A Case of Myelodysplastic Syndrome Associated with an Isolated del(5q) Chromosomal Abnormality Showing Poor Prognosis

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Typical myelodysplastic syndrome (MDS) associated with isolated del(5q) consists of an interstitial deletion of the band between q13 and q33 on chromosome 5. Generally, patients with isolated deletion 5q have better outcomes than those who have the deletion 5q with additional karyotypic abnormalities. Here we report a 47 year-old female with an isolated del(5q) chromosomal abnormality with an atypical breakpoint of 5q11q35 and rapid progression to acute leukemia, which had an exceptionally poor outcome. The peripheral blood revealed pancytopenia and occasional giant platelets, and the patient had hypercellular bone marrow with 4.8% blasts, as well as dysmegakaryopoiesis and dyserythropoiesis. Cytogenetically, the patient was del(5q)(q11.2q35)[18]/46,XX[2], showing that her deleted region was larger than that found for typical del 5q syndrome. Three months later, the patient presented with acute myelomonocytic leukemia with multilineage dysplasia. The cytogenetic findings were identical. Two months after allogeneic bone marrow transplantation, the patient died from severe graft-versus host disease. ***(Korean J Hematol 2007;42:43-47.)***

Key Words: Myelodysplastic syndromes, Isolated deletion(5q)

INTRODUCTION

Interstial deletion of 5q is the most common chromosomal aberration in patients with myelodysplastic syndromes (MDS),[1,2] with the proximal breakpoint usually being from q11 to q31 and the distal breakpoint from q21 to q33. The most common deletion is an interstitial deletion of the band from q13 to q33. MDS associated with isolated del(5q) is one of the seven categories of MDS by WHO definition. This disease shows favorable prognosis with long survival[1-4] and clinically the patients in this category is classified as refractory anemia.[5] We report here a case of MDS associated with isolated del(5q) which was associated with exceptionally poor prognosis.

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CASE REPORT

A 47-year-old woman visited hospital complaining of dyspnea. No abnormalities were noted during physical examination, but unexplainable pancytopenia was detected. The peripheral complete blood count was as follows: hemoglobin, 7.9g/dL; MCV, 97.6fL; white blood cells, 2.1×10^9/L with differentials of 1% band, 26% segments, 1% basophil, 1% eosinophils, 16% monocytes, 53% lymphocytes; and platelet, 31×10^9/L. Frequent giant platelets were noted. Bone marrow (BM) aspiration revealed hypercellular marrow, with 4.8% of all nucleated cells being blasts. The BM showed multilineage dysplasia involving cells of the megakaryocytic and erythroid lineages. Dysmegakaryopoietic features included hypolobulation, nu-

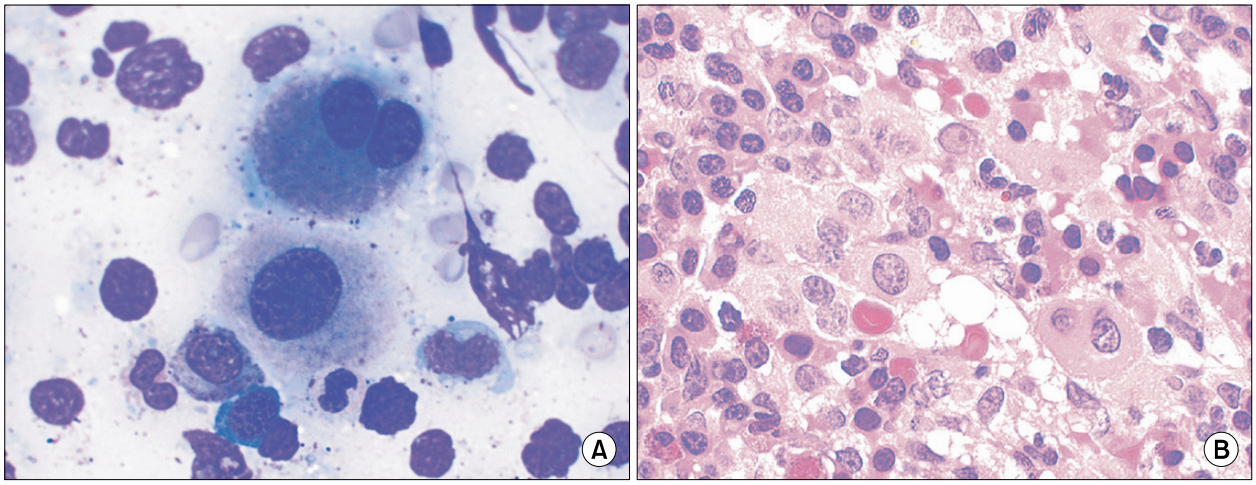

Fig. 1. The findings at the diagnosis of myelodysplastic syndrome associated with isolated del(5q). (A) Occasional micromegakaryocytes with hypolobulated nucleus in the bone marrow aspirates (Wright stain, ×1,000). (B) Numerous megakaryocytes of various sizes. Frequent hypolobulated micromegakaryocytes in the hypercellular bone marrow biopsy specimen (H&E stain, ×1,000).

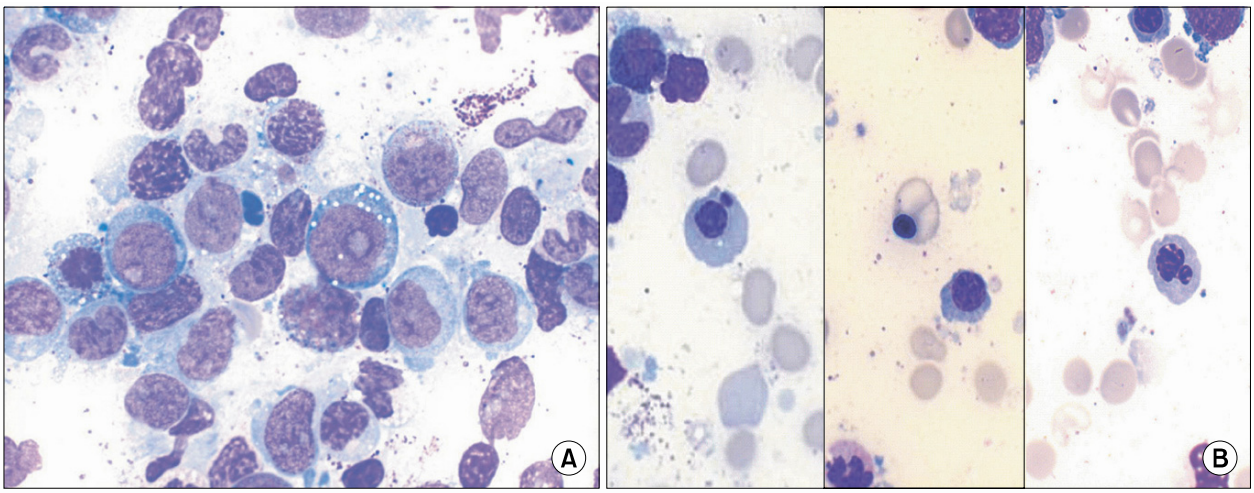

Fig. 2. The findings of bone marrow aspiration at the diagnosis of acute myelomonocytic leukemia with multilineage dysplasia (AML M4 according to the FAB classification). (A) Blasts with prominent nucleoli and relatively abundant cytoplasm with small vacuoles (Wright stain, ×1,000). (B) Erythroid dysplasia, including multinucleation, nuclear fragmentation, and basophilic stippling in the bone marrow aspirates (Wright stain, ×1,000).

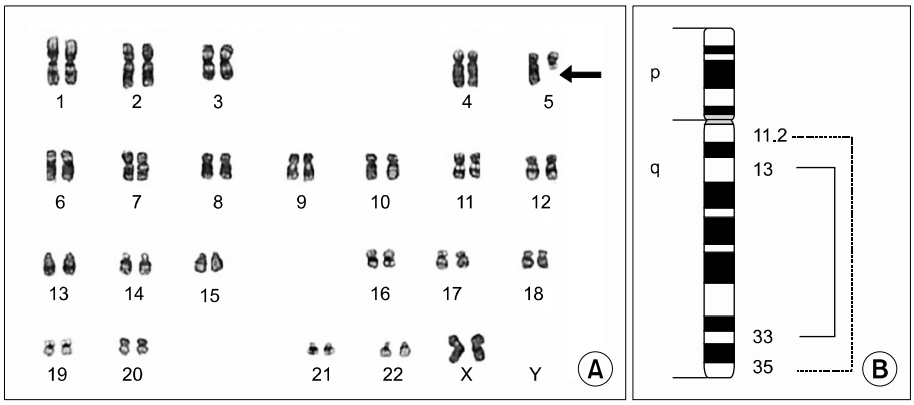

Fig. 3. (A) Karyotype analysis of the patient. del(5q)(q11.2q35) was observed in 18 of 20 metaphases, indicating that the deleted region was larger than that in typical 5q deletion. (B) Ideogram of chromosome 5: break point of the patient (dotted line) and ordinary break point of MDS associated with isolated del(5q) (solid line).

clear separation, and micromegakaryocytes, and dyserythropoiesis features included nuclear budding, multinucleation, basophilic stippling, and Howell-Jolly bodies (Fig. 1). Sideroblasts were not detected. Conventional cytogenetic analysis showed del(5q)(q11.2q35) in 18 of 20 metaphases and 46,XX in the remaining two. The deleted region was larger than that of typical MDS associated with isolated del(5q) (Fig. 2). Three months later without treatment, the peripheral blood showed 6% blasts and 24% monocytes with pancytopenia sustained The leukoerythroblastic reaction was noted. Repeated BM aspiration revealed 31% blasts with dysplastic features, and the patient was classified as acute myelomonocytic leukemia (AML M4 according to the French-American-British classification with multilineage dysplasia. The dysplasia became aggravated into three lineages with additional myeloid lineage (Fig. 3). Cytochemically, the blasts showed positive myeloperoxidase and non-specific esterase reaction. The blasts expressed CD13, CD33, CD117, CD14, and aberrant CD7. Repeated cytogenetic analysis showed del(5q)(q11.2q35), with no additional changes, in 18 of 20 metaphases. The patient received bone marrow transplantation (BMT) from unrelated donor after a scheduled pre-BMT BuCy regimen (Busulfan 4mg/kg/dx4, Cyclophosphamide 60mg/kg/dx2). But, 2 months after BMT, the patient died from severe graft-versus host disease (GVHD).

DISCUSSION

The MDS associated with isolated del(5q) classically, is characterized by hypolobulated micromegakaryocytic hyperplasia and a clonal cytogenetic abnormality, consisting of an interstitial deletion in the long arm of chromosome 5.[3] According to the new classification of MDS by World Health Organization (WHO), this is defined as a subgroup of MDS showing single cytogenetic abnormality of del(5q) and $<5\%$ blasts in the BM.[5] Cytogenetically, individuals with isolated del(5q) have a fairly good prognosis.[3,4] The significance of $>5\%$ BM blasts in a patient with an isolated del(5q) is not clear, but it has been suggested that these patients have poorer prognosis.[6]

Variable breakpoints of 5q have been reported in MDS associated with isolated del(5q), with the usual proximal breakpoint being from q11 to q31 and the usual distal breakpoint from q21 to q33. The most common form, del(5q)(q13q33), has the best prognosis.[4] In this patient, however, the deletion region was between bands q11.2 and q35, larger than that observed frequently in del(5q). It may be noteworthy that in this patient, MDS evolved into acute leukemia with multilineage dysplasia, without additional cytogenetic abnormalities, only 3 months after the initial diagnosis. Following the development of splenomegaly, she died from GVHD soon after BMT.

Although many genes that encode hematopo-

Table 1. Clinical and pathologic characteristics of MDS associated with isolated del(5q) and the comparison with this patient

Isolated del(5q)	This patient
• Clinical presentation	• Clinical presentation
Older age (median 68 years)	Old age (47 year-old)
Female predominance (7 : 3 female to male)	Female
Refractory anemia	Pancytopenia
Low risk of leukemic progression	**Leukemic progression**
Good prognosis	**Poor prognosis**
• Hematologic presentation	• Hematologic presentation
Macrocytic anemia	Normocytic anemia
Modest leukopenia	Modest leukopenia
Normal/High platelet counts	**Low platelet count**
del(5q)(q13q33)	**del(5q)(q11.2q35)**
BM erythroid hypoplasia	**No BM erythroid hypoplasia**
Hypolobulated megakaryocytes in BM	Markedly hypolobulated megakaryocytes in BM
<5% BM blast count	4.8% of BM blast count

ietic growth factors or their receptors have been localized to the long arm of chromosome 5, the importance of the deleted 5q bands in the development of MDS is not known. No single tumor suppressor gene responsible for MDS has been identified to date, although several interesting candidates have been localized to this location, including *MEGF1* and *G3BP*.[6-8] Loss of the 5q12 band has been reported to be an independent predictor of adverse outcome,[9] consistent with this finding of del(5q)(q11.2q35) in this patient. Other factors that influence the survival of deletion 5q patients include patient age, diagnosis, and acquisition of additional chromosome aberrations.

The typical clinical, hematologic, and pathologic presentations of MDS associated with deletion 5q are shown in Table 1,[6] together with findings in this patient. Interestingly, the patient described here lacked the typical morphology of megakaryocytes seen in MDS associated with isolated del(5q) and showed atypical breakpointof 5q11q35Moreover, the clinical course was more aggressive than even that of the unfavorable MDS subgroup.

In conclusion, we have described a patient with MDS associated with isolated del(5q), which was rapidly transformed to acute leukemia. In this patient, poor prognosis has been due to the 5q breakpoint, which included the band at 5q12.

요 약

5q단독결손골수형성이상증후군은 전형적으로 5번 염색체의 q13에서 q33 사이의 부분적 염색체소실을 특징으로 한다. 대개 5q 결손만을 나타내는 경우가 다른 염색체이상을 동반한 경우보다 경과가 양호하여 다른 골수형성이상증후군과 따로 분류된다. 저자들은 5q단독결손골수형성이상증후군으로 진단된 47세 여자 환자에서 비전형적인 5번 염색체 장완의 절단부위(5q11q35)가 관찰되면서, 급성백혈병으로 전환된 매우 불량한 임상경과를 보인 한 증례를 보고하고자 한다. 말초혈액도말상 범혈구감소증과 거대혈소판을 관찰하였고, 골수흡인과 생검상 4.8%의 골수모세포와 증가된 세포충실도, 거대핵세포형성이상과 적혈구형성이상이 관찰되었다. 골수세포로 시행한 핵형분석에서 del(5q)(q11.2q35)[18]/46,XX[2]를 나타내었는데, 이것은 이제까지 보고되었던 절단부(breakpoint)와 상이하였다. 3개월 후 환자는 다계열형성이상을 동반한 급성골수구단구성백혈병으로 진행하였다. 핵형분석은 5q단독결손골수형성이상증후군 진단 시의 소견과 같았다. 골수이식 2개월 후 환자는 이식편대숙주병으로 사망하였다. 본 증례는 5q단독결손골수형성이상증후군으로 독특한 절단부를 나타내면서 예외적으로 극히 불량한 예후를 나타내었다.

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