Hemophagocytic Lymphohistiocytosis in *RUNX1::RUNX1T1* Positive AML with Blast Count Below 20%

Blast Sayısı %20'nin Altında Olan *RUNX1::RUNX1T1* Pozitif Akut Myeloid Lösemi Olgusunda Hemofagositik Lenfohistiositoz

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To the Editor,

Hemophagocytic lymphohistiocytosis (HLH), a rare and life-threatening syndrome, is categorized as primary and secondary forms on the basis of genetic abnormalities or potential causes. Secondary HLH is triggered by multiple etiologies, including hematological malignancies, metastatic carcinoma, infections, and acquired immune deficiencies [1]. Malignancy-associated HLH is usually related to lymphoid neoplasms, while HLH in association with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) is rarely reported. According to the classification of the World Health Organization, patients with recurrent genetic abnormalities should be diagnosed with AML regardless of blast count. In this letter, we describe an uncommon case diagnosed as AML with *RUNX1::RUNX1T1*, with the coexistence of secondary HLH and a blast count below 20%.

A 58-year-old woman was admitted due to dizziness and fatigue for more than 20 days. Computed tomography scans of the chest and abdomen showed splenomegaly and extensive exudation, suggesting the possibility of pulmonary infection. A complete blood count showed leukocytosis, moderate anemia, and severe thrombocytopenia (leukocytes: 21.14×10^9/L, absolute monocyte count: 2.96×10^9/L, hemoglobin: 68 g/L, platelets: 4×10^9/L). Other laboratory results showed high levels of interleukin-6 (102.40 ng/L), serum procalcitonin (0.52 ng/mL), C-reactive protein (41 µg/mL), and high-sensitivity C-reactive protein (>5.0 µg/mL). Taken together, these findings collectively confirmed an initial diagnosis of severe pulmonary infection. Peripheral blood smears showed 5% promonocytes and 14% monocytes (Figure 1a). Bone marrow aspirate revealed hypercellular marrow with 2.5% myeloblasts and 2% promonocytes. The cytoplasm of partial abnormal cells was characterized by densely packed or even coalescent large granules and occasional large vacuoles close to the Golgi region (Figure 1b). Bone marrow aspirate showed striking histiocytic hyperplasia and hemophagocytosis (Figures 1c and 1d). Most of the histiocytes revealed marked hemophagocytic activity with phagocytosis of erythrocytes, nucleated red blood cells, platelets, and immature granulocytes (Figure 1d).

This patient also fulfilled the diagnostic criteria for HLH, meeting six of eight criteria including splenomegaly, cytopenia, hemophagocytosis, hypofibrinogenemia (0.65 g/L), hyperferritinemia (719.53 ng/mL), and a high level of sIL-2R (>7500 U/mL). *RUNX1::RUNX1T1* was identified by fluorescence in situ hybridization (Figure 1e) and cytogenetic analysis confirmed a karyotype of 46,XX,t(8;21)(q22;q22)[7]/46, XX[13] (Figure 1f). In spite of the blast count being lower than 20%, based on the presence of the *RUNX1::RUNX1T1* gene, a diagnosis of AML with *RUNX1::RUNX1T1* with concurrence of secondary HLH was established. The patient was hospitalized for 8 days and received dexamethasone at 10 mg/m^2/day and intravenous immunoglobulin at 0.4 g/kg/day. Meanwhile, in light of the severe pulmonary infection, the patient immediately underwent anti-infective treatment with meropenem and voriconazole, after which inflammatory markers did not decrease significantly and her respiratory function deteriorated progressively. Due to financial reasons and poor condition, the patient refused further chemotherapy for the leukemia and was discharged without follow-up.

The characteristic criteria of HLH include fever, cytopenia, hemophagocytosis, hyperinflammation, splenomegaly, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia. The diagnosis of HLH requires fulfillment of a minimum of five of these eight criteria as outlined by the HLH-2004 guidelines [1]. Our patient was diagnosed with secondary HLH in line with these diagnostic criteria. Of interest, her initial peripheral blood and bone marrow examination showed a very low blast count, along

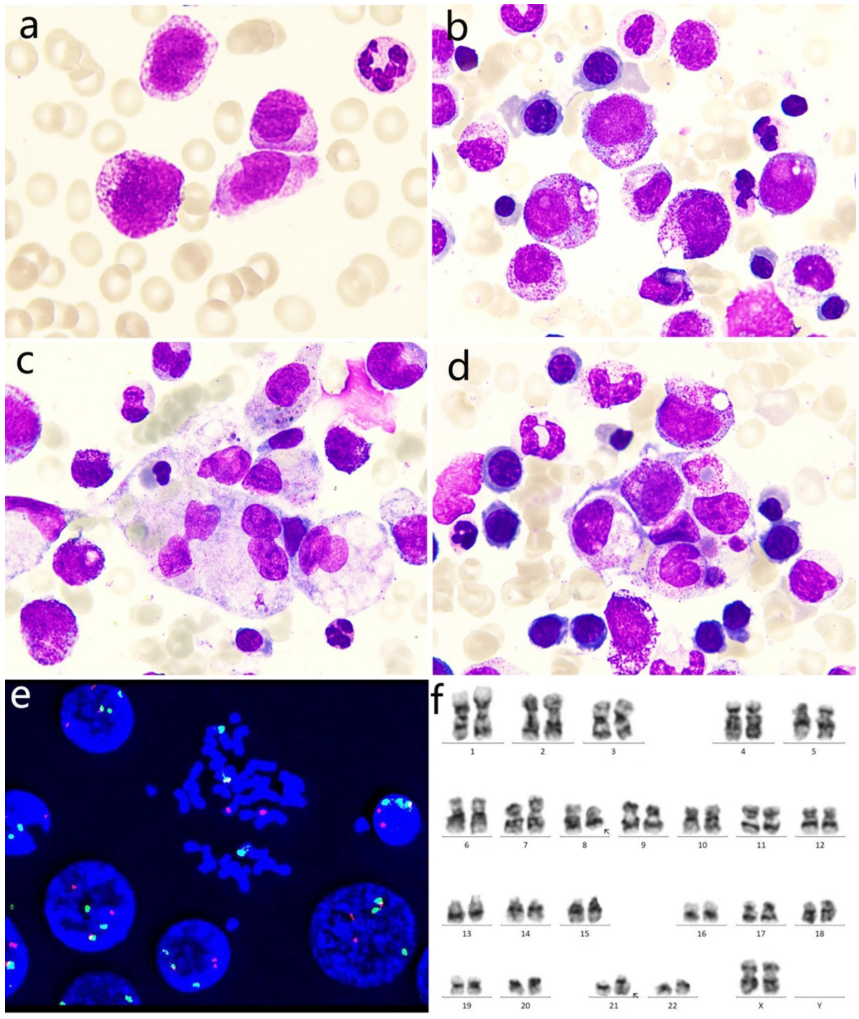

Figure 1. a) Peripheral blood smears showed 5% promonocytes and 14% monocytes (Wright-Giemsa stain, 1000x). b) Bone marrow aspirate revealed hypercellular marrow with 2.5% myeloblasts and 2% promonocytes. The cytoplasm of partial abnormal cells was marked by densely packed or even coalescent large granules and occasional large vacuoles close to the Golgi region. c, d) Bone marrow aspirate showed striking histiocytic hyperplasia and hemophagocytosis, with most histiocytes revealing significant hemophagocytic activity with the phagocytosis of erythrocytes, nucleated red blood cells, platelets, and immature granulocytes (Wright-Giemsa stain, 1000x). e) *RUNX1::RUNX1T1* was identified by fluorescence in situ hybridization. f) Cytogenetic analysis revealed a karyotype of 46,XX,t(8;21)(q22;q22)[7]/46, XX[13].

with moderate monocytosis, which can easily be misdiagnosed as chronic myelomonocytic leukemia. However, owing to the molecular biological detection of the *RUNX1::RUNX1T1* fusion gene, a timely diagnosis of AML was made.

The patient presented with cytopenia (both anemia and thrombocytopenia) at initial admission. She also fulfilled the diagnostic criteria for HLH, meeting six of eight criteria. It is known that secondary HLH may develop in association with various infections, exposure to toxins, malignancies, and autoimmune deficiency disorders. However, given the complexity of this patient's condition and the ineffectiveness of anti-infective therapy, it is unclear whether this case of HLH was due to AML or was associated with severe infection. It may have been the result of the simultaneous effects of infection and AML. Although the blast count was lower than 20%, the existence of the *RUNX1::RUNX1T1* fusion gene, together with the t(8;21)(q22;q22) translocation, led to a concomitant diagnosis of AML with *RUNX1::RUNX1T1* and HLH in this case. However, it is difficult to say whether cytopenia (anemia and thrombocytopenia) developed in relation to HLH or due to AML. There are few case reports of AML occurring with HLH in the literature to date, and a better understanding of the clinical course and pathophysiological features of AML with concurrent HLH and severe infection is needed.

Malignancy-related HLH has been reported in many studies and the most common malignancy types are hematological disorders with NK/T or B-cell lymphoma. Although a small number of cases of AML/MDS-related HLH have been recorded [2,3], AML

with low blast count is seen very rarely and accurate data are not available. Concurrent secondary HLH and blast count below 20% in AML with *RUNX1::RUNX1T1* is an extremely uncommon event. To date, only one pediatric case of AML with low blast count concomitant with HLH has been documented [4]. Thus, the rare adult case presented here highlights the importance of morphology and combining molecular techniques to characterize and confirm the diagnosis of AML with recurrent genetic abnormalities, especially in certain cases with low blast counts.

Keywords: Hemophagocytic lymphohistiocytosis, Blast count below 20%, Acute myeloid leukemia, *RUNX1::RUNX1T1*

Anahtar Sözcükler: Hemofagositik lenfohistiyositoz, Blast sayısı %20'nin altında, Akut myeloid lösemi, *RUNX1::RUNX1T1*

Ethics

Informed Consent: Informed consent was obtained from this patient.

Authorship Contributions

Concept- X.H., F.L., Y.Z., X.G., T.L.; Design- X.H., F.L., Y.Z., X.G., T.L.; Data Collection or Processing- Y.Z., X.G., X.H.; Analysis or Interpretation-Writing- T.L., F.L.

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