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Case Report .

Minimally Differentiated Acute Myeloid Leukemia (FAB M0) in a Child with Down Syndrome: A Case Report

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ABSTRACT

Children with Down syndrome (DS) have 10-100 fold increased risk of leukemia. >90% cases present with morphology and immunophenotype characteristic of acute megakaryoblastic leukemia (FAB M7). Other AML FAB described in DS include M0, M1/2 and M6. In addition, 10% of DS neonates manifest Transient Abnormal Myelopoiesis (TAM) which resolves spontaneously within 3 months. TAM is difficult to distinguish from AML and immunophenotyping along with the clinical course can give clues to final diagnosis. We present a case of DS presenting as AML M0 and experiencing a fatal outcome.

Key words: Downs Syndrome, Acute Myeloid Leukemia, Transient Abnormal Myelopoiesis.

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INTRODUCTION

Children with Down syndrome (DS) or Trisomy 21 have 10-100 fold increased risk of leukemia.[1] More than 90% cases present with morphology and immunophenotype characteristic of Acute Megakaryoblastic Leukemia (AMKL) highlighting the unique relationship between trisomy 21, leukemogenesis and a specific leukemia phenotype.[1] Other AML described in DS include M0, M1/2 and M6.[1] In addition, 10% of DS neonates manifest Transient Abnormal Myelopoiesis (TAM) which resolves spontaneously within 3 months.[1] TAM is difficult to distinguish from AML and immunophenotyping along with the clinical course can give clues to final diagnosis. We present a case of DS presenting as AML M0 and experiencing a fatal outcome.

CASE HISTORY

A neonate born with phenotypic features of DS (mongoloid slant, low set ears, epicanthic folds), had significant hepatomegaly and a palpable spleen. A routine hemogram done at day 8 of life showed hemoglobin 10.5g/dL, total leucocyte count 45,700/mm^3 and platelet count 2.53×10^9/L. On peripheral blood smear (PBS), 30% blasts were found. Blasts size was variable ranging from 2-5 times the size of small lymphocyte, high N/C ratio with scant basophilic cytoplasm, opened chromatin with 1-2 inconspicous nucleoli. Few blasts showed cytoplasmic blebbing and slight nuclear indentations (Fig 1). A clinico-morphological diagnosis of TAM was thought of. On cytochemistry, blasts were negative for MPO, SBB and PAS. On flow cytometry, blasts were positive for CD34, CD117, HLA-DR, CD38, CD33, CD7 and negative for cMPO, cCD3, CD79a, CD10, CD19, CD20, CD64, CD56, CD41 and glycophorin A (Fig 2,3). A final diagnosis of AML M0 was made. On follow up, the child did not receive any chemotherapy and had expired due to? respiratory arrest? sepsis within a month.

DISCUSSION

TAM found in newborns with DS, diagnosed on the detection of megakaryoblasts in PBS. These blasts have similar morphology and immunologic features as of megakaryocytic lineage (AKML cells)[1], are MPO negative and PAS positive on cytochemistry. The classical cytogenetic abnormality in TAM are GATA 1 mutations.[1] Detection of these mutations by PCR can confirm the diagnosis, help monitor clinical regression and may also identify cases which will ultimately progress to AML. The defining feature of TAM is spontaneous clinical resolution in majority of cases within 3 months with supportive care alone without use of chemotherapy (Favourable outcome).[1] However, the mechanisms of this unique phenomena are unknown. 20-30% of TAM develops a non-remitting acute megakaryoblastic leukemia within 1-3 years[1] and a fatal outcome is observed only occasionally.

Minimally differentiated acute myeloid leukemia (AML-M0) is a rare AML subtype in both children and adults. The French-American British (FAB) criteria for its diagnosis consist of the

presence of <3% MPO and/or SBB positive blasts in the bone marrow (BM) by light microscopy, myeloid-associated antigen positivity (CD13 and/or CD33) and lack of B-/T-cell lineage–associated antigen expression, with the exception of TdT, CD7, and CD4.[2] Despite the presence of these criteria, its diagnosis poses a challenge as there is no evidence of myeloid differentiation by morphology or cytochemistry. Its incidence has been reported to be 5.3% in DS children.[2] The most important differential is AMKL especially in DS children. Immunophenotyping by flow cytometry and cytogenetics can help differentiate these two entities. It has an unfavourable outcome in both adults and non-DS children but it does not appear to alter the excellent outcome of DS-associated AML. Although the etiology of the adverse outcome is unknown, it may relate to lack of favorable AML cytogenetic abnormalities {t(8;21), inv16} and a corresponding over-representation of high-risk (chromosome 5) abnormalities.[2] Literature in DS children is limited due to its rarity.

In the present case, the neonate had phenotypic features of DS, blasts with morphology resembling megakaryoblasts (basophilic cytoplasm with cytoplasmic blebbing) giving a clinico-morphologic impression of TAM. However, on cytochemistry the blasts were MPO, SBB and PAS negative. Flow cytometry confirmed the diagnosis as AML M0 (CD 41, cMPO, cCD3, CD 10, CD 19 negative and CD 34, CD117, HLA-DR, CD38, CD33 Positive). Though studies quote that leukemias in DS children respond better to chemotherapy and are associated with a favourable outcome (including AML M0)[1], the present neonate expired within a month in the absence of any treatment. The etiology of this adverse outcome may be similar to the unfavourable outcome seen in adults and non-DS children, the answer to which can only be provided by cytogenetics which could not be performed in this case.

To conclude, AML MO is a difficult diagnosis as no evidence of myeloid differentiation is seen by morphology or cytochemistry (<3% MPO positivity). The blasts need to be differentiated from those of AMKL especially in DS children. Immunophenotyping is essential is such a situation to arrive at a definitive diagnosis but only cytogenetics can provide answer to unforeseen outcomes.

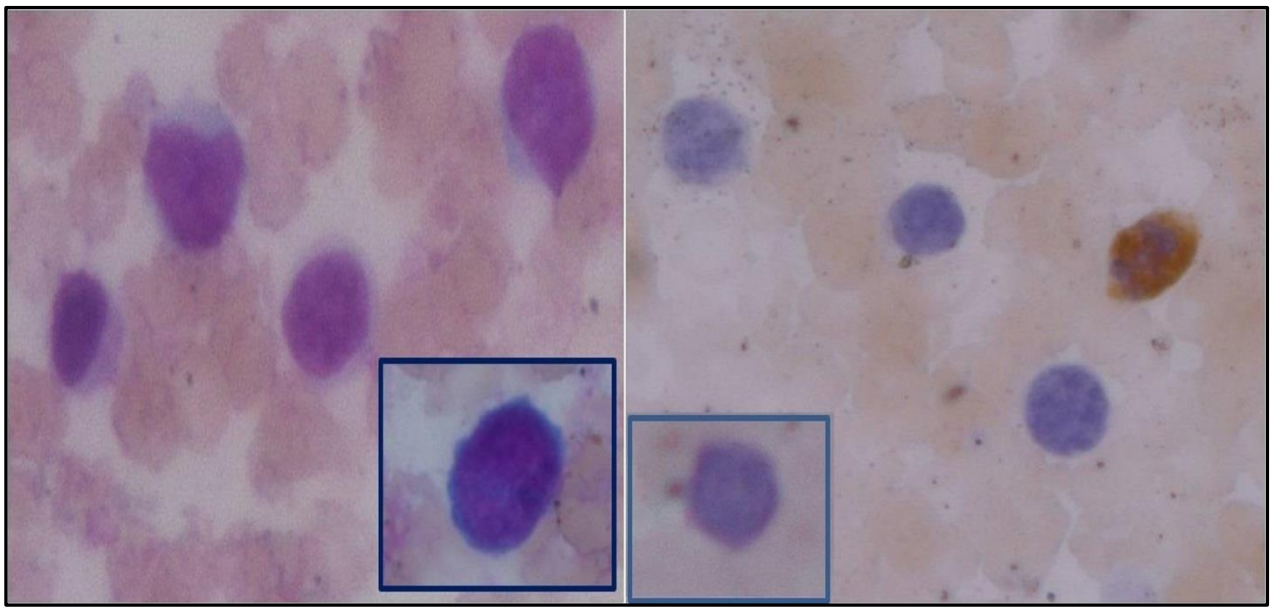

Figure 1 (a): Blasts: Variable size, high N/C ratio, scant basophilic cytoplasm, open chromatin, inconspicous nucleoli. Right Inset: Blast with cytoplasmic blebbing (MGG, 1000X) (b): MPO negative blasts. Left Inset: PAS negative blast

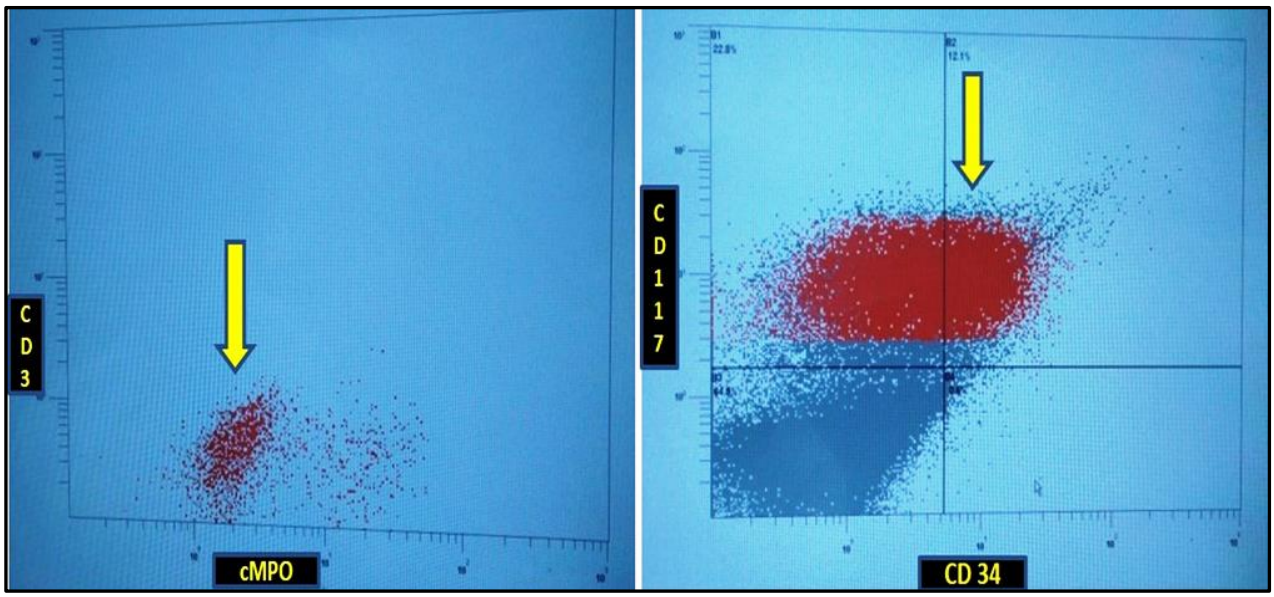

Figure 2 (a). CD 3 vs MPO: shows MPO negative blasts. (b). CD 117 vs CD 34: shows blasts positive for both the markers.

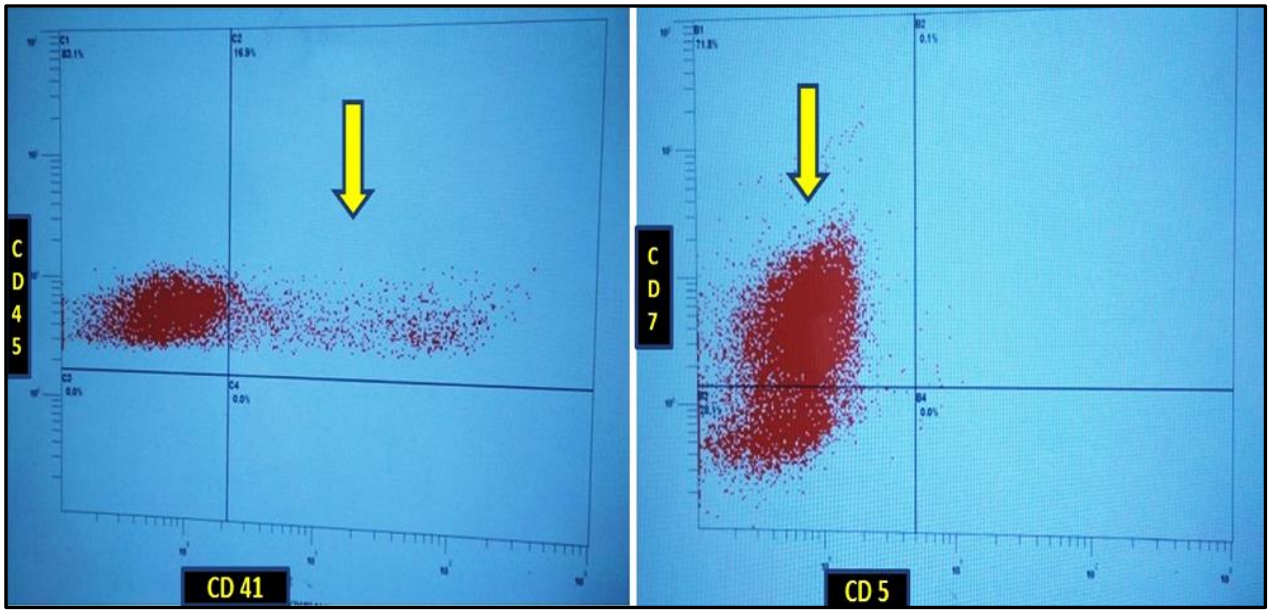

Figure 3 (a). CD45 vs CD41: shows CD 41 negative blasts. (b). CD 7 vs CD5: shows CD 7 positive blasts

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ETHICAL APPROVAL

The study was approved by ethical committee of the institute

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