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【 CASE REPORT 】

Very Late Relapse of Acute Promyelocytic Leukemia 17 Years after Continuous Remission

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Abstract:
The prognosis of acute promyelocytic leukemia (APL) has been improved by the combination of all-*trans* retinoic acid (ATRA) with chemotherapy. Nonetheless, relapse occurs in a certain proportion of patients, mostly within three to four years after treatment. We herein report a patient treated with ATRA and chemotherapy achieving remission who relapsed approximately 17 years after the treatment. A literature review identified 5 additional reported cases of APL relapse after more than 10 years. None of them presented with generally established risk factors for relapse, such as a high leukocyte count. The potential for late relapse of APL occurring more than 10 years after treatment should be recognized.

Key words: acute promyelocytic leukemia, late relapse, all-*trans* retinoic acid

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Introduction

Acute promyelocytic leukemia (APL) is a distinctive subtype of acute myeloid leukemia (AML) associated with the presence of reciprocal translocation between chromosomes 15 and 17, which generates PML/RARα genes. Owing to the introduction of all-*trans* retinoic acid (ATRA) as a differentiation-inducing therapy, the prognosis of APL has been dramatically improved. Nonetheless, the recurrence rate remains 10-15%, with recurrence occurring mostly within 3-4 years after the achievement of complete remission (CR) in patients treated with ATRA in combination with chemotherapy (1, 2).

We herein report a patient treated with ATRA and chemotherapy who relapsed approximately 17 years after achieving CR, together with a review of other cases of very late relapse occurring more than 10 years after the diagnosis.

Case Report

A 52-year-old Japanese man was diagnosed with APL in November 1999. At the diagnosis, his peripheral blood showed leukocytopenia (1.8×10^9/L with 4% atypical promyelocytes). A bone marrow examination showed an increase in atypical promyelocytes (70%) that possessed t(15; 17) and the PML/RARα gene (Figure a). An immunophenotypic analysis revealed positivity for CD13, CD33, and CD 38 antigens and negativity for CD34 and CD56. The patient received ATRA (45 mg/m^2/day) alone as induction therapy, followed by daunorubicin and behenoyl-cytarabine for progressive leukocytosis. However, he developed differentiation syndrome, which was treated with steroid therapy. He recovered, achieving molecular CR on day 36. He then underwent three cycles of consolidation therapy and six cycles of maintenance therapy according to the JALSG AML89 protocol, which did not contain ATRA (3). The last chemotherapy was started in April 2002. The patient was regularly fol-

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a) b)

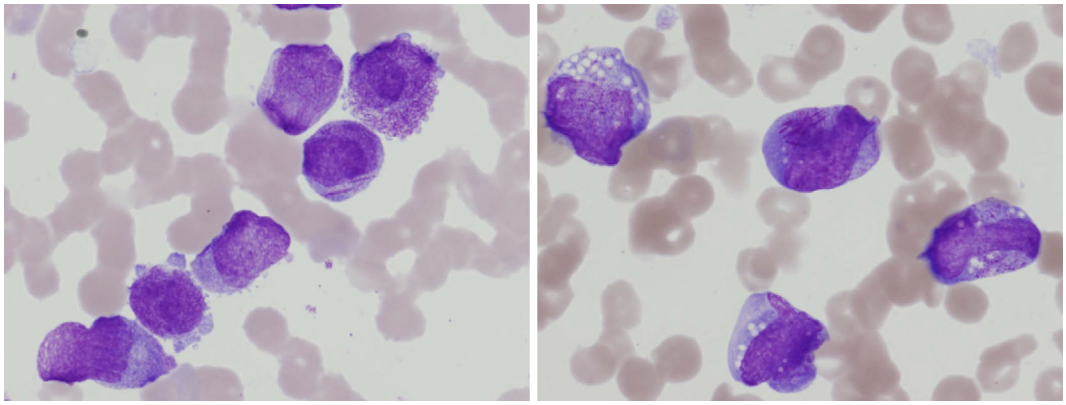

Figure. **The proliferation of atypical promyelocytes in the bone marrow (a) at the initial presentation and (b) at relapse.**

Table. **Reported Cases of Acute Promyelocytic Leukemia Relapsing More than 10 Years after Achieving First Remission.**

Case (Reference)	Sex	Age (year)	Leukocytes at diagnosis ($\times 10^9$/L)	Therapy at initial diagnosis	Years between diagnosis and relapse	Therapy at relapse	Outcome
1 (4)	Female	16	Not described	Chemotherapy alone	12.9	Chemotherapy+ATRA	Remission
2 (5)	Female	52	1.2	Chemotherapy+ATRA	11.3	ATRA+ATO	Remission
3 (6)	Female	23	Not described	Chemotherapy+ATRA	15.0	ATO+radiation	Remission
4 (7)	Female	42	Not described	Chemotherapy+ATRA	16.8	Chemotherapy+ATRA	Remission
5 (8)	Female	9	3.5	Chemotherapy+ATRA	15.2	ATRA+ATO	Remission
Present case	Male	52	0.3	Chemotherapy+ATRA	16.6	ATRA	Early death

ATRA: all-trans retinoic acid, ATO: arsenic trioxide

lowed up, and molecular CR was last confirmed in May 2007. For several years beginning in 2011, he was lost to follow-up.

In June 2016, 17 years after first achieving molecular CR, he developed *Legionella* pneumonia. Laboratory data revealed severe pancytopenia: a leukocyte count of 0.3×10^9/L with 2% promyelocytes, hemoglobin of 8.6 g/dL, and a platelet count of less than 0.5×10^9/L. His bone marrow demonstrated increased atypical promyelocytes (62%) that possessed a karyotype of t(15;17) and the PML/RARα gene (Figure b). An immunophenotypic analysis revealed positivity for CD13, CD33, and CD38 antigens and negativity for CD2, CD34, and CD56. The clonality could not be evaluated due to lacking a sample at the diagnosis. Although he was placed on ATRA 45 mg/m^2 together with an antimicrobial treatment, his respiratory failure progressed. He succumbed seven days after the diagnosis of pneumonia.

Our extensive literature review identified 5 reported cases of very late relapse occurring more than 10 years after the diagnosis, and their clinical courses are summarized in Table (4-8). One case was also identified in another report but lacked sufficient details and was therefore excluded (1). There was a female predominance, and the median age was 33 years, including 1 pediatric patient 9 years of age. The leukocyte counts at the diagnosis were available in 3 cases, all of which were less than 10×10^9/L. All patients but 1 were treated with ATRA in combination with chemotherapy and relapsed at a median of 15.1 years (range, 11.3-16.8) after the diagnosis. The treatments given after relapse were variable, including arsenic trioxide. All of these patients except ours successfully achieved second CR.

Discussion

Currently, newly diagnosed APL patients are generally treated with ATRA in combination with chemotherapy, which has resulted in a CR rate above 90% and a long-term disease-free survival rate above 80% (9). In addition, based on the published results of long-term follow-up data, patients who maintained CR for longer than five years have generally been considered to be cured (2). With regard to late relapse of APL, however, Kelaid et al. reported that 3.2% of 582 APL patients achieving CR relapsed more than 4 years after achieving CR, with a median time to relapse of 72 months (range, 50-120 months) (1). Although not clearly described, given this range, it is possible that only 1 (0.6%) of the 154 relapsed patients suffered a relapse more than 10 years after the initial diagnosis. These findings indicate that late relapse of APL does indeed occur in a small proportion of patients, but very late relapse occurring after more than 10 years is even rarer. With regards to other subtypes of AML, there are two large-scale studies showing the possibil-

ity of very late relapse (10, 11). These two studies showed that 3 (0.6%) out of 493 patients and 4 (0.4%) out of 942 patients with relapsed AML relapsed more than 10 years after the initial diagnosis. Based on these data, the difference in the rate of very late relapse among whole relapsed cases between APL and other subtypes of AML was considered comparable. However, since the whole relapse rate of APL is significantly lower than that of other subtypes of AML, it is plausible that the absolute number of very late relapse is smaller among APL patients than other subtypes of AML.

We unexpectedly experienced a patient with APL who relapsed approximately 17 years after achieving CR. The clonality could not be examined in our case due to a lack of a sample being obtained at the diagnosis. Therefore, whether this was indeed a case of relapse or the coincidence of APL originating from a different clone could not be conclusively determined, which was a major limitation of this report. However, this experience prompted us to review the reported cases of very late relapse of APL. Our extensive literature review identified only five additional cases. It was noted that there was a female predominance (male/female, 1/5), which was also demonstrated in late relapse cases by Kelaid et al. (7/12) (1). Since there are so few evaluated cases of late and very late relapse cases, these findings may be coincidental, and their clinical significance is unknown. Treatment agents given for APL at relapse varied among the cases, including arsenic trioxide. Except for our present case of early death due to preexisting bacterial pneumonia, all patients successfully achieved CR, suggesting that very late relapse is not associated with refractoriness to treatment.

A generally accepted risk factor for the relapse of APL is a high leukocyte count (i.e., 10×10^9/L) at the diagnosis (12, 13). Although data were available in only 3 of 6 cases of very late relapse of APL, these 3 patients presented with a leukocyte count of less than 10×10^9/L and thus were classified as at a low risk for relapse. Therefore, a high leukocyte count was suggested not to be a risk factor for very late relapse of APL. However, this is not conclusive due to the small number of patients evaluated. Several investigators have recently attempted to evaluate the effects of other factors on the relapse of APL, such as the expression of CD 56 (14), CD2, and CD34 (15, 16), and FMS-like tyrosine kinase 3 (FLT3) mutation (17). Such data were scarce in the reported cases of very late relapse of APL and thus could not be evaluated. Therefore, the impact of these novel risk factors on the occurrence of very late relapse should be investigated with the accumulation of more cases in a future study.

Physicians should be aware of the possible occurrence of very late relapse after achieving CR in patients with APL and should share this information with their patients. There are no established factors predicting the late or very late relapse of APL at present. The accumulation of cases with a longer follow-up is needed to further evaluate the clinical, phenotypic, and molecular characteristics of patients with very late relapse of APL.

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

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