A New Complex Translocation t(8;11;21)(q22;q24;q22) in Acute Myeloid Leukemia with RUNXI/RUNXIT1

Katsuya Yamamoto,* Kimikazu Yakushijin, Yohei Funakoshi, Yukinari Sanada, Shinichiro Kawamoto, Hiroshi Matsuoka, and Hironobu Minami

Keywords: acute myeloid leukemia, chromosome aberrations, complex translocation, RUNXI/RUNXIT1

TO THE EDITOR

The t(8;21)(q22;q22) translocation involving RUNXI at 21q22 and RUNXIT1 at 8q22 is found in 10% of cases of acute myeloid leukemia (AML) M2 subtype.1 This translocation results in the formation of a RUNXI/RUNXIT1 fusion gene, which contributes to leukemic transformation by transcriptional repression of normal RUNXI 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 RUNXI/RUNXIT1.

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 RUNXI/RUNXIT1 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 RUNXI/RUNXIT1 fusion signal on the der(8)t(8;21)(q22;q22) (Fig. 1D). Reverse-transcription polymerase chain reaction also confirmed the RUNXI/RUNXIT1 fusion transcript.

We have presented a complex three-way translocation t(8;11;21)(q22;q24;q22) and detected the RUNXI/RUNXIT1 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 RUNXI/RUNXIT1 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)(q22::21q22→21qter;11pter→11q24::8q22→8qter;21peter→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 RUNX1 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 FLII gene encoding an ETS transcription factor. This gene is known to form the EWSR1/FLII fusion product by t(11;22)(q24;q12) in Ewing’s sarcoma. However, at present, it is unclear whether FLII 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 RUNX1T1/RUNX1 may play a certain role in the progression of AML.\textsuperscript{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).\textsuperscript{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.\textsuperscript{3,11} Kim \textit{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).\textsuperscript{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).\textsuperscript{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).\textsuperscript{12} Continued observations will illuminate this issue.

### 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>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NA/F</td>
<td>AML M2</td>
<td>46,XX,t(8;11;21)(q22;p15;q22)</td>
<td>NA</td>
<td>Berger \textit{et al.}, 1987\textsuperscript{5}</td>
</tr>
<tr>
<td>2</td>
<td>NA/M</td>
<td>AML M2</td>
<td>45,X,Yt(8;11;21)(q22;q13;q22)</td>
<td>NA</td>
<td>Minamihisamatsu &amp; Ishihara, 1988\textsuperscript{6}</td>
</tr>
<tr>
<td>3</td>
<td>27/F</td>
<td>AML M2</td>
<td>46,XX,t(8;11;21)(q22;qt3;q22)[15]/46,XX[5]</td>
<td>46 +</td>
<td>Huang \textit{et al.}, 2006\textsuperscript{3}</td>
</tr>
<tr>
<td>4</td>
<td>5/M</td>
<td>AML M2</td>
<td>45,X,Yt(8;11;21)(q22;p15;q22)[10]/46,XY[1]</td>
<td>71 +</td>
<td>Betts \textit{et al.}, 2007\textsuperscript{7}</td>
</tr>
<tr>
<td>5</td>
<td>62/M</td>
<td>AML M2</td>
<td>46,XY,t(8;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 RUNXI (green) and RUNXIT1 (red) signals on these chromosomes are also shown.

**t(8;11;21)(q22;q24;q22)**

For **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