A variant of acute promyelocytic leukemia with t(4;17)(q12;q21) showed two different clinical symptoms

Takahisa Nakanishi,[1] Aya Nakaya,[1] Yusuke Nishio,[2] Shinya Fujita,[1] Atsushi Satake,[1] Yoshiko Azuma,[1] Yukie Tsubokura,[1] Ryo Saito,[1] Akiko Konishi,[1] Masaaki Hotta,[1] Hideaki Yoshimura,[1] Yoshihiko Kadosaka,[2] Kazuyoshi Ishii,[1] Tomoki Ito,[1] Koji Tsuta,[2] Shosaku Nomura[1]

[1]First Department of Internal Medicine, and [2]Department of Pathology and Laboratory Medicine, Kansai Medical University, Osaka, Japan

Abstract

A 63-year-old man was diagnosed with a rare variant of acute promyelocytic leukemia (APL) with t(4;17)(q12; q21) that showed atypical morphological features and two different clinical symptoms. He was started on standard induction chemotherapy for acute myeloid leukemia, which decreased myeloblast numbers; however, APL-like blasts remained. He then received a salvage therapy that added all-*trans* retinoic acid (ATRA). After ATRA commenced, APL-like blasts disappeared and cytogenetic analysis became normal. However, myeloblasts subsequently increased, and he became resistant. In summary, this patient exhibited two different clinical courses of acute myeloid leukemia and APL.

Introduction

Acute promyelocytic leukemia (APL) is characterized by the *PML-RARA* fusion gene that results from t(15;17)(q24.1;q21.2) rearrangements. *PML-RARA* is a specific fusion transcript that is present in >95% of APL cases.[1] Additionally, variant rearrangements involving *RARA* have previously been identified, and partners including *PLZF, NPM1, NUMA, SAT5b, PRKAR1A* and *FIP1L1* have been found.[2] The *RARA* fusion partner plays important roles in the morphology, clinical features, and response to all-*trans* retinoic acid (ATRA). In this case report, we document a rare t(4;17)(q12;q21) APL variant that showed atypical morphologic features and two different clinical courses.

Case Report

A 63-year-old man was admitted to our hospital because he had fever and thrombocytopenia. The initial laboratory evaluation of peripheral blood revealed that his white blood cell count was 31500 cells/µL with 58.5% blast cells, hemoglobin was 10.1 g/dL, and platelet count was 1,100 cells/µL. Coagulopathy was absent. Bone marrow examination showed a total nucleated cell count of 168,000 cells/µL with 31.6% myeloblasts and 28.0% promyeloblasts. Most myeloblasts had regular nuclei, and a few promyeloblasts contained azurophilic granules and Auer rods; however atypical APL cells were <1% of the total cells (Figure 1). Myeloperoxidase staining revealed that both myeloblasts and promyeloblasts were positive; however, the staining was not as strong as the typical APL pattern (Figure 2b). These morphological findings revealed features of both M2 and APL according to the French-American-British (FAB) Classification, and did not correlate with typical APL findings. Blasts were positive for CD13/34/HLA-DR, and negative for CD33 by flow cytometry. Wilms' tumor gene 1 (*WT1*) mRNA levels in peripheral blood were 39×10^4 copies/µg RNA. Reverse transcription polymerase chain reaction (RT-PCR) analysis was negative for *PML-RARA, AML1-MTG8, DEK-CAN, NUP98-HOXA9, CBFβ-MYH11, MLL-AF9, MLL-AF6, MLL-ENL, minor-BCR, BCR-ABL, MLL-AF4, ETV6-AML1, E2A-PBX1, SIL-TAL1, FLT-3,* and *C-KIT* (multi-kinase screening exam). Thus, he was initially diagnosed with acute myeloid leukemia with maturation according to the World Health Organization classification from 2008 (M2 in FAB).

An induction chemotherapy regimen consisting of idarubicin (12 mg/m²/d; days 1-3) and cytarabine (100 mg/kg/d; days 1-7) was administered (Figure 1). During induction therapy, the karyotype analysis from diagnosis arrived and revealed an abnormality: 46, XY, t(4;17)(q12;q21) in 6/20 cells (Figure 2c). After induction therapy, blasts in peripheral blood disappeared; however, 3.7% of myeloblasts and 24.0% of promyeloblasts remained in bone marrow. Karyotype analysis revealed: 46, XY, t(4;17)(q12;q21) in 12/20 cells. Fluorescence *in situ* hybridization (FISH) of PML2:RARA3 was 34% positive (2 intact *PML* signals and 3 split *RARA* signals; Figure 2d).

Vysis LSI PML/RARA dual-color, dual-fusion translocation probe was used for FISH analysis (Vysis). *WT1* mRNA levels in peripheral blood were 5.4×10^4 copies/µg

RNA; thus, he was diagnosed with induction failure. From the morphological features and FISH results, we diagnosed him as an APL variant with t(4;17)(q12;q21). We assumed there were two kind of blast stem cells of different origin, and that following initial treatment, blasts from the M2 origin decreased, while blasts of APL origin remained.

We then started a salvage treatment regimen to be effective for both M2 and APL: mitoxantrone (7 mg/m²/d; days 1–3) and cytarabine (200 mg/m²/d; days 1–5) were added to ATRA (25 mg/m²). With the salvage therapy, he achieved hematological remission in peripheral examination, FISH for PML2:RARA3 was 0%, and karyotype analysis was normal in bone marrow. However, blasts in bone marrow remained at 19.5%, the morphological features of which were normal myeloblasts without azurophilic granules or Auer rods. *WT1* mRNA levels in peripheral blood were 2.4×10^4 copies/µg RNA. Blasts were posi-

tive for CD13/34/HLA-DR by flow cytometry. Adding to them, CD71 and glycophorin-A were positive, those were not positive at the diagnosis. The second salvage treatment (high dose cytarabine: 4000 mg/m^2/d; days 1–5) was started with continuous ATRA. After this treatment, 45% of blasts, whose morphology was typical myeloblast, remained in bone marrow, and *WT1* mRNA levels in peripheral blood were 3.3×10^4 copies/µg RNA. Thus, he was diagnosed as resistant to second salvage treatment. At this time, he became so weak that he could not continue aggressive chemotherapy; thus, we changed to palliative therapy. The patient died of pneumonia eight months after diagnosis.

Discussion and Conclusions

Variant fusion genes containing *RARA* are frequently associated with APL. The *FIP1L1-RARA* fusion gene was reported to result from t(4;17)(q12;q21).[3,4] There are two APL cases with *FIP1L1-RARA*. Kondo *et al.*[3] reported a case of a 90-year-old woman where they found split *RARA* signals without a *PML-RARA* fusion signal by FISH. They examined the effect of *FIP1L1-RARA* on ATRA response and found that *FIP1L1-RARA* was ATRA responsive, similar to patients with *PML-RARA*. Consistent with this result, the patient achieved a complete remission by oral ATRA alone (50 mg/d). Menezes *et al.*[4] reported a case of a 77-year-old woman who was started on ATRA. The case revealed morphologically typical APL. Thus, they diagnosed her as *PML-RARA*-negative APL and started an APL protocol. Although we did not confirm the presence of a *FIP1L1-RARA* fusion gene in our case, the patient had the same karyotype abnormality as the two previous cases. Although the precise role of *FIP1L1-RARA* is unknown, the previous cases reported that patients with *FIP1L1-RARA* showed APL-like clinical symptoms. However, our case revealed atypical APL morphology at diagnosis and different clinical features. The most interesting point of our case is that it showed two different clinical characteristics. The induction therapy was standard regimen for acute myeloid leukemia and was effective for the M2 clone, as the number of blasts in bone marrow decreased. However, the APL clone remained, as the number of karyotype abnormalities increased and FISH remained positive. After ATRA was initiated, APL-like blasts disappeared, and karyotype and FISH analyses became normal. From these clinical responses, ATRA could be effective

for APL clones with t(4;17)(q12;q21). However, it is uncertain whether the different clinical features happened accidentally or were related to cytogenetic abnormalities. We tried to use *WT1* mRNA levels in peripheral blood as a biomarker. We expected it would reflect M2 clones, however, it did not. Our results showed that it responded in proportion to the number of bone marrow myeloblasts in induction therapy, how-

ever, it showed contradiction after salvage therapy. It decreased and remained low levels, although bone marrow myeloblasts increased (Figure 1).

In conclusion, we report a variant APL with t(4;17)(q12;q21) that demonstrated two different clinical symptoms. However, the relationship between genetic abnormalities and clinical symptoms for this patient is unclear. Further studies are required to elu-
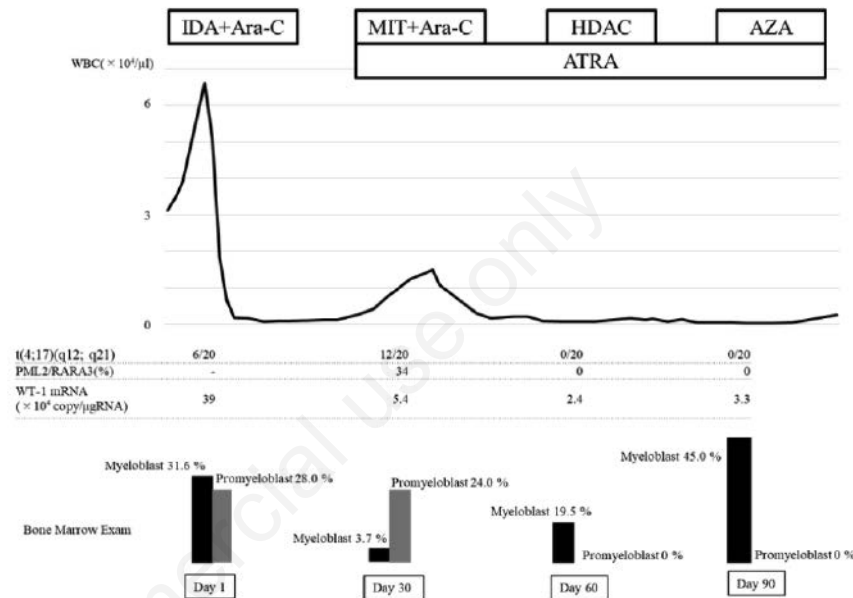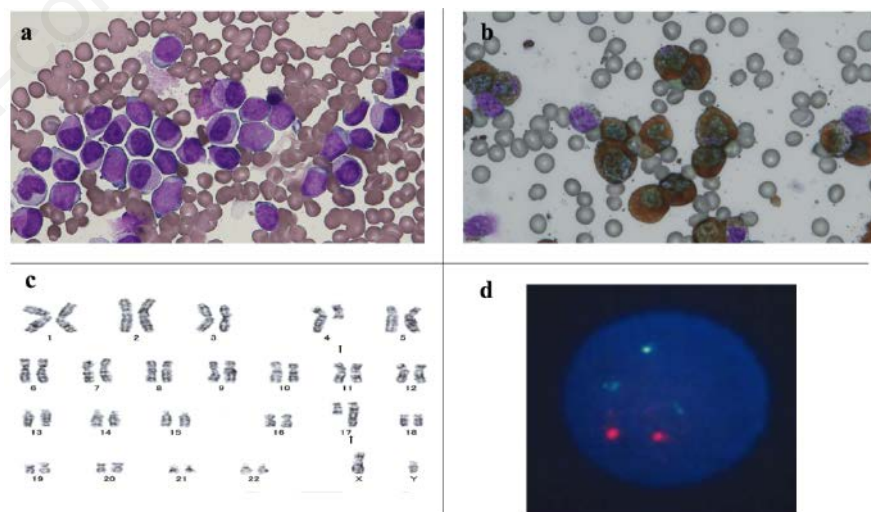

Figure 1. Clinical course.

Figure 2. Morphological and cytogenetic analysis. a) Bone marrow smear showing myeloblasts and promyeloblasts (magnification: 600×). b) Myeloperoxidase staining was positive; however, the straining was not as strong as the typical acute promyelocytic leukemia (APL) pattern (magnification: 600×). c) Karyotype analysis revealed 46, XY, t(4;17)(q12; q21) in blast cells. d) Fluorescence *in situ* hybridization (FISH) of PML2:RARA3 was 34% positive; two intact signals for *PML* (red) and three split signals for *RARA* (green) were identified.

cidate the pathogenesis of variant APL with t(4;17)(q12;q21).

References

1. de Thé H, Chen Z. Acute promyelocytic leukaemia: novel insights into the mechanisms of cure. Nat Rev Cancer 2010;10:775-83.
2. Zelent A, Guidez F, Melnick A, et al. Translocations of the RARalpha gene in acute promyelocytic leukemia. Oncogene 2001;20:7186-203.
3. Kondo T, Mori A, Darmanin S, et al. The seventh pathogenic fusion gene FIP1L1-RARA was isolated from a t(4;17)-positive acute promyelocytic leukemia. Haematologica 2008;93: 1414-6.
4. Menezes J, Acquadro F, Perez-Pons de la Villa C, et al. FIP1L1/RARA with breakpoint at FIP1L1 intron 13: a variant translocation in acute promyelocytic leukemia. Haematologica 2011;96: 1565-6.