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Case Report-II

Rare Association of Transient Myeloprolifierative Disorder and Imperforate Anus in a Neonate with Trisomy 21.

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ABSTRACT:

Transient myeloproliferative disorder is a disorder seen in Down's syndrome in neonatal period. A two day old neonate presented with features of Down's syndrome. He had imperforate anus as well. Blood investigation showed myeloblastosis which gradually subsided over 3 months.

INTRODUCTION

We report a rare trio of imperforate anus, trisomy 21 and transient myeloproliferative disorder (TMD)

CASE: A two day old full term normally delivered neonate was referred in view of absent anal opening. He was a product of non-consanguineous marriage. The mother was 25 years old and had normal antenatal period. She had not received any medications during pregnancy.

On examination baby had features of Down's syndrome – low set ears, protruded tongue, flattened nasal bridge, and mongoloid slant of eyes. Abdomen was distended. There was no hepatosplenomegaly or chloroma like cutaneous swellings. Patient had imperforate anus (Fig. 1). Rests of the systems were normal.

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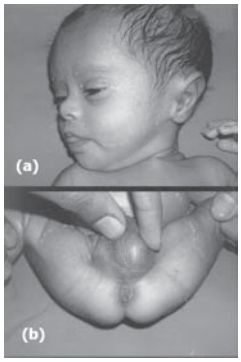

Fig-1: clinical picture showing (a) mongoloid features (protruded tongue, low set ears, depressed bridge) (b) imperforate anus.

On evaluation, invertogram revealed high anorectal malformation. Blood: 11g/dL, WBC 65600/ cumm and platelet count of 25,000/ cumm. The peripheral blood smear showed 74% myeloblasts, 5% myelocytes, 15% polymorphs, 6% lymphocytes. (Fig. 2 a) Bone marrow hypercellular marrow with predominant myeloid shift to left (85%) and increased myeloblast cells. Auer's rods were seen. Immunophenotyping was not done. (Fig-3) Rests of biochemical investigations (creatine, electrolytes, and blood gases) were normal.

High sigmoid loop colostomy was done after platelet transfusions. Blood counts were repeated every weekly for 4 weeks. Peripheral smear showed gradually decreasing trend of myeloblast cells with increasing polymorphs and lymphocytes in peripheral smear. Blood count showed only 1% myeloblast cells at the age

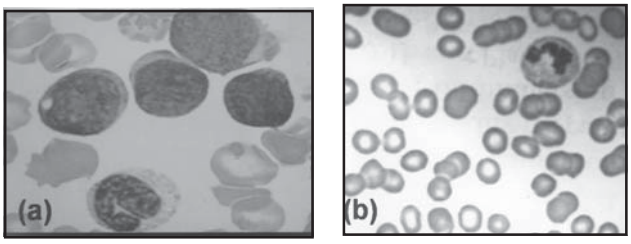

Fig-2: (a) peripheral blood film at day 2 showing the myeloblasts cells having basophillic cytoplasm, dispersed nuclear chromatin and several nucleoli. Azurophillic granules are present in one of the myeloblast. (b) smear at 3 months showing normal cell pattern.

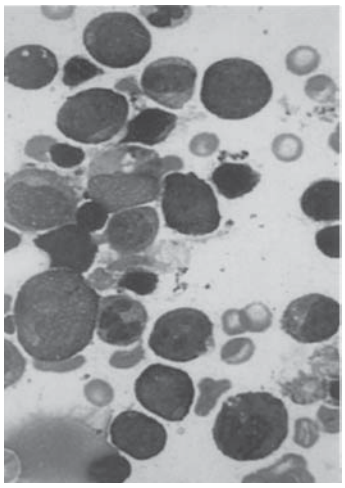

Fig- 3: bone marrow smear showing marked myeloid left shift and increased myeloblast cells.

of 3 months. (Fig-2b). Chromosomal study showed trisomy 21. Definitive surgery was done at the age of 8 months. Colostomy was closed 3 months later. Echocardiography done on follow up was normal. Patient was alright clinically at his one year follow up and was continent.

DISCUSSION

Down's syndrome is one of the commonest chromosomal anomalies seen in children. Patients of Down's syndrome are at higher risk of having imperforate anus.[1] Association of Down's syndrome and various hematological abnormalities is well known. The risk of leukemia in patients with Down's syndrome is 14 – 30 times more than in general population.[2]

Transient myeloprolifertive disorder (TMD) is mostly (although not exclusively) seen in Down's syndrome cases. There are reports of patients without Down's syndrome and TMD with identified GATA mutation in original blast cells.[3] It is characterised by presence of abnormal myeloblast cells in peripheral smear and bone marrow which is indistinguishable from acute leukaemia. Since in most circumstances it disappears gradually and is because of ineffective regulation of granulopoisis it is termed as transient myeloproliferative disorder.[4] TMD is seen 2 – 10 % of patients with Down's syndrome.[5,6]

The presence of extra chromosome in Down's syndrome is hypothesized to be cause for this disorder.[7] Several chromosomal abnormalities like unbalanced translocation between chromosomes 1 and 4 leading to trisomy 1q, trisomy 7q, monosomy 7p and a reciprocal translocation between chromosomes 10 and 16 are proposed to be associated TMD [8]. Down's syndrome and mutations in transcription factor GATA1 predispose neonates to TMD.[9]

Congenital leukemia is a rare malignancy diagnosed in a neonate. The following criteria, must be fulfilled for diagnosis (*i*) proliferation of immature leukemia cells; (*ii*) infiltration of these cells into non hemopoietic tissue; (*iii*) absence of other disease processes such as congenital hypoxia, erythroblastosis fetalis, congenital syphilis, bacterial infection which can cause a leukemoid or leukoerythro-blastic reaction, mimicking congenital leukemia.[4]

TMD is distinguished from congenital AML primarily by its spontaneous resolution within the first three months of life. Patients with TMD has lower blast percentages in their bone marrow than in their smear. Patients with AML have clonal cytogenetic abnormality which is not seen in TMD.[10] It is difficult to

differentiate between TMD and acute leukaemia in patients of Down's syndrome. The differentiation can be picked up only on follow-up.[5] If clinical or hematological deterioration continues, the possibility of TMD is ruled out and appropriate chemotherapy should be instituted.[4] However such patients are at high risk of developing acute leukaemia at later date and hence needs regular follow up and investigations. Upto 25% patients may develop myeloid leukaemia over a period of 3 years.[6] Little is known about markers predicting occurrence of leukemia. Expression levels of the Wilm's tumour gene (WT1) by real-time quantitative PCR (RQ-PCR) were studied in peripheral blood of five infants with TMD. It was found that the lack of normalization of WT1 gene level may be a predictor of leukemia development.[6] Individuals with +21 mosaicism are reported to be spared.

TMD is usually a benign self limited process that resolves spontaneously in the first few weeks of life[11] and requires supportive care only.[12] TMD occasionally results in severe and sometimes fatal complicatins, including progressive hepatic fibrosis with ultimate hepatic failure, hydrops fetalis with cardiopulmonary failure.[11] Low dose cytarabine therapy has been effective for treating TMD in some patients and should be considered for severe forms of the disease[12] Future therapy may involve nonimmu-nosuppresive and nongenotoxic inhibitors of signal transduction as well as targeted MAB or ligand conjugates.[10]

Studies have shown that 2% of Down's syndrome have imperforate anus.[13,14] In 95 % patients of Down's syndrome rectal pouch lies within 2 cms of perineal skin and are without urogenital or perineal fistula.[14,1] This type of imperforate anus may often be adequately treated by simple perineal anoplasty.[1] Prognosis remains good in terms of voluntary bowel control and urinary continence.[14]

In our patient no hepatospleenomegaly or any cutaneous manifestation of acute leukaemia were seen. Peripheral smear suggestive of leukaemia gradually subsided and normalised by 3 months. Screening the literature did not reveal the report of trio of Down's syndrome with myeloproliferative disorder with imperforate anus.

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