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Mixed Phenotypic Acute Leukemia

Amrita Bhattacharya[1]*, Anita Tahlan[2]
[1]Demonstrator, Department of Pathology, Government Medical College and Hospital, sector 32, Chandigarh, India
[2]Associate professor, Department of Pathology Government Medical College And Hospital, sector 32, Chandigarh, India

***Corresponding author**
Amrita Bhattacharya

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Abstract: To discuss biphenotypic leukemia. Mixed phenotype acute leukemia represents a small subset of acute leukemia that cannot be simply assigned as myeloid or lymphoid lineage, because of the ambiguous phenotype the leukemic cells exhibit. It encompasses leukemias containing separate populations of blasts of more than one lineage, or a single population of blasts co-expressing antigens of more than one lineage. The 2008 World Health Organization classification established strict criteria for diagnosis of mixed phenotype acute leukemia, emphasizing myeloperoxidase for myeloid lineage assignment, cytoplasmic CD3 for T lineage assignment, and CD19 and other B markers for B lineage assignment. We report a case of 45 year old female patient presenting with bleeding gums and echymotic patches to medicine emergency with 36% blasts in the peripheral blood film. Gated leukocytes in blast were highly positive for CD19, CD10, CD22, CD13, CD34, CD45, HLADR, TdT and moderately positive for CD33, CD7. Cytochemistry done on bone marrow imprint smears showed MPO positivity. Thus, she was diagnosed as mixed phenotypic leukemia based on cytochemical and flow cytometric findings. Mixed phenotype acute leukemia is associated with poor outcome compared with other types of acute leukemias, particularly in those with Philadelphia chromosome, and clinically presents challenges in diagnosis and treatment. Correct diagnosis requires suspicion and flow cytometric parameters.
Keywords: Leukemia, myeloid, lymphoid, biphenotypic.

INTRODUCTION

Most cases of acute leukemia can be classified based on the lineage of the leukemic cells as myeloid, B-lymphoblastic (B-ALL) or T-lymphoblastic leukemia (T-ALL). However, there are uncommon cases in which the blasts show differentiation towards more than one lineage. In the 2008 World Health Organization (WHO) classification these cases are identified as mixed phenotype acute leukemias (MPAL), under the category of acute leukemias of ambiguous lineage [1]. MPAL encompasses leukemias containing separate populations of blasts of more than one lineage (bilineal or bilineage), and a single population of blasts co-expressing antigens of more than one lineage (biphenotypic). Cases that can be classified in another category are excluded, including acute myeloid leukemia (AML) with recurrent translocations t(8;21), t(15;17) or inv(16), leukemias with *FGFR1* mutations, chronic myelogenous leukemia (CML) in blast crisis, myelodysplastic syndrome (MDS)-related AML and therapy-related AML, even if they have MPAL immunophenotype [2].

Mixed phenotype acute leukemia is a rare disease, representing only 3 - 5% of acute leukemias of all age groups, and 2.4 - 3.7% in children. However, the true incidence is difficult to establish due to problems with definition, and perhaps variation between different laboratories. It affects both adults and children, more frequently adults and has slight male preference. The prognosis for MPAL is poor comparing to other acute leukemias, with an overall survival of 18 months [3]. Here we present a case report of mixed phenotypic acute leukemia with t (9; 22) (q34; q11.2); BCR-ABL1 occurring denovo in a 45 year old female patient.

CASE REPORT

A 45 year old female patient presented in medicine emergency with complaints of breathlessness and weakness for the past 2-3 weeks. Patient also complained of joint pains. On examination there was pallor. However no lymphadenopathy or organomegaly was noted. A routine ultrasound also confirmed the same. On a complete blood examination haemoglobin was found to be 9.6 g/dl, total leucocyte count was raised with 37.7 * 10^9 /L and thrombocytopenia with 23*10^9/L platelets. The differential count revealed 54 blasts. The coagulation profile of the patient was markedly abnormal and the d-dimer test was found to be highly positive.

Morphology and cytochemistry

The blasts were of variable size with round, convulated nuclear configuration, one or more prominent nucleoli and moderate to abundant amount of basophilic cytoplasm with azurophilic granules and

vacuolations at places. Cytochemical staining with Sudan black B (SBB), MPO was positive with >3% blasts showing positivity on bone marrow aspirate smears. According to FAB criteria the blasts were M2 or M4.

Flow cytometry

Gated leukocytes in blast (50.0% of Acquired Events) region were highly positive for CD19, CD10, CD22, CD13, CD34, CD45, HLADR, TdT and moderately positive for CD33 and CD7. Rest of the markers Cyt.CD3, CD5, SIgM, CD20, CD14, and CD16 were negative (Table 1). Hence a diagnosis of mixed phenotypic acute leukemia was made.

Table-1: flow cytometric immunophenotyping of blasts

Marker	Result	Units
T-cell Markers		
CD3	0.2	% of Gated Leukocytes
Cyt.CD3	0.4	% of Gated Leukocytes
CD5	0.4	% of Gated Leukocytes
CD7	34.5	% of Gated Leukocytes
B-cell Markers		
CD19	83.8	% of Gated Leukocytes
CD10	66.0	% of Gated Leukocytes
CD22	66.3	% of Gated Leukocytes
SIgM	0.4	% of Gated Leukocytes
CD20	1.5	% of Gated Leukocytes
Myeloid/Monocytic Markers		
CD13	80.6	% of Gated Leukocytes
CD14	2.2	% of Gated Leukocytes
CD16	2.5	% of Gated Leukocytes
CD33	32.0	% of Gated Leukocytes
Others		
CD34	78.0	% of Gated Leukocytes
CD45	100	% of Gated Leukocytes
CD64	1.7	% of Gated Leukocytes
CD11b	14.3	% of Gated Leukocytes
CD117	1.3	% of Gated Leukocytes
HLADR	81.4	% of Gated Leukocytes
MPO	3.3	% of Gated Leukocytes
TdT	62.0	% of Gated Leukocytes
CD36	14.3	% of Gated Leukocytes

Cytogenetics

Structural chromosome abnormalities of the Philadelphia chromosome T (9; 22) BCR-ABL was detected by multiplex PCR. So a final diagnoses of MPAL with T (9; 22) (q34; q11.2); BCR-ABL1was made. The patient was treated with aggressive chemotherapy but she died in a course of 3 months.

DISCUSSION

According to WHO 2008 requirements for assigning more than one lineage in a single blast population is as follows [1].

Myeloid lineage Myeloperoxidase (flow cytometry, immunohistochemistry or cytochemistry) or Monocytic differentiation (at least 2 of the following NSE,CD11c,CD14, CD64, lysozyme)
T lineage cytoplasmic cd3 (flow cytometry with antibodies to cd3 epsilon chain; immunohistochemistry using polyclonal anti-CD3 antibody may detect CD3 zeta chain, which is not T cell specific) or surface CD3 (rare in mixed phenotypic acute leukemia)
B lineage (multiple antigens required) Strong CD19 with atleast 1 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10 or Weak CD19 with at least 2 of the following strongly expressed : CD79a, cytoplasmic CD22, CD10

Biphenotypic acute leukemias may affect adults or children. They may present as de novo or, rarely, they become apparent during a relapse following anti- AML or ALL therapy. The WBC is often high and most cases have a varying proportion of circulating blasts.

The most recent 2008 WHO classification has established new and strict criteria for the diagnosis of MPAL. Diagnosis of mixed phenotypic acute leukemia is based on immunophenotyping. The T lineage is recognized by the presence of specific T-lymphoid antigens, cytoplasmic CD3 (cCD3) or surface CD3. Cytoplasmic CD3 expression is best demonstrated by flow cytometry with antibodies to CD3 epsilon chain. It should be noted that polyclonal CD3 antibodies used in immunohistochemistry also react with the T-cell receptor zeta chain present in NK cells, and therefore considered not specific for T lineage. Surface CD3 is rare but indicative of the T-lineage. The myeloid lineage is demonstrated with the presence of myeloperoxidase (MPO) by flow cytometry, immunohistochemistry or cytochemistry, or monocytic differentiation (requiring at least two of the following: non-specific esterase (NSE), CD11c, CD14, CD64, lysozyme. Since there is no single marker sufficiently specific for B-cell lineage, multiple antigens are required, including strong expression of CD19 with one of the other B-cell markers (CD79a, cytoplasmic CD22, CD10), or weak CD19 expression with at least two of the other B-cell markers.

T (9;22)(q34;q11.2); BCR-ABL1 is the most frequent recurrent genetic abnormality occurring in MPAL and considered a distinctive entity. It accounts for 20% of all MPAL. It is a leukemia meeting the diagnostic criteria for MPAL with the blasts bearing the t(9;22)(q34;q11.2) translocation or *BCR-ABL1* rearrangement (Ph+) in patients with no history of CML. It occurs more often in adults than in children. Clinically, the patients present similarly as other patients with acute leukemias, with white blood cell counts likely to be high, resembling Ph+ ALL [4, 5].

In summary, MPAL is an uncommon type of leukemia which probably arises from a multipotent progenitor cell and carries a poor prognosis. Although there are no uniform criteria about whether to treat these patients as ALL or AML, it is likely that an intensive approach with high-dose therapy followed by bone marrow transplantation will be required to eradicate the disease permanently.

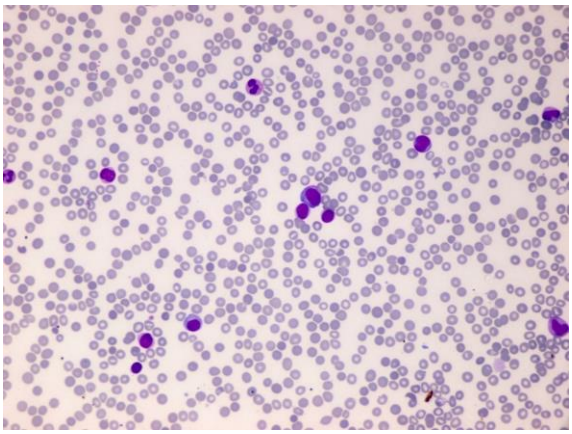

Fig-1: PBF showing 36% blasts of variable size, having high N:C ratio, lobulated nuclei and multiple prominent nucleoli with scanty granular cytoplasm. RBCs show mild anisopoikilocytosis including microcytes, tear drop cells and normocytes (transfused cells). Platelets are markedly reduced on smear.

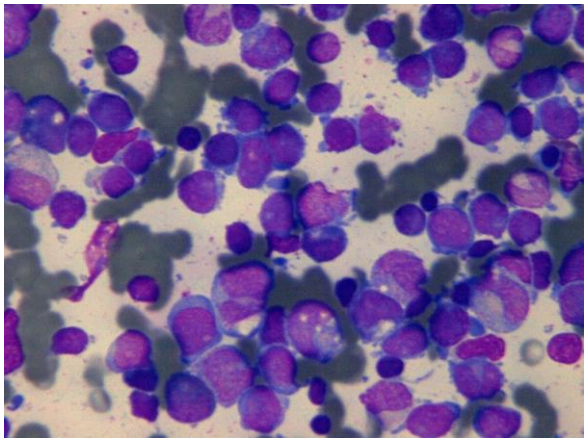

Fig-2: Hypercellular bone marrow aspirate showing 55% blasts

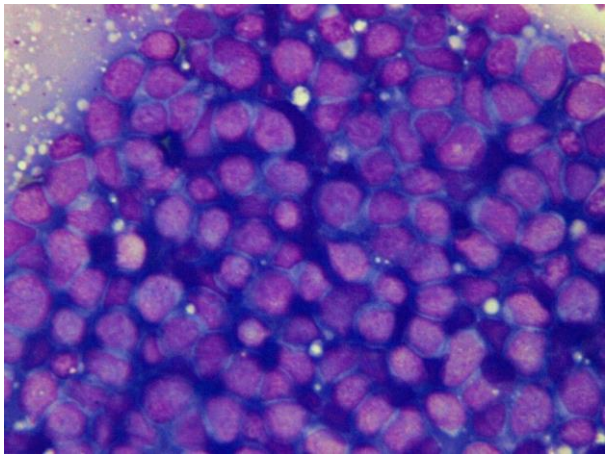

Fig-3: Hypercellular imprint smear showing blasts

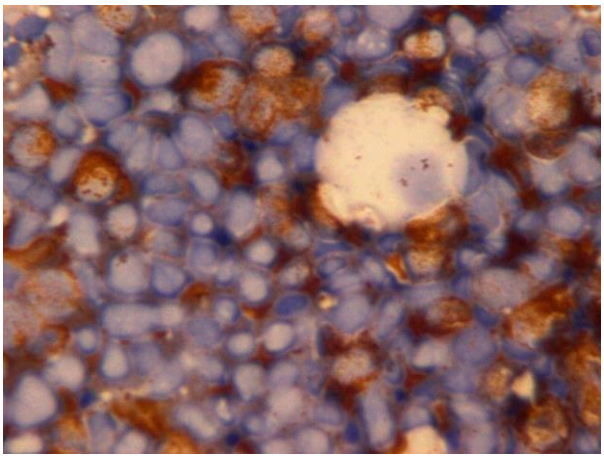

Fig-4: > 3% of blasts show MPO positivity

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