Case Study

Coexistent t(8;21)(q22;q22) Translocation and 5q Deletion in Acute Myeloid Leukemia

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The t(8;21)(q22;q22) translocation is specifically observed in acute myeloid leukemia (AML) M2 subtype, whereas del(5q) is one of the most common cytogenetic aberrations in myelodysplastic syndromes (MDS). Thus, t(8;21)(q22;q22) and del(5q) appear to be mutually exclusive, and the association between them has not been characterized yet. Here, we report an 81-year-old woman with coexistent t(8;21)(q22;q22) and del(5q) at initial diagnosis. The bone marrow was infiltrated with 18.4% myeloblasts, and showed marked myeloid and erythroid dysplasia. Myeloblasts were positive for CD19 and CD56 as well as CD13, CD33, CD34 and HLA-DR. G-banding and spectral karyotyping showed 46,XX,del(5)(q?),t(8;21)(q22;q22)[18]/46,XX[2]. Both del(5)(q?) and t(8;21)(q22;q22) were present in a single clone. Fluorescence in situ hybridization (FISH) on metaphase spreads detected a RUNX1/RUNX1T1 fusion signal on the der(8)t(8;21)(q22;q22), and confirmed deletion of CSF1R signaling at 5q33-q34 on the del(5)(q?). Furthermore, FISH on interphase nuclei revealed that the RUNX1/RUNX1T1 fusion signal and deletion of CSF1R signaling were found in 66.0% and 58.0% of interphase cells, respectively, suggesting that del(5) (q?) occurred in cells with RUNX1/RUNX1T1. These results indicated a diagnosis of AML with t(8;21)(q22;q22)/RUNX1/RUNX1T1 rather than MDS, even though the percentage of bone marrow myeloblasts was less than 20%. Based on these findings, together with those of other reported cases, del(5q) seems to be an extremely rare but recurrent secondary aberration in AML with t(8;21)(q22;q22). [J Clin Exp Hematop 55(2) : 181-185, 2015]

Keywords: acute myeloid leukemia, chromosome aberrations, coexistence, 5q deletion, RUNX1/RUNX1T1

INTRODUCTION

The t(8;21)(q22;q22) translocation involving RUNX1 at 21q22 and RUNX1T1 at 8q22 is observed in 10% of cases of acute myeloid leukemia (AML) M2 subtype.1 This translocation leads to the formation of a RUNX1/RUNX1T1 fusion gene on der(8)t(8;21)(q22;q22), thus causing leukemic transformation by transcriptional repression of normal RUNX1 target genes. On the other hand, deletion of the long arm of chromosome 5, del(5q), is one of the most common cytogenetic aberrations in myelodysplastic syndromes (MDS) and accounts for 10% and 40% of de novo and therapy-related MDS cases, respectively.1 Furthermore, according to the World Health Organization classification, del(5q) is defined to be one of the unbalanced abnormalities sufficient for the diagnosis of AML with myelodysplasia-related changes.1,2 At the diagnosis of AML with myelodysplasia-related changes, recurrent cytogenetic abnormalities, such as t(8;21)(q22;q22), inv(16)(p13.1q22), and t(15;17)(q22;q12), described as “AML with recurrent genetic abnormalities”, should be absent. Thus, t(8;21)(q22;q22) and del(5q) seem to be mutually exclusive in patients with AML. Here, we report an unusual case of AML with t(8;21)(q22;q22) and del(5q) at initial diagnosis.

CASE REPORT

An 81-year-old woman was admitted to our hospital because of fever, progressive anemia, and thrombocytopenia. Three years earlier, she had been diagnosed with mild anemia, but no specific treatment was given. Peripheral blood showed hemoglobin 7.4 g/dL (mean corpuscular volume 100 fL), platelets 66 × 10^9/L, and leukocytes 2.8 × 10^9/L with 2% myelocytes, 1% metamyelocytes, 9% band forms, 54% segmented neutrophils, 7% monocytes, 23% lymphocytes, and 4% myeloblasts. Bone marrow was normocellular with 18.4% myeloblasts, 61.4% mature myeloid cells, 1.0% monocytes,
5.2% lymphocytes, and 12.2% erythroblasts. Myeloblasts had few azurophilic granules and Auer rods in the basophilic cytoplasm (Fig. 1A & 1B). Marked myeloid dysplasia with hypogranulation, pseudo-Pelger-Huët anomaly, and separated nuclei, and erythroblasts with abnormal nuclear lobulation were also detected (Fig. 1C-1H). The number of megakaryocytes was low, and no dysplastic changes were apparent.

Myeloblasts were positive for myeloperoxidase, and immunophenotypically positive (> 20%) for CD13 (57.7%), CD19 (30.0%), CD33 (21.2%), CD34 (96.2%), CD56 (97.7%), and HLA-DR (93.7%). Initially, because of the low percentage of bone marrow blasts and marked bilineage dysplasia, we diagnosed the patient with MDS, refractory anemia with excess blasts-2, according to the World Health Organization.
classification. Furthermore, a computed tomography scan of the chest revealed multiple small nodules in both lungs. Because of her advanced age and suspected miliary tuberculosis, she did not receive chemotherapy and returned to the hospital closest to her home for comfort care.

G-banding analysis of bone marrow cells at diagnosis showed 46,XX;del(5)(q21)[8]/46,XY[2] (Fig. 1I). Both del(5q) and t(8;21)(q22;q22) were present in a single clone. Spectral karyotyping (SKY) confirmed del(5)(q21) and two derivative chromosomes, der(8)t(8;21)(q22;q22) and der(21)t(8;21)(q22;q22) (Fig. 1J). Specifically, del(5)(q21) was due to the deletion alone and not to an unbalanced translocation with another chromosome. However, precise breakpoints of del(5)(q21) could not be identified by G-banding and SKY because of inadequate quality of metaphase spreads. Fluorescence in situ hybridization (FISH) on metaphase spreads detected a RUNXI/RUNXIT1 fusion signal on the der(8)t(8;21)(q22;q22) in 15 of 20 metaphase spreads (Fig. 1K). In addition, FISH revealed deletion of CSF1R signaling at 5q33-q34 on the del(5)(q21) in 14 of 20 metaphase spreads (Fig. 1L). FISH on interphase nuclei demonstrated deletion of RUNXI/RUNXIT1 in situ fusion signal on RUNXI/RUNXIT1 hybridization (FISH) on metaphase spreads confirmed the RUNXI/RUNXIT1 fusion signal and deletion of CSF1R signaling were found in 66 of 100 cells and 58 of 100 cells, respectively (Fig. 1K & 1L, inset). The t(8;21)(q22;q22) translocation is defined to be one of the recurrent cytogenetic abnormalities specifically observed in AML. Morphological features such as granular blasts, Auer rods, myeloid dysplasia, and co-expression of CD19 seem to be typical findings of AML with t(8;21). Thus, we revised the final diagnosis to AML with t(8;21)(q22;q22)/RUNXI/RUNXIT1, even though the percentage of bone marrow myeloblasts was less than 20%.

**DISCUSSION**

Here we presented the coexistence of t(8;21)(q22;q22) and del(5q) at the initial diagnosis of AML with RUNXI/RUNXIT1. The t(8;21)(q22;q22) is a primary recurrent genetic event, with the exception of Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (CML). On the other hand, del(5q) could be an additional abnormality as part of a complex karyotype as well as a single aberration leading to 5q- syndrome. In the present case, FISH revealed that RUNXI/RUNXIT1 rearrangement was detected more frequently than CSF1R deletion in bone marrow interphase cells, suggesting that del(5q) occurred in cells with t(8;21)(q22;q22). Thus, we concluded that t(8;21)(q22;q22) and del(5q) were primary and secondary abnormalities, respectively, although both cytogenetic aberrations coexisted in all abnormal metaphase spreads analyzed by G-banding and SKY. Furthermore, the diagnosis was AML with t(8;21)(q22;q22) rather than MDS, even though the percentage of bone marrow myeloblasts was less than 20%. FISH on neutrophils in the peripheral blood may be useful for the differential diagnosis between MDS and de novo AML, but unfortunately, we could not perform this procedure.

Additional cytogenetic and molecular genetic abnormalities are frequently observed in AML with t(8;21)(q22;q22).5 Over 70% of patients have cytogenetic aberrations, such as loss of sex chromosomes, del(9)(q22), and trisomy 8; mutations of NRAS and KIT are also common. However, to our knowledge, the association between t(8;21)(q22;q22) and del(5q) has not been characterized yet. We searched the Mitelman database and found eight cases harboring coexistent t(8;21)(q22;q22) and del(5q) among 1,589 cases of AML with t(8;21)(q22;q22) (Table 1).6-14 As observed in the present case, both del(5q) and t(8;21)(q22;q22) were present in a single clone in these reported cases. Three cases (No. 1, 2 & 6) had del(5q) in their subclones, whereas other cases had coexistent del(5q) in the stem line. Only the present case showed del(5q) as a sole additional abnormality in the stem line. Therefore, del(5q) seems to be an extremely rare (8/183) case of AML with t(8;21)(q22;q22) and del(5q).

**Table 1.** Reported cases of hematological malignancies with coexistent t(8;21)(q22;q22) and del(5q)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ Sex</th>
<th>Diagnosis</th>
<th>Karyotypes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80/F</td>
<td>AML M2</td>
<td>46XX, t(8;21)(q22;q22)/46,sl,del(5)(q171q23)</td>
<td>Bernstein R, et al., 1982 [7]</td>
</tr>
<tr>
<td>2</td>
<td>13/F</td>
<td>AML M2</td>
<td>46XX,del(4)(q?),t(8;21)(q22;q22)/46,XX,del(5)(q?),t(8;21)</td>
<td>Prigogina EL, et al., 1986 [8]</td>
</tr>
<tr>
<td>3</td>
<td>62/M</td>
<td>AML</td>
<td>45XY,del(5)(q21q23),t(8;21)(q22;q22),del(11)(q23),add(12)(q23)</td>
<td>GFCH 1990 [9]</td>
</tr>
<tr>
<td>4</td>
<td>40/M</td>
<td>AML M2</td>
<td>46XY,der(1)(1;8)(p32;q23?),del(5)(q13),der(8)(t;8;21)(q22;q22),der(21)(t;8;21)(t;1;8)</td>
<td>Calabrese G, et al., 1996 [10]</td>
</tr>
<tr>
<td>5</td>
<td>31/M</td>
<td>LCH → AML M2</td>
<td>45X,-Y,del(5)(q21) t(8;21)(q22;q22)</td>
<td>Aslan V, et al., 2002 [11]</td>
</tr>
<tr>
<td>6</td>
<td>17/M</td>
<td>AML M2</td>
<td>45X,-Y, t(8;21)(q22,q22)/46,sl,add(3)(q26)</td>
<td>Viehmann S, et al., 2003 [12]</td>
</tr>
<tr>
<td>7</td>
<td>25/F</td>
<td>AML M2</td>
<td>46XX,t(1)(p36p11),del(5)(q22q34),der(8)(t;8;21)(q22;q22),der(21)(t;8;21)(t;1;8)</td>
<td>Xu W, et al., 2010 [13]</td>
</tr>
<tr>
<td>8</td>
<td>22/M</td>
<td>AML M2</td>
<td>45X,-Y,del(5)(q21),t(8;21)(q22;q22),i(9)(q10)</td>
<td>Gmiëdne A, et al., 2012 [14]</td>
</tr>
<tr>
<td>9</td>
<td>81/F</td>
<td>AML M2</td>
<td>46XX,del(5)(q21),t(8;21)(q22;q22)</td>
<td>present case</td>
</tr>
</tbody>
</table>

F, female; M, male; AML, acute myeloid leukemia; LCH, Langerhans cell histiocytosis; GFCH, Groupe Français de Cytogénétique Hématologique. The deletion 5q is indicated in bold letters.
1,589, 0.50%) but recurrent secondary aberration in AML with t(8;21)(q22;q22). One case (No. 5) showed similar hematological findings to the present case, such as low leukocyte count (1.9 × 10^9/L), intracytoplasmic granules and Auer rods of blasts, and positivity for myeloperoxidase, CD13, CD19, CD33, and HLA-DR; however, the bone marrow showed 80% of blast infiltrates, and myeloid dysplasia was not apparent.11 Unfortunately, common clinical and genetic features could not be detected because only limited data were available in the other reported cases.

With regard to the association between del(5q) and other recurrent genetic abnormalities, del(5q) was detected in 3 out of 899 cases of AML M3 with t(15;17)(q22;q12-21) (0.33%), and in 3 out of 888 cases of AML with inv(16)(p13q22) (0.34%).6 Coexistence of del(5q) with recurrent genetic abnormalities appears to be a very rare genetic event. In addition, del(5q) is often observed in Ph-positive CML as an unrelated cytogenetic abnormality after successful treatment with imatinib.15 On the other hand, Maekawa et al. reported a rare case of Ph-positive CML with del(5q) as a clonal evolution.16 Interestingly, this case progressed to erythroleukemia crisis. The present case also presented erythroid dysplasia, which is not a typical finding of AML with t(8;21). However, the association between an additional del(5q) and dyserythroidoisis is uncertain.

Deletion of 5q as a secondary change was also found in AML with another RUNXI-related translocation. The t(7;21) (p22;q22) translocation, which results in the fusion of RUNXI at 21q22 and USP42 at 7p22, is an uncommon but specific cytogenetic abnormality in AML: only 10 cases have been reported.17,18 Interestingly, 8 of 10 cases showed loss of 5q material as an additional abnormality at the initial diagnosis or at relapse. Leukemic cells in all 8 cases showed aberrant CD56 expression but lacked CD19 expression. Thus, the association between t(7;21) and del(5q) may be nonrandom, but the clinical significance of this connection remains to be elucidated.18 Although in the present case leukemic cells also expressed high CD56 and low CD19 levels, at the moment, it is unknown whether similar clinical findings are observed in AML with t(8;21) and del(5q). Future observations will clarify the possible association between RUNXI rearrangement and del(5q) in AML.

REFERENCES
18 Ji J, Loo E, Pullakat S, Yang L, Tirado CA: Acute myeloid leukemia with t(7;21)(p22;q22) and 5q deletion: a case report and literature review. Exp Hematol Oncol 3:8, 2014