LETTER TO THE EDITOR
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Acute Myeloid Leukemia Post Cytotoxic Therapy with *KMT2A* Rearrangement Mimicking Acute Promyelocytic Leukemia

Haiyang Wang[1], Jiulian Yuan[1], Ting Li[2*], Hui Wang[3*]
[1]Affiliated Hospital of Xuzhou Medical University, Department of Hematology, Xuzhou, China
[2]Beijing Lu Daopei Hospital, Department of Laboratory Medicine, Beijing, China
[3]Hebei Yanda Lu Daopei Hospital, Department of Laboratory Medicine, Langfang, China

Hui Wang, M.D., Hebei Yanda Lu Daopei Hospital, Department of Laboratory Medicine, Langfang, China
ldpwanghui2022@163.com

Ting Li, M.D., Beijing Lu Daopei Hospital, Department of Laboratory Medicine, Beijing, China
litingsysu@163.com

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Dear Editors,

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, 10.9×10^9/L, hemoglobin, 92 g/L, platelet count, 104×10^9/L, neuron-specific enolase, 21.1 ng/ml, fibrinogen, 5.22 g/L and lactate dehydrogenase, 307 U/L. Bone marrow aspirate smears revealed 92% hypergranular promyelocytes with bilobed/reniform nuclei, abundant cytoplasm containing large, coarse azurophilic granules, Auer rods, and occasional "frog cells" (Figure.1a-c). Myeloperoxidase staining was strongly positive (Figure.1d). Flow cytometric immunophenotyping showed the blasts were 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* as well as variant *RARA* translocations 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 identified 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 clinicopathologic entity arising as a late complication in patients previously exposed to cytotoxic chemotherapy or extensive radiation for non-hematologic conditions.

AML-pCT is generally categorized into 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 evolving 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 with the former, this subtype generally demonstrates a more favorable prognosis [1]. Our patient fits the latter category, having developed AML following prior chemotherapy with no evidence of antecedent MDS, and was found to harbor a *KMT2A* 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, *NPM1* or *IDH2* mutations [2-3]. However, the morphology in our case with *KMT2A*-rearranged AML-pCT mimicking APL was particularly rare.

This case underscores the diagnostic challenges posed by overlapping morphologic features among AML subtypes. It is well known that in patients presenting with clinical or pathological features suggestive of APL, early initiation of all-trans retinoic acid (ATRA) is recommended to prevent life-threatening coagulopathy, with discontinuation if subsequent cytogenetic or molecular studies exclude the diagnosis of APL, according to the NCCN Guidelines® Acute Myeloid Leukemia Version 2.2025 [4]. Integrating clinical history, morphologic evaluation, immunophenotyping, cytogenetic and molecular studies remains essential for accurate classification and guiding appropriate therapy in acute leukemia. Our findings underscore 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: AML-pCT, KMT2A rearrangement, acute promyelocytic leukemia, MICM workup, medical history

Declarations

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Authors' contributions All authors contributed to the paper conception and design. Clinical and histological data were collected by Haiyang Wang and Jiulian Yuan. The draft of the manuscript was written by Ting Li and Hui Wang, and all authors read and approved the final manuscript.

Conflict of Interest The authors that they have no conflicts of interest.

Informed consent Informed consent was obtained from this patient.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication Informed consent was obtained from the publication.

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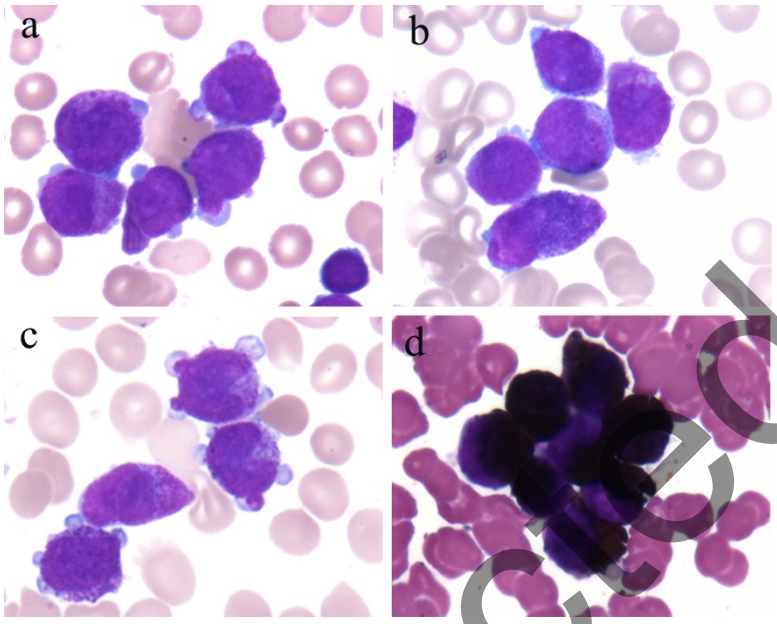

Figure 1. Bone marrow aspirate smears revealed 92% hypergranular promyelocytes with bilobed/reniform nuclei, abundant cytoplasm containing large, coarse azurophilic granules, Auer rods, and occasional "frog cells" (a-c, Wright-Giemsa staining, 1000× magnification). Myeloperoxidase staining was strongly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