Massive Ascites Associated with All-trans Retinoic Acid Treatment in Therapy-Related Acute Promyelocytic Leukemia

Munehiro Suzukawa, Tatsuki Nakazora, Yasufumi Kawasaki, Takayuki Tominaga and Kenji Shinohara

Abstract

A 77-year-old man who developed pancytopenia was administered granulocyte colony-stimulating factor (G-CSF) by another doctor, and referred to us for the evaluation of pancytopenia. He had hepatocellular carcinoma and was treated with transcatheter arterial chemoembolization (TACE) containing epirubicin (total dose: 300 mg over the last two years). Bone marrow aspiration smear demonstrated hypercellular marrow with promyelocytes. Cytogenetic analysis demonstrated del(7), t(15;17)(q22;q12), and a fluorescence in-situ hybridization (FISH) study demonstrated chimeric fusion genes of PML-RAR-α. He was diagnosed with therapy-related acute promyelocytic leukemia (APL), and treated with all trans-retinoic acid (ATRA). He showed the progressive accumulation of ascites with liver damage, without pulmonary symptoms of ATRA differentiation syndrome. After 60 days of ATRA treatment, complete hematological and cytogenetic responses were achieved. However, the patient died of septic circulatory failure.

Key words: acute promyelocytic leukemia, therapy-related, all-trans retinoic acid, ascites, liver damage

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Introduction

Therapy-related leukemia caused by systemic chemotherapy is increasing (1). Acute myeloid leukemia (AML) is one of the most frequent types (1), and there have been occasional cases of acute promyelocytic leukemia (APL): 30 cases as of 1995 have been reported including case reports and a literature review (2, 3). The precise incidence of therapy-related APL has not been described (1-3). These cases usually involve patients treated with systemic oral or intravenous administration of chemotherapeutic agents including alkylating agent and topoisomerase II inhibitor, and radiation.

For patients with hepatocellular carcinoma, a case of therapy-related AML was reported who was treated with intra-atrial and intravenous injections of chemotherapeutic agents, and radiation (4). This is the first reported case of therapy-related APL caused by transcatheter arterial chemoembolization (TACE) in a patient with hepatocellular carcinoma.

APL is usually treated with the administration of all-trans retinoic acid (ATRA) and chemotherapy (5). The adverse effect of ATRA, ATRA differentiation syndrome with pulmonary symptoms of acute respiratory distress syndrome (ARDS), is well known (5). The ATRA-related adverse effect of liver damage, through an increase in bilirubin and transaminase levels, is rarely observed. However, only one case of ascites-related adverse effects has been reported (6). We observed the accelerated accumulation of ascites after the administration of ATRA in a patient with therapy-related APL, who achieved complete remission by the administration of ATRA.

Case Report

A 77-year-old man developed hepatitis C in 2002. He was diagnosed with hepatocellular carcinoma in 2006. HBs anti-
gen was negative and HCV antibody was positive. The level of α-fetoprotein was elevated. He was treated with percutaneous ethanol injection therapy (PEIT) and transcatheter arterial chemoembolization (TACE) involving epirubicin hydrochloride (Far-morubicin, Kyowa-Kirin, Japan), each at 60 mg, performed 5 times (total dose of 300 mg from February 2007 to February 2009). In March 2009, pancytopenia was observed, and granulocyte colony-stimulating factor (G-CSF) at 75 μg/day was administered for 7 days by a doctor of hepatology, however, pancytopenia persisted. He was transferred to our department in early April for the evaluation of pancytopenia. Laboratory data on admission are shown in Table 1. The initial bone marrow aspiration was dry tap. Subsequent bone marrow aspiration demonstrated hypercellular marrow with increased promyelocytes. Flow cytometric analysis demonstrated increased expression of CD2, CD13, CD33 and CD 56, however, HLA-DR was negative. Cytogenetic analysis of bone marrow cells by G-banding demonstrated: 46, XY, del(7)(q22), t(15;17)(q22;q12). Interface in situ hybridization (FISH) demonstrated a fusion signal of PML-RARα. A hemostatic study demonstrated decreased fibrinogen and increased D-dimer levels. Blood chemistry identified elevated total bilirubin, decreased albumin, impaired renal function, and increased CRP. A diagnosis of therapy-related APL was made. The clinical course is shown in Fig. 1. He was started on treatment with all-trans retinoic acid (ATRA) (Vesanoid, Chugai, Japan) at 70 mg/day in the middle of April. After the start of ATRA administration, the accumulation of ascites was accelerated from the middle of May (Fig. 2). Other symptoms of ATRA differentiation syndrome including pulmonary symptoms were not observed. He had not previously undergone abdominocentesis for ascites. Ascites (approximately 4 liters) was removed in the middle of May, and the analysis of ascites demonstrated yellowish serous transudate. Subsequently, the levels of bilirubin and transaminase gradually increased. Ascites was initially removed twice a week. The administration of ATRA was stopped for one week, and the administration of prednisolone (PSL) and diuretics was performed. The administration of ATRA was resumed a week later at a reduced dose of 40 mg/day. After these treatments, the rate of ascites accumulation decreased, and thereafter, ascites (2-3 liters) was removed approximately every 10 days, totally 9 times. During the administration of ATRA, the plasma concentrations of interleukin-6 (IL-6), IL-8, and G-CSF were elevated, while those of IL-2 and tumor necrosis factor α(TNF-α) were not (Table 2).

The neutrophil count of the peripheral blood recovered, and promyelocytes in the bone marrow decreased gradually. After 60 days of ATRA administration, complete hematological and cytogenetic responses were achieved; cytogenetic analysis demonstrated a normal karyotype and FISH analysis showed 0% fusion signal for PML-RARα. In early July, leukocytosis, elevated procalcitonin, and hypotension were observed; however, chest X-ray and CT did not demonstrate an infiltrative shadow. The patient subsequently died of sep-
Table 2. Plasma Levels of Cytokines during the Administration of ATRA (Normal Range is Given in Parentheses)

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Level (U/mL)</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>&lt;0.8</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>IL-6</td>
<td>&lt;4.0</td>
<td>37.9</td>
</tr>
<tr>
<td>IL-8</td>
<td>&lt;2.0</td>
<td>26.8</td>
</tr>
<tr>
<td>G-CSF</td>
<td>&lt;18.1</td>
<td>45.4</td>
</tr>
<tr>
<td>TNF-α</td>
<td>&lt;5.0</td>
<td>4.9</td>
</tr>
</tbody>
</table>

tients with AML is usually contraindicated in the presence of leukemic blasts. The cause of pancytopenia should be carefully evaluated before the administration of G-CSF in patients with leukopenia.

In the present patient, APL was therapy-related rather than de novo, since chromosome analysis demonstrated del(7) in addition to t(15;17); the former is usually observed in patients with therapy-related leukemia (1). The loss of an entire chromosome or deletion of various parts of chromosome 7 or 5 has been frequently observed in therapy-related AML and myelodysplastic syndrome (1).

The frequency of chromosome 7 abnormality in therapy-related APL has been described only in one case report (3); however, cumulative data have not been reported in the literature reviews (2, 3).

About 30 patients with therapy-related APL caused by the alkylating agent, topoisomerase II inhibitor, and radiation, were reviewed in the literature (3). However, no patient with APL caused by epirubicin was reported. For patients with hepatocellular carcinoma, a case of therapy-related AML who was treated with intra-arterial injection of epirubicin, carboplatin and doxorubicin, intravenous administration of...
etoposide, and radiation was reported (4). The present patient is the first reported case of therapy-related APL in a patient with hepatocellular carcinoma caused only by injection of epirubicin by TACE.

APL has recently been treated by administration of leucocyte differentiation agents such as ATRA, with chemotherapy (5, 7). In the present patient, ATRA was initially administered since the patient had neutropenia. Complete hematological and cytogenetic responses were achieved only with the administration of ATRA.

The cause of the accelerated accumulation of ascites in patients treated with ATRA remains unknown, and also whether it is a symptom of ATRA differentiation syndrome or is due to liver damage remains to be elucidated.

Adult respiratory distress syndrome (ARDS) is frequently observed as ATRA differentiation syndrome (5, 7), resembling capillary leak syndrome. During the initial phase of ARDS, large numbers of neutrophils enter the lungs, and damage to the capillary endothelium and alveolar epithelium are early events, accompanied by interstitial and intra-alveolar edema and hemorrhage (7-9). The release of inflammatory cytokines, such as IL-2, IL-6, IL-8, TNF-α, and G-CSF, increases the expression of adhesion molecules on the myeloid cell surface including intracellular adhesion molecule 1 (ICAM-1), enhances the migratory capabilities of promyelocytes as they undergo differentiation into neutrophils, and increases the production of reactive oxygen, nitrogen species, and proteases, shown to be involved in the biochemical pathogenesis of ARDS (7-11). In the present patient, leukocytosis and pulmonary symptoms of ARDS in ATRA differentiation syndrome were not observed.

Ascites after ATRA treatment was reported in a case of APL (6), and the authors regarded it as a symptom of ATRA differentiation syndrome. That case showed no pulmonary symptoms, previous liver disorder, or liver damage during the clinical course. The present patient is the second reported case with ascites after ATRA treatment, although he previously suffered from chronic hepatitis and hepatocellular carcinoma.

APL was shown to express and secrete IL-1β, IL-6, and TNF-α, and TNF-α was incubated with ATRA (12). In the present patient, the plasma concentrations of IL-6, IL-8, and G-CSF were elevated. These increased cytokines might induce leakage from the hepatic capillaries to form ascites like capillary leak syndrome in ARDS. Alternatively, ATRA might cause liver damage, as was observed with an increase in total bilirubin and transaminase activities during the administration of ATRA, further accelerating the accumulation of ascites. Thus, the accumulation of ascites should be carefully monitored while administering ATRA, especially in cases such as the present patient, with previous chronic hepatitis and hepatocellular carcinoma.

References