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Case Report

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Mixed phenotype acute leukaemia: a case report of an unusual presentation

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ABSTRACT

Mixed phenotype acute leukaemias (MPALs), a varied group of disorders pose a diagnostic challenge to the physicians and pathologists alike. This rare subset of acute leukaemias are characterised by the presence of blasts which express markers of more than one lineage (B-lymphoid / T-lymphoid / Myeloid lineage), making the essentiality of immunophenotyping more pertinent. MPALs are included in the acute leukaemias of ambiguous lineage under the World health organization (WHO) classification of tumours of haematopoietic and lymphoid tissues. We describe here a case report of mixed phenotype acute leukaemia (T-Lymphoid/Myeloid).

Keywords: Acute leukaemia's of ambiguous lineage, Flow cytometry, Mixed phenotype acute leukaemia, T-Lymphoid/Myeloid

INTRODUCTION

Acute leukaemias which are clonal proliferation of hematopoietic stem cells, are characterised by the blasts of a specific of (lymphoid/myeloid). However, a small subset of acute leukaemias exist which exhibit more than one lineage and are termed as mixed phenotype acute leukaemia (MPAL). It is a rare entity so designated because of their features characteristic of multiple lineages and has been known previously by a multitude of names viz. mixed lineage leukaemia, acute hybrid leukaemia, bilineal leukaemia, and biphenotypic leukemias.²⁻⁵ The 2008 World health organization classification and European group for the immunological characterization of leukaemias (EGIL) have laid down certain criteria which must be met in order to diagnose a case as mixed acute leukaemia, thus helping distinguishing them from acute lymphoblastic leukaemia or acute myeloid leukaemia with aberrant antigen expression.6 An acute clinical awareness can prevent an

erroneous diagnosis especially when MPAL manifests with generalized lymphadenopathy, as seen in the case we describe here.

CASE REPORT

41-year-old female presented with complaints of bilateral neck swelling, fever which was on and off and bleeding gums for 6 months. Physical examination revealed generalized lymphadenopathy which included bilateral cervical, axillary and inguinal group of lymph nodes. Abdominal examination revealed no organomegaly. Her blood parameters were WBC-117,000/ μ L; RBC-2,850,000/ μ L; Hemoglobin-8.4 g/dL; Platelets-23,000/ μ L.

Peripheral smear revealed microcytic hypochromic RBCs with occasional nucleated RBCs. WBCs were markedly increased in count with preponderance of blasts having scant cytoplasm and 1-3 nucleoli which constituted 85% of WBCs. Platelets were reduced in number (Figure 1).



Figure 1: Peripheral smear presence of blasts.

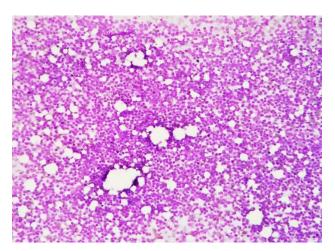


Figure 2: Bone marrow aspirate of a cellular marrow (40x, Leishman stain).

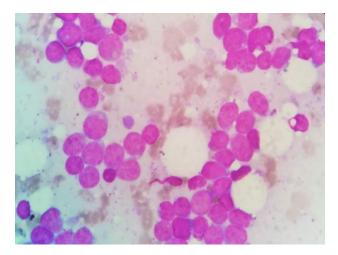


Figure 3: Bone marrow aspirate of an increase in the presence of blasts (1000x, Leishman stain).

Subsequently bone marrow aspiration and excision biopsy of cervical node was done. Bone marrow aspirate showed a cellular marrow with reduction in erythroid series and megakaryocytes and an increase in the presence of blasts with scant cytoplasm and 1-3 nucleoli

with few blasts exhibiting coarse cytoplasmic granules (Figures 2 and 3).

Histopathological examination of cervical lymph node showed effacement of lymph node architecture and diffuse proliferation of atypical cells exhibiting prominent nucleoli. Immunohistochemistry showed diffuse strong positivity for CD3 and negativity for CD20 (Figure 4A and 4B).

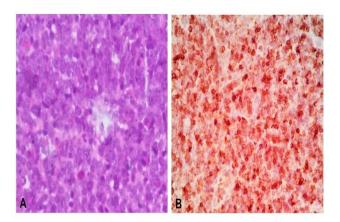


Figure 4: (A) Cervical lymph node biopsy (400x, H and E. (B) Cervical lymph node biopsy: CD3 positivity (400X).

Flow cytometric immunophenotyping analysis was done which showed positivity for CD3, CD7, CD10, MPO and CD33 in the blasts (Figure 5). Conventional karyotyping and fluorescent in situ hybridization (FISH) analysis to identify t (9;22) (q34; q11) using dual colour dual fusion BCR-ABL1 probe was performed on the bone marrow sample and she was found to have normal karyotype. The final diagnosis of mixed phenotype acute leukemia, T-lymphoid/myeloid, NOS was made.

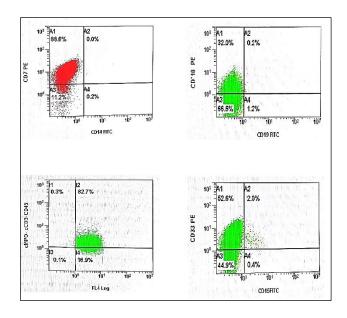


Figure 5: Flow cytometry plot.

DISCUSSION

Mixed phenotype acute leukaemias (MPALs) represent less than 5% of acute leukaemias.⁷ The previously defined separate entities like the biphenotypic acute leukaemia where a single blast cell population shows a mixed phenotype and the bilineal acute leukaemia where

two distinct blast cell populations exist each exhibiting a distinct phenotype are now included in the ambit of MPAL.⁸ The subtypes include B-Lymphoid/Myeloid, T-lymphoid/Myeloid, B-Lymphoid/T-Lymphoid and very rarely the possibility of trilineage differentiation (B-lymphoid/T-Lymphoid/Myeloid).⁹

Table 1: European group for the immunological characterization of leukaemia (EGIL) scoring system.

Score	B-lymphoid	T-lymphoid	Myeloid
2	CD79a	CD3 (Surface or cytoplasmic)	Myeloperoxidase
	Cytoplasmic CD22		
	Cytoplasmic IgM	TCR	
1	CD10	CD2	CD13
	CD19	CD5	CD33
	CD20	CD8	CD65
		CD10	CD117
0.5	TdT	TdT	CD14
	CD24	CD7	CD15
		CD1A	CD64
A score of more than 2 for each lineage is required			

Table 2: 2008 WHO criteria.

Lineage	Markers	
B-lymphoid	Strong CD19 expression and strong expression of at least one of the following markers: CD79a, cCD22, CD10 (or) Weak CD19 expression and strong expression of at least two of the following markers; CD79a, cCD22, CD10	
T-lymphoid	Cytoplasmic CD3 (or) Surface CD3	
Myeloid	Myeloperoxidase (or) Monocytic differentiation with at least two of the following markers: NSE, CD11c, CD14, CD64, lysozyme	

It affects both children and adults with a male predominance. MPALs are thought to arise from multipotent progenitor stem cells which can differentiate into lymphoid and myeloid lineages. Several diagnostic criteria have been proposed to distinguish MPAL from acute leukaemia with aberrant expression of differentiation antigens from another lineage.

The two most widely followed and accepted criteria are the 2008 WHO criteria and European Group for the immunological characterization of leukaemia (EGIL) scoring system (Tables 1,2). 8,12 In this case, the diagnostic criteria of both systems were satisfied with the expression of CD3 and myeloperoxidase (2008 WHO criteria) and a score of 3.5 for T-lymphoid lineage and a score of 3 for myeloid lineage (EGIL scoring system).

Cytogenetic studies have demonstrated many chromosomal abnormalities including t (9;22) (q34; q11), t (v;11q23) (MLL), monosomy 7 and trisomy 8 among others. ^{13,14}

The optimal therapy for MPAL has not been well defined and the prognosis remains unfavourable. ¹⁵ The treatment options include the combined AML+ALL therapy, CAG regimen (low-dose cytarabine, aclarubicin hydrochloride and granulocyte colony-stimulating factor) and allogenic hematopoietic stem cell transplantation. ^{15,16} Patients who have t (9;22) may benefit from the treatment with tyrosine kinase inhibitors. ^{15,17}

CONCLUSION

Mixed phenotype acute leukaemia being a very rare disease and when presenting with atypical clinical features like generalized lymphadenopathy, present a diagnostic dilemma. Flow cytometric immunophenotyping analysis and cytogenetic analysis are essential for the diagnosis, formulating treatment protocols and predicting the disease outcome.

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