Letter to the Editor

A New Complex Translocation t(8;11;21)(q22;q24;q22) in Acute Myeloid Leukemia with RUNXI/RUNXITI

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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 × 10⁹/L, and leukocytes 4.6 × 10⁹/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 RUNXI/RUNXITI according to the World Health Organization classification. 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 RUNXI/RUNXITI fusion signal on the der(8)t(8;21)(q22;q22) (Fig. 1D). Reverse-transcription polymerase chain reaction also confirmed the RUNXI/RUNXITI fusion transcript.

We have presented a complex three-way translocation t(8;11;21)(q22;q24;q22) and detected the RUNXI/RUNXITI 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). 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). 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 RUNXI/RUNXITI fusion gene on the der(8)t(8;21)(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::21q24→21qter;11pter→11q24::8q22→8qter;21qter→21q22::11q24→11qter) (Fig. 2).

In the present case, the reciprocal RUNX1/RUNX1T1 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 RUNXI on the der(21)t(11;21)(q24;q22), or to RUNXIT1 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. However, at present, it is unclear whether FLI1 at 11q24 is involved in
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 \( \text{RUNX1T1/RUNX1} \) may play a certain role in the progression of AML. However, the mechanism of t(8;11;21)(q22;q24;q22) in the present case suggests that \( \text{RUNX1T1/RUNX1} \) 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). However, the mechanism of t(8;11;21)(q22;q24;q22) in the present case suggests that \( \text{RUNX1T1/RUNX1} \) is not always required for the development of AML with t(8;21).

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 \( \text{RUNXI} \) (green) and \( \text{RUNXITI} \) (red) signals on these chromosomes are also shown.

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

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)/Sex</th>
<th>Diagnosis</th>
<th>Karyotypes</th>
<th>OS (month)</th>
<th>References</th>
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<tbody>
<tr>
<td>1</td>
<td>NA/F</td>
<td>AML M2</td>
<td>46.XX.q8(11:21)(q22;p15)q22</td>
<td>NA</td>
<td>Berger et al., 1987</td>
</tr>
<tr>
<td>2</td>
<td>NA/M</td>
<td>AML M2</td>
<td>45.X-Y.q8(11:21)(q22;q24)q22</td>
<td>NA</td>
<td>Minami et al., 1988</td>
</tr>
<tr>
<td>3</td>
<td>27/F</td>
<td>AML M2</td>
<td>46.XX.q8(11:21)(q22;q24)q22(15)/46.XY(5)</td>
<td>46+</td>
<td>Huang et al., 2006</td>
</tr>
<tr>
<td>4</td>
<td>5/M</td>
<td>AML M2</td>
<td>45.X-Y.q8(11:21)(q22;p15)q22(10)/46.XY(1)</td>
<td>71+</td>
<td>Betts et al., 2007</td>
</tr>
<tr>
<td>5</td>
<td>62/M</td>
<td>AML M2</td>
<td>46.XY.q8(11:21)(q22;q24)q22(20)</td>
<td>10+</td>
<td>present case</td>
</tr>
</tbody>
</table>

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 \( \text{RUNXI} \) (green) and \( \text{RUNXITI} \) (red) signals on these chromosomes are also shown.

regard to AML with t(8;11;21), two other cases showed favorable prognosis (Table 1). 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). 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). Continued observations will illuminate this issue.

REFERENCES


12 Ishida F, Ueno M, Tanaka H, Makishima H, Suzawa K, et al.: t(8;21;14)(q22;q22;q24) is a novel variant of t(8;21) with chimeric transcripts of AML1-ETO in acute myelogenous leukemia. Cancer Genet Cytogenet 132:133–135, 2002