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Letter to the Editor

A New Complex Translocation t(8;11;21)(q22;q24;q22) in Acute Myeloid Leukemia with *RUNX1/RUNX1T1*

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TO THE EDITOR

The t(8;21)(q22;q22) translocation involving *RUNX1* at 21q22 and *RUNX1T1* at 8q22 is found in 10% of cases of acute myeloid leukemia (AML) M2 subtype.[1] This translocation results in the formation of a *RUNX1/RUNX1T1* fusion gene, which contributes to leukemic transformation by transcriptional repression of normal *RUNX1* target genes, on der(8)t(8;21)(q22;q22). AML with t(8;21) is usually associated with a good response to chemotherapy and long-term disease-free survival.[1] It has been reported that variant translocations, the majority of which are complex three-way translocations, occur in approximately 3 to 4% of cases of AML with t(8;21).[2,3] However, clinical and hematological features of AML with variant t(8;21) remain to be completely characterized. Here, we describe a new complex translocation t(8;11;21)(q22;q24;q22) in a case of AML with *RUNX1/RUNX1T1*.

A 62-year-old man was admitted because of anemia and thrombocytopenia. He had no history of chemotherapy or radiotherapy. Peripheral blood analysis showed hemoglobin 7.8 g/dL, platelets 33 × 10^9/L, and leukocytes 4.6 × 10^9/L with 14% myeloblasts. Bone marrow was hypercellular with 18.2% myeloblasts, 60.0% mature myeloid cells, 5.6% eosinophils, 4.4% monocytes, 6.6% lymphocytes, and 2.6% erythroblasts. Myeloblasts had Auer rods and a few azurophilic granules in the basophilic cytoplasm. Myeloid dysplasia including the pseudo-Pelger-Huët anomaly was also found (Fig. 1A). Myeloblasts were positive for myeloperoxidase staining and immunophenotypically positive for CD13, CD19, CD33, CD34, CD56, and HLA-DR. In light of the cytogenetic and genetic abnormalities described below, we made a diagnosis of AML with *RUNX1/RUNX1T1* according to the World Health Organization classification.[1] Initial induction therapy with cytarabine and idarubicin failed, but the patient achieved hematological and cytogenetic complete remission (CR) after re-induction therapy with cytarabine and daunorubicin. The residual myeloblasts were negative for CD19 and CD56 after the attainment of CR. He received a further three courses of consolidation therapy with high-dose cytarabine, and remained in molecular CR for more than 10 months.

G-banding analysis of bone marrow cells at diagnosis showed 46, XY, t(8;11;21)(q22; q24; q22)[20] (Fig. 1B). Spectral karyotyping confirmed three derivative chromosomes: der(8)t(8;21)(q22;q22), der(11)t(8;11)(q22;q24), and der(21)t(11;21)(q24;q22) (Fig. 1C). Fluorescence *in situ* hybridization (FISH) on metaphase spreads detected the *RUNX1/RUNX1T1* fusion signal on the der(8)t(8;21)(q22;q22) (Fig. 1D). Reverse-transcription polymerase chain reaction also confirmed the *RUNX1/RUNX1T1* fusion transcript.

We have presented a complex three-way translocation t(8;11;21)(q22;q24;q22) and detected the *RUNX1/RUNX1T1* fusion gene in a patient with AML. In the Mitelman database, four AML M2 cases with t(8;11;21) involving 8q22 and 21q22 have been described (Table 1). Their breakpoints in chromosome 11 were clustered to 11p15 (two cases) and 11q13 (two cases).[3–7] Thus, to our knowledge, this is the first case with a complex t(8;21) translocation involving the breakpoint 11q24. With regard to breakpoints in other chromosomes, Kim *et al*. summarized 24 adult cases of AML with variant t(8;21), and demonstrated that there was no overlap of breakpoints in the involved chromosomes, except for 20p13 (two cases).[8] Thus, there seem to be few recurrent breakpoints involved in variant t(8;21).

The t(8;11;21)(q22;q24;q22) translocation generated only the *RUNX1/RUNX1T1* fusion gene on the der(8)t(8;21)(q22;

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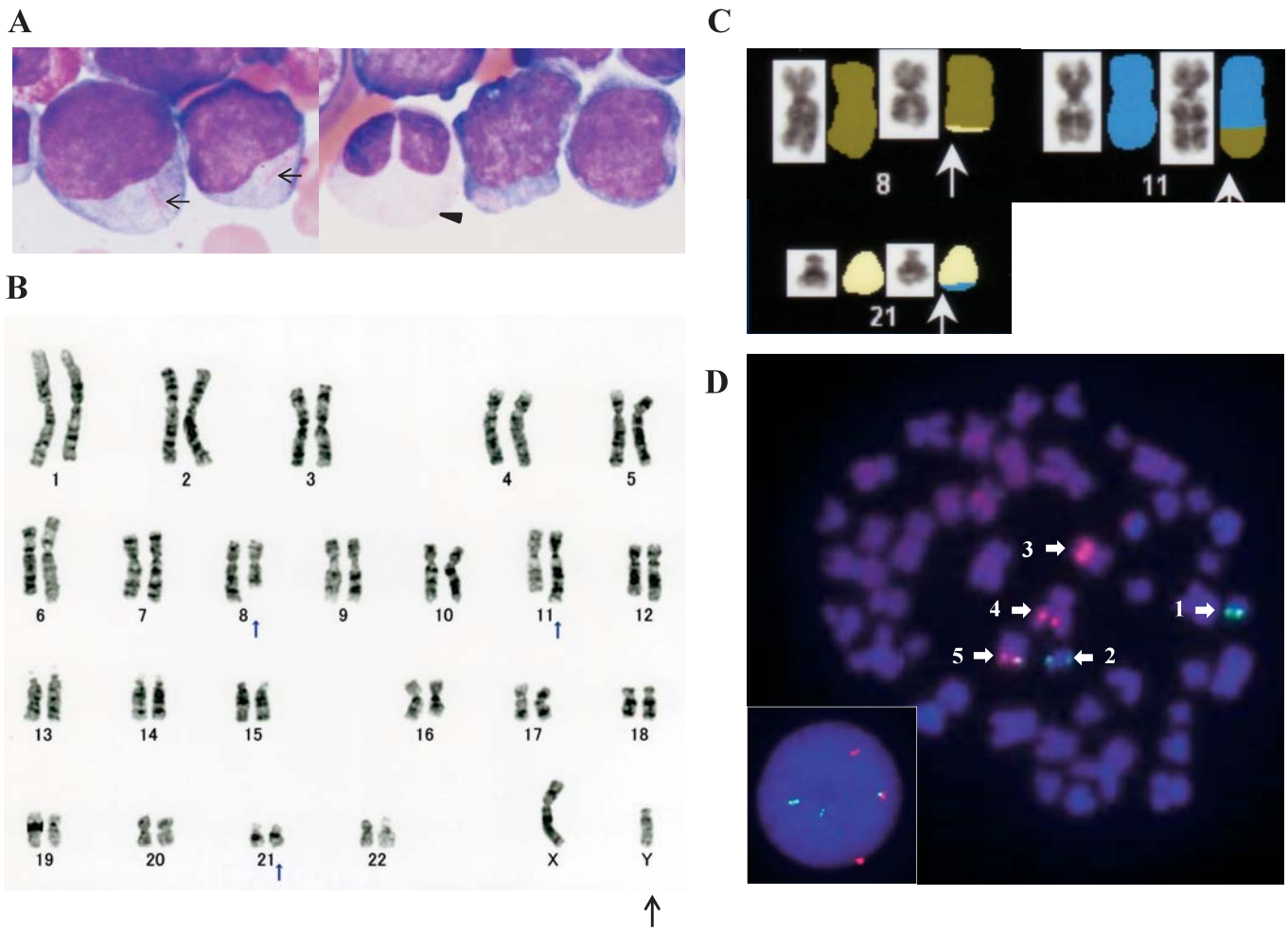

Fig. 1. Morphologic and cytogenetic findings of bone marrow cells. (***1A***) Bone marrow smears showing myeloblasts with Auer rods (*arrows*) and a hypogranular neutrophil with the pseudo-Pelger-Huët anomaly (*arrowhead*) (May-Grünwald-Giemsa staining, × 1,000). (***1B***) G-banded karyotype of bone marrow cells at the initial diagnosis: 46,XY,t(8;11;21)(q22;q24;q22). *Arrows* indicate rearranged chromosomes. (***1C***) Spectral karyotyping of the metaphase spreads after spectrum-based classification (*left side*, reverse DAPI; *right side*, SKY). Only chromosomes 8, 11, and 21 are shown. Three derivative chromosomes, der(8)t(8;21)(q22;q22), der(11)t(8;11)(q22;q24), and der(21)t(11;21)(q24;q22), are confirmed. *Arrows* indicate rearranged chromosomes. (***1D***) Fluorescence *in situ* hybridization analyses with Vysis LSI AML1/ETO Dual Color, Dual Fusion Translocation Probe (Abbott Molecular, Abbott Park, IL, USA) on metaphase spreads and interphase nuclei. *Arrows* indicate 1) *RUNX1* signal (*green*) on a normal chromosome 21, 2) partially deleted *RUNX1* signal (*green*) on the der(21)t(11;21)(q24;q22), 3) *RUNX1T1* signal (*red*) on a normal chromosome 8, 4) partially deleted *RUNX1T1* signal (*red*) on the der(11)t(8;11)(q22;q24), and 5) *RUNX1/RUNX1T1* fusion signal (*red*/*green*, *yellow*) on the der(8)t(8;21)(q22;q22). Similar signals are also detected on interphase nuclei (*inset*).

q22). This emphasizes the pathological significance of *RUNX1/RUNX1T1* in AML with t(8;21). We propose that the complex translocation evolved from a primary t(8;21)(q22;q22) followed by the second exchange between the der(21)t(8;21)(q22;q22) and a normal chromosome 11, although it is also possible that the t(8;11;21)(q22;q24;q22) occurred simultaneously. Finally, the karyotype can be described in detail as 46,XY,t(8;11;21)(8pter → 8q22::21q22 → 21qter;11pter → 11q24::8q22 → 8qter;21pter → 21q22::11q24 → 11qter) (Fig. 2).

In the present case, the reciprocal *RUNX1T1/RUNX1* fusion signal, which is usually observed on the der(21)t(8;21)(q22;q22), could not be detected. Instead, it is probable that an unknown gene located at 11q24 fused to *RUNX1* on the der(21)t(11;21)(q24;q22), or to *RUNX1T1* on the der(11)t(8;11)(q22;q24). As a possible candidate gene, the 11q24 region contains the *FLI1* gene encoding an ETS transcription factor. This gene is known to form the *EWSR1/FLI1* fusion product by t(11;22)(q24;q12) in Ewing's sarcoma.[9] However, at present, it is unclear whether *FLI1* at 11q24 is involved in

Table 1. Reported cases of acute myeloid leukemia with t(8;11;21) involving 8q22 and 21q22

Case No.	Age (years)/Sex	Diagnosis	Karyotypes	OS (month)	References
1	NA/F	AML M2	46,XX,t(8;11;21)(q22;**p15**;q22)	NA	Berger *et al*., 1987[5]
2	NA/M	AML M2	45,X,-Y,t(8;11;21)(q22;**q13**;q22)	NA	Minamihisamatsu & Ishihara, 1988[6]
3	27/F	AML M2	46,XX,t(8;11;21)(q22;**q13**;q22)[15]/46,XX[5]	46 +	Huang *et al*., 2006[3]
4	5/M	AML M2	45,X,-Y,t(8;11;21)(q22;**p15**;q22)[10]/46,XY[1]	71 +	Betts *et al*., 2007[7]
5	62/M	AML M2	46,XY,t(8;11;21)(q22;**q24**;q22)[20]	10 +	present case

F, female; M, male; NA, not available; AML, acute myeloid leukemia; OS, overall survival; + indicates alive. Breakpoints in chromosomes 11 are described in bold letters.

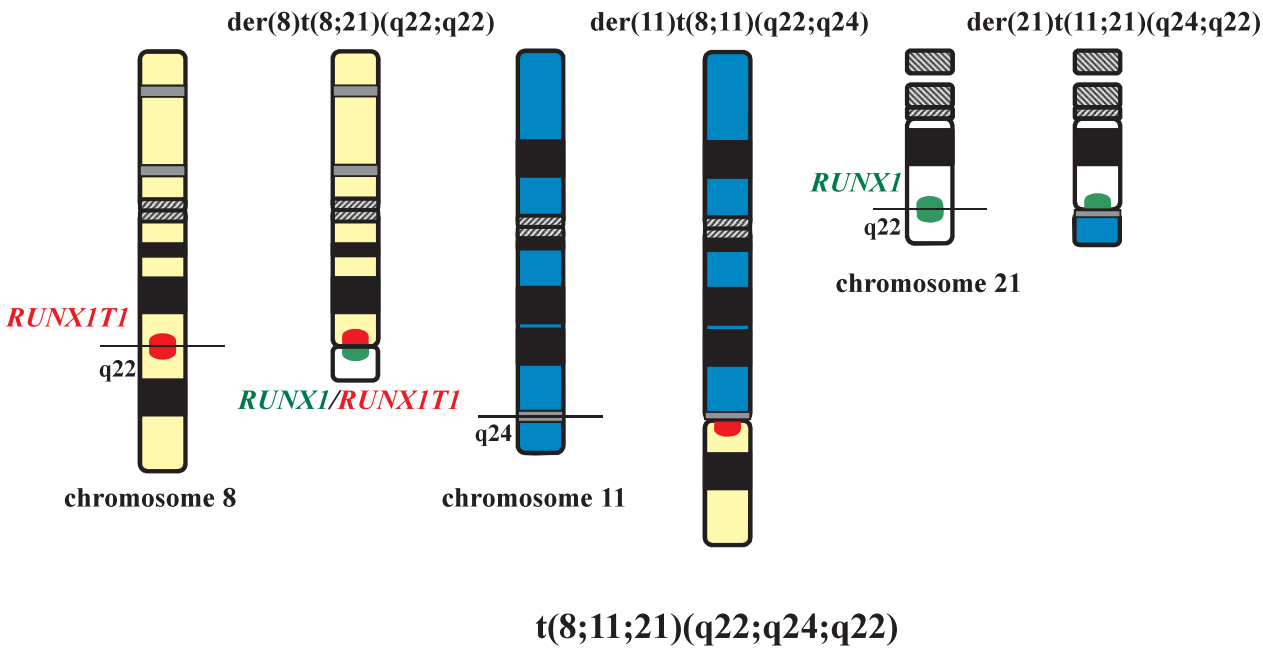

Fig. 2. Ideograms of G-banding patterns for the three-way translocation t(8;11;21)(q22;q24;q22) at 300-band levels. The three derivative chromosomes and normal chromosomes are presented. Locations of *RUNX1* (*green*) and *RUNX1T1* (*red*) signals on these chromosomes are also shown.

leukemogenesis of AML with t(8;11;21)(q22;q24;q22). Recently, we have reported that duplication of der(21)t(8;21)(q22;q22) is a rare but recurrent secondary abnormality in AML with t(8;21). That is, the reciprocal *RUNX1T1/RUNX1* may play a certain role in the progression of AML.[10] However, the mechanism of t(8;11;21)(q22;q24;q22) in the present case suggests that *RUNX1T1/RUNX1* is not always required for the development of AML with t(8;21).

Morphologic and immunophenotypic characteristics of the present case, including Auer rods in myeloblasts, myeloid dysplasia, and the positivity for CD19 and CD56, are often observed in AML with variant t(8;21).[3] These are also similar in AML with standard t(8;21). The prognosis of AML with variant t(8;21) appears to be controversial.[3,11] Kim *et al*. demonstrated that all 17 reported cases with variant t(8;21) achieved CR and only three cases died after relapse. With regard to AML with t(8;11;21), two other cases showed favorable prognosis (Table 1).[3,7] Unfortunately, because of limited information, it is difficult to conclude unequivocally that patients with variant t(8;21) have different clinical outcomes from those with standard t(8;21).[8] In the present case, in spite of an initial induction failure, at the time of writing, he has remained in CR after high-dose cytarabine, as observed in another case of AML with variant t(8;21).[12] Continued observations will illuminate this issue.

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