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Novel Four-Way t(8;14;15;21)(q22;q22;q15;q22.1) Translocation Variant in Acute Myeloid Leukemia with *RUNX1::RUNX1T1*

RUNX1::RUNX1T1 İçeren Akut Myeloid Lösemide Yeni Dört-Yol t(8;14;15;21)(q22;q22;q15;q22.1) Varyant Translokasyonu

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To the Editor,

Acute myeloid leukemia (AML) with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* is a distinct AML entity clinically characterized by extramedullary involvement and favorable prognosis with conventional chemotherapy. Variant t(8;21) translocations involving four chromosomes have been rarely described, and some researchers have suggested that the four-way t(8;21) translocation may predict poor prognosis [1,2,3,4,5,6]. Here, we report a case of AML with t(8;14;15;21)(q22;q22;q15;q22.1)/*RUNX1::RUNX1T1*.

A 71-year-old woman presented with a 2-week history of shoulder pain. A computed tomography scan showed a posterior mediastinal mass (long-axis diameter: 9 cm) extending to the spinal canal. The hemoglobin level was 11.9 g/dL; white blood cell count was 11.2×10^9/L with 53.5% blasts, 0.5% myelocytes, 0.0% metamyelocytes, 22.5% neutrophils, 0.5% basophils, 2.5% monocytes, and 20.5% lymphocytes; and platelet count was 187×10^9/L. A bone marrow aspirate smear showed hypercellular marrow with 72% myeloperoxidase-positive blasts with Auer rods. A multiplex quantitative real-time polymerase chain reaction panel revealed a chimeric *RUNX1::RUNX1T1* transcript. Leukemia cells expressed CD34, CD33, CD13, CD19, CD56, and HLA-DR and were characterized as 45, X, -X, and t(8;14;15;21)(q22;q22;q15;q22.1) in all 20 metaphases analyzed. Spectral karyotyping with interphase fluorescence in situ hybridization revealed that distal regions of the 8q22, 14q22, 15q15, and 21q22.1 chromosomes were transferred in a cycle, resulting in *RUNX1::RUNX1T1* fusion (Figure 1). *KIT*, *NPM1*, and *FLT3* mutations were not detected. A biopsy specimen of the mediastinal tumor showed proliferation of leukemic blasts. *RUNX1::RUNX1T1* AML with extramedullary involvement was diagnosed. Although the AML did not respond to two chemotherapy courses with cytarabine and anthracyclines (daunorubicin and idarubicin) and four courses of treatment with venetoclax combined with azacytidine, the patient achieved complete remission with partial hematological recovery of platelets to 90×10^9/L after single-agent gemtuzumab ozogamicin (GO) treatment.

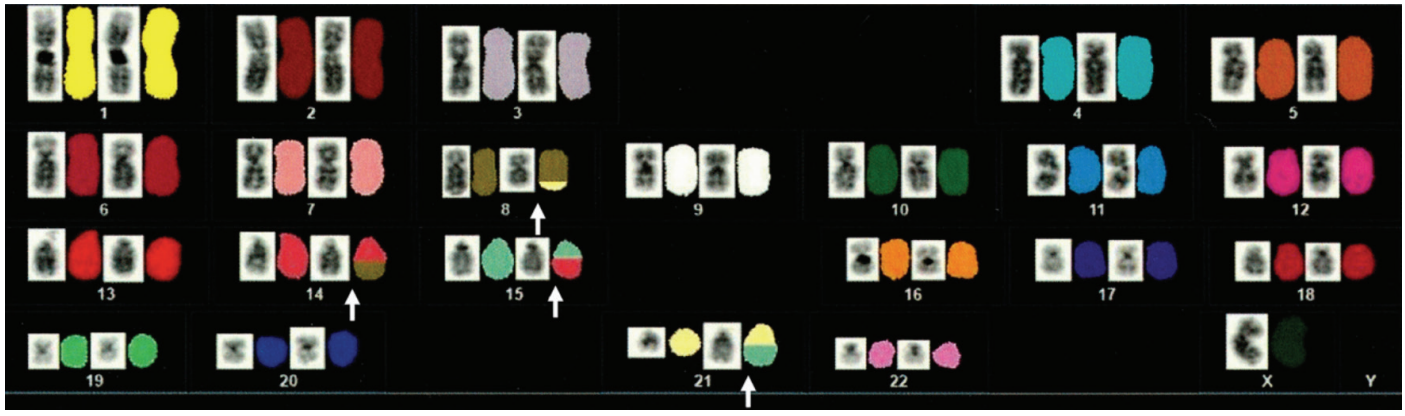

Figure 1. Spectral karyotyping with interphase fluorescence in situ hybridization reveals that distal regions of the 8q22, 14q22, 15q15, and 21q22.1 chromosomes were transferred in a cycle, resulting in t(8;14;15;21)(q22;q22;q15;q22.1). The arrows indicate rearranged chromosomal regions.

Excluding acute promyelocytic leukemia, there have been 8 AML cases presented to date with four-way translocations, including ours [1,2,3,4,5,6,7], among which 7 (88%) had t(8;21) translocations [1,2,3,4,5,6], indicating that four-way translocations are almost always associated with t(8;21) AML. The remaining case was acute megakaryocytic leukemia with t(1;22;17;18)(p13;q13;q22;q12) [7]. Cases of AML with four-way t(8;21) translocations do not share chromosomal regions, excluding 8q22 and 21q22, suggesting that *RUNX1::RUNX1T1* fusion plays a central role in the pathogenesis of AML with four-way t(8;21) translocations. From a clinical viewpoint, only 3 of 6 patients with four-way t(8;21) translocations achieved complete remission after conventional chemotherapy with cytarabine and anthracyclines or mitoxantrone [2,3,4,5,6], including our case, and 2 of the 3 patients who achieved complete remission eventually relapsed [2,4], supporting the conclusion that four-way t(8;21) is a poor prognosis factor in *RUNX1::RUNX1T1* AML. We used spectral karyotyping to demonstrate that the four-way t(8;21) translocations probably occurred consequent to cyclically ordered chromosomal translocations. The mechanisms remain unknown; however, they might be associated with single-event rearrangement via the simultaneous breakage of several chromosomes followed by mismatched joining. Our patient with refractory AML was successfully treated with CD33-targeting GO. In addition to high CD33 expression, *NPM1* mutations, and *FLT3* internal tandem duplication, core-binding factor rearrangements have been associated with favorable responses to GO [8]. In our case, the AML cells weakly expressed CD33 and had wild-type *NPM1* mutations and *FLT3*. Regardless of the CD33 expression levels in bulk AML cells, it has been reported that t(8;21) progenitors express CD33 and are sensitive to GO [9,10]. We suggest that GO is a viable treatment option for refractory AML with four-way t(8;21) translocation.

Keywords: Acute myeloid leukemia, Four-way translocation, t(8;21), *RUNX1::RUNX1T1*

Anahtar Sözcükler: Akut myeloid lösemi, Dört-yol translokasyonu, t(8;21), *RUNX1::RUNX1T1*

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication.

Authorship Contributions

Surgical and Medical Practices: N.T., F.O., T.K., S.Y., K.K.; Concept: T.K., S.Y., K.K.; Design: K.K.; Data Collection or Processing: N.T., F.O., K.K.; Analysis or Interpretation: N.T., F.O., T.K., S.Y., K.K.; Literature Search: N.T., F.O., K.K.; Writing: N.T., F.O., T.K., S.Y., K.K.

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