

Acute undifferentiated leukemia with myelofibrosis – A case report

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ABSTRACT

Acute undifferentiated leukemias (AUL) is the diagnosis of exclusion and is very rare, the morphology of leukemic cells is not specific. Here we report a rare case of AUL with myelofibrosis with an unusual morphology. A 40 year female presented with anaemia and hepatosple enomegaly with pancytopenia and leucoerythroblastic blood picture on peripheral blood smear underwent bone marrow studies. Bone marrow biopsy showed infiltration of blasts with scant cytoplasm, round to irregular nucleus, dispersed chromatin with grade 3 fibrosis by Reticulin stain and negative Masson trichrome stain. Immunohistochemistry (IHC) on bone marrow biopsy showed CD 34 positivity and negative for Tdt, MPO, CD3, CD20, CD61 markers. Thus diagnosed as Acute undifferentiated leukemia with myelofibrosis. AUL is the diagnosis of exclusion and before categorizing leukemia as undifferentiated, it is necessary to perform immunophenotyping with a comprehensive panel of monoclonal antibodies.

Keywords

Pancytopenia, hepatosplenomegaly, Immunohistochemistry

INTRODUCTION

Acute leukemia are clonal expansion of immature myeloid or lymphoid cells (blasts) in bone marrow, peripheral blood and other organs. The diagnosis and classification of acute leukemias rely on morphology, immunophenotyping with the expression of surface or cytoplasmic antigens, chromosomal abnormalities, and specific molecular genetic analyses.¹

The 2008 edition of the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues has described a special category called acute leukemias of ambiguous lineage', in which the AULs has been subcategorized. Here the leukemic cells express no more than one membrane marker of any

given lineage.² Acute undifferentiated leukemia is a rare subset of acute leukemias unclassifiable by the French-American-British classification, where the lineage origin of leukemic blasts cannot be established by the associations of morphology, cytochemistry, and immunophenotyping with an extensive panel of monoclonal antibodies.³⁻⁵

AUL is the diagnosis of exclusion and is very rare, the morphology of leukemic cells is not specific. Here we report a rare case of AUL with myelofibrosis with an unusual morphology.

CASE REPORT

A 40 year female presented to the outpatient department with anaemia and hepatosplenomegaly. The hematologic

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parameters were investigated with hemoglobin (Hb) 3.9 g/dl; platelet count is 53000 cells /cumm; and white blood cells (WBC) 2800cells/cumm having neutrophils 72%, myelocyte-2%, metamyelocyte-4% and lymphocytes- 22%. On peripheral blood smear red blood cells(RBC) showed normocytic normochromic cells with tear drop cells and 4 nucleated RBCs/100 WBCs. White blood cells showed leucopenia with neutrophilic predominance, toxic change and shift to left. Platelets were reduced in number. Retic count was 5%. Thus peripheral smear was reported as pancytopenia with leucoerythroblastic blood picture and advised for bone marrow studies. Bone marrow aspirate was done and the smears were diluted and no opinion was possible. The bone marrow biopsy showed infiltration of blasts with scant cytoplasm, round to irregular nucleus, dispersed chromatin.(Figure 1,2) Special stains such as reticulin stain showed grade 3 fibrosis (Figure 3) and Masson trichrome stain was negative. Immunohistochemistry (IHC) was done with a panel of markers on the bone marrow biopsy and showed CD 34 positivity (Figure 4) and negative for Tdt, MPO, CD3, CD20, CD61 markers. Erythroid and plasmacytoid cell lineage markers were also negative. There was no prior hospitalization or treatment history. In view of the above test results finally diagnosed as Acute undifferentiated leukemia with myelofibrosis. There was no follow up smears as the patient was discharged but later after 9 months patient came for follow up and for further treatment with symptoms of fever on and off, weight loss and myalgia. Hemogram showed Hb:3.6gms/dl with Normocytic normochromic red blood cells, tear drop cells, elongated cells, leucocytosis with 57% blasts, mild eosinophilia, myeloid left shift. Platelets were markedly reduced (5,000/cu mm). Periodic Schiff stain (PAS) stain was done on the peripheral smear and it showed block positivity in the blast cells. With these follow up investigations, it was later differentiated as acute lymphoblastic leukemia.

DISCUSSION

AULs arise presumably from clonal expansion from the most primitive hematopoietic cells or from the poorly differentiated hematopoietic cells. The incidence of AUL is probably less than 0.5%.⁶ Bassan et al had described about the largest study of 6 cases of AUL in 1992.⁷ AULs fall under the 2008 WHO classification of acute leukemia of ambiguous lineage. The leukemia classified into this category do not have a phenotype of a single cell lineage that allows for a simple clear cut classification and are therefore a diagnosis of exclusion.²

Figure1: Bone marrow biopsy showing hypocellular marrow with blasts (H&E,x40)

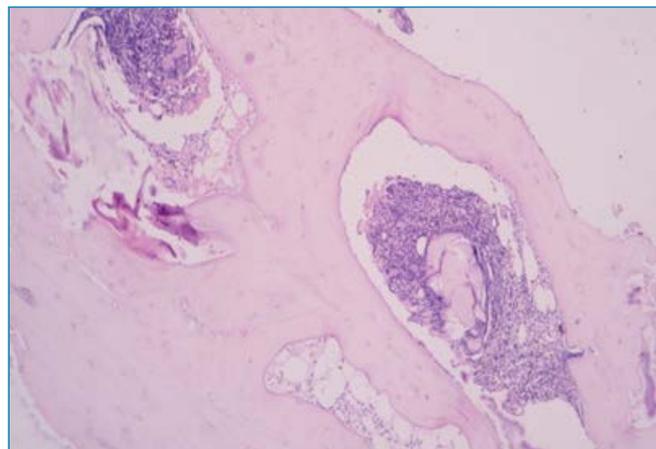


Figure 2: Bone marrow biopsy showing blasts with scant cytoplasm, round to irregular nucleus and few with prominent nucleoli (H&E,x400)

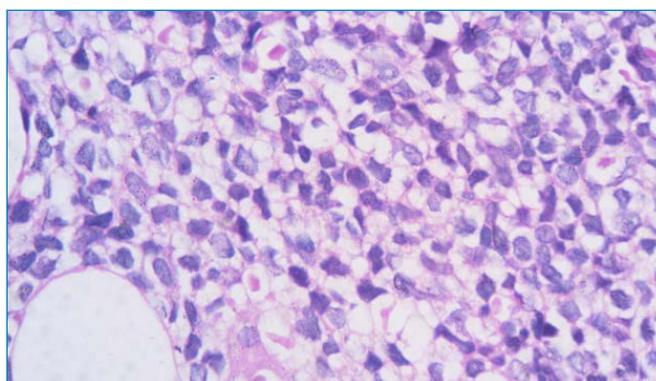
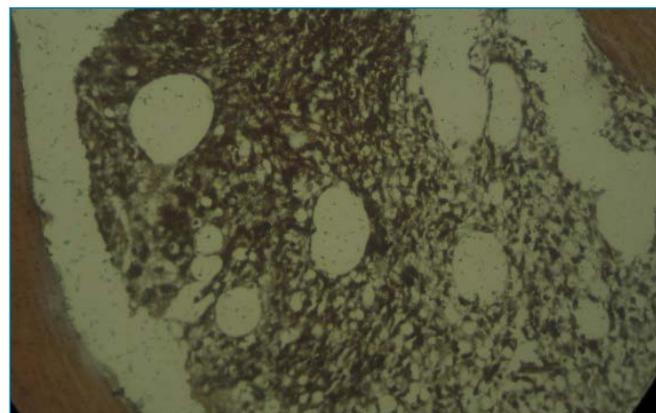
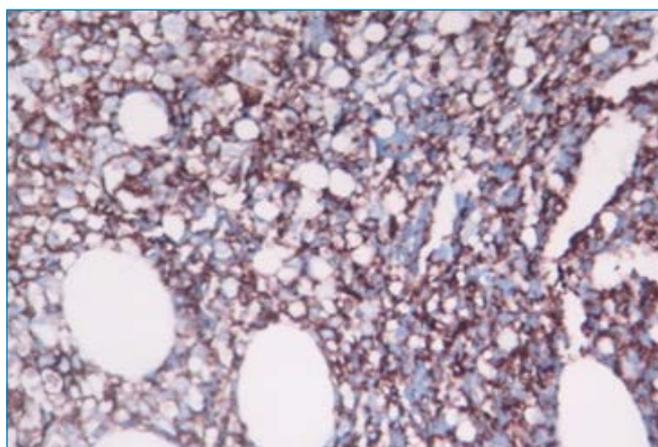


Figure 3: Reticulin stain showing grade 3 fibrosis (x400)



AULs typically express no more than one surface membrane antigen of any given lineage. Also, by definition they lack T-cell-specific, myeloid-specific, and B-lineage-specific markers, as well as other lineage-

Figure 4: Postive immunohistochemical marker for CD34 (x400)

specific markers (those for plasmacytoid dendritic cells, erythroid precursors, and megakaryocytes). AULs are usually negative for MPO and the esterases by enzyme cytochemistry. The blasts often express CD34, CD38, TdT and/or HLA-DR which are all non lineage-specific markers of immaturity or activation. If none of the uncommon lineage specific markers are present, the diagnosis of AUL can be made.⁸ Similar features were noted in our case, in addition with features of myelofibrosis.

AULs has been differentiated in few cases in the literature. More than half of the leukemias that are morphologically undifferentiated, has shown positive reaction with myeloperoxidase which points towards early myeloid differentiation, but the immunological markers were inconclusive. Hence these leukemias has also been referred to as AML-M0.⁹ Also these undifferentiated tumors has shown differentiation to Langerhans cell –like cells in lymph nodes.¹⁰ Our case has been differentiated to acute lymphoblastic leukemia and no literatures was found with this differentiation. Follow up AUL cases which has differentiated will be beneficial with better management options.

As AULs are rare, therefore much has not been elucidated about this hematopoietic neoplasm. Their frequency, predilection for involvement of sites other than blood and bone marrow, genetic abnormalities and progression/prognosis are not clearly known. In addition, the morphologic features of the blasts are indistinct and show no distinguishing features from blasts of other classifiable leukemias. It is important to diagnose and classify acute leukemias as it affects patient management options. Receptor studies, gene expression, and in vitro culture studies may, in the near future, contribute substantially to our knowledge about these undifferentiated blasts

The prognosis of AUL patients is generally considered as poor, although the information is too scanty to make any definitive statements.⁴ High frequency of unfavourable cytogenetic changes, high expression of immature markers, non lineage specific antigen receptor rearrangements may be responsible for poorer prognosis.

CONCLUSION

The present case had undifferentiated features with myelofibrosis morphologically as well as by Immunohistochemistry. Very few cases have been differentiated and has been found in literature. As only few cases of AUL has been described in literature the exact significance of AUL morphology was difficult to assess. However, before categorizing leukemia as undifferentiated, it is necessary to perform immunophenotyping with a comprehensive panel of monoclonal antibodies.

CONFLICTS OF INTEREST

None

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