

Case Report

MIXED PHENOTYPE ACUTE LEUKEMIA OF T/MYELOID TYPE WITH RARE MULTIPLE CYTOGENETIC ABNORMALITY OF CHROMOSOME 8, 9, 11, 12, 16 AND MARKER CHROMOSOME AND DUAL BLAST POPULATION: A RARE CASE.

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Abstract

Mixed phenotypic acute leukemia (MPAL) represent very rare and heterogenous group of acute leukemias comprising 2-5 % of all leukemias. Although WHO 2008 laid down stringent criteria for diagnosis but these still pose diagnostic challenge as It encompasses leukemias having separate populations of blasts of more than one lineage or a single population of blasts which co-express antigens of more than one lineage. Cytogenetics plays a major role not only in diagnosis but also determines the therapy and prognosis. We present a case of far unreported karyotype aberration in this type of acute leukemia 45, XY, -8, del (9)(p21),-11,add(12)(p13),add (16)(p13.3),+mar[20]with therapy resistant course.

Keywords: mixed phenotypic acute leukemia, complex karyotype, therapy

Introduction:

MPAL comprises 2-5% of all acute leukemias^[1]. The 2008 World Health Organisation classification established strict criteria for diagnosis of mixed phenotype acute leukemia, emphasizing myeloperoxidase for myeloid lineage, cytoplasmic CD3 for T lineage and CD 19 with other B markers for B lineage assignment^[1, 2]. MPAL are associated with poor outcome as compared to other acute leukemias and clinically presents challenges in diagnosis and treatment^[3, 4]. However, the true incidence is difficult to establish due to problems with definition, inter-laboratory

variations and non-availability of flow cytometry in most laboratories. There are four major categories listed under MPAL in the 2008 WHO classification. Although other types of cytogenetic aberrations have been recorded in this type of leukemia including 17p deletion^[4,5], MPAL with a 45, XY, -8, del (9)(p21),-11,add(12)(p13),add (16)(p13.3),+mar[20] complex karyotype has not been reported so far and may be of interest.

Case Report: A 38 yrs old male patient presented with cough, fever & headache for one month. CECT showed mediastinal mass (Fig 1) and hepato-splenomegaly. TLC was

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82,400/cumm, Hb was 12.5gm/dL & Platelets were 72,000/cumm. Peripheral blood film revealed 43 % blasts. Bone marrow examination revealed 90% blasts which were categorized into two types morphologically, large blasts with abundant cytoplasm, round to convoluted nucleus, fine lacy chromatin & prominent nucleoli

which were 66% of all cells and 24% blast which were smaller, had coarse chromatin and inconspicuous nucleoli with scant cytoplasm (Fig 2). Myeloperoxidase (MPO) positivity was seen in more than 3% blasts and thus diagnosis on morphology was Acute Myeloid Leukemia according to FAB.

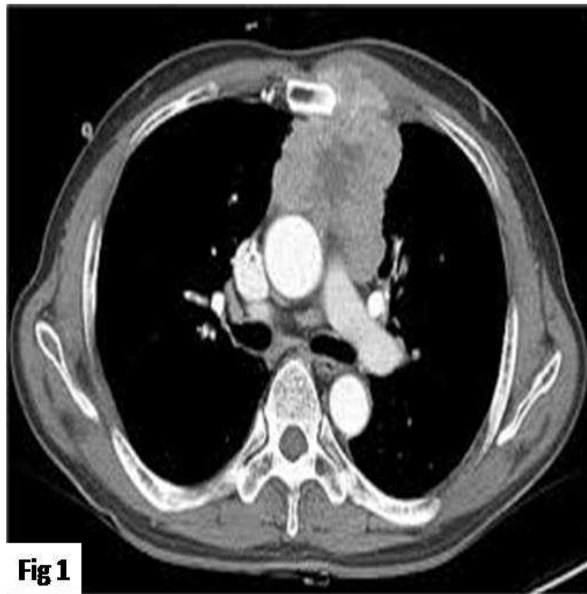


Fig 1

Fig 1 : CT scan showing anterior mediastinal mass

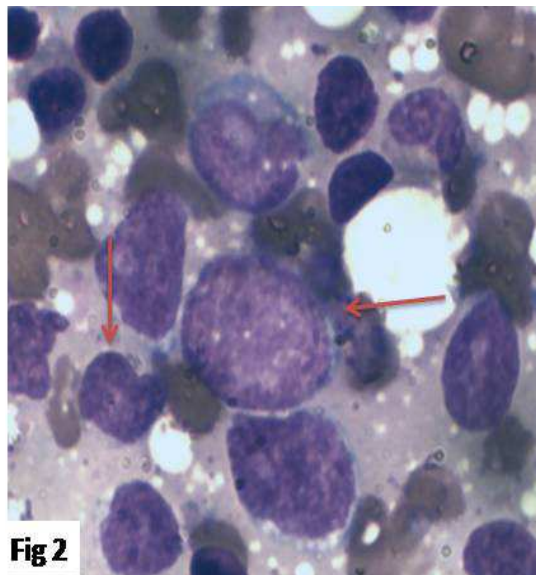


Fig 2

Fig 2: Bone marrow showing dual population of blasts

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Cytogenetic analysis showed complex karyotype of 45, XY, -8, Del (9) (p21),-11, add (12) (p13), add (16) (p13.3), +mar [20] (Figure 3).

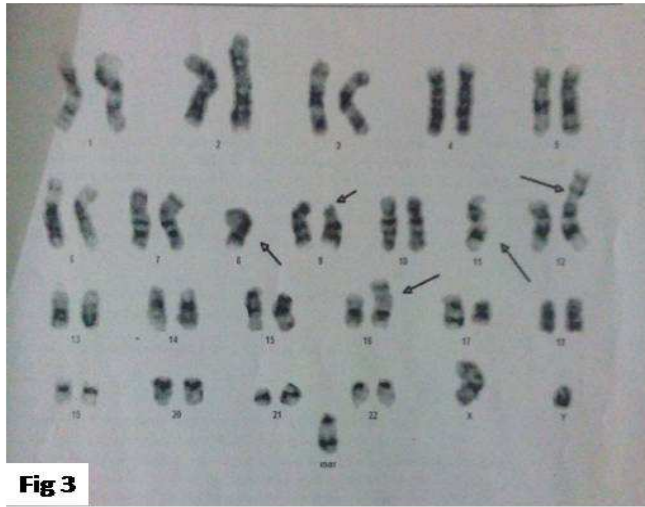


Fig 3

Fig 3 Interpretation: The analysis of 20 metaphases reveals 45, XY with loss of chromosomes # 8 and # 11, deletion on the short arm of chromosome # 9 at band 9p21, added material on the short arm of chromosome # 12 at band 12p13, and added material on the p arm of chromosome # 16 at 16p13.3 along with one marker chromosome of unknown origin.

Flow Cytometry was performed with back gating on CD34 positive population which revealed gated cells positive for CD45 (Dim), CD34, HLA-DR, cMPO, CD33, cCD3, CD7, TdT, CD5 (fig 4). Thus,

the final opinion was MPAL (T/myeloid) (Fig4). Other blasts populations with smaller cell diameter and less sizable in proportion expressed early T-lymphoid features with expression of cyCD3 (fig 4.)

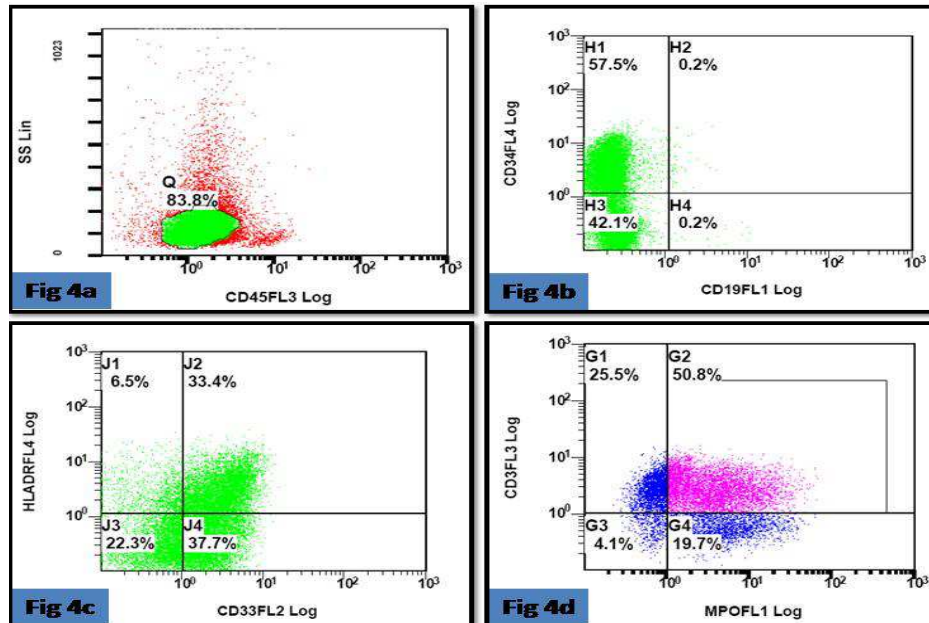


Fig 4 a SSC Vs CD45 and gated cells; **b.** gated cells were positive for CD34; **c.** Gated cells were positive for CD33 & HLA-DR ; **d.** 50.8% of gated cells were co-positive for Cytoplasmic MPO and cCD3

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The molecular analysis of FLT3 and NPM1 oncogenes, BCR/ABL gene rearrangement, t (12; 21) and t (4; 11) was negative. According to Immunophenotyping, our case was MPAL of T/myeloid type.

Patient was initially treated with ALL induction protocol with no response.

Thereafter AML protocol was instituted but the patient failed to respond and bone marrow still showed 31 % blasts. Flow cytometry now showed persistence of blasts with all the markers which were present earlier (Fig 5).

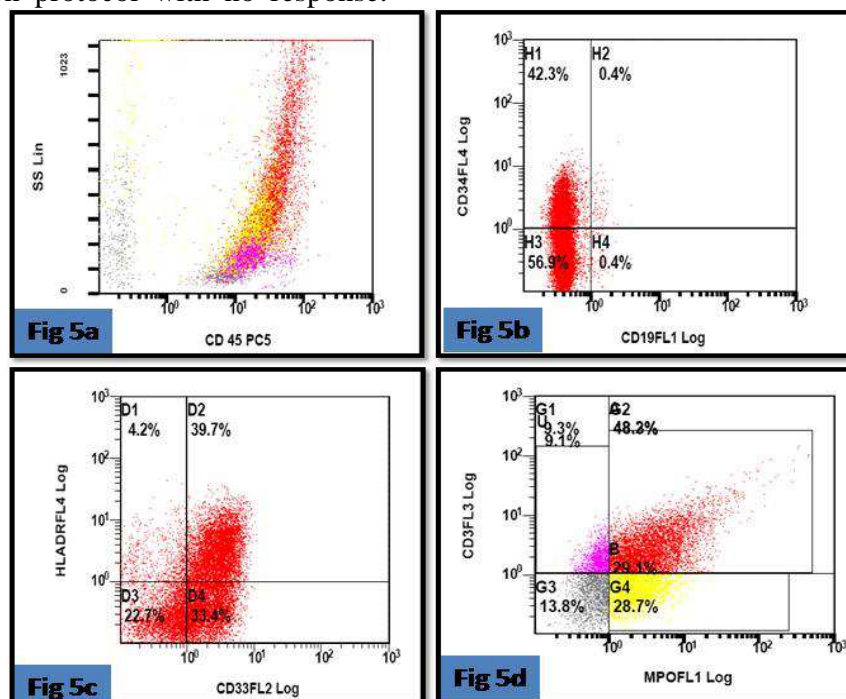


Fig 5a SSC Vs CD45; **b** Gated cells were positive for CD34; **c** Gated cells were positive for CD33 & HLA DR; **d** 48.3 % Gated cells were co-positive for Cytoplasmic MPO and CD3

Discussion

The rarity of MPAL and the lack of uniform diagnostic criteria have made it difficult to establish whether these leukemias have distinct characteristics and which is the best therapeutic approach for these patients [5]. Here, we present a rare case of an adult patient with MPAL of T/myeloid type, characterized by prominent immunophenotypic heterogeneity of leukemic cell population and the presence of a so far unreported karyotype aberration in this type of acute leukemia with therapy resistant course. Moosavi SA et al showed that karyotypes with high level amplification of RUNX1 were significantly characterized

by presence of marker chromosomes that harboured extra copies of RUNX gene contributing to pathogenesis and progression as was seen in our case⁶. Marker chromosomes have been reported in ALL, AML and MDS [6, 7].

Although the putative cell of origin in MPAL is unknown, it is possible that this leukemia arises in a very early hemopoietic progenitor with potential to undergo either on myeloid or lymphoid differentiation or rarely T- or B- cell differentiation [8]. The blast cell heterogeneity with a complex overlap of immunophenotypic profiles as well as CD7 antigen expression is in positive correlation

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with postulated origin of MPAL of T/myeloid type from a multipotential hematopoietic stem cell with preserved potential for T-and myeloid-lineage development^[1]. This patient had markedly drug resistant leukemia as he failed to respond to ALL followed by AML induction protocol. Also, the chromosome abnormality found in karyotyping suggested, but did not prove unequivocally, that blast subpopulations shared the same cytogenetic aberration.

Matutes E et al analyzed clinical, laboratory features and outcome in 100 cases defined as per WHO 2008 and documented poor outcome of MPAL in terms of achieving complete remission and overall survival^[4]. They also suggested that ALL directed therapy was more effective with higher response rate and comparatively better outcome. In the prognostic risk assessment two other variables might be considered as strong predictors for outcome, presence of Philadelphia chromosome and age^[4]. Studies have suggested that these are related to association of unfavourable markers like unfavourable karyotype and over-expression of p-glycoprotein. However because of small numbers included and patient heterozygosity the results should be taken with caution^[9].

The one marker chromosome of unknown origin provides a rare opportunity of observing an aggressive and therapy resistant MPAL with an unbalanced karyotype change.

Conflict of Interests

All authors have none to declare.

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