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CASE REPORT

Mixed Phenotype Acute Leukemia with B/T Lineage and BCR-ABL1 Rearrangement: a Case Report and Literature Review

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SUMMARY

Background: **We report a case of B/T mixed phenotype acute leukemia (MPAL) with BCR-ABL1 rearrangement in a 35-year-old male presenting with hemorrhage, infection, and hemodynamic instability.**
Methods: **Laboratory findings showed bicytopenia (hemoglobin 79 g/L, platelets 17 x 10^9/L), leukocytosis (7.7 x 10^9/L). Peripheral blood and bone marrow smears showed 22% and 66% myeloperoxidase-negative blasts, respectively. Immunophenotyping identified coexisting T-lineage (cytoplasmic CD3+, CD2+, CD5+) and B-lineage (CD19+, CD79a+, cytoplasmic IgM+) populations. Fluorescence in situ hybridization confirmed BCR-ABL1.**
Results: **The diagnosis for our case was B/T MPAL with BCR-ABL1 rearrangement. The patient achieved complete remission with tyrosine kinase inhibitors per GRALL-2014 protocol and is awaiting matched sibling donor transplantation.**
Conclusions: **This case demonstrates the diagnostic complexity and aggressive nature of BCR-ABL1-positive B/T MPAL.**
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KEYWORDS

mixed phenotype acute leukemia, leukemia, immunophenotypic, blast, BCR-ABL1

INTRODUCTION

Mixed-phenotype acute leukemia (MPAL) is a rare hematological malignancy affecting blood cells, accounting for approximately 2 - 5% of all cases of acute leukemia [1]. The diagnosis of MPAL is complex due to its mixed lineage characteristics. The World Health Organization (WHO) classification system (2016 update, revised 2022) and the International Consensus Classification (ICC 2022) introduced mixed-phenotype acute leukemia to replace and unify the concepts of biphenotypic and bilineal leukemia [2,3]. The prevalence of the BCR-ABL1 fusion gene in MPAL varies between studies and age groups. In adult populations, around 28 - 35% of MPAL cases present the BCR-ABL1 translocation. In contrast, pediatric studies report a significantly lower frequency, with around 3% of MPAL cases har-

boring the BCR-ABL1 fusion gene. A significant proportion of these cases present a dimorphic population of blasts, displaying predominantly B-lineage and myeloid features [4]. The presence of the BCR-ABL1 fusion gene in MPAL is generally associated with a more aggressive disease course and poorer prognosis compared with BCR-ABL1-negative MPAL [5]. We report here a rare case of B/T MPAL case with BCR-ABL1 rearrangement.

CASE PRESENTATION

A 35-year-old patient, with no prior medical history, particularly no indications of chronic myeloid leukemia, no pharmacological treatment, and no exposure to toxic agents, was admitted to the hospital due to hemorrhagic and infectious syndrome, accompanied by a deteriorated general condition and hemodynamic instability, in the absence of tumor syndrome. Hematological analysis revealed bicytopenia, characterized by normocytic normochromic anemia (hemoglobin: 79 g/L) and thrombocytopenia (platelet count: 17 x 10^9/L). The blood smear exhibited erythrocytic anisopoikilocytosis, and a white blood cell count of 7.7 x 10^9/L revealed 22% blast cells. These blasts were medium-sized, with a high nucleocytoplasmic ratio, irregular nuclei with fine chromatin, occasionally nucleated, and an agranular basophilic cytoplasm. The cytochemical reaction to myeloperoxidase (MPO) was negative in 100% of the blasts. Bone marrow aspiration demonstrated a hypercellular marrow with an absence of megakaryocytes and a 66% infiltration by abnormal cells (MPO negative), comprising two distinct populations: Population I, constituting 36%, consisted of medium to large cells with a high nucleocytoplasmic ratio, regular nuclei with dense, sometimes nucleated chromatin, and intensely basophilic cytoplasm, often containing small, rounded, and clear vacuoles. Population II, accounting for 30%, comprised medium-sized cells with a high nucleocytoplasmic ratio, irregular nuclei with fine, sometimes nucleated chromatin, and an agranular basophilic cytoplasm (Figure 1). Medullary immunophenotyping was performed using a *Sysmex XF-1600* 12-color multiparametric flow cytometer, with three-laser excitation optics, in conjunction with a *Sysmex PS10* for preparation of panels and specimens. The markers employed were monoclonal antibodies conjugated to fluorochromes: MPO-PE (R-phycoerythrin), CD79a-PerCP-Cy5 (peridinin chlorophyll protein-cyanine5), CD45-PO (Pacific Orange), IgM-ALEXA, CD22-PC7 (phycoerythrin cyanine7), CD117-PE (R-phycoerythrin), CD34 PerCP-Cy5.5 (peridinin chlorophyll protein-cyanine5.5), CD19-APC (allophycocyanin), CD3-PE LIHGT (R-phycoerythrin), CD1a-FITC (fluorescein isothiocyanate), CD8-ALEXA, CD4-PC7 (phycoerythrin-cyanine7), CD2-PE (R-phycoerythrin), CD5-PerCP (peridinin chlorophyll protein), CD7-PE (R-phycoerythrin). Immunophenotypic analysis identified 66% blastic cells exhibiting low CD45 expression. These blasts were categorized into two distinct subpopulations (Figure 2): the first subpopulation (Blast-1: 30%) demonstrated cytoplasmic CD3 expression and was positive for several T-lymphoid markers (CD2, CD5, CD8, CD7, CD1a, and TdT), while tests for other B-lineage and myeloid antigens were negative. These blast cells were classified as T-lymphoid, according to the scoring system of the European Group for Immunological Characterization of Acute Leukemias (EGIL) [6]. Notably, this T-lymphoid subpopulation is further divided into two cellular entities: CD4+/CD8+ and CD4-/CD8- (respectively, Blast-1a and Blast-1b in Figure 2). The second subpopulation (Blast-2: 36%) was entirely positive for CD79a and CD19, with no detection of T-lymphoid or myeloid antigens. Additional B lymphoid antigens (cyt IgM, sIgM, cyt CD22, CD22, CD10, CD24, and TdT) were also positive, as was HLA-DR. These blast cells were classified as B-lymphoid, according to the scoring system of the EGIL [6]. Table 1 outlines the integrated immunophenotypic criteria (EGIL 1995 and ICC/WHO 2022 guidelines) used to classify these two distinct subpopulations as T-lineage and B-lineage in B/T MPAL diagnosis [3,6,7]. The immunophenotypic analysis in Figure 2 shows only positive expression of markers for B and T-lymphoid lineages.

The cytological and immunophenotypic characteristics of the bone marrow were indicative of MPAL. Fluorescent in situ hybridization (FISH) analysis was performed on unstimulated interphase cells from a bone marrow sample using the XL BCR-ABL1 probe in conjunction with the Dual Color Dual Fusion Translocation Probe METASYSTEMS. A total of 200 cells were examined. In 100 of the 200 cells (50%) analyzed, the nuclear ISH (in situ hybridization) abnormalities (ABLx3), (BCR x3), (ABL con BCRx2) [100/200] were observed, indicating the presence of a BCR-ABL1 double fusion resulting from the t(9;22) translocation.

The patient was administered chemotherapy and treated with imatinib, which was subsequently replaced by nilotinib under the GRALL-2014 protocol. The patient remains alive and in complete remission while awaiting a hematopoietic stems cell allograft from his brother.

DISCUSSION

Mixed acute leukemia may present as a single population of blasts exhibiting both myeloid and lymphoid markers, or it may consist of two distinct populations of blasts. These cell populations express lineage specific antigenic markers. The advancement of flow cytometry techniques and the availability of a diverse array of antibodies have facilitated the differentiation between acute myeloid leukemia and lymphoid leukemia. The European Group for the Immunological Characterization of Leukemias (EGIL), the World Health Organization (WHO) 2008/2016/2022, and more recently, the International Consensus Classification (ICC), have en-

deavored to propose a scoring-based classification sys-

Table 1. Integrated immunophenotypic criteria for MPAL diagnosis: EGIL Scoring System (1995) and ICC/WHO 2022 Guidelines [3,6,7].

<table>
<tr><th>Lineage</th><th>EGIL Scoring System</th><th>ICC/WHO 2022 Diagnostic Criteria</th></tr>
<tr><td rowspan="3">Myeloid</td><td>2 Points: MPO, Lysozyme</td><td rowspan="3">- MPO (intensity > 50% of neutrophils/WHO) by flow cytometry (> 10% of blasts), immunohistochemistry, or enzyme cytochemistry (> 3% of blasts)

- OR Monocytic differentiation (at least 2 of the following: butyrate esterase, CD11c, CD14, CD64, lysozyme)</td></tr>
<tr><td>1 Point: CD117, CD33, CD13, CD65a</td></tr>
<tr><td>0.5 Points: CD14, CD15, CD64</td></tr>
<tr><td rowspan="3">B-Lymphoid</td><td>2 Points: CD79a, cyt IgM, cyt CD22</td><td rowspan="3">- Strong CD19 (intensity > 50% of mature B lymphocytes in cytometry /WHO, at least as intense as in mature B cells / ICC) with at least 1 of the following strongly expressed: CD79a, CD22, or CD10

- OR Weak CD19 (intensity < 50% of mature B lymphocytes in cytometry /WHO, least intense as in mature B cells / ICC) with at least 2 of the following strongly expressed: CD79a, CD22, or CD10</td></tr>
<tr><td>1 Point: CD19, CD20, CD10</td></tr>
<tr><td>0.5 Points: TdT, CD24</td></tr>
<tr><td rowspan="3">T-Lymphoid</td><td>2 Points: cyt/surf CD3, TCRα/β, TCRγ/δ</td><td rowspan="3">- CD3 cytoplasmic or surface (intensity > 50% of mature T lymphocytes in cytometry/WHO)</td></tr>
<tr><td>1 Point: CD2, CD5, CD8, CD10</td></tr>
<tr><td>0.5 Points: TdT, CD1a, CD7</td></tr>
</table>

cyt cytoplasmic, surf surface, IgM immunoglobulin M, MPO myeloperoxidase, TCR T-cell receptor, TdT terminal deoxynucleotidyl transferase.
Immunophenotyping positivity thresholds: 20% (surface) or 10% (cytoplasmic).
MPAL is diagnosed when scores are greater than 2 in 2 lineage columns (EGIL Scoring System). The case example (underlined) meets criteria for both B (9 points) and T (6.5 points) lineages.

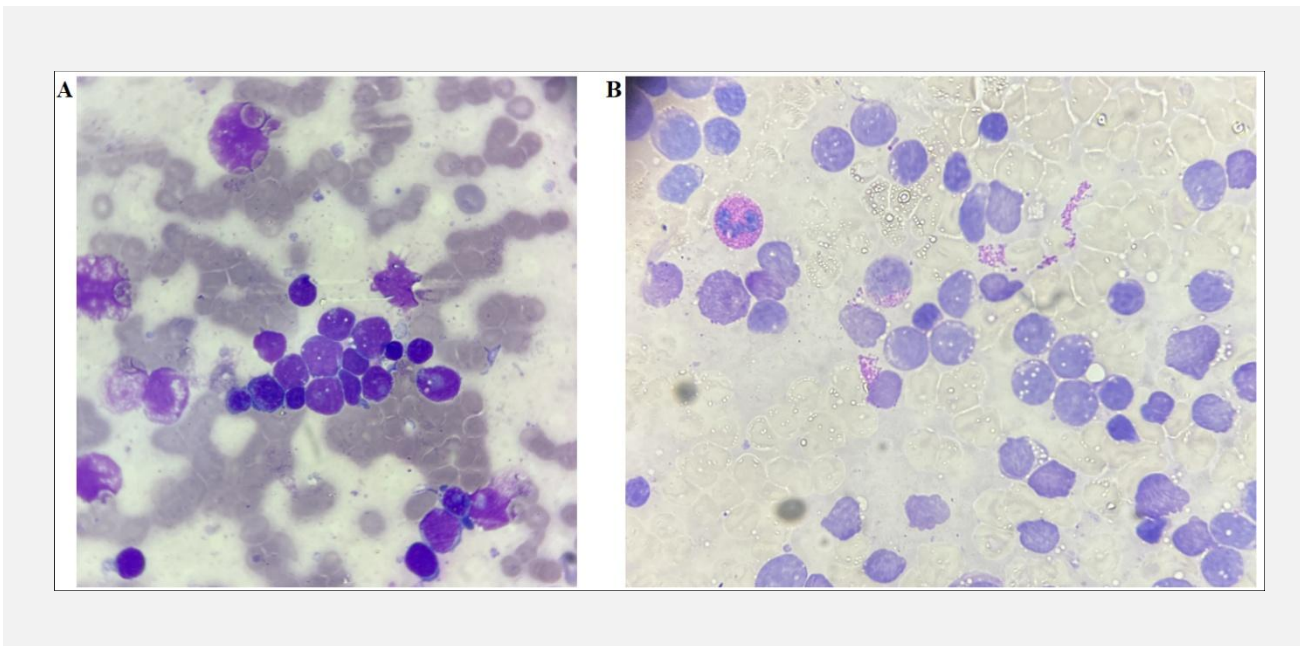

Figure 1. A) Medullary smear stained with May Grunwald Giemsa showing many heterogeneous circulating blasts (magnification x 1,000). The majority of blasts were medium-sized cells with a high nucleocytoplasmic ratio, irregular nuclei with fine, sometimes nucleated chromatin, and agranular basophilic cytoplasm, sometimes containing small, rounded, clear vacuoles. B) Medullary smear stained with MPO reaction showing myeloperoxidase-negative blast cells (magnification x 1,000). Iconography Central Hematology Laboratory of Ibn Sina Hospital, University Hospital, Rabat, Morocco.

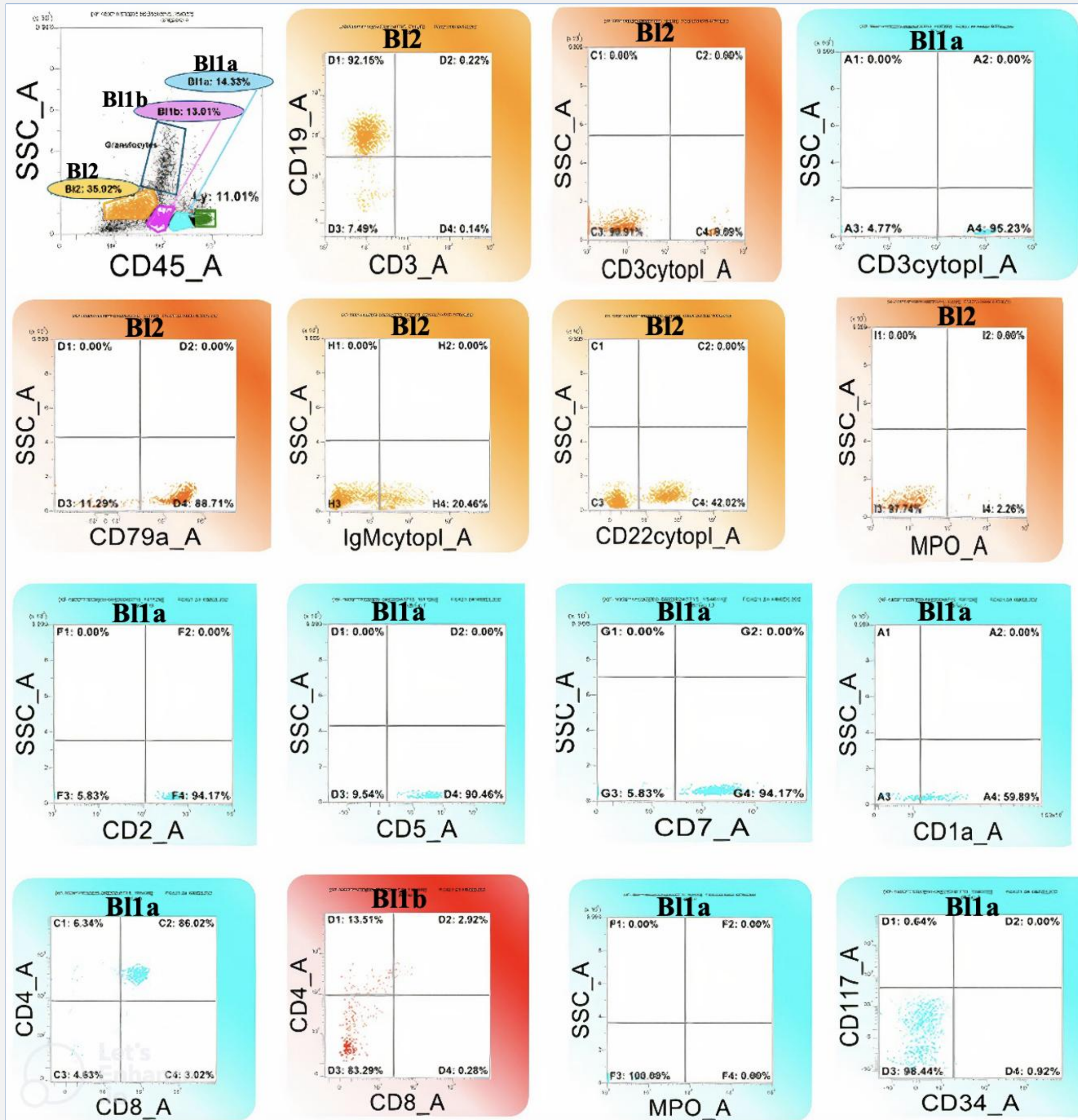

Figure 2. Medullary immunophenotyping.

Bl1a Blast-1a, Bl1b Blast-1b, Bl2 Blast-2.
Blastic populations: T lymphoid lineage made up of two sub-populations (Bl1a: double positive CD4/CD8 and Bl1b: double negative CD4-/CD8-), and B lymphoid lineage blastic cells (Bl2), which are identified by their low CD45 expression. Blast-1a, which is only shown because both Blast-1a and Blast-1b subpopulations have the same immunophenotypic expressions, with the exception of CD4/CD8, which is double positive for the Blast-1a subpopulation and double negative for Blast-1b (Central Hematology Laboratory of Ibn Sina University Hospital, Rabat, Morocco).

tem for mixed acute leukemia [2,3,6,8-10]. The World Health Organization (WHO) criteria for diagnosing MPAL are shown in Table 1 [3,6,7]. The majority of cases documented in the literature exhibit biphenotypic

B/T leukemia. Mi X et al. identified nine cases of biphenotypic B/T acute leukemia, with no reported instances of bilineal B/T [10]. This case represents a bilineal acute leukemia, characterized by two distinct populations: one expressing B-lineage markers and another comprising blasts with T-lineage markers.
With respect to the BCR-ABL1 fusion, existing literature, as reported by Matutes et al. and Yan et al. indicates that among a cohort of 217 patients, the prevalence of BCR-ABL1 in B/M cases was 20% (25/123), in M/B/T trilineage leukemia it was 33% (1/3), in B/T cases it was 5.5% (1/18), and in T/M cases it was 2.7% (2/73) [5,11]. However, these findings pertain to acute mixed biphenotypic leukemia, with a lack of data in the literature concerning bilineal leukemia. The Philadelphia chromosome (Ph) results in the production of the BCR-ABL1 fusion protein, which is characterized by enhanced tyrosine kinase activity, thereby facilitating the proliferation of leukemia cells. Prior to the advent of targeted therapies, the prognosis for patients with Ph+ MPAL was particularly poor. The introduction of tyrosine kinase inhibitors (TKIs), such as imatinib and ponatinib, has improved outcomes for patients with Ph+ leukemias. A 2018 case report documented a patient with Ph+ MPAL who achieved sustained remission following treatment with a TKI in conjunction with chemotherapy [12].
Furthermore, a 2020 analysis of 241 cases of MPAL demonstrated that the integration of TKIs into treatment protocols led to enhanced survival rates, as observed in our patient, albeit with a transition from imatinib to nilotinib [13]. Despite these advancements, the prognosis for Ph+ MPAL remains poor. Factors affecting outcomes include patient age, overall health, response to initial treatment, and the feasibility of allogeneic stem cell transplantation. A 2017 study reported a three-year overall survival rate of 56.3% for MPAL patients who underwent allogeneic hematopoietic stem cell transplantation following remission [14]. The present case bears similarities to that of Kohla et al., which represents the sole instance in the literature of a mixed bilineal acute leukemia with a comprehensive molecular cytogenetic analysis, including the presence of the BCR-ABL p190 protein [15].

CONCLUSION

Mixed phenotype acute leukemia (B/T) is an uncommon condition, particularly when associated with the BCR-ABL1 rearrangement. MPAL constitutes a complex leukemia subtype that necessitates precise diagnosis and individualized treatment strategies, though in our case, the lack of next-generation sequencing profiling prevented comprehensive molecular characterization of adverse genetic markers, limiting both risk stratification accuracy and personalized treatment options. Continued research incorporating advanced genomic technologies remains essential to enhance patient outcomes.

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Declaration of Interest:
The authors do not declare any conflict of interest.

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