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CORRESPONDENCE

Mixed Phenotype Acute Leukemia, B/Myeloid with t(9;22): Diagnostic and Therapeutic Challenges

Namrata P. Awasthi[1] · Poonam Singh[2] · Narendra Agrawal[3]

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Dear Editor,

Mixed phenotype acute leukemia (MPAL) account for 4% of all cases of acute leukemia. Extensive immunophenotypic analysis is required for evaluation of these neoplasms, as morphologically distinct blast populations may not be evident [1]. The 2008/2016 WHO established strict criteria for diagnosis of MPAL, emphasizing assignment of myeloperoxidase for myeloid lineage, cytoplasmic CD3 for T lineage and CD19 and other B markers for B lineage (Table 1). WHO recognizes 2 distinct categories: MPAL with the t(9;22)(q34;q11)/*BCR-ABL1* and MPAL with t(v;11q23)/*MLL* rearrangement. The remaining cases are designated as MPAL NOS (not otherwise specified).

Mixed phenotype acute leukemia (MPAL) with t (9;22) comprises less than 1% of acute leukemias. Chronic Myeloid Leukemia in Mixed Phenotype Blast Crisis (CML-MP-BC) can also be misdiagnosed as MPAL with t (9;22). No specific treatment guidelines are available for its management. The present case highlights the diagnostic and therapeutic challenges involved with MPAL with t(9;22).

✉ Poonam Singh
poonamkgmu07@gmail.com

Namrata P. Awasthi
namratapunit@yahoo.co.in

Narendra Agrawal
Narendra_ag1@rediffmail.com

[1] Department of Pathology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India

[2] Department of Lab Medicine, Sahara Hospital, Viraj Khand, Gomti Nagar, Lucknow 226010, India

[3] Rajiv Gandhi Cancer Institute, New Delhi, India

A 45 year/male with a history of ankylosing spondylitis, presented with complains of generalized weakness and fatigue for 1 month. His hemoglobin had dropped significantly from 112 to 86 g/L and WBC had increased considerably from 8.8 to 16.8 $\times$ 10^9/L 1 in three months. Examination showed pallor with no lymphadenopathy or organomegaly. Bone marrow aspirate smears demonstrated a hypercellular marrow with 40% blasts of dimorphic morphology (lymphoblast, myeloblasts/promonocytes) (Fig. 1a, b). Flow cytometric immunophenotyping on marrow aspirate revealed 40% blasts gated (R1) on CD45. Blasts were dim CD45 positive with strong expression of CD34, HLA DR (Immaturity). Blasts showed strong intensity for CD19, cyto CD22, cyto CD79a (B-lymphoid) and MPO (Myeloid) (Fig. 1c). Blasts were also positive for CD10, CD13, CD33, CD14 and CD64. Cytogenetics and conventional PCR revealed a t(9;22) BCR-ABL 1. Diagnosis of MPAL (B/Myeloid) with t(9;22) BCR-ABL 1 was rendered. He was treated with Dasatinib and ALL like chemotherapy and achieved molecular CR. He was taken for matched sibling donor allogeneic stem cell transplantation. Post-transplant cyclophosphamides along with tacrolimus were used for GvHD prophylaxis. He developed transplant associated thrombotic microangiopathy on day +22. He was managed with stopping tacrolimus and starting mycophenolate mofetil and FFP transfusions. He achieved neutrophil and platelet engraftment on day + 15 and 34 respectively. He started passing loose stools on day +32 of transplant. After thorough investigations, he was considered to have acute GvHD GI stage-IV, grade-III. He was started on Inj Methyl-Prednisolone 2 mg/kg/day. The symptoms of GvHD worsened and he succumbed to refractory GvHD on day + 61 of transplant.

MPAL is a rare entity, difficult to diagnose and to treat. MPAL is a heterogeneous category in the World Health

Table 1 World Health Organization 2008/2016 criteria for mixed-phenotype blasts

Lineage	Markers
Myeloid	MPO (flow cytometry, immunohistochemistry, or enzyme cytochemistry) –OR
	Monocytic differentiation (at least 2 of the following: NSE cytochemistry, CD11c, CD14, CD64, lysozyme)
T lineage	Strong cytoplasmic CD3
	-OR
	SurfaceCD3
B lineage	Strong CD19 with at least 1 of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10
	-OR
	Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10

Data derived from Borowitz et al. [2] and Arber et al. [3]

MPO myeloperoxidase, *NSE* nonspecific esterase

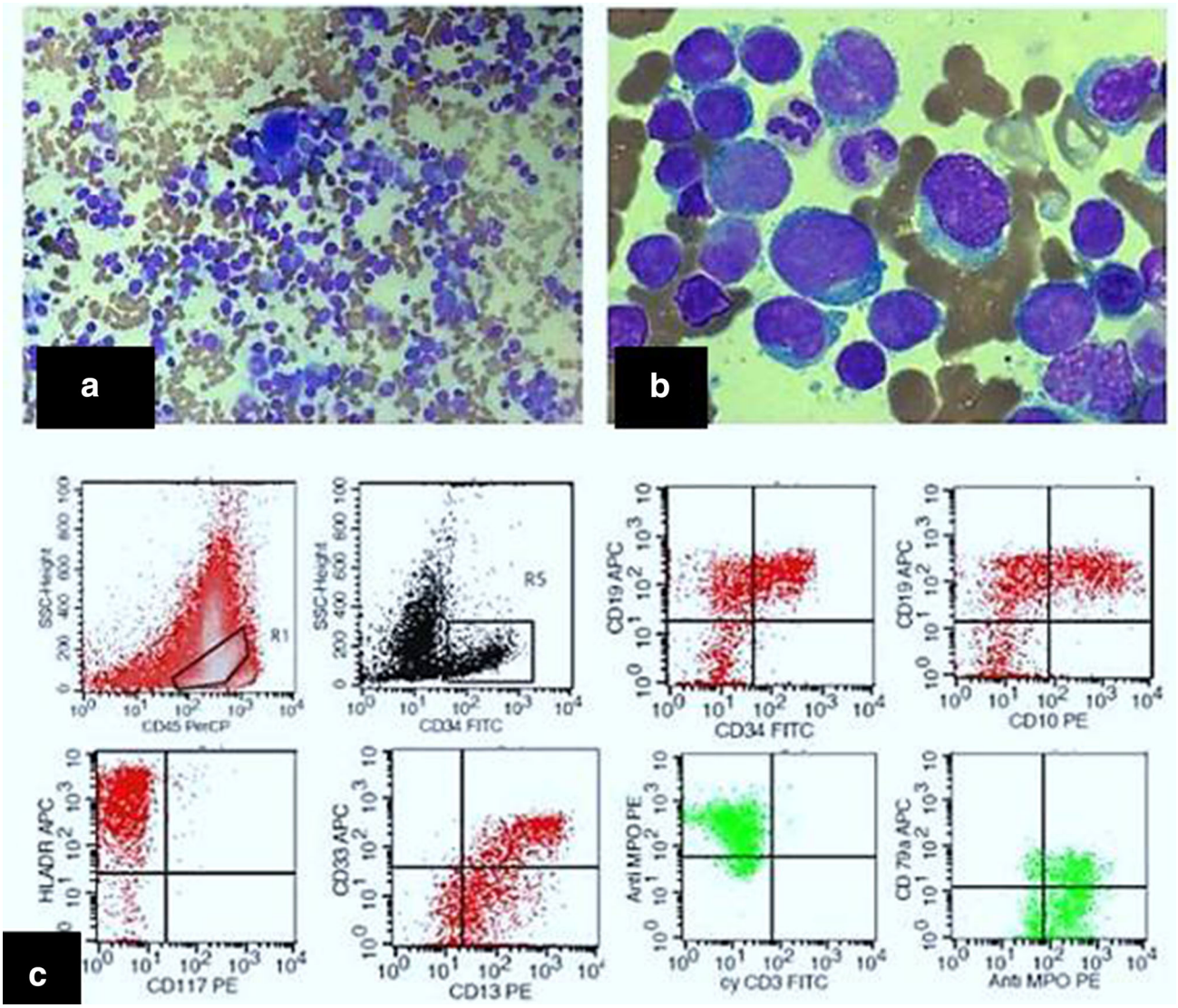

Fig. 1 May-Grunwald-Giemsa–stained BM smear showing a mixed-cell population of large and small blasts. **a** 10×, **b** 100×, **c** dot plots with the blast population highlighted in red (R1). These dot plots demonstrate the expression of CD 19, CD10, CD13, and coexpression of MPO with CD79a. Other positive markers are CD34, HLA DR, CD33

Organization classification that comprises acute leukemias with discrete admixed populations of myeloid and lymphoid blasts (''bilineal'') or with extensive coexpression of lymphoid and myeloid markers in a single blast population (''biphenotypic'') [2, 3]. In 2016 WHO classification, no new entities have been defined within acute leukemia of ambiguous lineage. The list of specific lineage markers for defining MPAL is unchanged (Table 1), but it is now emphasized that in cases with two distinct blast populations, each individual population should meet a criteria for either a B-ALL, T-ALL, or myeloid leukemia. It is not necessary that the specific markers be present [3]. Strict criteria to assign lineage do not universally apply for the diagnosis of otherwise typical AML or ALL, but only for MPAL [3]. It is recommended that cases of B-ALL with low-intensity myeloperoxidase (MPO) expression as only myeloid-associated feature should not be labelled as MPAL [3].

The WHO criteria for bilineal MPAL require that the sum of the 2 blast populations is at least 20% of nucleated cells [2]. Clinical presentation and genetic characteristic are similar in both biphenotypic and bilineal acute leukemia [4]. A comprehensive approach to immunophenotyping, using a large panel of antibodies is required to accurately establish the diagnosis of MPAL [1, 4, 5, 6]. Demonstration of lineage specific immunophenotypic markers of two or more lineages on the blast population is a prerequisite for diagnosis [1, 4, 5, 6].

B/myeloid acute leukemia accounts for 59% of all MPAL cases and about 1% of all leukemia. t(9; 22) BCR-ABL 1 is the most common recurrent genetic abnormality seen in MPAL [7]. Differential diagnosis of MPAL from CML-MP-BC is based on clinical history of normal hemograms, no history of CML-chronic phase, basophilia, splenomegaly and FISH analysis on mature granulocytes [8]. Chemotherapy protocols for ALL or AML along with Tyrosine Kinase Inhibitors for philadelphia positive MPAL and Bone Marrow Transplant have all been utilized for treatment. MPAL, specially adult patients should be considered candidates for consolidation with intensive chemotherapy and stem cell transplantation at first remission [4]. Bilineal acute leukemias portend a somewhat poorer prognosis than biphenotypic MPAL and have a higher risk of induction failure due to lineage switch [9].Cytogenetic and molecular genetic changes have emerged to be of greatest biological importance with most acute leukemias including MPAL. It is important to assess for the presence of mutations with prognostic and/or therapeutic relevance in leukemia and to rule out the presence of Ph-like signature, which could have eventual therapeutic implications in ALL. Collection of data may be retrospectively useful in learning about MPAL leading to new criteria for diagnosis and treatment of these disorders, based on more specific molecular genetic markers.

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Compliance with Ethical Standards

Conflicting interest The authors declare that they have no conflicting interest.

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