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Short communication

Paracentric inversion–associated t(8;21) variant in de novo acute myelogenous leukemia: characteristic patterns of conventional cytogenetics, FISH, and multicolor banding analysis

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Abstract Acute myelogenous leukemia (AML) with t(8;21)(q22;q22) demonstrates unique clinico-pathologic disease entity in patients with hematologic malignancies. The t(8;21), which results in fusion of the *AML1* gene on 21q22 and the *ETO* gene on 8q22 on a molecular level, is one of the most common nonrandom chromosomal changes, and it is found in about 5–12% of patients with AML. Among these cases, complex variants involving chromosomes 8 and 21, as well as a third or fourth chromosome, account for approximately 6–10% of patients with an *AML1*/*ETO* chimeric gene, and about 100 variant cases with *AML1*/*ETO* fusion transcript have been reported in the literature. Here, we describe a rare case report of reciprocal paracentric inversion–associated t(8;21) variant in a 28-year old male patient with de novo AML. The abnormal results of conventional cytogenetics and interphase fluorescent in situ hybridization in this patient drove us to perform further studies and a literature review. This report emphasizes the value of ''conventional'' cytogenetics, as well as ''newly developed'' molecular cytogenetic methods in the diagnosis of rare complex t(8;21) variant in patients with AML. ©2008 Elsevier Inc. All rights reserved.

1. Introduction

Recurrent cytogenetic abnormalities, including t(8;21), inv(16), or t(16;16), t(15;17) and various translocations involving the 11q23 breakpoint, are frequently identified aberrations in acute myelogenous leukemia (AML) [1]. Among these abnormalities, t(8;21)(q22;q22) is one of the most common structural aberrations, and is typically associated with the French–American–British (FAB) classification of acute leukemia subtype M2 (AML-M2). Recent molecular studies have shown that recurrent balanced chromosome rearrangements create a fusion gene encoding a chimeric protein, allowing t(8;21) to disrupt the *AML1* gene on 21q22 and the *ETO* gene on chromosome 8q22, resulting in a single transcriptionally active gene on the chromosome 8, the *AML1*/*ETO* fusion gene [2–4]. In the minority of AML, t(8;21) occurs as a complex variant involving chromosomes 8, 21, and a third or fourth chromosome [5,6]. To the best of our knowledge, approximately 100 case reports involving various chromosomes have been reported as the variant three-way or four-way translocation in the literature [6–8]. Until now, however, to our knowledge, only two cases of paracentric inversion-associated t(8;21) variant have been described in patients with AML as a masked t(8;21) and showed the location of fusion gene at 8q24 [9,10]. In this study, we describe a rare case of der(8)inv(8)(q22q24.3) t(8;21)(q22;q22) in a patient with de novo AML revealing a fusion gene at 8q22, in addition to a literature review.

2. Materials and methods

2.1. Case description

A 28-year-old Korean man with the chief complaint of flank pain and anemia was admitted to the Severance Hospital of Yonsei University for hematologic malignancy

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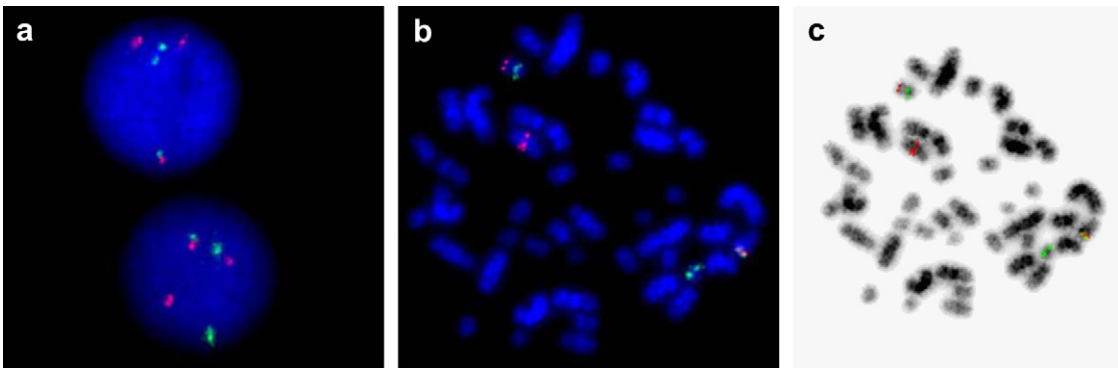

Fig. 1. Fluorescent in situ hybridization (FISH) analysis of the bone marrow cells using a *AML1/ETO* (LSI *AML1/ETO* Dual Color, Dual Fusion Translocation Probe, Abbot Molecular/Vysis, Des Plaines, IL) probe. (a) Interphase FISH shows an abnormal pattern of 2O2G1Y (2 *AML1*, 2 *ETO*, 1 *AML1/ETO*) in 96% of the nuclei examined. (b) Metaphase FISH with the *AML1/ETO* probe reveals an orange signal on a normal chromosome 8, a green signal on a normal chromosome 21, a fusion signal on a derivative chromosome 8, and an orange and green split signals on a derivative chromosome 21. (c) Inverted DAPI image of metaphase cell of figure (b).

evaluation. Complete blood count (CBC) showed a hemoglobin (Hb) level of 10.0g/dL, platelet count of 36,000/μL, and a white blood cell (WBC) count of 13,780/μL with 12% segmental neutrophils, 19% lymphocytes, 2% monocytes, 3% band neutrophils, 2% myelocytes, 1% metamyelocytes, and 61% immature cells. Initial bone marrow biopsy revealed markedly hypercellular marrow with massive infiltrates of myeloblasts with maturation, consistent with AML-M2 morphology. For further evaluation, chromosome, fluorescent in situ hybridization (FISH), immunophenotyping, and reverse transcriptase-polymerase chain reaction (RT-PCR) tests were performed. However, 5 days later, the patient experienced sudden back pain radiating to his lower extremities, and a whole spinal MRI was conducted. The MRI results demonstrated a soft tissue mass around sacral and paravertebral regions, which was highly suspicious of being granulocytic sarcoma. The patient was diagnosed with AML-M2 associated with suspicious granulocytic sarcoma, and was treated with chemotherapy (daunorubicin and cytosine arabinoside) and radiation therapy with follow-up. Two weeks from the patient's initial diagnosis a second bone marrow examination was performed, which revealed hypocellular marrow with a few immature cells (2.3%).

2.2. Conventional chromosome, FISH, and multicolor banding (mBAND) analysis

A standard culture technique for bone marrow cells was applied and chromosomes were analyzed using Giemsa banding of a synchronized high-resolution culture of bone marrow cells. The karyotypes were described according to the International System for Cytogenetic Nomenclature (ISCN 2005) [11].

FISH analysis was performed according to the manufacturer's instructions with commercially available FISH probes supplied by Abbott Molecular/Vysis (Des Plains, IL). The authors conducted FISH analyses for the *AML1/ETO* (LSI *AML1/ETO* Dual Color, Dual Fusion Translocation Probe;

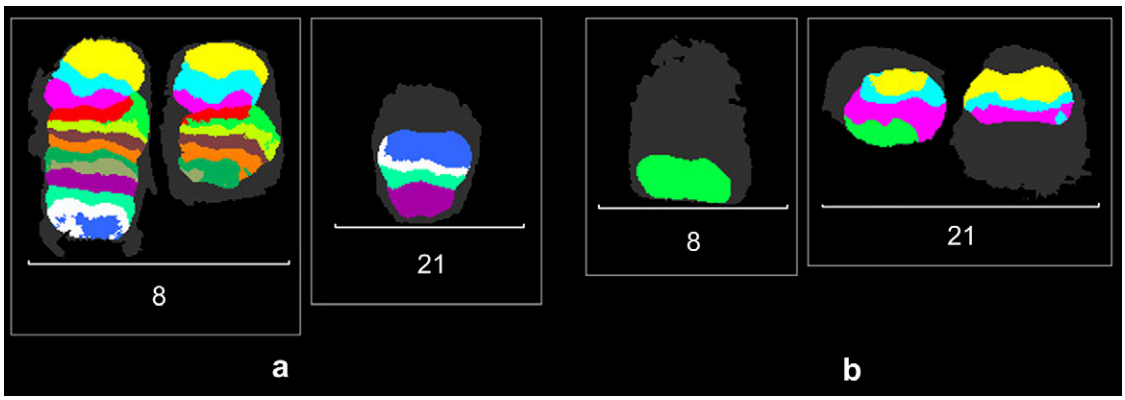

Fig. 2. (a) The chromosome 8 specific mBAND probe kit, XCyte 8 (MetaSystems, Germany), was hybridized to metaphase cells of bone marrow. This image represents three chromosomes that show signals after hybridization, the normal chromosome 8 (left), the derivative chromosome 8 (middle) and the derivative chromosome 21 (right), respectively. The mBAND analysis confirmed the inverted orientation of the part of chromosome 8 which is translocated to chromosome 21, consistent with the result of cytogenetics of inv(8)(q22q24.3)t(8;21)(q22;q22). (b) The chromosome 21 specific mBAND probe kit (XCyte 21) was hybridized to metaphase cells of bone marrow. This image shows three chromosomes, the derivative chromosome 8 (left), the normal chromosome 21 (middle), and the derivative chromosome 21 (right).