Case Report:
Concomitant Isochromosome 17q and Trisomy 14 in a Patient with Myelodysplastic Syndrome in Leukemic Transformation

Tae Sung Park,1* Jaewoo Song,1 Jong-Han Lee,1 Jin Seok Kim,2 Woo Ick Yang,3 and Jong Rak Choi1
Departments of 1Laboratory Medicine, 2Internal Medicine, and 3Pathology,
Yonsei University College of Medicine, Seoul, Korea
* Current address: Department of Laboratory Medicine, Kyung Hee University School of Medicine, Seoul, Korea

Abstract. We describe a novel case of simultaneous karyotypic abnormalities of isochromosome 17q and trisomy 14 in a patient with myelodysplastic syndrome (MDS) in leukemic transformation. A 66-yr-old Korean man was admitted to Severance Hospital for evaluation of pancytopenia. On the basis of bone marrow studies at 3 different stages, he was diagnosed with MDS in leukemic transformation. Chromosome karyotyping repeatedly showed the same main clonal abnormalities, including isochromosome 17q and trisomy 14. Isochromosome 17q and trisomy 14 have each been reported as rare, nonrandom recurrent chromosomal abnormalities in patients with MDS showing a poor prognosis. To our knowledge, this is the first report of concurrent i(17)(q10) and trisomy 14 in a patient with MDS in leukemic transformation.

Keywords: isochromosome 17q, trisomy 14, myelodysplastic syndrome, leukemic transformation

Introduction

The myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell diseases characterized by cytopenias, dysplasia in one or more of the major myeloid cell lines, ineffective hematopoiesis, and increased risk of development of acute myeloid leukemia (AML) [1]. The 2008 World Health Organization (WHO) classification system for MDS includes the following 7 entities: refractory cytopenias with unilineage dysplasia (RCUD), refractory anemia with ringed sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), refractory anemia with excess blasts-1 (RAEB-1), refractory anemia with excess blasts-2 (RAEB-2), myelodysplastic syndrome–unclassified (MDS-U), and MDS associated with isolated del(5q). Recently, the importance of subgroups with recurring clonal cytogenetic abnormalities such as “AML with recurrent genetic abnormalities” or “MDS associated with isolated del(5q)” has been emphasized on the basis of cancer genetics and prognostic significance. Common recurrent cytogenetic abnormalities found in MDS include del(5q), chromosome 7 abnormalities, del(20q), -Y, and trisomy 8 [2]. Among these, cytogenetic changes carry prognostic significance with normal cytogenetics, isolated del(5q), del(20q), and -Y conferring a relatively good prognosis, while chromosome 7 abnormalities and complex karyotypes confer a poor prognosis [2,3]. Isochromosome 17q and trisomy 14 have been reported as rare, nonrandom recurrent chromosomal abnormalities in patients with MDS showing a poor prognosis [4-12], and, as far as we know, there have been no reports of concurrent i(17)(q10) and trisomy 14 in patients with MDS. We report a novel case of isochromosome 17q concomitant with trisomy 14 in a 66-yr-old male patient with MDS in leukemic transformation showing a poor clinical course.
Materials and Methods

A 66-yr-old Korean man was brought to Severance Hospital for evaluation of hematologic malignancy in June 2005. Ultrasonography of the upper abdomen revealed mild splenomegaly (13.8 cm). A complete blood count (CBC) (June 9, 2005) showed a hemoglobin (Hb) level of 6.6 g/dl, a platelet count of 100,000 /μl, and a WBC count of 2,110 /μl with absolute neutrophil count of 300/μl. Pancytopenia compelled us to perform a bone marrow examination. His first bone marrow aspiration (June 2005) showed an 80% hypercellular marrow with 4.7% myeloblasts. Although dyspoietic micromegakaryocytes (dwarf form) were detected, no other distinct dysplasia was observed in his marrow. His second bone marrow biopsy (April 2006) showed dyserythropoiesis (megaloblastic maturation and sideroblasts) and increased micromegakaryocytes, as well as 14% myeloblasts of all nucleated cells (ANCs). Two years later, he was readmitted for treatment of pneumonia and epistaxis. On arrival (February 11, 2008), a CBC showed an Hb level of 3.7 g/dl, a platelet count of 9,000 /μl, and a WBC count of 720 /μl. His third bone marrow biopsy showed a 30-40% cellular marrow with 24% myeloblasts of ANC as well as marked trilineage dysplasia. The patient was diagnosed with MDS in leukemic transformation and he died one month later.

Chromosomes were prepared from a 24-hr unstimulated bone marrow culture. The bone marrow cells were grown in RPMI 1640 (Sigma, Schnelldorf, Germany) supplemented with 20% fetal bovine serum (Gibco, Grand Island, NY), Bone Marrow Growth Supplement (Genial Genetic Solutions, UK), and antibiotics (penicillin and streptomycin). The cultured cells were then exposed to colcemid for 20 min, and followed by 30 min of hypotonic treatment (KCl). A fixation procedure with ethanol and acetic acid (2:5:1) was performed. Chromosomes were analyzed with GTG-banding and the karyotypes described according to the International System for Human Cytogenetic Nomenclature (ISCN 2005) [13].

Immunophenotypes of the bone marrow cells were analyzed by 3-color flow cytometry with CD45/side scatter (SSC) gating using a Cytomics FC500 flowcytometer (Beckman Coulter, Fullerton, CA). Expression of each CD antigen on the gated cells was examined with monoclonal antibodies and defined as positive when ≥20% of gated cells showed fluorescence above the background control staining.

Results

This patient repeatedly exhibited the same main clonal abnormalities. The detailed results of the chromosome studies were as follows (Figs. 1 and 2): 47,XY,+14,i(17)(q10)[8] /46,XY[7] (June 2005), 47,XY,+14,i(17)(q10)[3] (April 2006) (Fig. 1), and 46,XY,i(17)(q10)[15] /46,idem,del(6)(q21),-7,+14[6] (February 2008) (Fig. 2). Immunohistochemical staining for p53 with bone marrow paraffin-embedded tissue was negative. No fluorescent in situ hybridization (FISH) studies were done due to lack.
of specimen. Flowcytometry showed the blasts to be positive for CD13, CD33, and CD45 and negative for CD3, CD7, CD10, CD14, CD19, CD20, cCD22, CD79a, MPO, and TdT. The laboratory and clinical data of this patient are summarized in Table 1.

Discussion

Although isochromosome 17q is the most common isochromosome and is a recurrent aberration in most tumors (medulloblastoma, gastric cancer, bladder cancer, breast cancer, and some hematologic malignancies), it is a relatively rare karyotypic abnormality in patients with MDS, with an incidence of 0.4-1.57% [4,5,14-16]. In general, the patients with MDS associated with i(17)(q10) share several features, such as severe anemia, prominent pseudo-Pelger-Huet neutrophils, increased micromegakaryocytes, and poor clinical prognosis [5], and they are regarded as a distinct category of disease [4,8]. In myeloid neoplasms, isochromosome 17q can occur both as a primary and as a secondary aberration [14]. When found with other aberrations, i(17)(q10) was particularly frequent together with t(9;22)(q34;q11.2) and t(15;17)(q22;q12). Nathan et al [17] reported a case of AML with i(17)(q10) and t(4;12)(q12;p13) simultaneously.

The p53 (located on chromosome 17p13) is one of the most representative tumor suppressor genes in normal and malignant hematopoiesis. This gene is considered the guardian of the genome and halts the cell cycle upon DNA damage as well as serving as a key regulator of apoptosis [18]. Mutations of p53 have been reported in solid tumors as well as in hematologic malignancies such as MDS, AML, acute lymphoblastic leukemia (ALL), and chronic lymphoblastic leukemia (CLL). However, the frequency of p53 mutations in hematologic malignancies is much lower than in solid tumors.
Although studies of therapy-related AML/MDS found p53 mutations in 30% of cases [18], with the majority of the mutated samples showing a loss of the wild type p53 allele, Fioretos et al [20] reported that there was no association between i(17q) and coding p53 mutations among 17 hematologic malignancies with i(17q): only one MDS displayed a homozygous deletion of p53 in their study. Therefore, although more case studies are needed, it seems that p53 mutations rarely occur in patients with MDS or other hematologic malignancies associated with i(17q).

Trisomy 14 is also an uncommon nonrandom chromosomal abnormality that has predominantly been found to be associated with myeloid disorders such as MDS, myeloproliferative disorders, atypical chronic myeloid leukemia, and AML [9,10]. Upon review of the Mitelman database, we found only 63 cases of trisomy 14 as the sole abnormality in hematologic malignancies [21]. Additional karyotypic abnormalities reported include t(1;3), +2, +13, del(20q), +21, i(Xq), and -Y [15]. Trisomy 14 is associated with poor prognosis and clinical features such as thrombocytosis, elderly patients, karyotypic mosaicism, and erythrocyte abnormalities [9].

The introduction of FISH analysis in the area of hematology or clinical cytogenetics generated a great revolution in the modern medicine. First, interphase FISH (iFISH) is a useful adjunct to conventional cytogenetics at diagnosis, particularly in cases of failed or apparently normal cytogenetics where the mitotic cells may not represent the malignant clone [22]. It is also valuable for identification of the breakpoints of consistent translocations associated with specific leukemia subtypes and follow up for minimal residual diseases. Second, multi-color FISH techniques such as mFISH (MetaSystems, Altlußheim, Germany) or spectral karyotyping (SKY; Applied Spectral Imaging, Migdal Haemek, Israel) allow visualization of the entire chromosome complement in 24 different colors [22,23].

Table 1. Summary of laboratory and clinical follow-up results in this patient.

<table>
<thead>
<tr>
<th></th>
<th>2005 (June)</th>
<th>2006 (April)</th>
<th>2008 (February)</th>
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<tbody>
<tr>
<td>CBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (/μl)</td>
<td>2,110</td>
<td>3,330</td>
<td>720</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>6.6</td>
<td>5.5</td>
<td>3.7</td>
</tr>
<tr>
<td>PLT (/μl)</td>
<td>100,000</td>
<td>99,000</td>
<td>9,000</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td>NA</td>
<td>Seg (48), Lym (52)</td>
<td>Seg (29), Lym (39), Mono (28), Aty Lym (4)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellularity %</td>
<td>80</td>
<td>NA</td>
<td>30-40</td>
</tr>
<tr>
<td>Blast % (ANCs)</td>
<td>4.7</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Associated dysplasia</td>
<td>micromegakaryocytes</td>
<td>micromegakaryocytes, dyserythropoiesis (megaloblastic maturation, sideroblasts)</td>
<td>micromegakaryocytes, dyserythropoiesis, dysgranulopoiesis (hypogranulation, pseudo-Pelger-Huet anomaly)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>RA</td>
<td>RAEB-2</td>
<td>AML with multilineage dysplasia</td>
</tr>
<tr>
<td>Treatment</td>
<td>azacitidine, oxymetholone</td>
<td>oxymetholone, exjade</td>
<td>medication for pneumonia (cefobactam, amikacin, meropenem, targocid)</td>
</tr>
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</table>

Abbreviations: CBC, complete blood count; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; NA, not available; Seg, segmental neutrophils; Lym, lymphocytes; Mono, monocytes; Aty Lym, atypical lymphocytes; ANC, all nucleated cells; RA, refractory anemia; RAEB-2, refractory anemia with excess blasts type 2; AML, acute myeloid leukemia.
attractive aspects of multi-color FISH is the ability to identify several targets simultaneously, using different colored fluorochromes. Such modern molecular cytogenetic methods have enabled us to detect several cryptic chromosomal abnormalities or novel breakpoints [24-27]. However, we did not perform any further FISH studies in this case due to lack of specimen.

Although the clinical significance of additional chromosomal abnormalities in patients with trisomy 14 is unclear, we consider the presence of trisomy 14 together with i(17)(q10) to be a poor prognostic factor for our patient. In addition, we think that both the subsequent clonal changes as well as the non-mosaic karyotypic aberration (increased cancer cell burdens) during the leukemic transformation were attributable to the rapid progression of the disease in this patient. Such simultaneous chromosomal abnormalities are extremely rare; however, further reports are necessary to evaluate treatment response and prognosis of MDS patients with these rare chromosomal abnormalities. To the best of our knowledge, this is the first report of concurrent i(17)(q10) and trisomy 14 in a patient with MDS in leukemic transformation.

References


