CONGENITAL LEUKEMIA IN A NEWBORN WITH DOWN SYNDROME; A CASE REPORT WITH REVIEW OF LITERATURE

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ABSTRACT

Congenital leukemia is a very rare disorder accounting for less than 1% of all childhood leukemias. Transient Myeloproliferative Disorder (TMD) occurs in 4 to 10% of infants with Down Syndrome (DS) characterized by numerous circulating blast cells and spontaneous resolution within a few weeks. We present a 3day old male baby with DS presenting with clinical features of shock and high percentage of blast cells in peripheral smear. This case is presented to highlight the clinical and laboratory diagnostic dilemma.

Keywords: Down Syndrome (DS), Transient Myeloproliferative Disorder (TMD), Transient Abnormal Myelopoiesis (TAM), congenital leukemia (CL)

INTRODUCTION

Congenital leukemia is an exceedingly uncommon disease in the newborn. Congenital leukemia occurs at the rate of 1 per 5 million births. Down syndrome (DS) is a common genetic disorder characterized by a numerical chromosomal abnormality 47, XX or XY, +21 with an incidence of 1 in 700 live births. On hematology DS children show macrocytosis, abnormalities in platelet count and an increased prevalence of leukemia. Infants with DS infrequently develop a condition known as Transient Myeloproliferative Disorder (TMD) also known as Transient abnormal Myelopoiesis (TAM). It is characterized by non-specific symptoms requiring a high index of suspicion for further investigations and diagnosis. We report here a rare case of congenital acute myeloblastic leukemia / TMD with Down syndrome in a 3 day old male baby.

CASE REPORT

A 3 day-old male baby was admitted with the complaints of loose stools 5-6 times/day, refusal of feeds, and decreased activity since 2 days. The parents had noticed that the child developed abdominal distension and shortness of breath a day prior to admission. The antenatal, birth and immediate postnatal history were uneventful. There was no history of maternal fever with rash & lymphadenopathy during the first trimester of pregnancy (to rule out TORCH infections). He was delivered by full term normal vaginal route, cried immediately after birth. Birth weight was 3kg and he had been breastfed since birth. At admission, the child was sick, pale looking, tachypnoeic, poor cry and suck activity with signs of severe dehydration. There was some evidence of facial dysmorphism in the form of round head, depressed nasal bridge, hypertelorism, lowset ears, high arched palate, generalised hypotonia. There was no evidence of cataract, lymphadenopathy or skin lesions. He was in severe respiratory distress with subcostal, intercostal recession and grunting. Auscultation of chest revealed bilateral rales. The abdomen was distended with a hepatomegaly of 7 cms below costal margin, firm, nontender and splenomegaly of 2 cms. External genitalia were normal. He had feeble peripheral pulses with prolonged capillary refill time. Heart sounds were normal. He was drowsy and no focal

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neurological deficits. Fundoscopy was normal with no evidence of chorioretinitis.

The blood count at 3rd day of life showed leukocytosis (1, 09000/mm3) with haemoglobin of 18.3gm%. The peripheral blood smear showed marked leukocytosis with 80% of blastcells, 4%metamyelocytes, 6% bandforms, 6% neutophils & 4% lymphocytes.Blast cells showed enlarged nucleus with open chromatin and 2 to 4 nucleoli (fig-1). On cytochemistry blast cell showed myelo peroxidase positivity. Erythrocytes show macrocytosis and nucleated RBC 12/100 WBCS. Platelet count is 2.62 lakhs/mm3. Serum creatinine level was 0.95 mg/dL; blood urea was 51mg/dl. Serum electrolytes revealed hyponatremia (sodium: 121.6 meq/l) and hyperkalemia (potassium: 5.87mg/dl). Serum calcium was 9mg/dl.CRP was 48 mg/l and an arterial blood gas analysis was suggestive of severe metabolic acidosis. Chest x-ray revealed infiltrates bilaterally, more in the right upper zone. HbsAg and HIV-1 & HIV-2 by were negative by ELISA. No growth on first subculture. Chromosomal analysis suggested Down syndrome (karyotype: 47, XY, +21). Management was initiated as for fulminant sepsis with shock. Supportive therapy also included correction of electrolytes and metabolic acidosis. Subsequent to admission, he was successfully resuscitated thrice from cardiac arrest. Despite aggressive intensive care support he continued to deteriorate and died on fourth day of admission. After much persuasion and time, parents agreed for a limited postmortem investigation, inclusive of liver and lung biopsy only. Parents refused special investigations for diagnosis of inborn errors of metabolism and a bone marrow study. On microscopy lung showed congestion and liver showed infiltration by leukemic cells

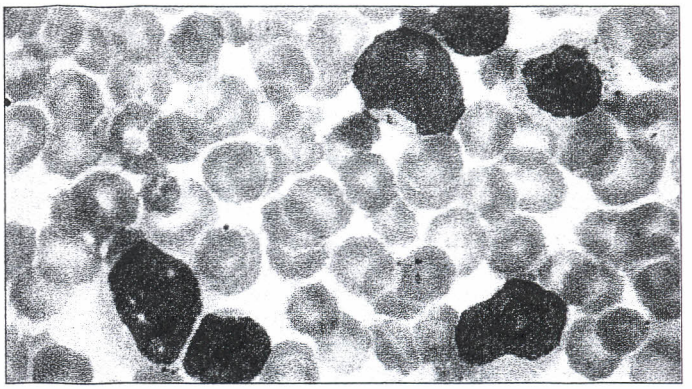

Fig 1. Peripheral blood smears showing blast cells with 2-3 prominent nucleoli and scanty cytoplasm. (X 1000, Leishman stain)

DISCUSSION

Congenital leukemia is a very rare disorder. It accounts for less than 1% of all childhood leukemias[1]. The majority are Non-Lymphocytic type (80%), while acute lymphoblastic leukemia (ALL) comprises only < 20%. Congenital leukemia is occasionally associated with number of congenital anomalies and with chromosomal disorders such as Down syndrome, Edward and Patau syndrome and a number of nonspecific chromosomal abnormalities. The clinical signs of leukemia may be evident at birth with leukemia cutis[2]. Clinically, it is important to differentiate congenital leukemia from other leukoerythroblastic conditions, which are seen in response to bacterial infection, hypoxemia and severe hemolysis in the neonate[3]. Other differential diagnosis includes congenital syphilis, intrauterine viral disease, neuroblastoma and the transient myeloproliferation syndrome associated with Down syndrome[4,5,6].

TMD is more commonly associated with DS. It has been estimated that between 4 to 10% of infants with DS are born with TMD which is characteristically manifest in the first few days of life with numerous circulating blast cells and spontaneous resolution within a few weeks[7,8].

Despite the high rate of spontaneous regression, TMD can be preleukemic disorder in 20-30% of children in DS. Incidence of ALL in DS is approximately 20 fold higher than in general population, while incidence of acute megakaryoblastic leukemia is 500 fold higher. Mutation of the gene encoding for haemopoeitic transcription factor GATA1, which is localized on X chromosome is commonly associated with TMD in DS new borns. TMD neonates may be asymptomatic other than elevated blood count and hepatomegaly. Less commonly infants may present with jaundice, bleeding disorder,ascities,pleural effusion, signs of heart failure and skin infection. The course of congenital leukemia is one of rapid deterioration and death from hemorrhage and infection. Specifically, it is a more aggressive disease with increased incidence of leukocytosis, massive hepatosplenomegaly, CNS involvement, thrombocytopenia, hypo-gammaglobenimia, disseminated intravascular coagulopathy (DIC) and less frequent remission induction by 14 days[9]. In Massey et al study 8 out of 47(17%) child died at a mean age of 90 days[10]. Unfortunately our patient died on 7th day of life and molecular genetics for GATA1 mutation was not done. Therefore possibility of TMD associated with DS couldn't be ruled out in our case.

Diagnosis of congenital leukemia and TMD requires high degree of clinical suspicion and hematological investigations for better prognosis.

REFERENCES

1. Bader JL, Miller RW.US cancer incidence and mortality in the first year of life. Am J Dis Child. 1979 Feb; 133(2):157-9.
2. Campwell W A, Macafee AL, Wade WG: Familial neonatal leukemia. Arch Dis Child 1962; 37: 93-98.
3. Nathan O: Congenital leukemia. In: Haematology of Infancy and Childhood. 3rd ed. Philadelphia: WB Saunders; 1987; 1052-1053.
4. Conen P E, Erkman B: Combined mongolism and leukemia.Report of eight caseswith chromosomal studies. Am J Dis Child 1966; 112(5):429-443.
5. Al Mulhim I: Down's syndrome with transient myeloproliferative syndrome. Ind J Paediatr 1990; 57:253-255.
6. Malinge S, Izraeli S, Crispino JD. Insights into the manifestations, outcomes, and mechanisms of leukemogenesis in Down syndrome. Blood. 2009 Mar 19; 113(12):2619-28. Epub 2009 Jan 12.
7. Pine SR, Guo Q, Yin C et al. Incidence & clinical manifestation of GATA1 mutation in newborns with Down syndrome. Blood.2007; 110:2138-2131.
8. Zwaan MC, Reinhardt D, Hitzler J, Vyas P.Acute leukemias in children with Down syndrome. Pediatr Clin North Am. 2008 Feb; 55(1):53-70.
9. Heerema N A, Arthur D C, Sather H et al: Cytogenetic features of infants less than 12 months of age at diagnosis of acute lympho-blastic leukemia. Impact of the 11q 23 break-point on outcome. A report of children cancer group. Blood 1994; 83: 2274-2281.
10. Massey GV, Zipursky A, Chang MN, et al. A prospective study of the natural history of transient leukemia in neonates with Down syndrome: a children's oncology group (COG) study POG- 9481. Blood 2006; 107:4606-13.