched to tacrolimus and 1 mg/kg of prednisone was restarted on day 112. Although the rash again subsided, she started to feel malaise with slightly elevated serum transaminase on day 124. She developed high fever on day 140. On day 142, her alanine aminotransferase (ALT) was elevated at 1030 U/l. Imaging studies of the liver revealed no apparent space-occupying lesion. On day 159, she complained of abdominal cramp and developed grade IV hepatic coma. Her laboratory data at that time is shown in Table 1. Virological examinations, including IgM type anti-hepatitis A antibody, IgM anti-HBc antibody, anti-HBs antibody, anti-hepatitis C antibody and cytomegalovirus antigenemia all tested negative. Polymerase chain reaction (PCR) tests for herpes simplex virus, varicella zoster virus, parvovirus B19, human herpes virus 7, and HCV-RNA were also negative in the plasma. The Epstein Barr (EB) virus DNA load was 6,460 copy/μg DNA in whole blood, but, later on, EBV was revealed to be negative in the hepatocytes according to in situ hybridization methods. The ADV viral load in peripheral blood measured with real-time PCR assays was positive: with more than 5× 10^7 copies/ml. There were no signs nor symptoms of hemorrhagic cystitis or colitis. A bone marrow study showed that she was still in complete remission. Plasma exchange did not improve the degeneration, and the patient died from fulminant hepatic failure on day 160. Postmortem liver necropsy was performed with the family’s consent.

Methods

Histological evaluation of liver necropsy specimen

The postmortem liver specimen was processed for hematoxylin-eosin stains using standard protocols. Immunoperoxidase studies were performed on formalin-fixed paraffin sections using avidin-biotin peroxidase complex methods with a panel of purified monoclonal antibodies against ADV (Chemicon International, Inc, USA), HSV-I (DaltoCytomation, Glostrup, Denmark), HSV-II (DaltoCytomation, Glostrup, Denmark) and CMV (DaltoCytomation, Glostrup, Denmark). All antibodies were applied after being retrieved with microwave oven heating. Translucent electron microscopic examination was performed on formalin-fixed, paraffin-embedded tissue using the standard method.

Literature search

We extensively searched the previously published (up to September 2005) reports on ADV fulminant hepatic failure after HCT, using PubMed. Meanwhile, fulminant hepatic failure is a clinical syndrome of decompensated liver dysfunction caused by viral infection or drug toxicity with a progressively deteriorating clinical course. However, several terminologies seem to exist to designate the fulminant hepatic failure, such as fulminant hepatitis, fulminant hepatic necrosis, fulminant liver failure or hyperacute liver failure in the previous literature. Because the nomenclature of fulminant hepatic failure may differ among the authors, we searched, among the post-HCT patients, for the cases described as fulminant hepatic failure by the authors, or so cited in subsequent reports.

Results

Hematoxylin-eosin staining of the liver necropsy specimens showed large and random foci of coagulative hepatocyte necrosis with mild canicular and cytoplasmic cholestasis and some steatosis, surrounded by hepatocytes with ill-defined intranuclear basophilic inclusions and chromatin margination, or ‘smudge cells’, characteristic of adenovirus infection (Fig. 1a). The infiltration of inflammatory cells was scarce. No bile duct damage or loss was observed. The portal areas were enlarged with mild fibrosis and with only minimal amounts of lymphocytic infiltration. Small to large adipose deposits were moderate. No leukemic cell infiltration was seen.

With immunohistochemical methods, there were negative findings for HSV-I, HSV-II and CMV, but strongly positive stains were confirmed for ADV in the nuclei of the hepatocytes (Fig. 1b). Electron micrographs showed a combination of intranuclear ring-like inclusions and virus particles of approximately 60-70 nm within the nucleus, highly indicative of ADV (Fig. 1c). The crystalline arrays were not observed.
in this specimen. Taken together, she was diagnosed with fulminant hepatic failure with ADV-associated disseminated ADV disease.

We have found, through PubMed, sixteen cases with ADV fulminant hepatic failure after allogeneic HCT (Table 2). The patients were 20.4 years of age on average, with nine males, six females, and one not specified. The present case is the most advanced age ever reported. The relationship between the underlying disease and ADV fulminant hepatic failure is weak. As for the conditioning regimen, seven cases with TBI and two cases without TBI have been documented. The GVHD prophylaxes entailed CYA+short MTX in five cases, only CYA in two cases, CYA+pantoxyfylline in one case, and ATG in one case. T-cell depletion was utilized in five of the documented cases. The stem cell sources are all bone marrow: from ten related donors (five HLA matched, one mismatched, four not specified), three unrelated donors and three undescribed donors. None of the cases were autologous transplants. The engraftment was dated between day 12-20 in five cases. Acute or chronic GVHD was documented in six cases (8, 11-13), and suspected in three cases (5, 14, 15), one of which was treated with steroids (14); the treatment was not described in the other cases.

The clinical pictures of ADV fulminant hepatic failure depicted in the previous reports are almost identical. The elevation of liver enzyme is prominent; up to 205 times the upper limit of the normal value for alanine aminotransferase (ALT) (16), up to 269 times the upper limit of the normal value for aspartate aminotransferase (AST) (16), up to 8 times the upper limit of the normal value for alkaline phos-

Table 2. Previous Cases with Adenoviral Fulminant Hepatic Failure after Hematopoietic Cell Transplantation

<table>
<thead>
<tr>
<th>case number</th>
<th>age/year</th>
<th>sex</th>
<th>underlying disease</th>
<th>donor/HLA-match</th>
<th>TBI*</th>
<th>T-cell depletion</th>
<th>aGVHD†</th>
<th>ATG‡</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24 F</td>
<td>AML</td>
<td>n.m./n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>+/-/n.m.</td>
<td>n.m.</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>13 M</td>
<td>AA</td>
<td>n.m./n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>+/-/n.m.</td>
<td>n.m.</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>19 M</td>
<td>X linked LP</td>
<td>related/matched</td>
<td>n.m.</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>34 M</td>
<td>NHL</td>
<td>related/matched</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 F</td>
<td>AML</td>
<td>related/mismatched</td>
<td>-</td>
<td>+</td>
<td>n.m./+</td>
<td>-</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.9 n.m.</td>
<td>ALL</td>
<td>related/matched</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.66 M</td>
<td>infantile osteopetrosis</td>
<td>n.m./n.m.</td>
<td>-+</td>
<td>n.m./n.m.</td>
<td>-</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>22 M</td>
<td>CML</td>
<td>related/matched</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3 M</td>
<td>AML</td>
<td>related/matched</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>24 F</td>
<td>ALL</td>
<td>unrelated/matched</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>8</td>
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</tr>
<tr>
<td>11</td>
<td>44 M</td>
<td>CML</td>
<td>unrelated/matched</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>22 F</td>
<td>n.m.</td>
<td>related/matched</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>43 M</td>
<td>n.m.</td>
<td>unrelated/matched</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>10 F</td>
<td>AML</td>
<td>related/matched</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>21 M</td>
<td>ALL</td>
<td>n.m./n.m.</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>35 F</td>
<td>HD</td>
<td>related/n.m.</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>57 F</td>
<td>ALL</td>
<td>unrelated/matched</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>


TBI*, total body irradiation; aGVHD†: acute graft versus host disease; ATG‡: anti-T lymphocyte globulin

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phatase (5), and the elevation occurred rapidly. Of note, the AST level was higher than the ALT level, except in one report (14). The serum bilirubin level was not necessarily high when the other liver markers reached significance (16). The prolonged prothrombin time started at a moderate level, up to 1.4 to 1.8 times the upper limit of the normal value (5, 14, 17), and became prominent when liver failure ensued, reaching 6.1 times the upper limit of the normal value (14). As for the physical signs and symptoms, fever (14, 16-18), tender hepatomegaly (16), or abdominal and back pain (18) were described at the onset in the previous cases. The present case also presented with fever and abdominal cramping, which might have been the signs and symptoms of the disease, although both were also non-specific.

In terms of diagnosis, liver biopsy was performed in only one case (5), where liver GVHD was suspected. In the rest of the cases, liver pathology was examined only with autopsy or necropsy specimens. The present case was diagnosed as disseminated ADV disease with fulminant hepatic failure, and the diagnosis was also made with liver necropsy. The ADV PCR assays were found to be positive after her death. Six of the sixteen patients with fulminant hepatic failure were documented to have had grade II-IV acute GVHD at the time of diagnosis. One case developed refractory grade 1 GVHD in skin associated with fever. Another case showed no evidence of acute GVHD, except for chronic GVHD of the localized skin. Three cases were treated with ribavirin (11, 19), one case with donor lymphocyte infusion (20), and the others without. All of the patients died.

Discussion

Among ADV diseases after HCT, fulminant hepatic failure is a rare manifestation (21). We searched the literature extensively using PubMed Central, and found sixteen reported cases, summarized in Table 2. Despite its rarity, adenovirus fulminant hepatic failure poses diagnostic and therapeutic challenges after HCT, due to its aggressive clinical course and extremely poor prognosis. In addition to HCT, some patients were reported to have developed fulminant hepatic failure after liver transplantation (22-27) or renal transplantation (28), or after chemotherapy without undergoing HCT (29-33). Moreover, other cases were reported without having had any immunosuppressive treatment (34), or some were immunocompetent cases (35, 36).

Bordignon et al (7) revised the Wisconsin criteria, which defines definite ADV disease as the presence of typical ADV nuclear inclusion in routine histopathology and/or a positive culture from affected tissue, originally described by Flomenberg et al (12), reflecting the new diagnostic modalities, such as PCR assays or immunohistological staining. In addition, disseminated ADV disease is defined as the presence of systemic disease involving two or more organ systems with positive ADV tests, or positive PCR or blood culture (10).

In accordance with the above criteria, histopathology is mandatory in diagnosing ADV fulminant hepatic failure. However, liver biopsy may carry too great a risk of bleeding. The necropsy or autopsy, not biopsy, was contributory in most of the previous cases, as well as the present case. Hence, it might be imperative to identify the risk factors, early signs and symptoms of the adenovirus fulminant hepatic failure, and, at the moment it is suspected, to perform liver biopsy effectively and expeditiously to lead to the prompt initiation of its available therapy (37). In addition, ADV fulminant hepatic failure might even have been underestimated, partly because of the lack of liver autopsy or necropsy (2, 12, 38). However, laboratory data and clinical signs and symptoms at the early stage of the disease, such as fever or abdominal cramp, may not be specific and may not always be sufficient for the early diagnosis of the disease.

Although identifying the risk factors for ADV disease are expected, those described in the previous reports are still controversial: including, moderate to severe acute GVHD and/or steroid therapy (2, 8, 11-13, 21, 39), the intensity of immunosuppressive therapy (38), the isolation of ADV from two or more sites (12, 39), HLA-mismatched or unrelated transplants (1, 21), T-cell depletion transplants (11) with/without ATG, CD34+ positive selection transplant, lympho- cytopenia (11), ADV antibody status of the donors (2), allogeneic transplantation (38, 39), and a conditioning regimen with TBI (8). No single serotype has been identified as indicating a risk of developing disseminated disease, either. Even though serotypes 1 (12), 2 (17, 19), 5 (14-16, 18), and 32 (40) have been demonstrated to be causative agents for ADV hepatic failure in previous reports, it is not yet clear which serotype is more prone to developing fulminant hepatic failure. It is not known what underlying disease is more prone to developing ADV disease; about half of the previous reports (Table 2) are lymphoid malignancies, though this is not significant.

Recently, monitoring of the ADV viral load with realtime PCR assays in peripheral blood (41), serum (42, 43), or urine (42, 44) has appeared to be promising. Echavarria et al discussed the association of serum ADV and the development of disseminated disease (43). Teramura et al argued that positive tests with both serum and urine are highly likely to progress to disseminated disease (42). Lion et al demonstrated a ten-fold increase in the viral load preceded the ADV disease three weeks in advance; and, therefore, argued that the repeated detection of ADV in the blood and the documentation of the increase in viral load may become an early sign of the progressive disease (41).

Therapeutic options for ADV disseminated disease are still very limited (1, 7, 10, 36, 38, 39, 41, 43, 45-47). Intravenous or aerosolized ribavirin (1, 7, 19, 38, 45, 47), vidarabine (7), and cidofovir (7, 36, 45-47) are included in antiviral agents, and the intravenous administration of immunoglobulin (12), the discontinuation of antibiotics (36), donor lymphocyte infusion (7) and the modification of immuno- suppressive agents have also been documented. Unfortu-
nately, none of them is definitively promising, and the development of new therapeutic strategies is mandatory. Some cases with spontaneous recovery from ADV disease also make it difficult to evaluate some of the anti-viral drugs (38). Although limited, however, early diagnosis and preemptive therapy might be the best hope (39, 43). It is important to develop a clinical marker to monitor the progressive disease to initiate, effectively and expeditiously, the necessary diagnostic and therapeutic approaches. Positive PCR in the peripheral blood or serum might lead to preemptive therapy of disseminated ADV diseases, but it has yet to be clarified whether the positive PCR may precede the deterioration in the liver.

In summary, we report a case of disseminated adenovirus disease presented with fulminant hepatic failure after allogeneic HCT for ALL. Unlike other presentations of ADV disease after HCT, fulminant hepatic failure is rare, and it exhibits one of the most severe morbidities and highest mortalities among the non-relapse post-HCT complications. A high level of caution for early detection is needed, though its treatment options are unsatisfactory. The development of more effective antiviral therapies, as well as preemptive therapy strategies, are warranted for this clinically challenging disease. In the current situation, one method might be monitoring of the ADV viral load with quantitative PCR of the blood, and the suspicion of ADV hepatitis from elevation of liver enzyme or abdominal symptoms for the early consideration of ADV hepatitis and fulminant hepatic failure, especially when liver biopsy is difficult to perform.

References