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Case Report

ETP ALL or mixed phenotype acute leukemia: Diagnostic dilemma in acute leukemia with simultaneous expression of thymic and myeloid markers

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ABSTRACT

Early T precursor acute lymphoblastic leukemia (ETP ALL) is rare and has a characteristic phenotype. Mixed phenotype acute leukemia (MPAL), as per World Health Organization, needs to have two different lineages. On cytochemistry, myeloid lineage is designated by more than 3% blast cells positivity for cytochemical myeloperoxidase (MPO). Flow cytometric analysis of MPO an arbitrary cutoff of 10% has been described in the literature for this purpose by some authors. Many laboratories performing flow cytometric immunophenotyping of hematolymphoid neoplasms do not use cytochemical MPO. The differential diagnosis between ETP ALL with myeloid antigen expression and T/Myeloid MPAL is tricky. Here, we describe a case where in cytochemistry and morphology favor myeloid lineage and flow cytometry findings in isolation favored ETP ALL, thereby highlighting the benefits of cytochemical MPO staining of bone marrow/blood smears in the diagnostic workup for acute leukemia.

Keywords: Early T precursor acute lymphoblastic leukemia, Mixed phenotype acute leukemia, Cytochemical myeloperoxidase.

INTRODUCTION

Early T-cell precursor, acute lymphoblastic leukemia (ETP-ALL) is the most immature subtype of thymic (T) precursors cell ALL, capable of expressing one or more stem cell markers, and/or myeloid markers. Among T-cell lineage markers, ETP-ALL blasts are negative for CD1a, CD8, and surface CD3. CD5 expression is dim and partial (<75% cells positivity) or negative. This entity is not adequately described in the 2008 World Health Organization (WHO) classification of hematolymphoid neoplasms.[1,2] ETP-ALL has a poor treatment outcome and a high relapse rate.[3] Cytogenetic findings are not disease specific but may have some myeloid lineage associated mutations.[4] On the other hand, the T/Myeloid subtype of mixed-phenotypic acute leukemia (MPAL), as defined by the WHO 2008 classification, can resemble ETP-ALL. Flow cytometric immunophenotyping is considered essential for the diagnosis of MPAL. For assigning T-lineage to the blast cells, either cCD3 or sCD3 should be positive and for myeloid lineage, either myeloperoxidase (MPO) or monocytic markers should be expressed by these cells.[1] Here, we report the case of a 35-year-old female whose blast cells had immunophenotypic features favoring the diagnosis of ETP-ALL but cytochemical findings showed MPO positivity

in these cells along with the presence of "Auer" rods thereby questioning their ETP phenotype and suggesting the diagnosis of MPAL.

CASE REPORT

A 35-year female presented with fever, weakness, and petechial hemorrhage. Laboratory investigations showed leucopenia (0.82 × 10^6/dL), low hemoglobin (4.8 g/dL), and low platelet count (15 × 10^6/dL). Morphological examination of bone marrow revealed ~75% blast cells with coarse cytoplasmic granules in a number of these cells. Some of the blasts also showed slender "Auer" rods that were more evident in MPO-stained bone marrow smears [Figure 1].

In flowcytometric immunophenotyping , CD45/ SSC dot plot reveal approximately 70% blast cells with low SSC and dim CD45. On gating these cells express immaturity markers (CD 34 and CD117), myeloid marker (CD33), and T lymphoid markers (cytoplasmic CD3, CD7, and CD5 [dim and partial]). Other T-lymphoid markers such as CD1a, CD4, CD8, and surface CD3 were absent in blast cells thereby suggesting their early T-precursor phenotype. Interestingly, cytoplasmic MPO (K window) was expressed only in a subpopulation (9%) of the gated CD34 positive blast population, corresponding to the low percentage (6%) MPO positivity in blast cells in the bone marrow smears [Figures 2a and 2b]. Based on cytochemical MPO positivity, the presence of "Auer" rods (which suggested their neoplastic phenotype) and the above immunophenotypic features of the blast cells, the diagnosis of MPAL – T/Myeloid was preferred to ETP-ALL.

DISCUSSION

In flow cytometric immunophenotyping of acute leukemia, positivity for a surface marker is based on the expression of the marker in more than or equal to 20% of blast cells and for the cytoplasmic markers the cutoff of 10% or more has been suggested in some studies.[3,5] However, there is a lack of consensus on these cutoffs, especially for the cytoplasmic markers. According to the 2008 WHO guidelines, MPO is a myeloid lineage specific marker but the guidelines did not define the cutoff for percentage positivity for MPO by flow cytometry. On the other hand, the cutoff of 3% MPO positivity has been in use in morphological/cytochemical analysis of bone marrow smears for decades to label blast cells as "myeloid." Furthermore, the outcome and interpretation of immunophenotyping data can be affected by the type of sample, aging of the sample, hemodilution of the bone marrow sample, the presence and percentage

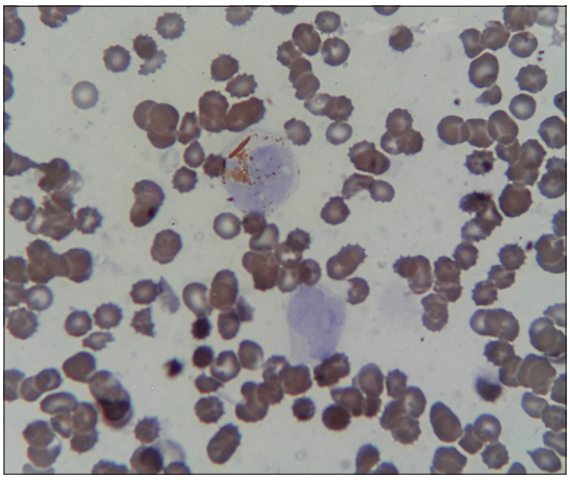

Figure 1: Blast cells with cytoplasmic myeloperoxidase positivity and presence of "Auer" rod.

of normal myeloblasts, reagents and fluorochromes used, method and techniques followed, etc. One or more of these variables can lead to false positive or negative results. In our experience, cytochemical MPO staining in conjunction with flow cytometry data has been found more useful in sorting out the abovementioned issues than either modality of diagnosis alone. However, in some cases, the dilemma could persist despite applying both modalities of diagnosis. This is well demonstrated in the case under discussion in that the presence of MPO-positive "Auer" rods in addition to ~6% MPO-positive blast cells in bone marrow smears and ~9% MPO positivity in flow cytometry confirmed the concomitant "myeloid" phenotype of a subset of blast cells and their neoplastic nature, in addition to their early T-precursor phenotype, that is, T/Myeloid MPAL phenotype. The blast cell phenotype of CD33, CD117, CD34, cCD3, CD7 positivity, dim CD5 expression, and CD4, CD8, CD1a, and sCD3 negativity in the absence of other B cell markers prima facie favored the diagnosis of ETP-ALL in our case [Figures 2a and 2b]. This is the most immature subtype of T-ALL associated with myeloid antigen expression. Distinguishing these cases from true T/Myeloid MPAL is difficult due to similar immunophenotype of blast cells in the two conditions complicated by nebulous diagnostic criteria as outlined above. However, this distinction is important because of the different therapeutic approaches in the two conditions.[6,7] All of the above however, also point to the fact that in ontogeny, cells of myeloid, and T-lineages share a common origin at the stem cell level and leukemic blast cells expressing both T-lymphoid and myeloid phenotypes represent neoplastic cells at an early stage of maturation and differentiation in the common T/Myeloid lineage. This possibility is also supported by other cellular and molecular evidence – both old and new.[8]

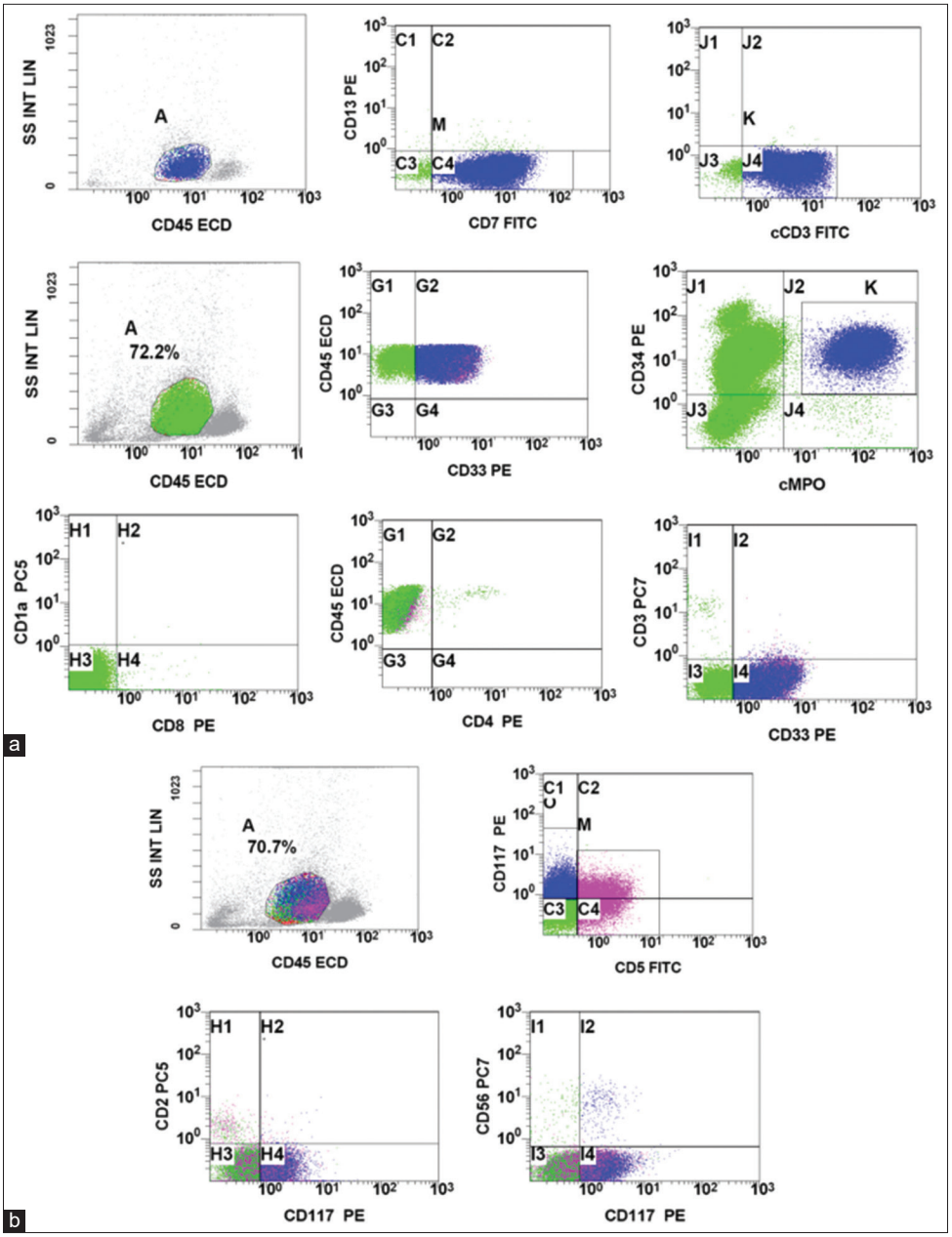

Figure 2: (a) ETP phenotype with subset of CD34 positive blasts expressing cytoplasmic MPO (K approximately 9%). (b) Flowcytometry plots show dim CD5 and expression of dim CD117. ETP: Early T precursor, MPO: Myeloperoxidase.

CONCLUSION

Early T precursor ALL is a distinct and immature subtype of T cell origin with overlapping marker expression of myeloid series/stem cells and has a poor prognosis. The presence or absence of MPO/Auer rods is crucial to define mixed phenotypic leukemia in such cases. Because of the low positivity for cytoplasmic MPO observed by flowcytometry, the careful microscopic evaluation of cytochemical MPO is crucial for a more reliable and definitive characterization of mixed phenotypic acute leukemia.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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