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Mixed Phenotypic Acute Leukemia (B/Myeloid) , Post Cytotoxic Therapy with Residual Myeloma

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Introduction

Mixed phenotypic acute leukemia (MPAL) is indeed a rare and complex form of leukemia that seen in <4% of all acute leukemia cases (1). It is characterized by the presence of two or more different cell lineages within the population of leukemic blasts, and classified as follow:

Biallelic MPAL: characterized by presence of two different populations of leukemic blasts, each expressing a different phenotypic lineage (e.g., one population showing myeloid markers, while the other expresses T or B cell lymphoid markers).

Bi-phenotypic MPAL: characterized by presence of single population of leukemic blasts that phenotypically express markers of two or more distinct hematopoietic lineages (e.g., myeloid, and lymphoid).

MPAL can show a significant diagnostic and therapeutic challenges, as the combination of multiple lineages can lead to ambiguous classification.

Case Description

Here in we present a 65-year-old male with a history of multiple myeloma (MM), who has undergone multiple lines of treatment, and currently presents with pancytopenia. His laboratory results reveal a white blood cell count of 0.71 k/µL, red blood cell count of 2.19 million/µL, hematocrit of 29.1%, hemoglobin of 7.7 g/dL, mean corpuscular volume (MCV) of 103.1 fL, and a platelet count of 84 k/µL.

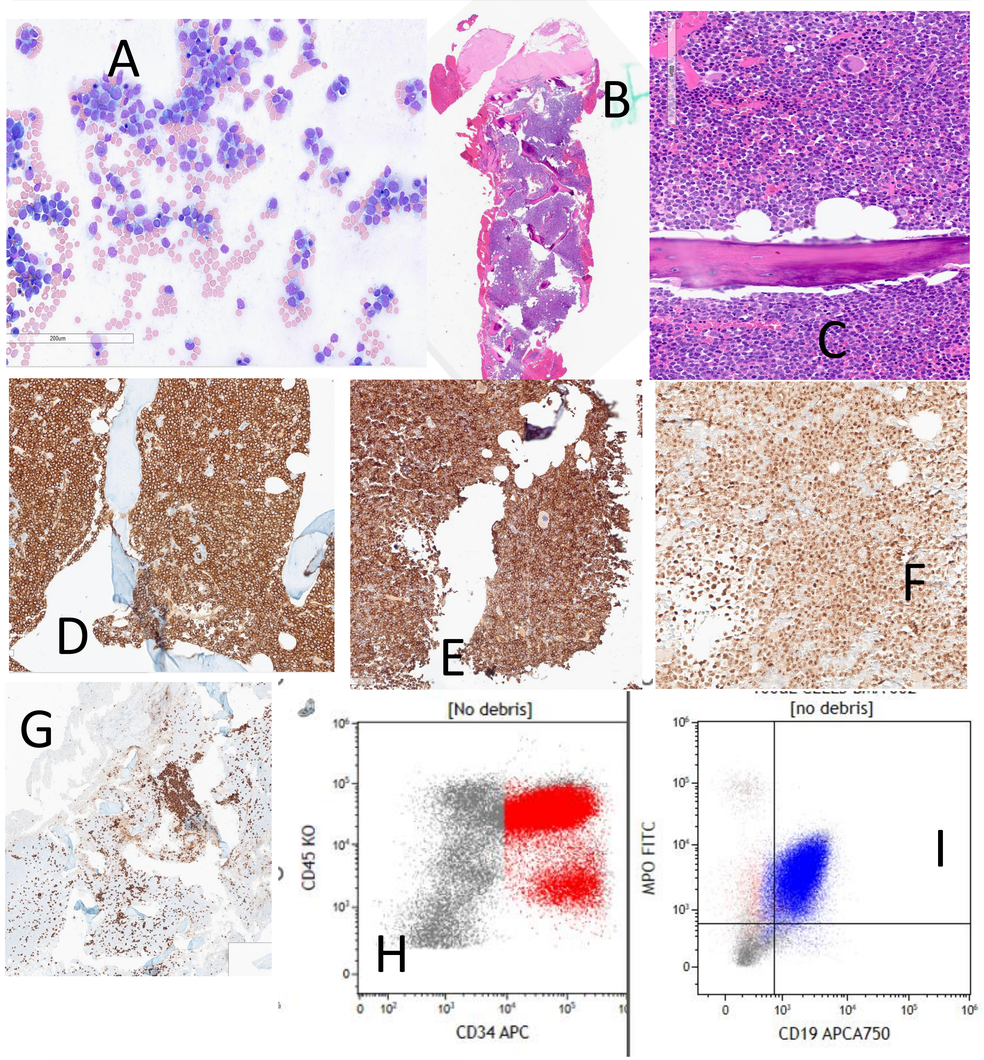
Peripheral blood examination shows significant pancytopenia with anisopoikilocytosis, and rare circulating blasts. A bone marrow aspirate reveals small-to-medium-sized blasts with high nucleus-to-cytoplasm (N/C) ratio, immature chromatin, and occasional visible nucleoli(A). The bone marrow core biopsy shows markedly hypercellular marrow with extensive infiltration by leukemic cells, accounting for approximately 70% of the marrow content (B, C).

CD34 highlights blast population(D) which co-expressing CD19(E), and TdT(F). TCF4 is weekly positive and CD303 is negative. CD138 highlights clusters of plasma cells (~5%)(G).

Flow cytometry analysis reveals CD34 positive (H) blast population co-expressing myeloperoxidase (MPO) and CD19 (I), indicating a myeloid lineage, and lymphoid lineage, respectively.

Taken together, these findings, along with the patient's prior history of multiple myeloma, led to a diagnosis of Mixed Phenotypic Acute Leukemia (B/Myeloid), Post-Cytotoxic Therapy, with evidence of Residual Myeloma.

Results



Discussion

MPAL patients typically present with symptoms related to bone marrow failure. The pathogenesis of MPAL is driven by genetic abnormalities such as BCR-ABL1 fusions, MLL rearrangements, or RUNX1 mutations which leads to disruptions in lineage commitment and differentiation. Diagnosis requires a thorough evaluation using flow cytometry, immunohistochemistry, and cytogenetic or molecular studies to confirm the co-expression of lineage-defining markers.

In this case cytogenetic analysis revealed a complex karyotype, including 46,XY,del(20)(q11.2q13.1) in 7 cells, 47,XY,del(7)(p15p13),+8 in 4 cells, and a normal male karyotype (46,XY) in 9 cells. Fluorescence in situ hybridization (FISH) identified gain or amplification of 1q21 in 40% of analyzed cells and deletion of 17p in 55.5% of cells, with no evidence of MLL gene rearrangement. Next-generation sequencing (NGS) revealed two pathogenic variants: a FLT3 missense mutation (p.Y842C, c.2525A>G) with a variant allele frequency (VAF) of 16.8%, and a PAX5 frameshift mutation (p. Y315Cfs*19, c.942_943dupGT) with a VAF of 13.1%. These molecular findings, combined with structural chromosomal abnormalities, highlight the disease's complexity, and suggest an aggressive clinical course.

Managements and Outcomes

MPAL remains a challenging condition to treat due to its aggressive nature and dual-lineage characteristics. Current treatment strategies often involve combining chemotherapy protocols designed for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)(2). For eligible patients, hematopoietic stem cell transplantation (HSCT) is considered a cornerstone of therapy.

Despite these intensive treatments, MPAL generally has a poorer prognosis compared to isolated ALL or AML, with high relapse rates. MPAL-B/Myeloid (MPAL-B/M) is classified as a high-risk acute leukemia, with outcomes falling between those of AML and B-lymphoblastic leukemia (B-ALL)(2). Research indicates that ALL-type treatment regimens are associated with higher remission rates compared to AML-type regimens (3).

Advances in understanding the molecular mechanisms underlying MPAL, as well as the development of targeted therapies, provide hope for improving outcomes in this complex and challenging disease.

References

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