

A variant acute promyelocytic leukemia with t(11;17) (q23;q12); *ZBTB16-RARA* showing typical morphology of classical acute promyelocytic leukemia

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A subgroup of acute leukemia with morphology resembling acute promyelocytic leukemia (APL) shows variant translocations involving *RARA* and has a different morphology from that of classical APL. The variant APL with t(11;17)(q23;q12); *ZBTB16-RARA* subgroup has been reported to have leukemic cells with regular nuclei, many granules, absence of Auer rods, an increased number of Pelgeroid neutrophils, strong myeloperoxidase (MPO) activity, and all-trans-retinoic-acid (ATRA) resistance. Here, we report a case of variant APL with t(11;17)(q23;q12); *ZBTB16-RARA* showing typical morphological features of classical APL, including numerous Auer rods and faggot cells. The leukemic cells expressed CD13, CD33, CD117, human leukocyte antigen (HLA)-DR, and cytoplasmic-MPO on the immunophenotyping study. The diagnosis was confirmed by cytogenetic and molecular studies. To distinguish variant APL cases from classical APL cases, regardless of whether morphologically the findings are consistent with those of classical APL, combining morphologic, immunophenotypic, cytogenetic, and molecular studies before chemotherapy is very important.

Key Words APL, t(11;17), *ZBTB16-RARA*, *PLZF*

INTRODUCTION

Acute promyelocytic leukemia (APL) with t(15;17)(q22;q12); *PML-RARA* is characterized by the presence of promyelocytes and multiple Auer rods, hemorrhagic tendency, and *PML/RARA* fusion mRNA [1-4]. A subgroup of acute leukemia that has a similar morphology as APL shows variant translocations involving *RARA*. These variant fusion partners include *ZBTB16* at 11q23, *NUMA1* at 11q13, *NPM1* at 5q35, and *STAT5B* at 17q11.2 [5-8]. Some of the variant APL with t(11;17)(q23;q21) cases that are associated with the *ZBTB16-RARA* fusion gene have been reported as being resistant to all-trans-retinoic acid (ATRA) [9]. Therefore, differential diagnosis of variant APL with t(11;17)(q23;q12) from classical APL with t(15;17)(q22;q12); *PML-RARA* is very important. Variant APL cases usually show different morphological characteristics. The variant APL with t(11;17)(q23;q12); *ZBTB16-RARA* subgroup has been reported to have leukemic cells with regular nuclei, many granules, absence of Auer rods, an increased number of Pelgeroid neu-

trophils, and strong myeloperoxidase (MPO) activity [10]. Therefore, when leukemic cells show typical morphology of classical APL with t(15;17)(q22;q12); *PML-RARA*, the possibility of variant APL is very low. We report a case of variant APL with the t(11;17)(q23;q12); *ZBTB16-RARA* showing typical morphology of classical APL.

CASE REPORT

In January 2010, a 52-year-old man was referred to our hospital because of pancytopenia. Complete blood count (CBC) showed pancytopenia with white blood cells, 1,620/ μ L (segment neutrophils, 12.3%; lymphocytes, 60.5%; monocytes, 27.2%; eosinophils, <1%; basophils, <1%; leukemic cells, 8%); hemoglobin, 8.8 g/dL; and platelets, 98,000/ μ L. Bone marrow biopsy revealed about 100% cellularity, and that 80% of the nucleated elements were leukemic cells. The leukemic cells showed medium to large size, irregular shape, finely chromatinized nuclei with distinct nucleoli, and moderate amount of blue cytoplasm with azurophilic



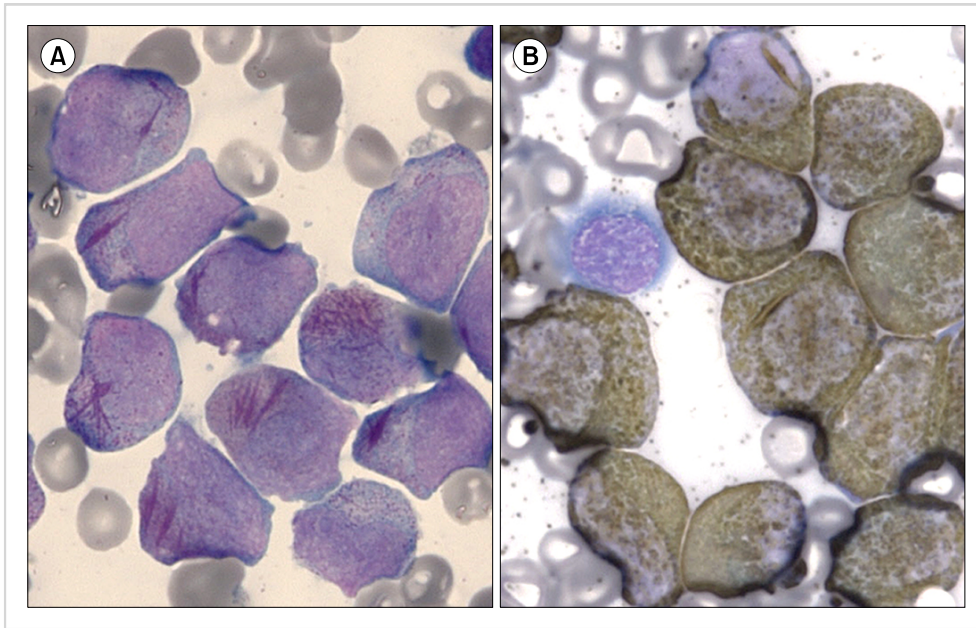


Fig. 1. Bone marrow aspirates showing typical acute promyelocytic leukemia morphology, including numerous leukemic promyelocytes with faggot cells (A) Wright stain; $\times 1,000$ and strong myeloperoxidase activity (B) myeloperoxidase stain; $\times 1,000$.

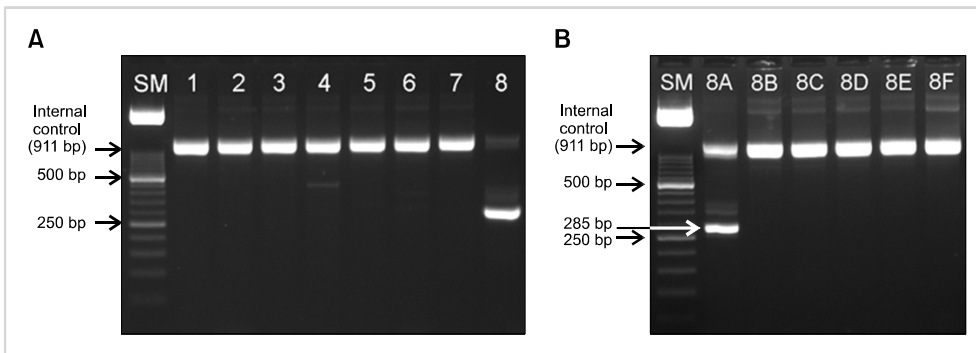


Fig. 2. In the first PCR (A) for screening of leukemia-associated genes, there is a positive band in lane 8 (between 250-300 bp). In the split-out reaction (B) using a single specific primer pair, a *t(11;17)(q23;q21)*; *ZBTB16-RARA* fusion (285 bp) is confirmed, as revealed by the bands in lane 8A.

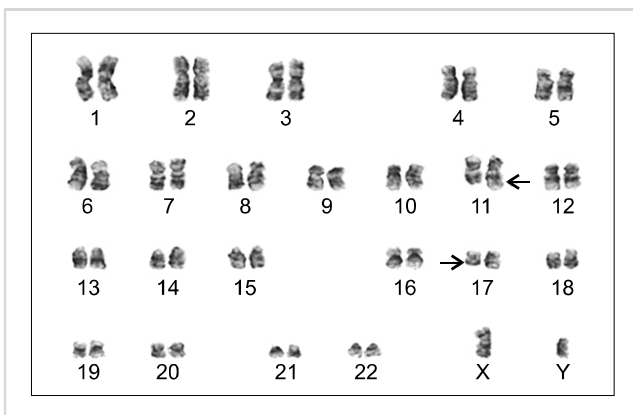


Fig. 3. The karyotype of the patient was 46,XY,t(11;17)(q23;q21)[17]/46,XY[3].

granules. The leukemic cells showed multiple Auer rods and frequently showed faggot cells (Fig. 1A). They were strongly positive to MPO stain (Fig. 1B). The leukemic cells expressed CD13, CD33, CD117, human leukocyte antigen (HLA)-DR, and cytoplasmic-MPO, as revealed by the im-

munophenotyping study. *ZBTB16-RARA* translocation was detected on the leukemia gene screening test by reverse transcription-nested polymerase chain reaction (Fig. 2; Hemavision, DNA technology, Denmark). Cytogenetic study revealed *t(11;17)(q23;q21)* (Fig. 3). The patient is being treated with chemotherapy without ATRA.

DISCUSSION

Most APLs show typical morphology, including irregular and variable nuclei that are often kidney-shaped or bilobed; cytoplasm containing densely packed or even coalescent large granules that stain bright pink, red, or purple in Romanowsky stains; and multiple Auer rods [1-4, 10]. Therefore, APL can be easily diagnosed at the time of morphologic evaluation. However, variant APL *t(11;17)(q23;q21)* has been reported to have atypical APL morphology, and Auer rods are seldom observed [9, 10]. Absence of Auer rods or faggot cells is especially considered as a characteristic morphologic feature of this subtype [9, 10]. In variant APLs, including variant *RARA* translocation, the diagnosis can be made by chromo-

some analysis or molecular study [11-13]. The results may show the typical karyotype t(15;17)(q22;q12); *PML-RARA* or the variant *RARA* translocation [11-13]. However, in our case, the typical morphology of classical APL, including multiple Auer rods in numerous leukemic cells and frequent faggot cells, was observed, and the karyotype and molecular studies showed t(11;17)(q23;q12) and *ZBTB16-RARA* fusion. At the time of morphologic evaluation, our case showed findings consistent with those of APL with t(15;17)(q22;q12), before chromosome analysis and molecular study were performed. The typical immunophenotype of APL has been reported to be distinctive unlike those in other acute myeloid leukemia (AML) cases. The leukemic cells in the former express myeloid antigens such as CD13 and CD33 but show weak or negative reaction to CD34 and HLA-DR [14]. Some of the microgranular variant APL cases express CD34 and/or HLA-DR [15]. However, variant APL with t(11;17)(q23;q12); *ZBTB16-RARA* subgroup has been reported to show the same immunophenotype as that in classical APL [10]. Interestingly, in our case, the leukemic cells expressed HLA-DR in addition to CD13, CD33, and CD117, unlike other cases that have previously been reported [10]. The variant APL with t(11;17)(q23;q12); *ZBTB16-RARA* subgroup usually shows resistance to ATRA therapy [9]. Therefore, our patient is being treated with alkylating agents rather than the classical APL regimen that includes ATRA. The present study emphasizes the importance of combining morphologic, immunophenotypic, cytogenetic, and molecular studies to distinguish variant APL cases from classical APL cases before initiating chemotherapy, regardless of whether the morphological study reveals findings consistent with those of classical APL.

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