Congenital Acute Lymphoblastic Leukemia: A Rare Presentation in a One Month Old Boy

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Abstract

A one month old boy of non-consanguineous parents was admitted with gradual distension of abdomen, yellow coloration of whole body, progressive pallor and respiratory distress since birth. Septic investigations were done and found negative. His complete blood count with peripheral blood film examination revealed hyperleukocytosis, thrombocytopenia and presence of significant number of blasts cell. Cerebrospinal fluid (CSF) examination showed central nervous system (CNS) status 3 (>5 WBC/cm³ with blasts). Other causes of leukemoid reaction were ruled out. Karyotyping had done and found normal chromosomal pattern (46XY). Bone marrow aspiration findings were suggestive of ALL-L, His myeloperoxidase (MPO) and Sudan black stain was negative but periodic acid schiff (PAS) stain was positive. Immunophenotype showed blasts cells which were positive for CD5(1.10%), CD8(0.4%), CD10(0.74%), CD13(13.7%) and CD19(62.4%). Finally, the boy was diagnosed as congenital acute lymphoblastic leukemia (ALL-L, B-lineage, CNS status 3). Following chemotherapy, the child suddenly deteriorated and on the second day of therapy suddenly he expired possibly due to leukostasis or coagulopathy or non-responsive of drugs or MLL gene translocation. So, congenital acute lymphoblastic leukemia (CALL) should be kept in mind in a newborn child with clinical features of sepsis, leukocytosis, thrombocytopenia, huge hepatosplenomegaly.

Keywords: Congenital acute lymphoblastic leukemia; Cerebrospinal fluid; Central nervous system; Myeloperoxidase; Periodic acid Schiff; Cluster of differentiation

Abbreviations: CALL: Congenital Acute Lymphoblastic Leukemia; CSF: Cerebrospinal Fluid; CNS: Central Nervous System; MPO: Myeloperoxidase; PAS: Periodic Acid Schiff; CD: Cluster of Differentiation

Introduction

CALL is an exceedingly uncommon disease in the newborn baby and it is usually diagnosed at birth or within one month of life [1]. It is a rare entity with reported incidence between 4.3 to 8.6 per million live births [2]. The criteria for diagnosis of CALL are: a) disease presentation at or shortly after birth (<30 days), b) proliferation of immature white cell, c) infiltration of cells into extrahemopoietic tissues and d) absence of any other condition that mimics congenital leukemia [3].

The etiological considerations in CALL have included chromosomal defects, intrauterine environmental insults, viral infections and exposure to radiation during pregnancy. CALL has also been reported in association with Down’s syndrome, Turner’s syndrome, Klippel-Feil syndrome and Ellis-van Creveld syndrome [4]. The congenital abnormalities (CAs) and chromosomal syndromes have frequently been associated with childhood cancers and leukemia in particular. Most notably, Down’s syndrome is firmly established as a risk factor for leukemia [5].

Infantile acute lymphoblastic leukemia (ALL) is uncommon, occurring in approximately 2-4% of cases of childhood ALL. ALL in infants appears to be biologically distinctive from the disease in older children. Infants are much more likely to present with high leukocytes counts, hepatosplenomegaly and overt CNS disease [6,7]. T-cell phenotypes are much less common in infants, while myeloid antigen co-expression and the absence of CD10 expression are more frequent in infants than in older children [7].

In large scale clinical trials in childhood ALL have resulted in the recognition of certain clinical features at the time of diagnosis that appears to have profound prognostic significance [8,9]. One such feature is age at the time of diagnosis. It is well established that an age peak exists with respect to the frequency of childhood ALL [10,11] and that children with ALL between the age of 2 and 10 years have a significantly better prognosis when compared with children outside this age range [12]. Previous reports suggested that infants with ALL have a decidedly worse prognosis when compared with older children [13-16].

Leukemia in infants has unique epidemiological, biological and clinical characteristics. The majority of cases of ALL in infant is characterized by high white blood cell count, bulky extramedullary disease, a propensity to express lymphoid markers and molecular translocation of MLL (ALL-L1, HRX, Htrx-1) gene at chromosomes band 11q23 [17-20]. The MLL gene translocations are associated with poor outcome, especially in ALL [21,22]. MLL gene translocations are believed to be leukemogenic by the mechanism of gene fusion rather than by gene activation [23].

At initial diagnosis, ALL in infant is characterized by a median white cell count of >50x10⁹/L, frequent hepatosplenomegaly and involvement of CNS. 14 to 41% of infants have CNS disease at diagnosis, compared with approximately 5% of children [24]. T-cell ALL is exceptional in infants compared with that in children, where T-cell ALL accounts for up to 20% of ALL [25].

ALL in infancy is clinically aggressive in character and spontaneous remission is usually uncommon. There is a single case report of
spontaneous remission after marrow relapses in one twin of a pair of monozygous twins both with congenital ALL associated with (4:11) but the spontaneous remission was followed by a second relapse five months later [26]. High white blood cell count, younger age, bulky extramedullary disease, CNS disease at diagnosis and MLL gene translocations has significant unfavorable characteristics [27].

Till now, to the best of my knowledge and following extensive literature search we found no such rare publication of congenital acute lymphoblastic leukemia in a one month old boy in Bangladesh. So, to highlight this issue, the study is carried out to disseminate our findings.

Case Report

A one month old boy weighing 4 kg from Dhaka, Bangladesh was admitted in the Department of Pediatric Hematology and Oncology, BSMMU, Shahbag, Dhaka, Bangladesh on the 28th April, 2013 with the complaints of gradual distension of abdomen since birth, yellow coloration of the whole body for last 25 days, progressive pallor for 15 days and respiratory distress for last 8 days. Prior to admission at BSMMU, he was admitted at a private hospital in Dhaka city where the following investigations and management were given without any significant improvement, rather deteriorating his clinical status.


After admission in Pediatric Hematology and Oncology Department, the child was ill looking, weighing 4 kg, lethargic, pale, anicteric, dyspnoeic (RR 80/min), febrile (Tem101°F) and tachycardia (HR 150/min). There was no evidence of microcephaly, cataract, facial dysmorphism, lymphadenopathy or purpuric spot. His anterior fontanelle was normal. There was severe respiratory distress with sub costal and intercostals recession. On auscultation, bilateral course crepitation found on both lung fields. The abdomen was hugely distended and liver was palpable about 6 cm from the right costal margin along the mid-clavicular line, margin was sharp, firm in consistency, surface was smooth, non-tender and not fixed to the underlying structures. Spleen was also palpable about 5 cm from the left costal margin along its long axis, surface was smooth, non-tender, free from underlying structures. Heart sounds were audible in all four areas. External genitalia were normal. The child had feeble peripheral pulse with prolonged capillary refill time (3 seconds). Other systems revealed no abnormalities. His hemoglobin level was 9.6gm/dl, total WBC count 437×10⁹/L, neutrophil 05%, lymphocyte 05% and lymphoblasts 90% (Figure 1). Platelet count was 22×10⁹/L. Peripheral blood film reported as normocytic hypochromic red cells with marked leukocytosis and marked shift to the left. Serum creatinine was 0.87 mg/dl and SGPT 29 U/L, serum electrolyte report revealed features of tumor lysis syndrome (Serum Na+: 120 mEq/L and serum potassium 6.5 mmol/L), TCO₂18.5 and oxygen saturation was 90%. The radiograph of chest showed bilateral extensive patchy opacities in both lung fields resembles to leukemic cell infiltration.

Bone marrow aspiration materials showed hypercellular marrow with increased M: E ratio, erythropoiesis and granulopoiesis were depressed and megakaryocytes were scanty. Bone marrow was infiltrated more than 90% lymphoblasts (Figure 2).

Cytochemistry of the aspirated marrow material showed MPO and Sudan black as negative but periodic PAS stain was positive. CSF study was positive for blasts cells, CNS status 3 (≥5WBC/cmm² with blasts) (Figure 3). Immuno phenotype showed blasts cell which was positive for CD5 (1.10%), CD8 (0.4%), CD10 (0.74%), CD13 (13.7%), CD19 (62.4%), CD33 (0.0%). Karyotyping showed normal chromosomal pattern, 46XY.

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Reviewing all the findings and investigations, the boy was finally diagnosed as congenital acute lymphoblastic leukemia (ALL-L₁, B-lineage, CNS status 3).

The parents were counseled about the nature, consequence of treatment and prognosis of the disease. Following proper hydration (3 litre/m²/day) with intravenous fluid and alkalinization with sodium
includes congenital syphilis, intrauterine viral disease, neuroblastoma infection, hypoxemia and severe hemolysis in the neonate [34]. In leukoerythroblastic condition, which is seen in response to bacterial infection, bi-carbonate, protocol based (Infantile protocol) induction of remission was started with inj. Vincristine1.5 mg/m² iv on day one as flush method, Triple intrathecal (TIT):Inj. Methotrexate (MTX) 7.5 mg. Inj. Hydrocortisone 25 mg, Inj. Cytarabine 30 mg on day one, Inj. Donorubicine 45 mg/m² on the same day. Suddenly his physical condition deteriorated following the day of chemotherapy and expired on the second day of therapy.

**Discussion**

CALL is a term applied to leukemia diagnosed at birth or within the first month of life [1]. CALL is a very rare disorder [28]. The majority of non lymphocytic type found (80%), while ALL comprises only less than 20%. Familial neonatal leukemia is extremely rare and no child born to a mother with leukemia has been found to have the disease during the neonatal period [29]. Clinical signs of leukemia may be evident at birth with hepatosplenomegaly, petechiae and ecchymosis. Twenty five to thirty percent of infants with CALL have specific cutaneous infiltration (leukemia cutis) [30], which usually appear as firm blue or red nodules (‘Blueberry Muffin’) [31,32]. No leukemia cutis was found in my case. In a study of 6 cases of CALL, all of which were acute myeloid leukemia (AML), autopsy showed leukemic cell infiltrations in the lungs and other organs [33].

Clinically, it is important to differentiate CALL from other leukoerythoblastic condition, which is seen in response to bacterial infection, hypoxemia and severe hemolysis in the neonate [34]. In this index case, there was no such feature. Other differential diagnosis includes congenital syphilis, intrauterine viral disease, neuroblastoma and transient myeloproliferative disorders associated with Down’s syndrome [35-37], but in this study, Rubella virus Ab: IgG and Cytomegalovirus Ab: IgG were positive.

Cellular morphology, immunophenotype and chromosomal study differentiate CALL from acute non-lymphoblastic leukemia (ANLL) in newborn [30]. Franch-American-British (FAB) classification based on the cellular morphology reveals that the most common subtype in infantile and neonatal ANLL is the monocytic variety [38], which was not consistent with my observations, where it was found morphologically (FAB) and immuno phenotypically ALL-L1, B-lineage with CNS status 3.

The prognosis of CALL is poor; with only 23% surviving at 24 month [39], but this index case expired on the second day of chemotherapy which was not consistent with their observation.

The course of CALL is one of rapid deterioration and death from hemorrhage and infection. Specifically, it is more aggressive disease with increased incidence of leukostasis, massive hepatosplenomegaly, CNS involvement, thrombocytopenia, hypogammaglobulinemia; disseminated intravascular coagulation (DIC) and less frequent remission of induction by 14 days [22]. These findings are consistent with their observations.

The current improved success of induction of remission with treatment of ANLL in infant younger than 1 year is similar to that in older children using combination chemotherapy. However, the experience with newborns is limited, but between 1984 to1989, 5 of 12 newborns with ANLL sustained complete remission with chemotherapy and all were in the myelomonocytic or monocytic variety [40]. In ALL, the treatment outcome is significantly poorer in infants younger than 1 year at diagnosis (23%) disease free survival as compared to 70% for older children and may be even lower in newborn. Only 10 to 20% survival for infants younger than 6 months of age at diagnosis has been reported as compared to 40% those who were more than 6 months of age [22]. My index case expired on the second day of chemotherapy possibly because of leukostasis, coagulopathy or DIC. Two year event free survival and survival of CALL patients treated on the Interfant-99 protocol was 20% [41] but in comparison the outcome of our index case is very much poor because of limited number of case and the baby expired on the day second of chemotherapy.

**Conclusion**

CALL in children may mimic several neonatal conditions when patients are first seen by a neonatologist or any other pediatrician. CALL should be kept in mind in a newborn with clinical features of sepsis, leukocytosis, thrombocytopenia, huge hepatosplenomegaly. Infant with CALL are at high risk of treatment failure.

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**References**

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