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(Citation)
International Journal of Laboratory Hematology,46(6):988-990

(Issue Date)
2024-12

(Resource Type)
journal article

(Version)
Accepted Manuscript

Near-triploidy with four Philadelphia chromosomes in adult B-lymphoblastic leukemia with *BCR::ABL1* fusion

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Short title: Triploidy with four Ph in ALL

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The acquisition of additional Philadelphia (Ph) chromosomes, such as double Ph chromosomes, is an uncommon finding at the initial diagnosis of Ph-positive acute lymphoblastic leukemia (ALL). Cases harboring three or more Ph chromosomes are rare.

A 69-year-old male was admitted for the precise examination of anemia and leukocytosis. Three months ago, his peripheral blood counts were normal. Peripheral blood tests on admission were hemoglobin 68 g/L, platelets 122 × 10^9/L, and leukocytes 11.0 × 10^9/L: 17% blasts, 1% myelocytes, 2% metamyelocytes, 4% stab cells, 48% segmented neutrophils, 26% lymphocytes, and 2% monocytes. Bone marrow aspirate showed hypercellular marrow, consisting of 73.2% blasts, 10.6% myeloid cells, 7.8% erythroblasts, and 7.8% lymphocytes. These blasts had bizarre and large shapes (Figure 1A), and were negative for myeloperoxidase staining (Figure 1B). They were immunophenotypically positive for TdT, CD34, CD10, CD19, CD22, CD79a, and CD33. G-banding analysis demonstrated near-triploidy as follows:

46,XY,t(9;22)(q34.1;q11.2)[1]/69~78,XXY,+5,−7,+8,−9,t(9;22)×2,+12,+14,+15,+18,−20,+22,+5mar[cp12]/46,XY[7] (Figure 1C). Fluorescence *in situ* hybridization (FISH) on metaphase spreads revealed four *BCR::ABL1* fusion signals on double der(22)t(9;22)(q34.1;q11.2) and two small marker chromosomes in 13 of 20 cells, indicating that two marker chromosomes were also der(22)t(9;22) (Figure 2A). Namely, four Ph chromosomes resulting in four *BCR::ABL1* fusions were generated. Furthermore, two *BCR::ABL1* fusion signals were found in 2 out of 20 metaphases. FISH on interphase nuclei confirmed four *BCR::ABL1* fusion signals (Figure 2B). Molecular screening detected a minor *BCR::ABL1* fusion transcript but no major *BCR::ABL1* fusion. We made a diagnosis of near-triploid B-ALL with *BCR::ABL1* fusion.

The patient received induction therapy with prednisolone and dasatinib and achieved hematological complete remission (CR). Molecular CR was obtained after one course of con-

solidation therapy with hyper-CVAD/MA regimen plus dasatinib. However, he died of severe pneumonia during myelosuppression after the third course.

Near-triploidy (66−80 chromosomes) and near-tetraploidy (>80) are rare cytogenetic abnormalities observed in 1% to 2% of childhood and adult ALL cases.[1] Near-triploidy/tetraploidy is specifically associated with t(12;21)(p13;q22)/*ETV6::RUNX1* fusion in childhood B-ALL. In contrast, other chromosomal translocations, including t(9;22)(q34.1;q11.2), t(1;19)(q23;p13), and t(4;11)(q21;q23), are seldom observed in adult ALL with near-triploidy/tetraploidy.[1] To our knowledge, only one case of near-triploid ALL with Ph chromosomes has been reported.[2] This case was a 3-year-old boy with T-ALL L1, and the karyotype was 63−75 chromosomes with two Ph chromosomes. Thus, this is the first case of B-ALL harboring near-triploidy and four Ph chromosomes.

Near-triploidy usually arises from doubling of hypodiploidy with 30−39 chromosomes.[1] In the present case, an initial occurrence of t(9;22)(q34.1;q11.2) was followed by the duplication of der(22)t(9;22)(q34.1;q11.2) and the loss of one normal chromosome 9. This pseudodiploid clone with double Ph chromosomes probably duplicated to near-tetraploidy with four Ph chromosomes. Afterward, the near-triploidy most likely arose by subsequent random chromosome losses from near-tetraploidy rather than by the doubling of hypodiploidy.[2]

The presence of four Ph chromosomes is expected to enhance tyrosine kinase activity. Actually, *BCR::ABL1* amplification by double Ph was shown to be associated with primary refractoriness to imatinib in Ph-positive ALL.[3] However, in this case, the response to initial treatment using dasatinib was not poor.

(495 words<500 words)

Conflict of interest

No conflicts of interest.

References

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Figure legends

Figure 1.

(A) Bone marrow smear (May–Grünwald–Giemsa staining, ×1000). Large and bizarre lymphoblasts have irregular nuclei, nucleoli, fine nuclear chromatin, and basophilic cytoplasm.

(B) These lymphoblasts are negative for myeloperoxidase staining, while myeloid cells are positive (×1000).

(C) The karyotype of bone marrow cells by G-banding: 78,XXY,+5,−7,+8,−9,t(9;22)(q34.1;q11.2)×2,+12,+14,+15,+18,−20,+22,+5mar. Arrows indicate the rearranged chromosomes, der(22)t(9;22)(q34.1;q11.2) and der(9)t(9;22)(q34.1;q11.2). Arrowheads in marker chromosomes also indicate der(22)t(9;22)(q34.1;11.2).

Figure 2. Fluorescence *in situ* hybridization (FISH) using Vysis LSI BCR/ABL ES Dual Color Translocation Probe Kit (Abbott, Abbott Molecular, IL). FISH was performed on (A) metaphase spreads and (B) interphase nuclei. Two types of fusion signals (green/red, red/green) indicate minor-breakpoint (m-bcr) signal patten.

(A) Arrows indicate four *BCR::ABL1* fusion signals (green/red, yellow) on four der(22)t(9;22)(q34.1;q11.2). Furthermore, two *BCR* signals (green) on normal chromosomes 22 and two *ASS1-ABL1::BCR* fusion signals (red/green) on the der(9)t(9;22)(q34.1;q11.2) are observed.

(B) Two *BCR* signals (green), two *ASS1-ABL1::BCR* signals (red/green) and four *BCR::ABL1* fusion signals (green/red, yellow) are observed in an interphase nucleus. Arrows indicate four *BCR::ABL1* signals.

Figure 1

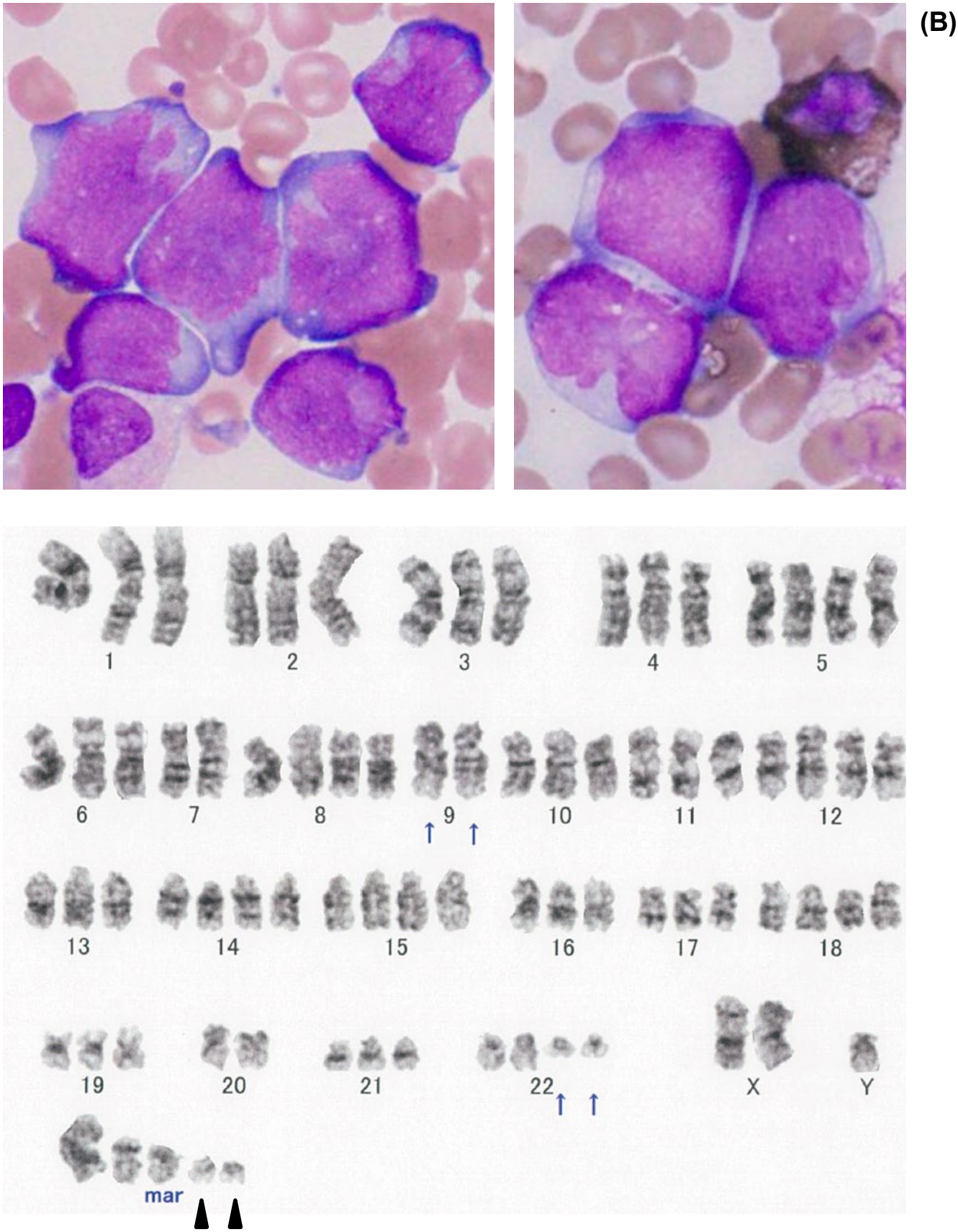

Figure 2