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골수성질환에서 단독 염색체 이상으로 19번 삼염색체를 보인 2예

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Two Cases of Trisomy 19 as a Sole Chromosomal Abnormality in Myeloid Disorders

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Trisomy 19 is frequently encountered in cases of chronic myeloid leukemia (CML) as a secondary abnormality: however, trisomy 19 rarely occurs as a sole chromosomal abnormality and, to date, it has only been reported in 48 hematopoietic malignancies, 1 case of adenocarcinoma and 1 case of astrocytic tumor. Here, we report two additional cases of trisomy 19 as a sole karyotypic aberration in myeloid malignancies. One of these cases involved a 6-month-old male who was diagnosed with acute myeloid leukemia minimally differentiated. His karyotype was 47,XY,+19[20]. He expired 5 days after diagnosis. Another case occurred in an 80-yr-old female who had refractory anemia with excess blasts. Her karyotype was 47,XX,+19[16]/46,XX[4]. Four months later, her peripheral blood smears suggested that the disease had progressed, but she refused further evaluation. Based on a review of the existing literature and the results of this report, trisomy 19 not only as a secondary abnormality but also as a sole karyotypic aberration is strongly associated with myeloid disorder; however, it is not preferentially found in specific FAB subgroups of myelodysplasic syndrome or acute myeloid leukemia. *(Korean J Lab Med 2008;28:174-8)*

Key Words : *Trisomy 19, Sole chromosomal abnormality, Myeloid malignancies*

INTRODUCTION

Numerical chromosomal aberrations are frequently observed as clonal chromosome abnormalities that are associated with hematologic disorders. Several numerical aberrations lack morphologic-cytogenetic specificity, and more frequently, they are found as secondary changes, which obscure their role in the leukemogenic process. However, it is well known that there is a nonrandom association of trisomic clones with some specific diseases. Consistent association of trisomic states with neoplastic conditions includes trisomy 4 in cases of acute myeloid leukemia (AML), trisomy 9 in cases of polycythemia vera (PV), trisomy 11 in myeloid disorders, and trisomy 12 in cases of B-cell chronic lymphocytic leukemia (CLL)[1]. Trisomy 19 as a sole abnormality is a rare event that may be associated with myeloid malignancies, and it was previously described in only 48 cases that involved various hematologic malignancies, a

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case of adenocarcinoma, and a case of astrocytic tumor[2]. We encountered two cases in which trisomy 19 occurred as the sole anomaly. One of these was a case of refractory anemia with excess blasts (RAEB) and the other was a case of acute myeloid leukemia minimally differentiated (AML-M0). Based on a review of the existing literatures, no report describing the occurrence of trisomy 19 as a sole anomaly in cases of hematologic disorders in Korea existed. Herein, we present the clinical and morphological findings of these cases and compare them with previously published cases in which isolated trisomy 19 was involved.

CASE REPORTS

1. Case 1

A 6-month-old male was referred to our center after experiencing fever and vomiting for one week. Although he had been born as a 4.1 kg, full term baby that was previously healthy, he appeared very ill when he presented at our center. His complete blood cell count revealed an Hb concentration of 7.2 g/dL, a platelet count of 320×10^9/L and a WBC of 7.7×10^9/L with 89% blasts. His bone marrow showed marked hypercellularity and an increase of blasts up to 96% (Fig. 1). The blasts were not stained by myeloperoxidase, PAS, or α-naphthyl butyrate. Flow cytometric analysis revealed that leukemic cells were positive for CD7, CD33, CD13, HLA-DR, and CD34. Therefore, he was diagnosed with AML-M0 according to the FAB classification. The liver and spleen were palpable upon physical examination. Cytogenetic analysis was performed using 24-hr unstimulated cultures with peripheral blood specimen, and karyotype was described according to the International System for Human Cytogenetics Nomenclature (ISCN) 2005. His karyotype was 47,XY,+19[20] from the unstimulated cultures (Fig. 2). We failed to obtain interpretable mitoses from the phytohemagglutinin (PHA)-stimulated lymphocyte culture. Although he received chemotherapy and antibiotics, he expired 5 days after diagnosis.

2. Case 2

An 80-yr-old female with previous history of myocardial

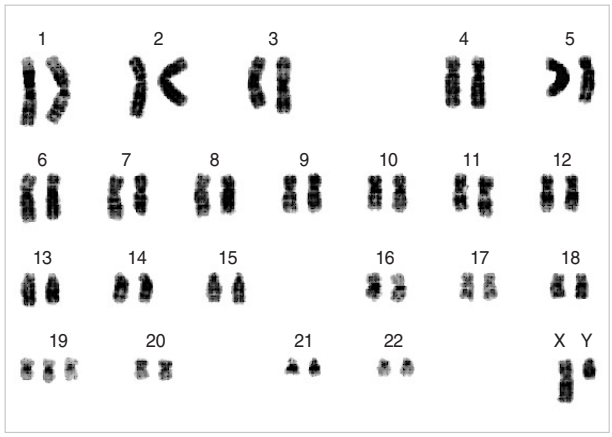

Fig. 2. The representative karyotype of case 1 shows 47,XY,+19.

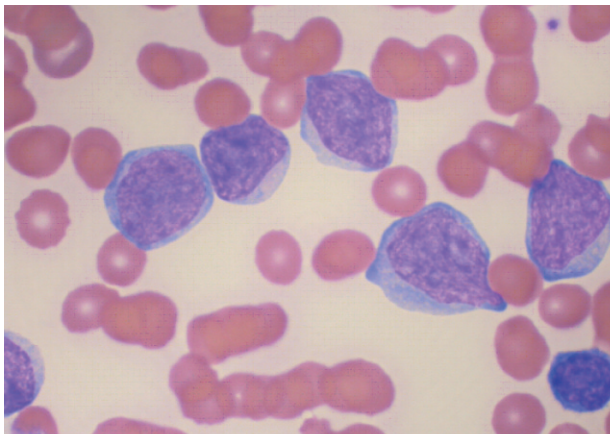

Fig. 1. The bone marrow aspirate of case 1 showed increase of blasts up to 96% (wright stain, ×1,000).

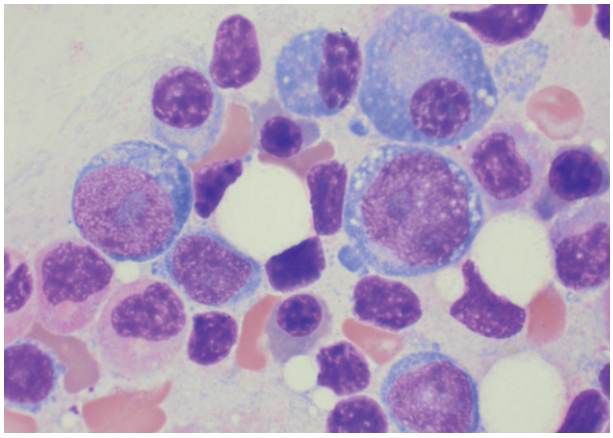

Fig. 3. The bone marrow aspirate of case 2 was normocellular and contained 5.5% blasts (wright stain, ×1,000).

infarction and congestive heart failure was admitted to our center due to aggravation of dyspnea. Her complete blood cell count revealed a Hb concentration of 7.4 g/dL, a platelet count of 110×10^9/L, a WBC of 3.17×10^9/L with segmented neutrophils 24%, band form neutrophils 3%, lymphocytes 54%, monocytes 14%, atypical lymphocytes 2%, metamyelocytes 1%, and myelocytes 2%. Her bone marrow was normocellular and contained 5.5% blasts (Fig. 3), which were stained by myeloperoxidase. Therefore, she was diagnosed with myelodysplastic syndrome (MDS), RAEB. Cytogenetic analysis of bone marrow revealed 47,XX,+19[16]/46,XX[4]. Four months later, her peripheral blood smears showed a leukoerythroblastic reaction with 3% blasts and 10 normoblasts/100 WBCs. She refused further evaluation and was discharged.

DISCUSSION

Despite the relatively frequent occurrence of numerical abnormalities, they have received less attention than structural abnormalities, because several numerical anomalies are found to cause secondary changes. Secondary cytogenetic abnormalities are indistinct in their role in the tumorigenic process, and the molecular consequences of gains and losses of entire chromosomes are virtually unknown[3]. However, several numerical abnormalities have been found to be the sole karyotypic abnormalities in malignancies, and often specifically associated with particular tumor types. Further, sole cytogenetic abnormalities have received attention, because the term sole refers not only to the fact that these are the first cytogenetic changes to occur in neoplastic cells, but also because of their causal role in tumorigenesis[4].

Trisomy 19 has frequently been encountered as a secondary anomaly in case of chronic myeloid leukemia (CML). Although it is not as common as trisomy 8, i(17q) and extra Philadelphia chromosome, trisomy 19 has also been observed in up to 15% of CML patients with additional anomalies and may therefore also be considered as a major route change. The presence of an extra copy of chromosome 19 has been correlated with myeloid blast crisis of CML[4, 5]. In addition, an additional chromosome 19 or 19q also detected in 13.2-33.3% of patients with acute megakaryoblastic leukemia (AML-M7) and it occurs as a secondary anomaly in all cases[6]. As indicated above, the presence of an extra copy of chromosome 19 is associated with myeloid malignancies; however, the presence of trisomy 19 as a sole karyotypic aberration is rare, and it has only been reported in 48 hematopoietic malignancies, 1 case of adenocarcinoma, and 1 case of astrocytic tumor. Among these 48 cases of hemotopoietic malignancies, 15 were AML, 11 were MDS, 5 were chronic myelomonocytic leukemia (CMMoL), 3 were acute biphenotypic leukemia (ABL), 1 was acute undifferentiated leukemia (AUL), 10 were acute lymphocytic leukemia (ALL), and 3 were multiple myeloma (MM) (Table 1)[2]. In addition we report here a case of AML-M0 and a

Table 1. The summary of previously reported and our cases with trisomy 19 as sole cytogenetic abnormality

Diagnosis	N of cases	Mean age (range)	M/F	AA/AN	Mean % of abnormal clone
AML					
M0	3	2 (1-3)	2/1	1/1	90.0
M1	5	28.2 (1-76)	5/0	2/3	54.9
M2	1	1	1/0		
M4	3	45.6 (6-74)	1/2	2/0	83.8
M5a	1	6	0/1	0/1	5.7
NOS	3	1	2/1	1/0	9.5
MDS					
RA	6	58.6 (16-76)	5/1	0/3	46.3
RARS	1	43	1/0	1/0	95.0
RAEB	5	60.6 (1-80)	2/3	1/4	55.2
MDS/MPD					
CMMoL	5	70 (61-75)	4/1	2/3	
AUL	1	2			
ABL	3	3 (1-5)	2/1		
ALL	10	17 (1-34)	6/4		
MM	3		2/1	3/0	10.2
Adenoca	1	52	0/1	0/1	50.0

Abbreviations: AML, acute myeloid leukemia; M0, acute myeloid leukemia minimally differentiated; M1, acute myeloid leukemia without maturation; M2, acute myeloid leukemia with maturation; M4, acute myelomonocytic leukemia; M5a, acute monoblastic leukemia; NOS, not otherwise specified; MDS, myelodysplastic syndrome; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; MDS/MPD, myelodysplastic/myeloproliferative disease; CMMoL, chronic myelomonocytic leukemia; AUL, acute undifferentiated leukemia; ABL, acute biphenotypic leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; Adenoca, adenocarcinoma; M, male; F, female; AA, abnormal metaphases only; AN, abnormal and normal metaphases.

case of RAEB associated with the presence of trisomy 19 as a sole karyotypic aberration. It should also be noted that this anomaly of trisomy 19 is strongly associated with myeloid disorder.

A review conducted by Johansson et al.[3] revealed that, the 14 AML cases included in their review had had a preleukemic myelodysplastic phase; however, the clone containing trisomy 19 had occurred around the time that leukemic transformation occurred in all these cases. One of our cases who was diagnosed as RAEB suggested progression of disease. A similar association between trisomy 19 and leukemic transformation occurs in cases of CML. It has been suggested that the appearance of an extra copy of chromosome 19 in cases of CML results in the impediment of myeloid leukemic transformation. However, our review revealed that 8 of 11 patients with MDS and isolated trisomy 19 did not develop acute leukemia; therefore, it is difficult to determine if the presence of an isolated trisomy 19 can be used to predict leukemic transformation. None of the MDS, CMMoL or AML cases had a history of exposure to radiotherapy or chemotherapy and the occurrence of isolated trisomy 19 was associated with a subgroup of de novo myeloid disorders.

Even though Daskalakis et al.[7] concluded that trisomy 19 as a sole anomaly was a recurrent change in CMMoL, particularly in the proliferative type that frequently evolved to AML, no clinical features seem to characterize patients of MDS or CMMoL with isolated trisomy 19 by our review. However, in cases of AML, the mean age of patients with isolated trisomy 19 appears to be young. Eight of the 15 patients that possess the isolated trisomy 19 were less than 10 yrs old, and four of these patients were infants, in spite of the occurrence of acute leukemia in infants was not common. A similar result was described in a report by the United Kingdom Cancer Cytogenetic Group (UKCCG)[1] regarding primary, single, autosomal trisomies associated with hematological disorders. Five of the cases described by the UKCCG report showed the presence of an isolated trisomy 19, and the mean age of these patients was significantly younger than that of the entire study group (18.2 yr compared with 51.8 yr). Based on their report, six of the 13 patients, which included eight previously reported cases were aged eight months to 6 yrs. The two youngest patients with trisomy 19 in the UKCCG study each had relatives with leukemia. Taken together, the results of the UKCCG study suggested that there was a subgroup of patients who were very young and had a familial history of isolated trisomy 19. Hartley and Sainsbury reported the same chromosome abnormality of trisomy 19 in monozygotic twins diagnosed with AUL, one of whom presented with AUL at the age of 17 months, while the other presented at the age of 36 months [8]. One of our patients with AML was also less than 1 yr. Although we failed culture to evaluate the peripheral blood cytogenetics, we can exclude the presence of constitutional trisomy 19 because he had no phenotypic abnormality. The most reported cases of constitutional trisomy 19 were those that involved partial trisomy 19q and were associated with a distinctive phenotype that usually includes low birth weight, growth and psychomotor retardation, and facial dysmorphism etc[9]. Because no live birth with complete trisomy 19 has been reported, it can be assumed that trisomy 19 has a pathogenetic relationship with leukemia in this case of infantile AML.

The biologic relevance of trisomy 19 may relate to a gene dosage effect. For example, the human DNA methyltransferase 1 gene has been mapped to the short arm of chromosome 19 (19p13.2), which catalyzes "maintenance" methylation of mammalian genomic DNA. Overexpression of the mRNA for DNA methyltransferase-1, and -3A has been reported in MDS, which may contribute to the aberrant hypermethylation that occurs in MDS patients[10]. A case of CMMoL showed the presence of a strongly hypermethylated promoter and a response to demethylation therapy[11]. However, it is still unclear which gene(s) located on chromosome 19 might have a functional role in the development of hematologic malignancies.

In summary, although the occurrence of trisomy 19 as a sole cytogenetic abnormality is rare, it is associated with myeloid hematologic malignancies such as MDS, CMMoL, and AML. However, trisomy 19 has not been reported in patients with chronic myeloproliferative disorder (CMPD). It is not associated with characteristic morphologic or clin-

ical features except that the mean age of patients with isolated trisomy 19 appears to be young in cases of AML. At present, it is unclear which gene(s) on chromosome 19 is associated with tumorigenesis. Because a small number of cases have been reported and the clinical outcomes of most patients have been poorly described, the clinical implications and prognostic impact of isolated trisomy 19 require further elucidation.

요 약

19번 삼염색체는 만성골수성백혈병에서 이차적 염색체 이상으로 흔히 관찰되지만, 단독 염색체 이상으로 나타나는 경우는 매우 드물어 현재까지 48예의 혈액 종양, 1예의 샘암종과 1예의 별아교세포종에서 보고되었다. 저자들은 최근 골수성 혈액종양에서 단독 염색체 이상으로 19번 삼염색체을 보인 2예를 경험하여 보고하는 바이다. 1예는 미분화 급성골수백혈병으로 진단받은 생후 6개월의 남아로 핵형은 47,XY,+19[20]이었으며 항암치료와 항생제 치료를 받았으나 진단 후 5일째 사망하였다. 다른 1예는 골수형성이상증후군 중 모세포과다 불응성 빈혈로 진단받은 80세 여자 환자로 핵형은 47,XX,+19[16]/46,XX[4]이었다. 진단 4개월 후 말초혈액에서 백적혈구모세포반응을 보여 질병의 진행이 의심되었으나 환자의 거부로 더 이상의 평가는 하지 못했다. 이제까지 보고된 문헌과 본 증례에 근거하면, 단독염색체 이상으로서의 19번 삼염색체는 골수성 혈액 질환과 관련이 깊은 것으로 생각되지만, 골수형성이상증후군이나 급성골수성백혈병의 특정 형태학적 아형과 연관성은 없었다.

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