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Case Report

Transient myeloproliferative disorder and hepatic failure in a newborn with Down syndrome

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Approximately 10% of Down syndrome (DS) newborn develops transient leukemia (TL) also known as transient myeloproliferative disorder (TMD). Rarely, hepatic fibrosis (HF) and severe hepatic dysfunction have been reported in a patient with TL/TMD. Platelet-derived growth factor (PDGF) in combination with TGF-β1 is responsible for HF in such patients. Not only fibrosis of liver, diffuse fibrosis of other organ such as lung, kidney and pancreas are also seen in TMD patients. The triad of DS, TMD and HF is extremely rare. We report a DS neonate with endocardial cushion defect who developed TMD and died due to hepatic failure.

Keywords: Down's syndrome, transient leukemia, endocardial cushion defect, platelet-derived growth factor.

INTRODUCTION

Approximately 10% of Down syndrome (DS) newborn develops transient leukemia / transient myeloproliferative disorder (TL/TMD), which usually undergoes sponta-neous remission within 3 months (Zipursky et al., 1999). Rarely, hepatic fibrosis (HF) and fatal hepatic dysfunction have been reported in patients of DS with TMD (Matthias et al., 1998; Ogawa and Hirokazu, 2008). Platelet-derived growth factor (PDGF) in combination with TGF-β1 is responsible for HF in such patients (Ogawa and Hirokazu, 2008; Hattori et al., 2001). The triad of DS, TMD and HF is extremely rare (Matthias et al., 1998). We report a DS neonate with endocardial cushion defect who developed TMD and ultimately died due to hepatic failure.

CASE REPORT

A 25 days old male neonate with typical stigmata of DS was admitted with history of jaundice for 2 weeks. He had been born out of non-consanguineous marriage and normally delivered after an uncomplicated full term pre-gnancy (38 weeks) with birth weight of 2.3 kg. His mother was 34 years old and had normal antenatal period and she reported no exposure to infection, alcohol, tobacco or any drugs. Her other two children were normal. She was a booked case but only antenatal clinical assessment was done without any Ultrasonological (USG) screening and / biochemical profile.

Clinical examination detected; features of Down's syndrome: low set ears, protruded tongue, flattened nasal bridge and mongoloid slant of eyes (Figure 1). Pallor and icterus with few ecchymotic spots over skin were detected. Systemic examination revealed hepatomegaly (4 cm) and splenomegaly (2.5 cm) with minimum ascites. Mild precordial bulging with multiple visible pulsations was seen. Prominent heave at left sternal border with palpable thrill in left parasternal region were detected. An ejection systolic murmur was audible in the upper left sternal border. Other systemic examination was unremarkable.

Investigations detected; Hb-6.44 g/dl, total leukocyte count was 38,500/cumm, peripheral blood smear showed 63% of myeloblasts, 9% myelocytes, 20% polymorphs, 8% lymphocytes. RBC series were normocytic normo-chromic. Blast cells were large had scanty cytoplasm with round nucleus which were containing open chromatin and prominent 1-2 nucleoli. Few cells showed Auer rod in their cytoplasm. Platelet count was decreased to 80,000/cumm with few large forms were also visible. Possibility of acute myeloproliferative disorder was

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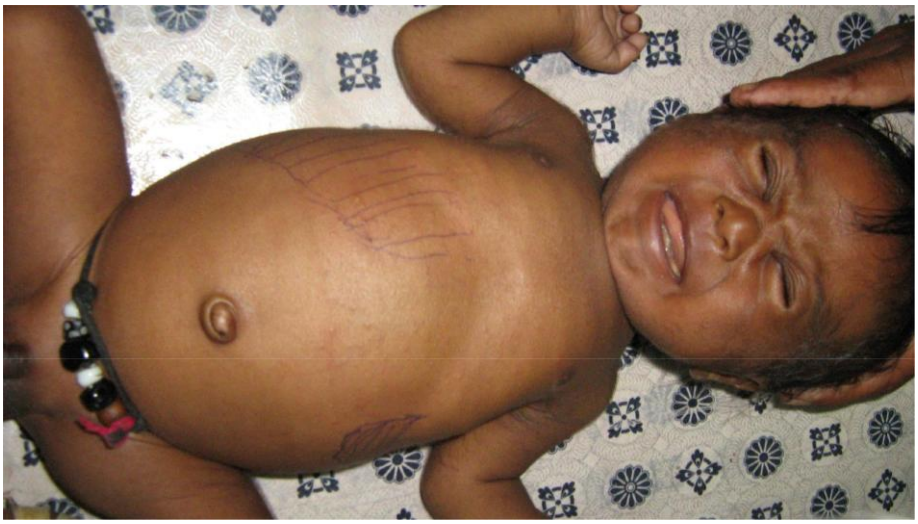

Figure 1. Showing image of newborn with features of Downs's syndrome with precordial bulging and abdominal distension.

considered and bone marrow examination was suggested. Blood for ESR and CRP were increased. Renal function tests, serum electrolytes and blood gases were within normal limit. Liver function test detected serum bilirubin of 8.5 mg/dl (conjugated 6.5 mg/dl, unconjugated 2 mg/dl), ALT 1550 U/L (normal 0-40 U/L), AST 360 U/L (normal 0-40 U/L) and alkaline phosphatase was 663 U/L. Total protein was 6.2 g/dl (Serum albumin 3.2 g/dl, globulin 3 g/dl). Lactate dehydrogenase (LDH) was hugely increased to 7455 U/L. Prothrombin time (PT) was 16.1 second with International normalization ratio (INR) of 1.6. Activated partial prothrombin time (APTT) and Fibrin Degradation Products (FDP) were within normal limit. Malarial Parasite (MP) and Malaria dual antigen was negative. TORCH screening and Hepatitis B (HBsAg) and Anti-Nuclear Antibody (ANA) were non-reactive. Thyroid profile and Serum Alpha Fetoprotein (AFP) was within normal limit. Urine for routine and microscopy had shown only bile salt and bile pigment without reducing substance. Urine and blood culture were sterile. Ultrasonography of abdomen revealed hepatosplenomegaly with ascites. 2D Echocardiography detected; complete Atreo-Ventricular (AV) canal defect with inlet Ventricular Septal Defect (VSD) (0.93 cm), Atrial Septal Defect (ASD) (0.55 cm), Patent Foramen Ovel (PFO) and trivial Mitral Regurgitation (MR) with mild Tricuspid Regurgitation (TR), fenestrated septal tricuspid leaflet with Pulmonary Arterial hypertension (PAH) and all chambers were enlarged. Bone marrow examination had done which revealed; hypercellur smears with moderate increased in myeloid erythroid ratio (M: M-19:1) with mild to moderate depression of erythroid, megakaryocytic and lymphoid precursor cells. There was considerable increased in myelopiosis. Blast cells accounted for 28% of marrow nucleated cells. Most of the other cells were precursor or mature cells of granulocytic series. Blast cells were large, round with moderate amount of bluish cytoplasm. Granularity of the cytoplasm was evident in some of the blasts and occasional cells show cytoplasmic vacuolation. Nucleus of those cells were round with open chromatin pattern and prominent multiple nucleoli. Features were suggestive of acute myelogenous leukemia (Figure 2).Chromosomal study showed trisomy 21(47XX+21) (Figure 3).

Treatment initiated with intravenous vitamin K and antibiotics. Fresh frozen plasma (FFP), platelets and packed red blood cell were transfused over next few days. Blood counts were monitored bi-weekly. Peripheral smear was showing gradually decreasing trend of myeloblast cells with increasing polymorphs and lymphocytes. Blood count had shown only 1% myeloblast cells over next 3 weeks. However, his liver function para-meters were deteriorating continuously. Serum bilirubin along with hepatic enzymes and PT was gradually increasing. Clinically jaundice was deepening and multiple ecchymoticspots were appeared. His bleeding diathesis remained uncontrolled even with by repetitive FFP transfusion. Finally he succumbed to his illness on day 66 of life.

DISCUSSION

Down's syndrome (DS) is the most common disorder of autosomal chromosome. It is due to an extra copy of the long arm region of q22.1 to q22.3 on chromosome no 21, causing trisomy 21.5In 95% of cases of Trisomy 21, the extra chromosome are of maternal origin. It results from meiotic non-disjunction. In a smaller percentage, normal number of chromosomes (46) with extra chromosomal material is present as a translocation, such as a Robertsonian translocation (Earle et al., 1992). In these

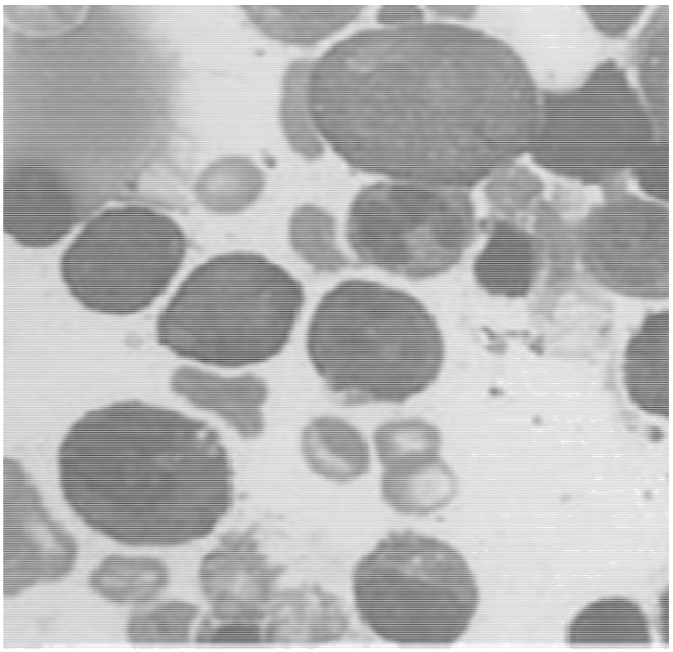

Figure 2. Image of bone marrow smear showing increased proportion of myeloid cells with presence of blast cells having large vesicular nuclei and prominent nucleoli.

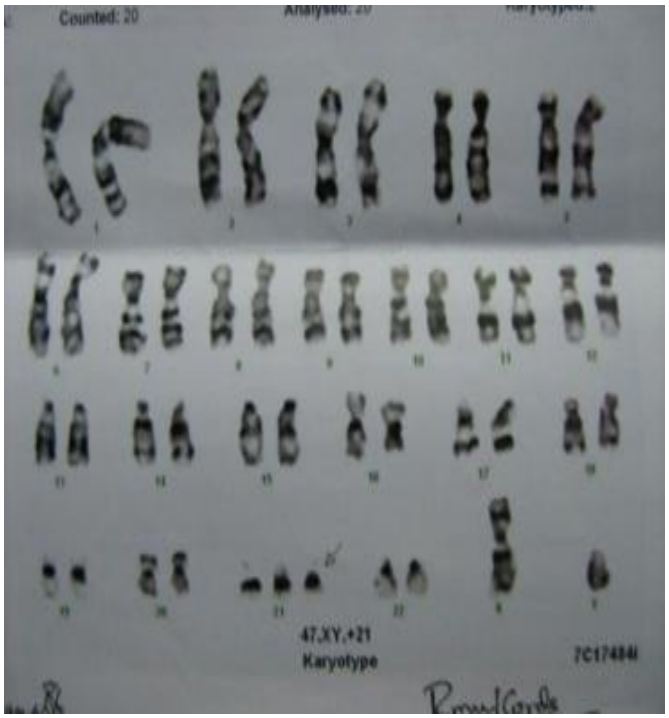

Figure 3. Chromosomal study showing trisomy 21(47XX+21).

cases; the translocated chromosome is inherited from one of the parents, usually from the mother. The fertilized egg has two copies of chromosome 21 and the extra translocated material acts as a triple gene dosage. Approximately 10% of newborn with trisomy 21 (DS) develops TL also known as TMD or transient abnormal myelopoiesis (TAM) (Zipursky et al., 1999). TMD blasts are believed to be of fetal derivation and normally reside in organs of fetal hematopoiesis such as liver (Suda et al., 1987). Due to this reason higher percentage of TMD blasts are seen in the peripheral blood in comparison to the bone marrow. That explains presence of 28% blast cell in BM and disproportionately higher number of blasts (65%) in peripheral blood in our patient. DS patients have 10 to 20 fold increased risk of developing acute leukemia, particularly acute megakaryoblastic leukemia (AMKL) (Hitzler et al., 2003). AMKL a subtype of acute myeloid leukemia (FAB classification M7) which occurs with an incidence estimated to be 500 fold greater in DS children than in the general pediatric population. Both in TMD and AMKL, blasts have been accumulated in blood and BM with abnormal megakaryocytic differentiation. The blasts in TMD are almost always megakaryoblasts and are virtually indistinguishable to the blasts of AMKL. Typically, the blasts are medium to large sized with round to occasional binucleation, fine to slightly condensed chromatin, numerous cytoplasmic blebbing, scant to moderate basophilic cytoplasm, and occasional fine azurophilic granules consistent with platelet granules (Zipursky et al., 1999). TMD may be presented with only circulating blasts without clinical symptoms (Massey et al., 2006). In contrast to AMKL, TMD undergoes spontaneous remission, which occurs within 2 to 194 days with a mean of 58 days (Massey et al., 2006). TMD is associated with neonatal death secondary to liver failure, heart failure, sepsis, hemorrhage, hyperviscosity and disseminated intravascular coagulation in 11 to 52%. Death correlates with leukocytosis (100,000/μl), increasing organomegaly, worsening liver function and visceral effusions. After resolution of TMD, approximately 13 to 29% may develop AMKL after 6 months of age with a mean age of 20 months (Massey et al., 2006).

AMKL occurs more frequently in TMDs that initially had additional cytogenetic abnormality beyond trisomy 21 (Massey et al., 2006). Other TMD findings such as complete blood count, percentage of blasts, liver enzyme activities, age and sex are not predictive of eventual development of AMKL (Massey et al., 2006). It is difficult to differentiate between TMD and acute leukemia in patients of DS at presentation. The treatment of neonates with DS who developed TMD remains controversial. Mostly, conservative management is preferred, without chemotherapy. Sometime, if patient is suffering with progressive organomegaly or liver dysfunction, low-dose chemotherapy with cytosine arabinoside (cytarabine) is administered (Massey et al., 2006). However, AML in DS is treated according to the AML-Berlin-Frankfurt-Muenster protocol for children with DS, which includes a dose-reduced treatment schedule compared with the schedule for patients without DS. In comparison with non-

DS children with AML, children with DS and AML have a better clinical outcome with this therapy. The blast cells in children with DS are extremely sensitive to cytosine arabinoside, may be due to decreased expression of a cytarabine-catabolizing enzyme, or increased expression of certain genes found on chromosome 21. Our patient's hematological parameters had been improved and 3 weeks after admission, his peripheral blood picture detected absence of blast cells. Likely he was suffering from TMD. However, such patients are at high risk of developing AMKL and hence needs regular follow up. Up to 25% patients may develop myeloid leukemia over a period of 3 years (Awasthi et al., 2005). The pathogenesis of TMD is not fully understood, proposed hypothesis is that the DS and mutations in transcription factor GATA1 predispose neonates to TMD. Somatic mutations of the gene encoding the hematopoietic transcription factor GATA1 were found in AMKL blasts of patients with DS, suggesting a significant role for these mutations in the development of leukemia and TMD. GATA1 has essential functions during the normal erythroid and megakaryocytic differentiation of hematopoietic stem cells. Lack of GATA1 function in hematopoietic cells has been shown to result in the accumulation of abnormally differentiated megakaryocytes and thrombocytopenia with or without leukemic transformation (Hitzler et al., 2003).

The clinical presentation is variable. Features such as congenital heart disease and gastrointestinal anomalies are secondary to DS and unrelated to TMD. However, hepatosplenomegaly and effusions are secondary to TMD and unrelated to DS in the absence of TMD. Although uncommon, TMD can causes severe diffuse lobular hepatic fibrosis with high mortality rate (Miyauchi et al., 1992). Our patient had recovered from TMD but ultimately died due to hepatic failure. As like our patient, fatal hepatic dysfunction is reported in literature (Matthias et al., 1998; Hattori et al., 2001; Miyauchi et al., 1992. That suggests a close association between hepatic lesions and TMD. The triad of DS, TMD and HF is extremely rare but known entity (Miyauchi et al., 1992). The hepatic fibrosis is characterized by diffuse intralobular sinusoidal fibrosis and extramedullary hematopiosis, in which megakaryocytes are prominent (Miyauchi et al., 1992). It is considered that PDGF in combination with TGF- **β**1 is responsible for organ fibrosis in TMD (Ogawa and Hirokazu, 2008) not only liver but other organ fibrosis are also documented in TMD. Severe fibrosis in the lung, kidney and pancreas are documented. Immuno histochemical analysis revealed high expression of PDGF receptor in the severe fibrotic areas of the fibrotic tissues.

A real-time polymerase chain reaction (PCR) analysis demonstrated the expression of PDGF in the peripheral blood samples of the patient which indicates that the PDGF pathway has an important role in the fibrosis of several organs in patients with TMD.

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