Somatic 15q Break After Long-Term Stable Disease in Acute Myeloid Leukemia

Kayo Harada-Shirado,[1] Kazuhiko Ikeda,[1] Hayato Matsumoto,[1] Yutaka Shiga,[2] Miki Furukawa,[1] Hiroshi Takahashi,[1] Hiroshi Ohkawara,[1] Hideyoshi Noji,[1] Yuko Hashimoto,[3] Satoshi Waguri,[4] Shinya Watanabe,[4] Kazuei Ogawa,[1] Yasuchika Takeishi[1]

Clinical Practice Points

- Acute myeloid leukemia (AML) is characterized by a rapid increase of myeloid blasts with severe reduction of normal hematopoiesis.
- Conventional chemotherapy is essential to decrease blasts and facilitate recovery of normal hematopoiesis in almost all patients with AML.
- We report a patient with AML who showed an extremely indolent clinical course with neither chemotherapy nor blood transfusion for > 5 years.
- When his leukemia progressed, a novel somatic chromosomal translocation developed involving 15q, t(15;15)(q13;q15), resembling an inherited translocation reported in patients with the congenital neural disorder Prader-Willi syndrome.
- When this translocation was detected, leukemic cells showed deregulated expression of the necdin (*NDN*) gene in chromosome 15q, which is crucial for the pathogenesis of Prader-Willi syndrome.

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Introduction

Acute myeloid leukemia (AML) is a hematologic malignancy characterized by a rapid increase of myeloid blasts, which severely reduces normal hematopoiesis. Therefore, conventional chemotherapy is essential to decrease leukemic blasts and facilitate recovery of normal hematopoiesis in nearly all cases of AML.[1-3]

We report a unique patient with AML who demonstrated an extremely indolent clinical course with normal platelet count and mild anemia despite consistently increased blasts for more than 5 years without any chemotherapy. Six years after the onset of AML, the patient showed disease progression with a novel chromosomal translocation involving 15q, t(15;15)(q13;q15), which resembles the abnormality in the congenital neural disorder Prader-Willi syndrome.[4,5] When this translocation was detected, leukemic cells showed deregulated expression of necdin (*NDN*), which is located on chromosome 15q and plays a crucial role in the pathogenesis of Prader-Willi syndrome.[6]

[1]Department of Cardiology and Hematology, Fukushima Medical University, Fukushima, Japan
[2]Department of Hematology, Kita-Fukushima Medical Center, Fukushima, Japan
[3]Department of Pathology and Diagnostic Pathology
[4]Translational Research Center
Fukushima Medical University, Fukushima, Japan

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Address for correspondence: Kazuhiko Ikeda, MD, PhD, Department of Cardiology and Hematology, Fukushima Medical University, 1 Hikariga-oka, Fukushima, Fukushima, 960-1295, Japan
Fax: +81-24-548-1821; e-mail contact: kazu-ike@fmu.ac.jp

Case Report

In the beginning of 2007, medical examination of a 63-year-old man showed peripheral leukopenia (1.6×10^9/L) with presence of blasts (5%) and mild anemia (hemoglobin value, 9.7 g/dL). May-Giemsa staining of a bone marrow (BM) smear showed increased middle-sized blasts with clear cytoplasm (Fig. 1A). Most of these blasts were positive for CD13, CD34, and CD117 (Fig. 1, B and C). Based on the proportion of BM blasts (73%) and their partial positivity for myeloperoxidase (Fig. 1A), he was diagnosed as having AML without maturation. At this point, BM chromosome analysis did not show an abnormal karyotype. He initially received chemotherapy, including a remission-induction regimen with cytarabine and daunorubicin,[3] but the proportion of BM blasts did not decrease at all. In the middle of 2007, despite a high proportion of blasts (80% in BM and 10% in peripheral blood), he discontinued chemotherapy for personal reasons. Since then, unexpectedly, both the proportion of peripheral blasts (5%-15%) and the leukocyte count ($2.0\text{-}5.0 \times 10^9$/L) have not changed significantly for more than 5 years, although he did not

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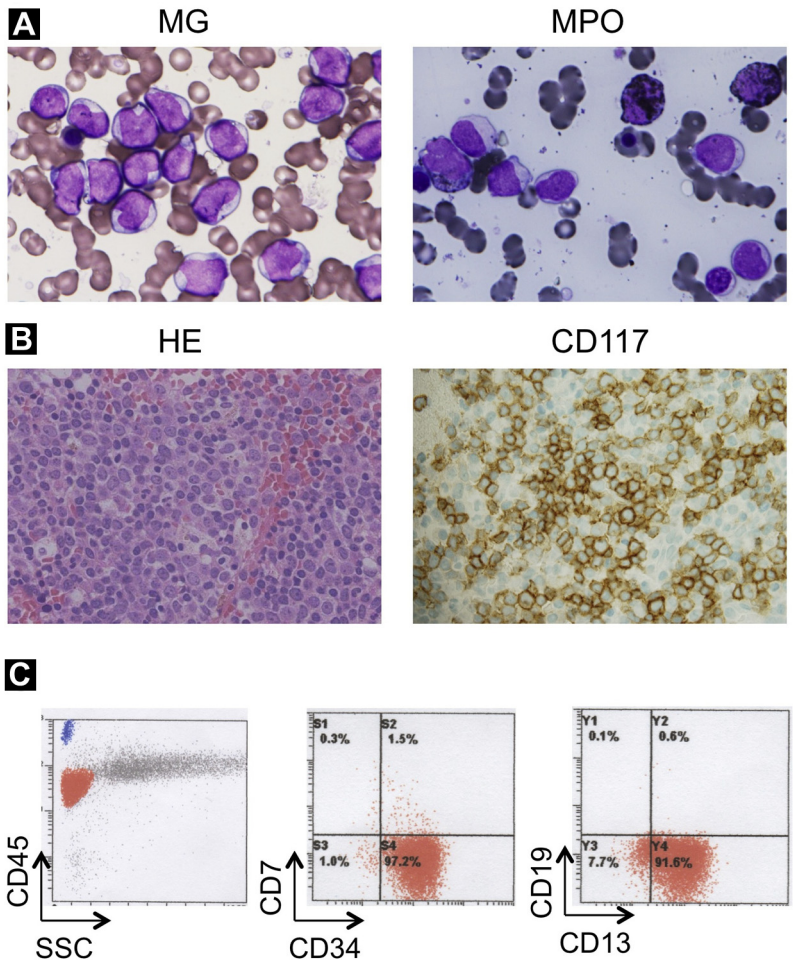
Figure 1 Bone Marrow (BM) Findings. (A) BM Smear With May-Giemsa (MG) Staining Showed Proliferation of Middle-Sized Blasts With Clear Cytoplasm. Proportion of Blasts in the BM had Been 60% to 80% From the Time of Onset and Throughout an Observation Period of Approximately 6 Years (2007-2013). About 10% of Blasts Were Positive for Myeloperoxidase (MPO). Original Magnification was ×600. (B) Hematoxylin and Eosin (HE) Staining of Paraffin-Embedded BM Showed Hypercellular Marrow With Diffuse Infiltration of Leukemic Blasts, Which Stained Positively for CD117 (×400). (C) Flow Cytometry of BM Cells. Leukemic Cells, Gated by low Side Scatter (SSC) and Weak CD45 Expression ($SSC^{low}CD45^{weak}$ Blasts), are Shown as Orange Dots in Each Panel. Proportion of $SSC^{low}CD45^{weak}$ Blasts in the Total BM Cells was 61% (Left Panel). More Than 90% of These $SSC^{low}CD45^{weak}$ Blasts Were in the $CD7^{-}/CD34^{+}$ (Middle Panel) and $CD13^{+}/CD19^{-}$ Fractions (Right Panel)



receive any chemotherapy. In addition, his general condition had been stable without any blood transfusion. However, in 2012, when both the proportion (50%-80%) and absolute number (10-20 × 10^9/L) of peripheral blasts increased, a new chromosomal translocation t(15;15)(q13;q15) was present in 15 of 20 cells in the analysis without addition of mitogen (Fig. 2A). He then received hydroxyurea, which controlled his blast count for 9 months. Thereafter, his peripheral blast count increased and he began combination chemotherapy in June 2013.

Discussion

Indolent Clinical Course

An indolent clinical course without chemotherapy is extremely rare in AML. In fact, there have been only 8 patients reported with smoldering AML who survived more than 12 months without requiring conventional chemotherapy.[7-9] Most of these 8 patients showed mild leukopenia and nonsevere anemia as well as the initial findings seen in our patient. Severe thrombocytopenia was seen in only 1 of these patients. Cytogenetic analysis was performed in 5 of these 8 patients with indolent AML, and only 1 of them had an abnormal karyotype of del(6)(q21).[9] At the onset, our patient also had a normal karyotype. Thus, mild cytopenia with normal cytogenetic features at the onset might be associated with a slowly progressive indolent AML. However, the detailed cause of such an indolent course is unclear in our present patient.

Cytogenetic and Genetic Abnormality at Disease Progression

The novel translocation t(15;15)(q13;q15) was observed 6 years after the onset of AML in our patient. When this translocation was