

급성림프모구성백혈병에서 급성골수성백혈병으로의 계열 변환 1예

정희정¹ · 박찬정¹ · 장성수¹ · 지현숙¹ · 서울주¹ · 서종진²

울산의대 서울아산병원 진단검사의학과, 소아과²

A Case of Lineage Switch from Acute Lymphoblastic Leukemia to Acute Myeloid Leukemia

Hee-Jung Chung, M.D.¹, Chan-Jeoung Park, M.D.¹, Seongsoo Jang, M.D.¹, Hyun-Sook Chi, M.D.¹, Eul Ju Seo, M.D.¹,
and Jong-jin Seo, M.D.²

Departments of Laboratory Medicine¹ and Pediatrics², University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea

Lineage switch from acute lymphoblastic leukemia (ALL) to acute myeloid leukemia (AML) is very rare. We report a case of a 9 yr-old ALL patient relapsed as acute myelomonocytic leukemia. At the initial diagnosis, the blast cell morphology and immunophenotype were consistent with the diagnosis of typical ALL (L1 subtype according to FAB classification). The *BCR-ABL* fusion gene was not found by reverse transcription-PCR. Complete remission (CR) was achieved after induction and consolidation chemotherapy (Children's Cancer Study Group 1891 protocol, CCG1891). Nine months, which is a very short time compared with other cases in the literatures, after the diagnosis of ALL, she relapsed with completely different blasts (typical AML, M4 according to FAB classification) in morphology, cytochemistry, and immunophenotyping. The karyotype has changed from 56,XY,+X,+Y,+Y,+4,+8,+10,+14,+17,-20,+21,+21,+21[6]/57, idem,+Y[19] to 46,XY,t(8;16)(p11.2;p13.1)[19]/46,XY[1], showing unrelated chromosomal abnormality to the karyotype at the initial diagnosis. Moreover, both findings were quite specific for each common cell ALL and acute myelomonocytic leukemia. These findings support that this case is completely different leukemic clones occurred at each leukemic expression. The treatment with AML 2000 protocol chemotherapy failed, and he underwent the chemotherapy with the combination of high dose cytarabine and mitoxantrone and has been in CR state for 21 months, until now. (*Korean J Lab Med* 2007;27:102-5)

Key Words : Lineage switch, Acute lymphoblastic leukemia, Acute myelomonocytic leukemia

INTRODUCTION

Lineage switch from acute lymphoblastic leukemia (ALL)[1] to acute myeloid leukemia (AML) is very rare[2-4]. The conversions can occur in both directions from ALL to AML and vice versa[4-9]. And the for-

mer conversions are reported mainly in children[4, 8]. We report herein a case of child having had ALL at 9 yr of age who relapsed as acute myelomonocytic leukemia with a complete change of karyotype and immunophenotype.

CASE REPORT

A 9-yr-old boy presented with complaint of easy bruisability. The spleen was slightly enlarged, and neither lymphadenopathy nor hepatomegaly was found. He had no history of the previous exposure to toxic drugs. Lab-

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교 신 자 : 박 찬 정
우 138-736 서울시 송파구 풍납2동 388-1
울산의대 서울아산병원 진단검사의학과
전화 : 02-3010-4508, Fax : 02-478-0884
E-mail : cjpark@amc.seoul.kr

oratory studies revealed a white blood cell count of $20 \times 10^9/L$ with 44% blasts, the hemoglobin level of 8.0 g/dL, and the platelet count of $44 \times 10^9/L$. Bone marrow examination showed massive infiltrate of blast cells (98% among nucleated marrow cells). The blasts showed small to medium size, round nucleus, clumped nuclear chromatin, 0-1 indistinct nucleolus, and small amount of cytoplasm without granules (Fig. 1A).

Cytochemical stains showed block-dot positive reaction for periodic acid-Schiff (PAS), and negative reaction for myeloperoxidase (MPO) and α -naphthyl butyrate esterase (ANBE). Immunophenotypic analysis of blast cells showed the positivity of CD45, HLA-DR, terminal deoxynucleotide transferase (TdT), CD19, CD22, CD10 and the negativity of CD34, CD13, CD33, CD20, cytoplasmic IgM, surface IgM, CD3 and CD7. These findings were consistent with B-lineage common cell ALL. ALL, L1 subtype was diagnosed according to the FAB classification. Cytogenetic

study was performed on a 24-hr bone marrow culture. Six metaphase cells revealed the karyotype of 56,XY,+X,+Y,+Y,+4,+8,+10,+14,+17,-20,+21,+21,+21 and nineteen cells showed 57,idem,+Y, which were usual findings in common cell ALL (Fig. 2A). The RNA extraction and reverse transcription PCR were performed, but *BCR-ABL* fusion gene was not found. Complete remission (CR) was achieved and the chemotherapy was maintained in compliance with Children's Cancer Study Group (CCG) 1891 protocol. Nine months after the initial diagnosis, the patient presented with continuous fever. There was no interval change of mild splenomegaly and other physical findings. The peripheral blood showed $0.7 \times 10^9/L$ white blood cells without blasts, hemoglobin 10.4 g/dL, and platelet count $70 \times 10^9/L$. Bone marrow study revealed a homogeneous population of large blasts (84.8% among nucleated marrow cells) with relatively abundant amount of basophilic cytoplasm, and lobated nuclear configuration. Some blasts

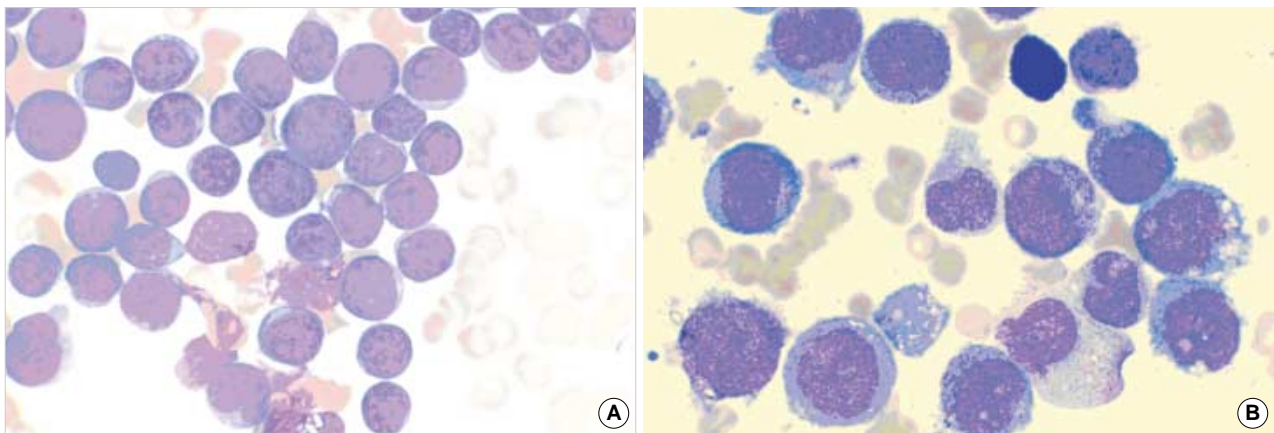


Fig. 1. Bone marrow aspirate findings (Wright stain, $\times 1,000$) (A) Acute lymphoblastic leukemia at the initial diagnosis, (B) Acute myelomonocytic leukemia at the relapse.

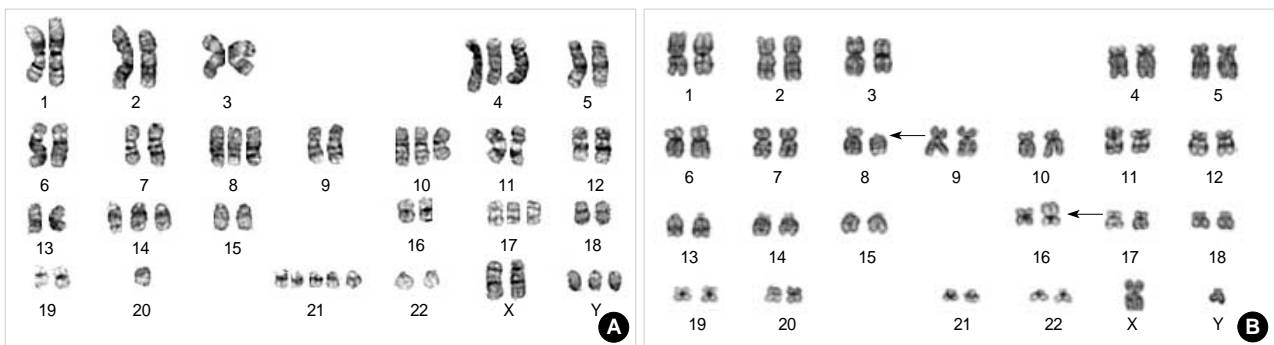


Fig. 2. The change of karyotype with bone marrow aspirates. (A) The karyotype at the diagnosis of acute lymphoblastic leukemia revealed 56,XY,+X,+Y,+Y,+4,+8,+10,+14,+17,-20,+21,+21,+21[6]/57,idem,+Y[19]. (B) The karyotype at the relapse as acute myelomonocytic leukemia revealed 46,XY,t(8;16)(p11.2;p13.1)[19]/46,XY[1] showing unrelated abnormality to the karyotype at the initial diagnosis.

contained granules but no Auer rods (Fig. 1B). Cytochemical stains showed positive reaction for MPO in about 42% of the blasts and for ANBE in about 80%. Immunophenotyping showed coexpression of CD14 and CD33 on leukemic blasts. The blasts showed the positivity of HLA-DR, CD13, CD33, CD14 and the negativity of CD34, TdT, CD117, CD41, CD10, CD19, CD3, CD7 and CD56, which was consistent with acute myelomonocytic leukemia. Repeated cytogenetic studies with bone marrow aspirates revealed 46,XY,t(8;16)(p11.2;p13.1)[19]/46,XY[1], which is common in acute myelomonocytic leukemia (AML M4) and acute monoblastic/monocytic (AML M5) leukemia (Fig. 2B). Induction chemotherapy with AML 2000 protocol and repeated reinduction therapy failed, showing persistent bone marrow blasts up to 30.8%. The patient achieved CR with the treatment of high dose cytarabine and mitoxantrone, and has been alive for 34 months from the diagnosis of AML.

DISCUSSION

The frequency of lineage switch among patients with acute leukemias at the relapse is estimated to be about 6% to 9%[8, 10]. Cases of conversion from ALL to AML are very rare. To our knowledge, only a few cases of conversion from B-lineage ALL to AML have been previously reported world-widely[5, 11, 12] although there has been some switching within the myeloid lineage, occasionally[13]. In this case, the leukemic clone at relapse had completely different morphology, cytochemistry, and phenotypic lineage. The different findings to be noticed in this patient from other reports are like these. First, the interval between the treatment and the conversion was very short as 9 months. In other literature, it is known to be after median 3.0 yr (ranged from 1.2 to 6 yr)[6, 7, 14]. The patient has not been treated with drugs which could cause therapy-related AML such as alkylating agent or topoisomerase II inhibitor. The patient treated according to the CCG protocol 1891 (vincristine, prednisolone, L-asparaginase, and methotrexate); however, these agents are generally not considered as leukemogens. Second, the blasts at the relapse showed absolutely different karyotype and immunophenotype from those at the diagnosis, suggesting the emergence of a new independent clone at the conversion. Especially cytogenetic study showed totally

unrelated abnormality without any similarity between the diagnosis and the relapse. Moreover both findings were quite lineage specific for each common cell ALL and acute myelomonocytic leukemia. The t(8;16)(p11.2; p13.1) which is found at the relapse in this patient, is observed in about 0.4% of AML with M4-M5 subtype[15]. Immunophenotyping also revealed striking changes between the initial presentation and the subsequent relapse: loss of lymphoid markers such as CD10, CD19, CD22 and TdT, and gain of myeloid markers such as CD13, CD33 and CD14. These two findings support that this case is completely different leukemic clones occurred at each leukemic expression.

There are several hypotheses to explain lineage switch of acute leukemia, but the precise mechanism remains obscure. One supportive hypothesis is a mixed lineage leukemia model. That is, chemotherapy might suppress the leukemic clone apparent at the diagnosis, but subsequently allow the expansion of a subclone with a different phenotype. It is appropriate with some cases with the mixed lineage at the diagnosis, and the lineage switch may be the part of the biologic spectrum of the mixed lineage leukemia. But in fact, the lineage switch is not necessarily restricted to the mixed lineage leukemia. Another hypothesis is the change of leukemic entity. Chemotherapy after the first diagnosis could modify the original leukemic clone, thus causing a shift in the expression of the phenotypic features[10]. An alternative model could be provided by chronic myeloid leukemia at the blast transformation. In that hypothesis, pluripotent stem cell malignancy may be capable of an acute transformation into either myeloid or lymphoid cell lines[16]. In this case, *BCR-ABL* fusion gene was not found by RT-PCR analysis. Chromosomal abnormalities, particularly those involving 5, 7, and especially 11q23 band occur preferentially at the malignant transformation of a pluripotential stem cell[4, 14]. However, it has been shown that the molecular abnormalities in the lineage switch of acute leukemias are heterogeneous and they can represent the emergence of a second new clone[4].

Although it is very rare, the lineage switch in acute leukemias exists and its frequency could be underestimated because sometimes myeloperoxidase cytochemistry and immunophenotypic analyses were not fully performed at the time of relapse. Early recognition of lineage switch can lead to appropriate therapy and allow such patients to achieve the remission state like this case.

요 약

급성림프모구백혈병에서 급성골수성백혈병으로의 계열 변환은 매우 드물다. 저자들은 급성림프모구백혈병으로 진단 후 급성골수단구성백혈병으로 계열이 변환된 9세 환아를 경험하였다. 초진시 환아의 골수 백혈병모세포는 형태학적으로나 면역표현형 검사 결과상 ALL에 합당하였다(FAB분류상 L1아형). 역전사중합효소연쇄반응에서 *BCR-ABL* 융합 유전자는 관찰되지 않았다. 유도요법과 공고요법 치료(Children's Cancer Study Group 1891 protocol, CCG1891) 후 완전관해에 도달하였다. ALL 진단 9개월 후, 형태학적으로나 면역표현형검사상이나 세포화학 반응양상으로 완전히 다른 AML, M4 모세포의 특징을 나타내면서 재발되었는데, 기존의 계열 변환 문헌과 비교하였을 때 상당히 짧은 기간이었다. 세포유전학적 분석결과 56,XY,+X,+Y,+Y,+4,+8,+10,+14,+17,-20,+21,+21,+21[6]/57,idem,+Y[19]에서 46,XY,t(8;16)(p11.2;p13.1)[19]/46,XY[1]로 초진시와 연관성이 없는 염색체이상을 나타내었다. 또한 각각의 결과는 common cell ALL과 myelomonocytic leukemia에 매우 전형적인 소견이었다. 이러한 소견들은 본 증례의 각 백혈병 발현시 모세포가 다른 clone이라는 것을 뒷받침한다. 환자는 AML 2000 protocol 화학요법으로 치료에 실패하여 고용량 cytarabine과 mitoxantrone으로 혼합화학요법으로 치료 후 현재까지 21개월 간 완전관해상태를 유지하고 있다.

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