Letter to the editor

Association between acute promyelocytic leukemia and ring chromosome 6

After the first report of a ring chromosome in a case of human leukemia by Sandberg et al., ring chromosomes have been infrequently (<10%) detected in hematopoietic neoplasias [1,2]. In most cases, however, ring chromosomes were part of a more or less complex karyotype associated with a poor prognosis [2]. As far as we know, there was no detailed, confirmatory report on an association between a certain leukemia subtype and a specific ring chromosome. Here, we describe a rare, recurrent case of acute promyelocytic leukemia (APL) with simultaneous t(15;17)(q22;q12) and ring chromosome 6 in addition to a relevant literature review.

A 47-year-old Korean female with mild fever, myalgia, easy bruising, and toothache was admitted to Severance Hospital of Yonsei University. Initial complete blood count showed a hemoglobin level of 9.3 g/dL and a platelet count of 36,000/μL with a white blood cell count of 10,890/μL with 1% myelocytes, 10% lymphocytes, and 89% promyelocytes. Coagulation studies revealed a fibrinogen level of 202 mg/dL (reference range, 200–400 mg/dL) and a D-dimer level of 11,701 ng/mL (reference range, 0–243 ng/mL). APL was suspected and a bone marrow examination was performed the very next day. Bone marrow aspiration and biopsy showed a hypercellular marrow replaced by leukemic promyelocytes, consistent with APL morphology.

Analyses for chromosome, fluorescent in situ hybridization (FISH), flow cytometry, and reverse transcriptase-polymerase chain reaction (RT-PCR) for PML/RARA rearrangement, as well as multicolor FISH (mFISH), were conducted. The initial karyotype of this patient was a 46,XX,—6,t(15;17)(q22;q12),+mar in 20/21 cells (Fig. 1). FISH signals from CBFB/MYH11, AML1/ETO, BCR/ABL, and MLL rearrangements were within reference ranges, whereas FISH signals from PML/
Table 1
Summary of APL patients in association with ring chromosomes

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/Age/Country</th>
<th>Karyotype</th>
<th>References</th>
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<tbody>
<tr>
<td>1</td>
<td>Male/ND/UK</td>
<td>46,XY,r(6)t(15;17)(q22;q21)</td>
<td>Swansbury et al., 1985 [4]</td>
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<tr>
<td>2</td>
<td>Male/34/UK</td>
<td>46,XY,r(6)t(15;17)(q10;del(17)(q?)</td>
<td>Russell et al., 1988 [5]</td>
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<tr>
<td>3</td>
<td>Male/35/China</td>
<td>46,XY,t(15;17)(q22;q12)/46,iderm,r(17)</td>
<td>Xue et al., 1992 [6]</td>
</tr>
<tr>
<td>4</td>
<td>Female/24/ Germany</td>
<td>47,XX,r(7n)+t(15;17)(q22;q11-12)</td>
<td>Gebhart et al., 1993 [7]</td>
</tr>
<tr>
<td>5</td>
<td>Male/18/UK</td>
<td>46,XY,r(6)t(15;17)(q22;q21)</td>
<td>Hiiorns et al., 1997 [8]</td>
</tr>
<tr>
<td>6</td>
<td>Male/57/Canada</td>
<td>46,XY,add(1)(q21),t(1;4)(p22;q31),add(5)(q33),r(7)(p12q36),del(17)(q21q23),</td>
<td>Forrest et al., 1998 [9]</td>
</tr>
<tr>
<td>7</td>
<td>Male/ND/Italy</td>
<td>46,XY,t(15;17),(del(17)(q5;17)/45,iderm,r(1)-5,45,iderm,der(1)(q12)-5</td>
<td>Frenny et al., 2003 [10]</td>
</tr>
<tr>
<td>8</td>
<td>Female/47/Korea</td>
<td>46,XX,r(6)t(15;17)(q22;q12)</td>
<td>Park et al., 2009 [this study]</td>
</tr>
</tbody>
</table>

Abbreviations: APL, acute promyelocytic leukemia; ND, not described; UK, United Kingdom.

RARA (LSI PML/RARA Dual-Color, Dual-Fusion Translocation Probe, Abbott Molecular/Vysis, Des Plaines, IL) probe showed nuc ish(PML × 3),(RARA × 3),(PML con RARA × 2)[139/175], consistent with the typical signal patterns of APL in 79.4% of nuclei examined. mFISH analysis revealed that the round marker chromosome of this patient was a ring chromosome 6 (Fig. 1). Therefore, the revised karyotype result was a 46,XX,r(6)t(15;17)(q22;q12). Flow cytometry showed the blasts to be positive for CD13, CD33, CD45, CD117, and MPO, and negative for CD3, CD7, CD19, CD14, CD20, cCD22, CD56, CD79a, HLA-DR, and TdT. In addition, RT-PCR for PML/RARA rearrangement showed a positive result (L-form). She was diagnosed with APL, and treated with ATRA and anthracycline. One month after the initial diagnosis, a second bone marrow examination was performed, revealing a slightly hypocellular marrow (20–30% cellularity) with complete hematologic remission.

Here we present a 47-year-old female with APL associated with ring chromosome 6. Initial results of bone marrow, chromosome, FISH, and RT-PCR analysis were consistent with the diagnosis of APL. The initial karyotype of this patient, however, was a 46,XX,-6,t(15;17) (q22;q12),+mar in most of the analyzed cells. After conducting mFISH analysis, we found that this round marker chromosome was a ring chromosome 6. When we reviewed the Mitelman database and the literature [3–10], we found seven APL patients associated with ring chromosomes. Among these cases, five patients were associated with ring chromosome 6. Although the number of reported cases is too limited, patients ranged in age from 18 to 57 years (median 35.8) with a male predominance (75%). Interestingly, most of ring chromosome 6 in APL cases was not associated with the complex karyotype (Table 1).

A ring chromosome, which appears to be a rare event in prenatal or cancer patients, can be formulated by fusions between both arms of the same chromosome with or without loss of genetic material. According to one recent review by Gebhart et al. [2], ring chromosome 11 (15%) was most often involved in hematologic malignancies, followed by ring chromosomes 7 (14%), 21 (~9%), and 5 (~6%). In addition, ring chromosome 11 (23%) was also clearly dominant in acute myeloid leukemia (AML), followed by ring chromosomes 7 (11%) and 21 (10%). Acquired ring chromosome 6 is a very rare chromosomal abnormality, and only 33 cases with solid or hematologic malignancies have been reported until now [3]: solid tumors (12 cases), AML (12 cases), myelodysplastic syndrome (1 case), chronic myelogenous leukemia (1 case), acute lymphoblastic leukemia (1 case), multiple myeloma (1 case), idiopathic myelofibrosis (1 case), mature B-cell neoplasm (1 case), juvenile myelomonocytic leukemia (1 case), and lymphomas (2 cases). As mentioned above, most of ring chromosomes were part of a complex karyotype, and solitary rings are infrequent (~13%). In their extensive review, Gebhart et al. [2] mentioned that there were a few (three sporadic cases of AML-M3 accompanied by r(6), but there have been no other confirmatory reports or reviews on an association between a certain leukemia subtype and a specific ring chromosome. Although further studies are needed, on the basis of this study and literature review, we think that there could be a close association between APL and ring chromosome 6.

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