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8번 염색체 사체성을 보인 급성단구성백혈병 1예

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Tetrasomy 8 in a Patient with Acute Monoblastic Leukemia

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Trisomy 8 is one of the most frequent numerical chromosomal abnormalities observed in hematological malignancies, whereas tetrasomy 8 is a clonal aberration seen mainly in myeloid disorders such as acute myelod leukemia (AML) and myelodysplastic syndromes. In contrast to trisomy 8, tetrasomy 8 is a rare chromosomal aberration, in that only 17 reported AML cases with isolated tetrasomy 8 have been documented. Interestingly, the majority of reported cases were associated with monocytic-lineage leukemias. According to recent reports, tetrasomy 8 is regarded as a poor prognostic factor, and most patients having this abnormality relapsed and died within 1 yr. Here, we report a patient with acute monoblastic leukemia having tetrasomy 8 and a very aggressive disease course. *(Korean J Lab Med 2008;28:262-6)*

Key Words : *Acute myelogenous leukemia, Tetrasomy 8, Poor prognosis*

INTRODUCTION

Tetrasomy 8 is a rare chromosomal abnormality observed in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)[1, 2]. Only 17 reported AML cases with isolated tetrasomy 8 have been documented, with all AML subtypes in French American British (FAB) classification being reported at least once[1]. Recently, it has been considered as a poor prognostic factor and showed short survival[3, 4]. Here, we describe a patient with acute monoblastic leukemia having tetrasomy 8 and a very aggressive disease course, and review the previous reports. To the best of our knowledge, this is the first report of tetrasomy 8 in hematological malignancies in Korea.

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CASE REPORT

A 48-yr-old Korean man with poor oral intake and severe abdominal pain for 4 days was admitted to the emergency department of Severance Hospital. An initial complete blood count (CBC) showed a Hb level of 114 g/L and a platelet count of 25×10^9/L with a white blood cell (WBC) count of 64×10^9/L; with 3% neutrophils, 7% lymphocytes, 7% monocytes, 1% atypical lymphocytes, and 82% immature cells (monoblasts). Blood chemistries also yielded abnormal results: blood urea nitrogen (BUN), 48.4 (reference interval 5.0-25.0)

mg/dL; creatinine, 2.7 (0.5-1.4) mg/dL; and lactate dehydrogenase (LDH), 2,116 (225-455) IU/L. High leukocytosis and thrombocytopenia compelled us to perform a bone marrow examination. The bone marrow was markedly hypercellular and replaced by many large vacuolated monoblasts showing strong positive non-specific esterase activity (Fig. 1). Flow cytometry showed the blasts to be positive for CD13, CD33, CD14, CD45, MPO, and HLA-DR and negative for CD3, CD7, CD10, CD19, CD20, cCD22, CD79a, and TdT. Ultrasonography of the upper abdomen showed an enlarged liver and no definite evidence for focal mass lesion or enlargement of the spleen. Because acute renal failure was suspected, conventional hemodialysis was performed. The patient was diagnosed as acute monoblastic leukemia (AML-M5b) with acute renal failure. After completing hemodialysis, his renal function progressively recovered. However, his general condition worsened due to bacterial sepsis, pulmonary hemorrhage, and pneumonia. Although intensive management was promptly initiated, the patient died of septic shock on the 23rd day of the admission.

METHODS AND RESULTS

1. Conventional cytogenetic analysis

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) [5]. The result of karyotyping was a 48,XY,+8,+8 in 18 of 20 cells analyzed (Fig. 2). Two other analyzed cells showed 46,XY, which is a normal male karyotype.

2. FISH study

FISH analysis was performed on bone marrow cells according to the manufacturer's instructions and the protocol described by Pinkel et al.[6]. The LSI IGH/MYC, CEP 8 Tri-color set DNA probe (Vysis, Downers Grove, IL, USA) was used for hybridization. This probe is designed to detect the juxtaposition of immunoglobulin heavy chain (IGH) locus on chromosome 14 and *MYC* gene on chromosome 8. In addition, the SpectrumAqua CEP 8 probe serves as an indicator of chromosome 8 and targets the alpha satellite sequences on human chromosome 8 (band region 8p11.1-q11.1). Six hundred metaphase cells were scored for signal patterns, using a fluorescence microscope. Four aqua and orange signals were visualized in 95.5% of the nuclei examined, revealing the presence of tetrasomy 8 (Fig. 3); three aqua and orange signals, showing trisomy 8, were seen in 3.3% of the nuclei; two aqua and orange signals, showing normal chromosome 8, were seen in 1.1% of the nuclei. Unfortunately, no material was available to perform either the FISH or RT-PCR for the MLL gene.

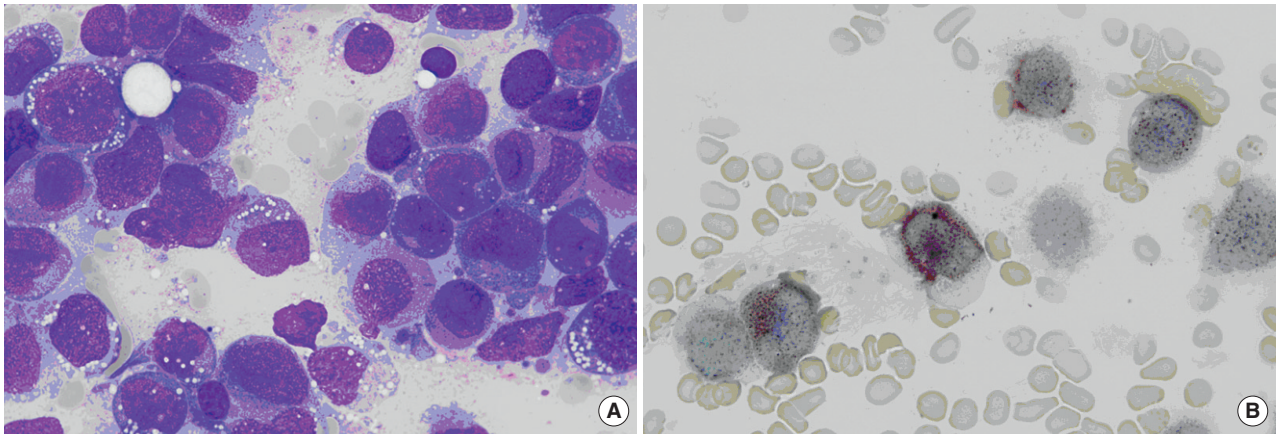

Fig. 1. (A) Bone marrow smear (Wright-Giemsa, ×1,000) showing many large vacuolated monoblasts. (B) Monoblasts showing intense non-specific esterase activity (Non-specific esterase, ×1,000).

3. Molecular study

Reverse transcriptase (RT)-PCR was performed to detect gene rearrangement of *BCR/ABL* major and minor, *AML1/ETO*, and *CBFB/MYH11*. The results of the RT-PCR analysis were all negative.

DISCUSSION

Although trisomy 8 is a common chromosomal abnormality in AML and MDS, tetrasomy 8 is very rare[7-10]. Recently, Beyer et al. reviewed polysomy (tetrasomy, pentasomy, and hexasomy) 8 and characterized 103 patients with tetrasomy 8 as a sole or complexed karyotype abnormalities in detail[1]. According to their report, AML was diagnosed in 83 patients, MDS in 12, and MPD in 8. Interestingly, tetrasomy 8 was associated with myelomonocytic or monocytic involvement in 46 of the 103 patients (45%); 36 with AML-M5, 8 with AML-M4, and 2 with chronic myelomonocytic leukemia. Only 17 reported AML cases with isolated tetrasomy 8 have been documented, with all AML subtypes being reported at least once[1-4, 7, 9-21].

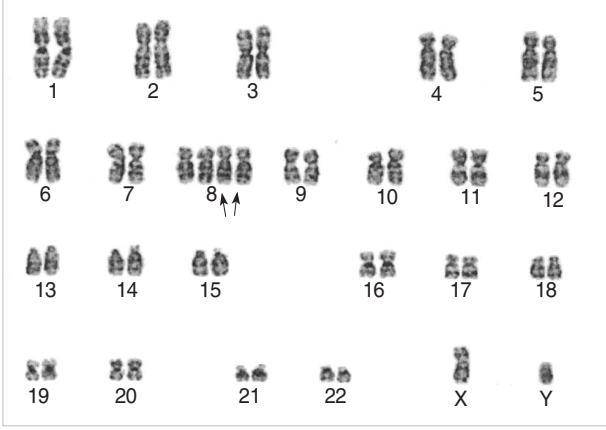

Fig. 2. Giemsa-banding karyotype of the bone marrow cells: 48, XY,+8,+8.

Trisomy 8 was undetectable with conventional cytogenetics in most of the reported cases[4]. In some tetrasomy 8 cases, further examination with FISH, using probes specific for the centromeric region of chromosome 8, revealed a concurrent trisomy 8 in almost all of the examined cases [3]. In our case, we also found a few clones of trisomy 8 (3.3%) with FISH analysis, which were not detected by conventional cytogenetics. We believe our FISH results are in agreement with other previous reports, suggesting that tetrasomy 8 is always accompanied by trisomy 8 clones[3, 7, 10]. Some authors suggested that tetrasomy 8 could occur by either of the following mechanisms: 1) two consecutive events of single nondisjunction of chromosome 8 or 2) a single event of double nondisjunction of chromosome 8[3, 4, 11, 12, 22]. Because most reported cases showed that tetrasomy 8 was accompanied by trisomy 8 clones, we also consider the first mechanism more likely. In addition, the

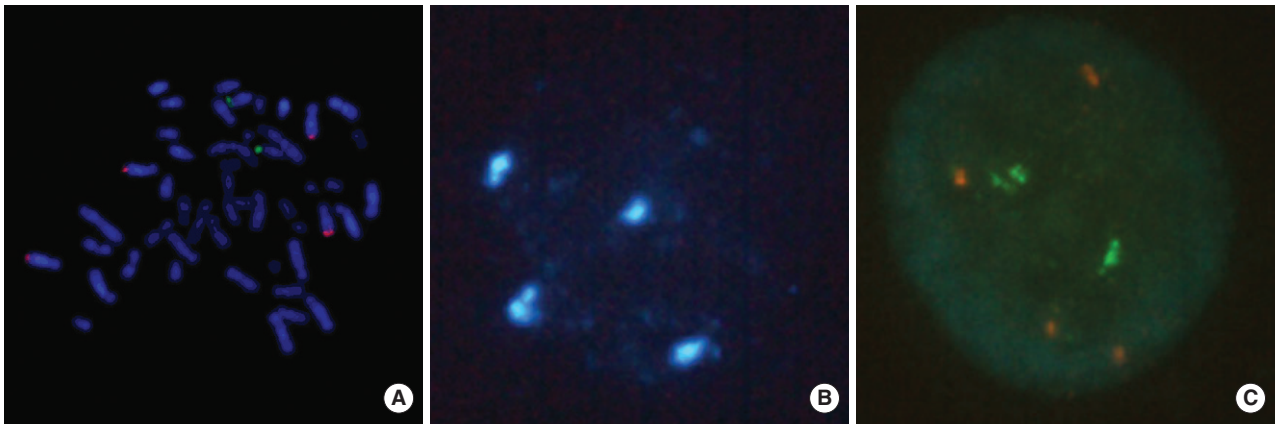

Fig. 3. Metaphase FISH of the bone marrow cells using a LSI IGH/MYC, CEP 8 Tri-color set DNA probe (Vysis, Downers Grove, IL, USA). (A) A metaphase cell was analyzed by a Metafer4-MetaCyte scanning system (MetaSystems, Germany). The four orange fluorescent spots indicate tetrasomy 8. The other two green signals indicate immunoglobulin heavy chain (IGH) locus on chromosome 14. (B) The SpectrumAqua CEP 8 probe shows centromere-specific 4 aqua signals of chromosome 8. (C) A LSI IGH/MYC, CEP 8 Tri-color set DNA probe showing 4 orange signals (chromosome 8) and 2 green signals (chromosome 14) (Vysis).

polysomy cases detected by conventional chromosomal study should be confirmed by more sensitive tests such as FISH to ensure the possible existence of other clones that may contribute to the aggressive nature of the disease.

AML with tetrasomy 8 is considered to have a highly aggressive nature, and the overall median survival has been estimated at 6-7 months by some reports[1-4]. Recently, Cho et al. reported a hexasomy 8 in a patient with AML-M5, who also showed a short survival[23]. The pathogenetic mechanisms are not clear, however, genes that may be involved in leukemogenesis located on chromosome 8, such as *MYC* in 8q24, *MOS* in 8q22, and *RUNX1T1* should be considered as potential causes of malignant transformation [3]. More studies are needed to investigate this rare numerical abnormality in hematological malignancies. To our knowledge, this is the first report of tetrasomy 8 in a patient with AML in Korea.

요 약

8번 염색체 삼체성은 혈액종양에서 발견되는 흔한 염색체 이상의 하나이며 8번 염색체 사체성은 급성골수성백혈병이나 골수이형성증후군 등과 같은 골수구성 질환에서 주로 발견되는 클론성 변이로 알려져 있다. 8번 염색체 사체성은 8번 염색체 삼체성과는 달리 매우 드물게 보고되고 있으며 지금까지 단 17예의 급성골수성백혈병에서 8번 염색체 사체성이 단독 이상으로 보고되었다. 더욱 흥미로운 사실은 대부분의 증례가 단핵구성 백혈병과 연관되어 나타난다는 것이다. 최근에 보고된 바에 의하면 8번 염색체 사체성은 나쁜 예후 인자에 속하며 대부분의 환자들에서 재발하여 1년 안에 사망하는 것으로 나타났다. 저자들은 급진적인 경과를 보인 8번 염색체 사체성을 동반한 급성단핵구성백혈병 1예를 경험하여 보고하는 바이다.

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