Case Study

Persistent Hypoplastic Acute Promyelocytic Leukemia with a Novel Chromosomal Abnormality of 46, XY, t(15;17), t(9;11)(q13;p13)

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A diagnosis of acute promyelocytic leukemia (APL) is usually made when normal hematopoietic cells are substituted by APL cells. We encountered a unique APL patient who presented with persistent hypoplastic features of APL. An 84-year-old man presented with leukopenia (2.2 × 10^9/L) and anemia (Hb 12.5 g/dL). Five months later, the bone marrow (BM) was hypoplastic with a normal proportion of blasts and promyelocytes (5.2%), although the latter cells were hypergranular. The karyotype of BM cells was 46, XY, t(15;17)(q22;q12), t(9;11)(q13;p13). Two months later, the BM remained hypoplastic with 8.5% hypergranular promyelocytes, some of which contained faggot of Auer rods. RT-PCR examination yielded the PML- RARA transcript, and its sequencing revealed the breakpoint of PML to be bcr2. The patient was treated with all-trans retinoic acid under a diagnosis of APL with improvement of the bicytopenia. FISH analysis of BM cells yielded a negative result regarding t(15;17), although RT-PCR was positive for PML-RARA mRNA. Six months later, APL recurred with the same karyotypic abnormalities and therapeutic resistance, and the patient died of pneumonia. A persistent hypoplastic state of APL may be a rare event, and the association of t(15;17) and t(9;11) is novel. (J Clin Exp Hematop 55(2) : 71-76, 2015)

Keywords: acute promyelocytic leukemia, t(15;17), t(9;11), hypoplastic APL, bcr2

INTRODUCTION

Acute promyelocytic leukemia (APL), which was first reported in 1957,1 is a type of acute leukemia showing the extensive proliferation of neoplastic promyelocytes, rapid progression, severe coagulopathy, and an association with a poor prognosis. The prognosis of APL patients, however, has been greatly improved by differentiation-inducing therapy with all-trans retinoic acid (ATRA).2,3 The pathogenesis of APL was elucidated soon after the development of ATRA therapy.4-6

The clinical manifestation of APL is usually the extensive proliferation of APL cells in both peripheral blood and bone marrow. However, exceptional APL cases manifest as a prolonged early state of leukemia or low-percent leukemia. Here, we report a rare APL patient who showed sustained hypoplastic features of APL, which was associated with mild coagulopathy.

CASE REPORT

An 84-year-old man was found to have a low white blood cell (WBC) count of 2.2 × 10^9/L in a hospital in March 2011. He was admitted to the hospital 3 months later because of pneumonia. At that time, his WBC count was 0.82 × 10^9/L with 71% neutrophils. A bone marrow aspirate taken in August 2011 showed hypocellularity without an increase of myeloblasts or promyelocytes, or dysplastic features of hematopoietic cells. The cytogenetic analysis of marrow cells, however, showed an abnormal karyotype of 46, XY, t(15;17)(q22;q12), t(9;11)(q13;p13) in 4 of the 20 cells analyzed (Fig. 1). Therefore, he was referred to our hospital and admitted in August 2011 under a tentative diagnosis of APL. As the medical history, he had had pulmonary tuberculosis, undergone partial gastrectomy because of a perforated ulcer, and developed cerebral infarction, at the ages of 23, 42, and 74, respectively. He also had diabetes mellitus, hypertension, and hepatitis C with an unclear onset.
Physical examination on admission revealed a height of 150 cm, body weight of 48.5 kg, and body temperature of 36.6°C, without signs of a bleeding tendency. Hematologic examination revealed a WBC count of $1.5 \times 10^9$/L with a differential count of 0.3% blasts, 46.3% neutrophils, 2.0% monocytes, and 43.7% lymphocytes, a hemoglobin concentration of 10.4 g/dL, and a platelet count of $198 \times 10^9$/L. Hemostatic examination showed that the prothrombin time was 12.1 seconds, prothrombin time-international normalized ratio 1.04, activated partial thromboplastin time 27.2 seconds, fibrinogen 318 mg/dL, D-dimer 5.9 µg/mL (normally 0 to 1 µg/mL), plasmin-α₂ plasmin inhibitor complex 2.4 µg/mL (normally less than 0.8 µg/mL), and thrombin-antithrombin complex 4.1 ng/mL (normally less than 3.0 ng/mL), indicating mild coagulopathy. The amount of Wilms’ tumor 1 (WT-1) mRNA in the peripheral blood was 7,000 copies/µg RNA (normally fewer than 50 copies).

We reviewed the bone marrow on a smear preparation made in the former hospital, and found a small number of abnormally hypergranular promyelocytes (Fig. 2A). Then, we performed bone marrow aspiration, and the aspirate showed a nucleated cell count of $0.6 \times 10^9$/L with a differential count of 0.4% myeloblasts and 5.2% promyelocytes, 49.5% granulocytes, 21.1% erythroblasts, 24.0% lymphocytes, and 1.9% plasma cells. Although no dividing cells were obtained on chromosomal analysis, fluorescent in situ hybridization (FISH) analysis showed that cells carrying the PML-RARα fusion signal comprised 4.1%. From these findings, a diagnosis of hypoplastic APL was made.

Clinical course (Fig. 3A, 3B)

Although a diagnosis of APL was made, we did not start chemotherapy because of the low percentage of marrow promyelocytes, normal platelet count, mild anemia, and mild coagulopathy. The leukemia, however, gradually progressed with severe anemia (Hb: 6.1 g/dL) and the appearance of a few circulating promyelocytes with Auer rods or faggot cells in October 2011. Therefore, we performed bone marrow examination again to confirm the diagnosis of APL molecularly. Although the bone marrow was hypoplastic, the percentage of abnormal promyelocytes, some of which were faggot cells, was increased to 8.5%, while that of myeloblasts was 1.0%. Reverse transcriptase polymerase chain reaction (RT-PCR) analysis of the marrow cells demonstrated a chimeric transcript of PML-RARα, and the PCR product was revealed to be the variable long form of the PML-RARα isozyme, confirmed as bcr2 by sequence analysis of the product. After molecular confirmation of the diagnosis of APL, we started to treat the patient with ATRA (45 mg/sqm), with improvements of the leukopenia, anemia, and coagulopathy. At the beginning of December 2011, the percentage of PML-RARα-positive bone marrow cells was within normal limits on FISH analysis, with the disappearance of abnormal promyelocytes, although RT-PCR showed the PML-RARα transcript. We discontinued ATRA, and the patient was
transferred to a hospital for general medical care. However, the APL recurred in August 2012, and the patient was readmitted to our hospital. In the bone marrow, abnormal promyelocytes with fine but not coarse azurophil granules comprised 6.8% of nucleated cells and PML-RARA-positive cells were 7.2% on FISH analysis. The patient was treated again with ATRA (45 mg/sqm) with the progression of leukemia, showing 20% bone marrow promyelocytes and 67.6% PML-RARα-positive cells. Chromosomal analysis showed the same karyotypic abnormality of 46, XY, t(15;17)(q22;q12), t(9;11) (q13;p13) in 18 of the 20 cells analyzed. Therefore, we switched from ATRA to tamibarotene (8 mg/day), with the further progression of leukemia and the appearance of many blast-like cells in the peripheral blood (Fig. 2B) (65.6% in 7.4 × 10⁹/L WBC). We then started treatment with arsenic trioxide (6.4 mg/day) at the end of October 2012; however, the patient died of pneumonia without the improvement of leukemia.

**DISCUSSION**

The present APL patient had 2 very characteristic clinical features. Firstly, the number of bone marrow PML-RARα-positive cells at the initial diagnosis was very small. Secondly, the APL showed very slow progression after the diagnosis. Therefore, the present case showed an unusual clinical picture of persistent hypoplastic APL.

To the best of our knowledge, there have been 3 similar cases of APL diagnosed at an early stage or exhibiting unusual smoldering evolution. One of these 3 cases was suggested to have transformed from myelodysplastic syndrome (MDS). One of the 2 cases of smoldering APL was associated with sarcoidosis, and the authors speculated that the activation of the immune system by the sarcoid may have inhibited the progression of leukemia. The remaining case was associated with therapy-related MDS. This patient was treated with ATRA and arsenic trioxide, with the improvement of both APL and dysplastic features of hematopoietic cells. In other clinical studies of APL, although not well documented, 3 cases of therapy-related APL appeared to be smoldering APL, which progressed to overt leukemia after the period of therapy-related MDS. In 2 of the above-mentioned cases, cytopenia was the first clinical manifestation, and marrow PML-RARα-positive cells proliferated 1 year or 3 months after the initial diagnosis. Collectively, cytopenia could occur irrespective of the small number of APL cells in such early APL cases, including the present patient. Slow progression also appears to be characteristic of these APL cases.

More than 90% of APL patients carry t(15;17)(q22;q12),
Fig. 3. Clinical course of the present patient. (3A) Clinical course from presentation to the complete remission of promyelocytic leukemia. (3B) The course from relapse of the leukemia to the terminal period. WBC, white blood cell; Hb, hemoglobin; PLT, platelet; RCC, red cell concentrate; PC, platelet concentrate; pro.; promyelocyte.
and a chimeric gene of PML-RARA is generated as a result of reciprocal translocation between the PML gene located on 15q22 and the RARA gene located on 17q12. In this reciprocal translocation, 3 breakpoints within the PML gene have been identified, that is, in intron 3, intron 6, and exon 6, called bcr3, bcr1, and bcr2, respectively. The frequencies of the PML-RARA isoform derived from bcr3, bcr1, and bcr2 have been reported to be 30%, 65%, and 5%, respectively.7 APL cases with the bcr3 isoform are associated with a high relapse rate and, consequently, with a poor prognosis when compared with those with the bcr1 isoform.12 APL cases with the bcr2 isoform, which was observed in the present patient, are rare and associated with a poor response of APL cells to ATRA in vitro.13 The present patient, however, was initially treated with ATRA alone and showed a favorable response.

Chromosomal abnormalities in addition to t(15;17) are observed in 26% to 39% of APL patients.14,15 Among these abnormalities, trisomy 8 is the most common, being observed in 28% to 36% of APL patients. Other abnormalities involve number 7, 9, and 16 chromosomes;14,15 however, the association of t(9;11)(q13;p13), which was observed in the present patient, has not been reported, and thus appears to be novel. Furthermore, t(9;11) itself with the breakpoints of (q13;p13) has not been reported in hematologic malignancies. It has been reported that APL patients showing additional chromosomal abnormalities are associated with more marked coagulopathy and a poor prognosis.15 However, several clinical trials reported that there were no significant differences in the complete remission and overall survival rates between APL patients with solely t(15;17) and additional abnormalities.17,18

The mechanisms of the persistent hypoplasia in APL are unclear. The association of t(9;11)(q13;p13) may have contributed to the characteristic clinical picture in the present patient, while differences in the PML-RARA isoform may not be related to the early form of APL because no relationship between the isoform and early picture of APL has been described. As another possibility, immune-mediated suppression of APL cells, either by cytotoxic T cells or humoral factors, as observed in myelodysplastic syndrome, might have acted in the present patient.19 Thus, the accumulation of APL cases exhibiting hypoplastic features and slow progression and their in-depth molecular investigation will be required to elucidate the characteristics of this unique type of APL.

**DISCLOSURE**

The authors declare no conflicts of interest with any individuals or companies.

**REFERENCES**


4 Rowley JD, Golomb HM, Dougery C: 15/17 translocation, a consistent chromosomal change in acute promyelocytic leukemia. Lancet 1:549-550, 1977


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