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□ 증례 □

Acute Myeloid Leukemia with t(8;21)(q22;q22) (AML1/ETO) in a Patient with Marked Hypocellularity and Low Blasts Count

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－Abstract－

According to the World Health Organization (WHO) classification system, cases with t(8;21)(q22;q22) should be diagnosed as acute myeloid leukemia (AML) even with a blast count of less than 20 percent in blood or bone marrow. It is an uncommon manifestation, moreover hypocellularity is rarely observed in this subtype of leukemia. Here, we report a case of t(8;21) in a patient with marked hypocellularity of less than 5 percent and a blast count of less than 20 percent. This patient responded relatively well to chemotherapy. An allogeneic bone marrow transplantation was performed with good engraftment . This case suggests that hypocellular AML with a t(8;21) has as good a prognosis as hypercellular AML with t(8;21).

Key Words: Acute myeloid leukemia, t(8;21)(q22;q22), Hypocellularity

Introduction

The translocation t(8;21)(q22;q22) is one of the most common structural aberrations in acute myeloid leukemia (AML). It was found in 5-12 percent of cases of AML and in one-third of karyotypically abnormal cases of AML with maturation (M2). This type of AML usually shows common morphological features, which include the presenceof large blasts with abundant basophilic cytoplasm, and which often contain numerous azurophilic

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granules. Auer rods are frequently found and may be detected in mature neutrophils.[1-3] According to the World Health Organization (WHO) classification system, rare cases with t(8;21) and bone marrow blasts count of less than 20 percent should be classified as AML and not as refractory anemia with excess blasts (RAEB).[1] Here, we describe our experience of a case of t(8;21) in a patient with marked hypocellularity of less than 5 percent and blasts count of less than 20 percent. By a review of literatures, hypocellular AML is a rare manifestation of AML with t(8;21).[4]

Case report

A 49-year-old male was referred to us in July 2005, because of dizziness and fatigue of duration 1 month. His complete blood cell count revealed bicytopenia (hemoglobin 7.5 g/dL and platelets 21 × 10^9/L). His white blood cell (WBC) count was 5.98 × 10^9/L with segmented neutrophils 83%, myelocytes 1%, lymphocytes 13% and blasts 3%. A bone marrow biopsy showed marked hypocellularity of less than 5 percent (Fig. 1A), and on bone marrow aspirate smears, all three lineages were suppressed and blasts were relatively increased up to 16 percent (Fig. 1B). Moreover, these blasts revealed myeloperoxidase positivity. We initially diagnosed the present case as hypocellular myelodysplastic syndrome (MDS) RAEB type based on blast percentage. A cytogenetic analysis of bone marrow was performed using 24-hour unstimulated cultures, and karyotypes were described according to the International System for Human Cytogenetics Nomenclature (ISCN) 2005. A clone was defined as at least two cells with the same additional numerical and/or structural abnormalities, or as three cells with the loss of the same chromosome. His karyotype was 46,XY,t(8;21)(q22;q22)[3]/46,idem,del(9)(q22)[8]/46,XY

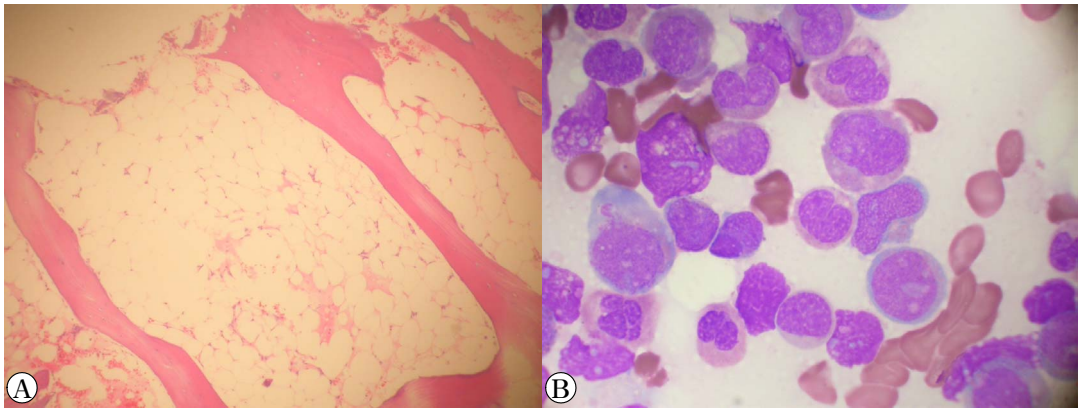

Fig. 1. A bone marrow biopsy showed marked hypocellularity (A, H-E stain x 40) and blasts were increased on bone marrow aspirates (B, wright stain x 1000).

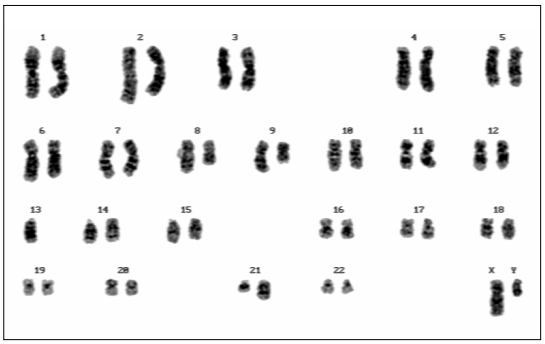

Fig. 2. The representative karyotypes showed 46, XY,t(8;21)(q22;q22),del(9)(q22).

[9] (Fig. 2). Fluorescence in situ hybridization (FISH) was performed using an AML1/ETO dual color, dual fusion translocation probe (Vysis, Downers Grove, IL) and 60 percent of interphase cells (120 per 200 cells) revealed the AML1/ETO rearrangement (Fig. 3), which was also demonstrated by reverse transcription-polymerase chain reaction (RT-PCR). Thus, a final diagnosis of AML with t(8;21)(q22;q22);(AML1/ETO) was made using the WHO classification. He received allogeneic stem cell transplantation from a human leukocyte antigen (HLA)-matched sibling donor (a younger sister) in October 2005. At the time of writing (19 months after transplantation), his complete blood cell count is hemoglobin 12.4 g/dL, platelets 132 × 10^9/L and WBCs 8.57 × 10^9/L. He achieved complete chimerism by the variable-number tandem repeat analysis method (VNTR) and microchimerism (0.2 percent of XY signal) by FISH of CEP X/Y probe kit.

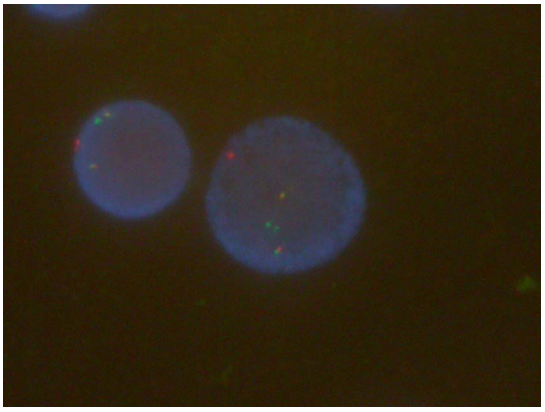

Fig. 3. AML1/ETO rearrangement is demonstrated as fusion signals by fluorescence in situ hybridization using an AML1/ETO dual color, dual fusion translocation probe.

Discussion

The WHO, in conjunction withthe Society for Hematology and the European Association of Hematopathology, published a new classification for hematopoietic and lymphoid neoplasm in 2001. In this WHO classification, the blast threshold for a diagnosis of AML is reduced from 30 percent to 20 percent in blood or marrow. Moreover, four well-defined recurring genetic abnormalities are allocated to the subgroup “AML with recurrent cytogenetic abnormalities.” Nearly 30 percent of patients with AML have one of four recurring genetic abnormalities, and these patients show a strong correlation between genetic and morphological findings. For example, morphological features of AML with t(8;21) include large basophilic blasts with prominent Auer rods, numerous large azurophilic granules, pseudo-Chediak granules and vacuoles, mature neutrophils with

pseudo-Pelger-Hüet anomaly, homogenous pink-colored cytoplasm and basophilic rim.[1)]

Before the WHO classification was published, a small number of cases of t(8;21) positive MDS had been reported and most of these cases were classified as refractory anemia with excess blasts in transformation (RAEB in T) according to the French-American-British (FAB) classification. The arguments were posed that t(8;21) positive MDS could be called a MDS, because the clinical manifestations of t(8;21) positive MDS that had been described in the literatures were similar to that of de novo AML with t(8;21).[2, 5-7)] First, they had often evolved into typical M2-AML relatively rapidly. Second, the complete remission (CR) rate of over 80 percent shown for conventional antileukemic therapy was similar to that of AML M2. Such a high CRrate on AML-type chemotherapy is uncommon for MDS and may indicate that these patients with t(8;21) positive MDS should receive immediateantileukemic treatment. Third, in some cases, Auer rods can be identified not only in blasts but also in mature neutrophils, thus providing morphologic evidence of the terminal differentiation of leukemic progenitors. One of the important changes of WHO classification compared to FAB classification is that patients with recurring abnormalities t(8;21)(q22;q22), inv(16)(p13q22) or t(16;16)(p13;q22) and t(15;17)(q22;q12) should be considered as having AML regardless of blast percentage.

This case is also of interest because the patient suffered from so-called hypocellular AML. Marked hypocellularity less than 5 percentwas rarely reported in AML with t(8;21). Hypocellular acute leukemia (HAL) had been described as a subset of acute leukemia characterized pancytopenia and an increased number of blasts in hypocellular bone marrow. Bone marrow cellularity is a critical determinant of recognizing this entity. The majority of previous reports have defined the threshold for “hypocellular” as below 40% or 50% or occasionally 30%. However, because most patients were elderly and might have low cellularity due to aging, bone marrow cellularity cut-off values remain controversial, and the precise incidence and natural history of HAL have not been established. True HAL according to age adjustment is extremely rare.[4, 8-10)] The WHO classification defines “hypocellular” or “hypoplastic” acute leukemia as a marrow cellularity of less than 20 percent and a marrow blasts count of more than 20 percent. Hypocellular AML must be differentiated from aplastic anemia. Bone marrow hypocellularity in aplastic anemia is usually more pronounced without evidence of increased blasts, and interstitial cells are well differentiated lymphocytes, plasma cells, mast cells, and scattered maturing hematopoietic cells. The differentiation of HAL and hypocellular MDS may be difficult though possible by blast percentage.[1)] The cytogenetic findings

of HAL have rarely been reported. The frequency of karyotypic abnormalities (31%) is slightly lower than in AML in the elderly (60%) or in MDS (55%). Abnormal karyotypes in HAL are similar to those commonly seen in MDS or in AML of the elderly cases, but no specific non-random abnormalities for HAL have been discovered because of small number of reports. To the best of our knowledge, t(8;21) has not been described before in HAL.[4)]

The present case did not achieve complete remission (CR) by first remission induction chemotherapy but achieved CR on reinduction. Thereafter, he received an allogeneic stem cell transplantation, and at the time of writing his complete blood cell counts are within normal limits and he has maintained complete chimerism by VNTR for 19 months after transplantation.

This patient responded relatively well to chemotherapy and engrafted well after an allogeneic bone marrow transplantation. Thus, this case suggests that hypocellular AML with t(8;21) also need intensive antileukemic therapy and has as good a prognosis as hypercellular AML with t(8;21).

요 약

세계보건기구의 분류에 따르면 8번 염색체와 21번 염색체의 전위인 t(8;21)(q22;q22)를 가진 경우는 말초혈액이나 골수에 모세포가 20% 미만이더라도 급성골수성백혈병으로 분류하여야 하며, 이는 흔하지 않은 소견이다. 뿐만 아니라 이런 아형의 백혈병에서 골수의 저세포충실도는 매두 드물다. 저자들은 골수세포충실도가 5% 미만으로 심하게 감소되어 있고, 골수의 모세포도 20% 미만인 환자에서 t(8;21)을 관찰하여 급성골수성백혈병으로 진단한 1례를 보고하는 바이다. 항암치료에 잘 반응하고 동종골수이식의 생착이 잘 이루어져, t(8;21)을 가진 일반적인 고세포충실성 급성골수성백혈병과 유사하게 좋은 예후를 가지는 것으로 생각된다.

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