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REVIEW ARTICLE

AMEGAKARYOCYTIC LEUKEMIA IN DOWN SYNDROME-A CASE REPORT

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ABSTRACT

Children with trisomy-21 have predisposition to develop Myeloid Leukemia of Down syndrome.(ML-DS). ML-DS is associated with TAM (Transient Abnormal Myelopoiesis) a haematological disorder of infancy, thought to originate in utero, as an identical mutation in GATA1 gene Most TAM cases will undergo spontaneous resolution without treatment, they don't require chemotherapy unless there is life threatening complication. We present a case of 16 month old female presented with complaints of fever &decreased activity, down's facies. On Complete blood count Hb-3.7, total count-19400, differential leukocyte count –blast-50%, & neutrophil 21%, lymphocyte-25%, eosinophil 1%, monocyte-3%, basophil-0%. Immunophenotyping of pheripheral blood by flow cytometry showed CD34, CD45, CD33, CD13, CD117, aberrant CD7, CD36, CD56, Cyto CD61-positive. s/o amegakaryocytic leukemia M7.Karyotyping confirmed DS. Patient completed 4 cycle of chemotherapy out of 4 cycles. Subject Area: paediatrics

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INTRODUCTION

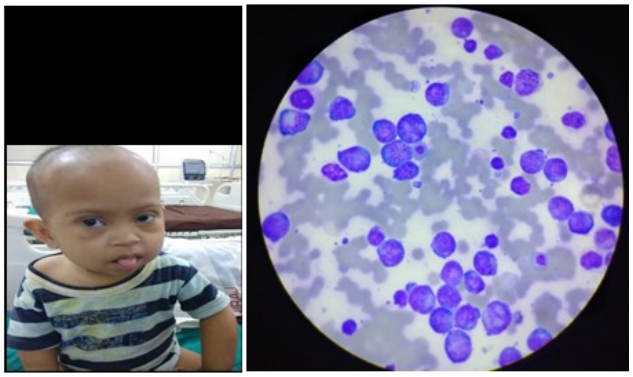
- Children with trisomy-21 have predisposition to develop Myeloid Leukemia of Down syndrome.(ML-DS).
- ML-DS is associated with TAM (Transient Abnormal Myelopoiesis) a haematological disorder of infancy, thought to originate in utero, as an identical mutation in GATA1 gene.(1-5)
- TAM is characterized by leukocytosis with increased circulating megakaryoblasts that harbour N-terminal truncating mutations in GATA1 gene.

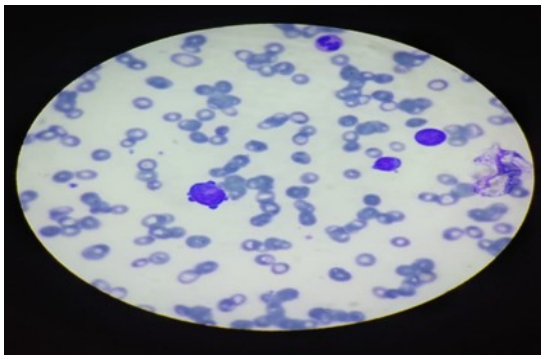
CASE REPORT

16 month old female presented with complaints of fever &decreased activity.On further examination child has Down's facies (figure1) and no lymph nodes.On examination liver 3cm palpable & spleen 2cm & grade 3 pansystolic murmur heard over tricuspid area. On *Complete blood count* Hb-3.7, total count-19400, differential leukocyte count –blast-50%, & neutrophil 21%,lymphocyte-25%, eosinophil 1%, monocyte-3%, basophil-0%. *Peripheral smear* showed moderate anisopoikilocytosis, polychromasia, tear drops, elliptocytes and target cells with leucocytosis with shift to left, blast cells showed high N:C ratio, fine chromatin, prominent 1-2 nucleoli and scanty cytoplasm with some having blebs,platelet anisocytosis and megakaryocyte fragment(figure2). *Bone marrow aspiration and biopsy* M: E ratio-7:1,DC showed blast 60%,promyelocyte 2%, myelocyte & metamyelocyte 8%, band cell & neutrophil 11%, lymphocyte 12%,eosinophil 3%,monocyte 4%. It also revealed depressed erythropoesis, multiple megakaryoblasts with cytoplasmic blebing constituting about 60% of marrow nucleated cells. *Immunophenotyping* of pheripheral blood by flow cytometry showed CD34, CD45, CD33, CD13, CD117, aberrant CD7, CD36, CD56, CytoCD61-positive. s/o amegakaryocytic leukemia M7. An impression of acute megakaryoblastic leukemia (AML M7) by morphology and immunophenotypically was made. Karyotyping confirmed DS. Patient completed 4 cycle of chemotherapy out of 4 cycles

DISCUSSION

Children with DS have 150 fold increased risk of developing acute myeloid leukemia before 5 years of age. The World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues (6) recognises the unique clinical and molecular features and the central role of GATA1, and defines TAM(TL-DS) as 'increased peripheral blood blast cells in a neonate with Down syndrome'. Cellular and Molecular Pathogenesis of TAM and ML-DS The cellular and molecular events involved in initiation and evolution of





TAM and ML-DS can best be understood as a three-step model which requires the presence within a fetal liver-derived haematopoietic stem or progenitor cell of (i) trisomy 21, (ii) an acquired GATA1 mutation, and (iii) at least one additional oncogenic mutation.There are at least three distinct steps in the pathogenesis of ML-DS. First, trisomy 21 perturbs fetal haematopoiesis, providing the ideal cellular context for the second step: transformation of these fetal haematopoietic cells by acquired N-terminal truncating mutations in the GATA1 gene to produce the clinical syndrome TAM. While the majority of cases of TAM resolve without sequlae as the GATA1 mutation is lost, ~10 % of children harbour residual GATA1-mutant cells which then, in the third step, acquire transforming mutations in additional oncogenes leading to ML-DS Around 10-15% of neonates with DS have diagnosis of TAM characterized by blast cells in peripheral smear, thrombocytopenia and hepatomegaly (7).

No single clinical feature is entirely specific to TL-DS because each of these features may also occur in the absence of TL-DS . However, there are several characteristic features that are seen relatively frequently in TL-DS but are uncommon in DS neonates without GATA1 mutations, including organomegaly, hepatopathy (raised transaminases with conjugated hyperbilirubinaemia), skin rash, pericardial and pleural effusions, extreme leucocytosis and coagulopathy (8,9). Presence of one or more of these features in the absence of a clear alternative explanation should lead to the early consideration of a diagnosis of TL-DS. Morphology, immunophenotyping and bone marrow Examination TL-DS originates from abnormal megakaryocyte-erythroid precursors in the fetal liver (10,11). Circulating blast cells are pleomorphic, often having prominent nucleoli and basophilic,blebbed cytoplasm, in keeping with their erythroid-megakaryocytic origin, and megakaryocyte fragments are often a prominent feature. Immunophenotypically they have a phenotype distinct from other leukaemias, showing variable co-expression of stem cell markers (CD34 and CD117), myeloid markers CD33/CD13 and platelet glycoproteins (CD36, CD42 and CD61). TAM and ML-DS blast cells are extremely sensitive cytarabine (12,13) Patients with Down syndrome demonstrate a remarkable sensitivity to methotrexate and other antimetabolites, which can result in substantial toxicity if standard doses are administered. Most TAM cases will undergo spontaneous resolution without treatment, they don't require chemotherapy unless there is life threatening complication. 20-23% of TAM will develop ML-DS in 1st 4years of life. Earliest sign of incipient ML-DS with history of TAM is falling platelet counts. In AML, however, patients with Down syndrome have much better outcomes than non–Down syndrome children, with a >80% long-term survival rate. After induction therapy, these patients receive therapy that is less intensive to achieve better results .Patients who have Down syndrome and who develop this transient leukemia or myeloproliferative disorder require close follow-up, because 20-30% will develop typical leukemia (often acute megakaryocytic leukemia) by 3 yr of life (mean onset, 16 mo). *GATA1* mutations (a transcription factor that controls megakaryopoiesis) are present in blasts from patients with Down syndrome.

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