LETTER TO THE EDITOR

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Acute Myeloid Leukemia Post Cytotoxic Therapy with *KMT2A* Rearrangement Mimicking Acute Promyelocytic Leukemia

Sitotoksik Tedavi Sonrası *KMT2A* Yeniden Düzenlenmesi ile Akut Promiyelositik Lösemiyi Taklit Eden Akut Miyeloid Lösemi

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To the Editor,

A 58-year-old female patient with a 4-year history of small-cell lung cancer treated with etoposide and cisplatin presented with fatigue, poor appetite, and intermittent fever. Laboratory findings were as follows: white blood cell count of $10.9x10^9$/L, hemoglobin of 92 g/L, platelet count of $104x10^9$/L, neuron-specific enolase of 21.1 ng/mL, fibrinogen of 5.22 g/L, and lactate dehydrogenase of 307 U/L. Bone marrow aspirate smears revealed 92% hypergranular promyelocytes with bilobed/reniform nuclei, abundant cytoplasm containing large and coarse azurophilic granules, Auer rods, and occasional "frog cells" (Figures 1a-1c). Myeloperoxidase staining was strongly positive (Figure 1d). Flow cytometric immunophenotyping showed blasts positive for MPO, CD117, CD123, CD33, CD13, CD38, and CD15 and negative for CD34 and HLA-DR. The morphologic and immunophenotypic findings were highly suggestive of acute promyelocytic leukemia (APL). However, no evidence of *RARA* or variant *RARA* translocation was found by *RARA* break-apart fluorescence in situ hybridization (FISH) or RNA sequencing. Notably, FISH confirmed the *KMT2A* rearrangement, but the partner was not determined by reverse transcription polymerase chain reaction. Chromosomal karyotype analysis revealed 46,XX,t(4;11)(q21;q23),t(16;21)(p13;q11)[10]. Considering the patient's prior medical history, a diagnosis of acute myeloid leukemia (AML) with *KMT2A* rearrangement post cytotoxic therapy (pCT) was made.

AML-pCT is a distinct clinicopathological entity arising as a late complication in patients previously exposed to cytotoxic chemotherapy or extensive radiation for non-hematological conditions. AML-pCT is generally categorized within two major subtypes based on the class of causative agents and associated genetic features. One subtype is linked to prior exposure to alkylating agents or ionizing radiation, typically arising from a preceding myelodysplastic syndrome (MDS). These cases often present with complex karyotypes and unbalanced chromosomal aberrations and are associated with poor clinical outcomes. The second subtype is more commonly associated with DNA topoisomerase II inhibitors. These cases usually lack a prior MDS phase and are characterized by balanced chromosomal translocations, particularly rearrangements involving the *KMT2A* (*MLL*) gene at 11q23. Compared to the former subtype, this subtype generally has a more favorable prognosis [1]. Our case fell within the latter category, the patient having developed AML following prior chemotherapy with no evidence of antecedent MDS and being found to harbor a *KMT2A*

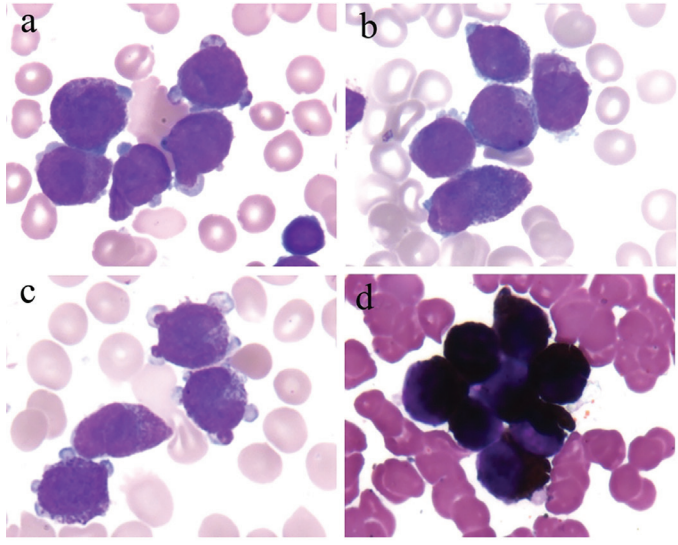

Figure 1. Bone marrow aspirate smears revealed 92% hypergranular promyelocytes with bilobed/reniform nuclei, abundant cytoplasm containing large and coarse azurophilic granules, Auer rods, and occasional "frog cells" (a-c, Wright-Giemsa staining, 1000× magnification). Myeloperoxidase staining was strongly positive (d, 1000× magnification).

rearrangement. Interestingly, the leukemic blasts in this case displayed morphological features reminiscent of APL, such as abundant cytoplasmic granules and Auer rods. Although rare, such APL-like morphology has been reported in AML cases with *NUP98* rearrangements and *NPM1* or *IDH2* mutations [2,3]. However, the morphology in our case of *KMT2A*-rearranged AML-pCT mimicking APL was particularly rare.

This case underscores the diagnostic challenges posed by overlapping morphological features among AML subtypes. For patients presenting with clinical or pathological features suggestive of APL, early initiation of all-trans retinoic acid is recommended according to current guidelines to prevent life-threatening coagulopathy, with discontinuation if subsequent cytogenetic or molecular studies exclude the diagnosis of APL [4]. The integration of clinical history, morphological evaluation, immunophenotyping, and cytogenetic and molecular studies remains essential for achieving accurate classification and guiding appropriate therapy in cases of acute leukemia. Our findings reflect the importance of maintaining a high index of suspicion for therapy-related leukemias with atypical morphologies and reinforce the need for molecular confirmation in all suspected cases.

Keywords: Acute myelocytic leukemia post cytotoxic therapy, AML-pCT, *KMT2A* rearrangement, Acute promyelocytic leukemia, MICM workup, Medical history

Anahtar Sözcükler: Sitotoksik tedavi sonrası akut miyelositik lösemi, AML-pCT, *KMT2A* rearranjmanı, Akut promiyelositik lösemi, MICM değerlendirmesi, Tıbbi öykü

Ethics

Informed Consent: Informed consent was obtained from this patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ha.W. J.Y.; Concept: Ha.W. J.Y., T.L., Hu.W.; Design: Ha.W. J.Y., T.L., Hu.W.; Data Collection and Processing: Ha.W. J.Y.; Analysis or Interpretation: Ha.W. J.Y., T.L., Hu.W.; Literature Search: T.L., Hu.W.; Writing: T.L., Hu.W.

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