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Case Report Open Access

Congenital Acute Leukemia: A Rare Hematological Malignancy

Vishal Vishnu Tewari[1*], Ritu Mehta[2] and Kunal Tewari[3]

[1]*Department of Pediatrics, Army Hospital (Referral and Research), New Delhi, India*

[2]*Department of Pathology, All India Institute of Medical Sciences, New Delhi, India*

[3]*Department of Anaesthesia, Base Hospital, New Delhi, India*

[*]**Corresponding author:** Vishal Vishnu Tewari, Department of Pediatrics, Army Hospital (Referral and Research), New Delhi, India, Tel: +91-8826118889; E-mail: docvvt_13@hotmail.com

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Abstract

Background: Acute leukemia presenting in the neonate and the young infant is a rare hematological malignancy. It may present at birth or within few days (congenital) or it may be diagnosed in first 4-6 weeks of life (neonatal) and may be myeloid or lymphoid in origin. High index of suspicion along with bone marrow studies, cytochemistry and immunophenotyping is the mainstay of diagnosis.

Case presentation: We report two cases of congenital acute leukemia presenting in second month of life. The first case, a female infant presented with fever, inconsolable crying, loose stools and vomiting of two weeks duration with pallor and hepatosplenomegaly. Lab investigations revealed anemia, leucocytosis and thrombocytopenia with 80% blasts seen on peripheral blood smear. The bone marrow aspirate was hypercellular with greater than 3% of the blasts positive for myeloperoxidase. Based on morphology and immunophenotyping by flow cytometry a diagnosis of acute myeloid leukemia M2 was made. The infant was managed with BFM intermediate risk induction protocol. Maintenance therapy was given for 18 months. The infant is in complete clinical and hematological remission. The second infant presented with fever, lethargy, poor feeding and palpable organomegaly. She had similar findings of leucocytosis with 90% blasts on peripheral smear which were negative for myeloperoxidase. She was diagnosed as a calla-positive B cell acute lymphoblastic leukemia. She was managed as per the Interfant collaborative group protocol but succumbed to her illness.

Conclusion: Congenital leukemia is characterized by a rapidly progressive nature of illness, greater achievement of remission in acute myeloid leukemia as compared to acute lymphoblastic leukemia, higher relapse rate, poor prognosis and difficulty in instituting combination chemotherapy. We report two infants diagnosed with congenital acute myeloid leukemia M2 and calla-positive B cell acute lymphoblastic leukemia based on cytochemistry and immunophenotyping. Resistance of leukemic cells in congenital acute lymphoblastic leukemia to chemotherapeutic drugs entails using a hybrid chemotherapeutic regimen.

Keywords: Congenital acute leukemia; Congenital lymphoblastic leukemia; Congenital myeloid leukemia

Abbreviations ALL: Acute Lymphoblastic Leukemia; AML: Acute Myelocytic Leukemia; BFM: Berlin Frankfurt Munster; CL: Congenital Leukemia; IPT: Immunophenotyping; LDH: Lactate Dehydrogenase; MLL: Mixed Lineage Leukemia; MPO: Myeloperoxidase; PAS: Periodic acid Schiff, PBS: Peripheral Blood Smear; TAM: Transient Abnormal Myelopoiesis; TLC: Total Leucocyte Count; Tdt: Terminal deoxynucleotidyl transferase

Introduction

Congenital leukemia (CL) is an extremely uncommon malignancy, occurring at a rate of 1 per 5 million births and represents less than 1% of all childhood leukemia [1]. It is diagnosed on the basis of presence of leukemic blasts in the bone marrow and/or extra haematopoietic tissue. The term congenital leukemia was originally applied to cases of leukemia that developed at birth, while neonatal and infantile leukemia were used to describe leukemia developing within the first 4 weeks of life or from 4 weeks to 1 year of life respectively. However CL is usually diagnosed at birth or within the first month of life as making the distinction between congenital and neonatal leukemia may be difficult [2]. Newborns usually present with elevated white blood cell counts accompanied with immature cells/ blasts in the peripheral blood. It has to be differentiated from various in-utero infections (TORCH infections), sepsis, hemolytic disease of newborn and other neoplasms like neuroblastoma. Acute myeloid leukemia (AML) is more prevalent in neonates in contrast to predominance of acute lymphoblastic leukemia (ALL) in older children. Acute lymphoblastic leukemia and mixed phenotypic leukemia though common in childhood are very rare in early life. Various cytogenetic abnormalities have been detected in cases of CL. Congenital leukemia's are a diagnostic dilemma and high index of suspicion on part of clinician is required whenever an infant presents with features of sepsis and leucocytosis. Combination chemotherapy can achieve remission induction rates in congenital AML similar to those in older infants and children. In congenital ALL, induction failure rates are not significantly different from older infants [3,4]. Herein we report two cases of congenital acute leukemia who presented to our tertiary care hospital.

Case Presentation

Case 1

A two month old female infant, second product of non-consanguineous marriage, was admitted to our hospital with complaints of loose stools, vomiting and excessive crying of 15 days duration. She was a full term normal delivery with birth weight of 3 kg. Antenatal and postnatal period was uneventful. There was no history of in-utero radiation exposure. One week prior to admission the infant was treated in pediatric outpatient department of a local hospital with fluids, oral antibiotics and supportive care, without any significant improvement. At our hospital, general physical examination at time of admission revealed that the baby was pale, lethargic and weighed 5.2 kg. There were no dysmorphic features, microcephaly, cataract or jaundice. Her temperature recorded was 99.4°F. She was tachypneic with a respiratory rate of 58 per min and also had tachycardia with heart rate of 168 per min. On systemic examination the infant had hepatosplenomegaly without significant lymphadenopathy. There were no skin lesions identified. Other systems were normal. Investigations done showed Hb 7.2 g/dl, total leucocyte count (TLC) 1,55,000 per cu mm and platelet count as 45,000 per cu mm. Peripheral blood smear (PBS) examination showed a differential leucocyte count of polymorphs 05%, lymphocytes 10% and blasts 85%. Bone marrow aspirate done was hypercellular showing replacement of normal hematopoietic elements by atypical cells accounting to approximately 80% (Figures 1a and 1b). Erythroid precursors and megakaryocytes were suppressed. PBS and aspirate showed blasts accounting to 80% of nucleated cells. The blasts were large, had high N:C ratio, dispersed chromatin with 1-2 nucleoli (myeloblasts). Cytochemical staining on both PBS and marrow with myeloperoxidase (MPO) showed >3% blasts to be MPO positive. Lactate dehydrogenase (LDH) was 550 U/L (normal range 200-450U/L) and other biochemical and serological investigations including TORCH titres were within normal limits. Urine analysis was also normal. Ultrasonography abdomen showed enlarged liver and spleen measuring 3 cm and 2 cm from right and left costal margin respectively. Immunophenotyping (IPT) by flow cytometry was done on bone marrow aspirate in EDTA by standard lyse wash procedure and data was analyzed. The abnormal cells were gated on CD 45 side scatter dot plot which comprised of 78% of total leucocyte population. The blasts were bright positive for CD45, CD13, CD33, CD117, HLA-DR, anti-MPO and negative for both B and T cell markers (Figures 2a-2c). Hence based on morphology and IPT a diagnosis of acute myeloid leukemia M2 (AML-M2) was made. Patient was started on Berlin Frankfurt Munster (BFM) intermediate risk induction protocol comprising of cytosine arabinoside (ara-c) 100 mg/m^2/day on day 1 and 2 followed by 30 min infusion every 12 h on days 3 through 8, etoposide (VP-16) 150 mg/m2 as 120 min infusion from days 6 to 8 and idarubicin 12 mg/m^2 30 min infusion daily from day 3 to 5. After achievement of complete remission HAM therapy was given which comprises of high doses of ara-c with mitoxantrone. Consolidation therapy was given for 6 weeks with following drugs: 6-thioguanine, prednisolone, vincristine, daunorubicin, ara-c and cyclophophamide. Maintenance therapy was given for 18 months with 6-thioguanine and ara-c. The infant required two packed red blood cell and five platelet concentrate transfusions during this period. After completion of remission induction there was clinical amelioration of symptoms and her hematological parameters normalized. Repeat bone marrow done showed bone marrow to be in complete remission.

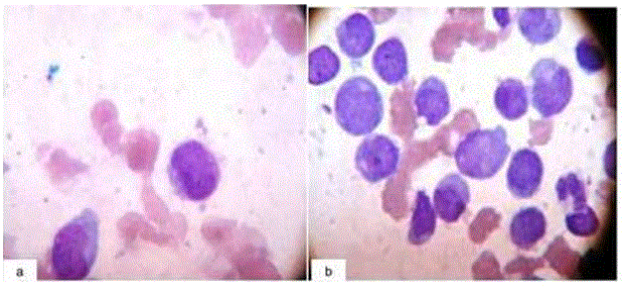

Figure 1: (a and b) Bone marrow aspirate showing diffuse infiltration by myeloblasts (stained with Leishman's and magnified at x40).

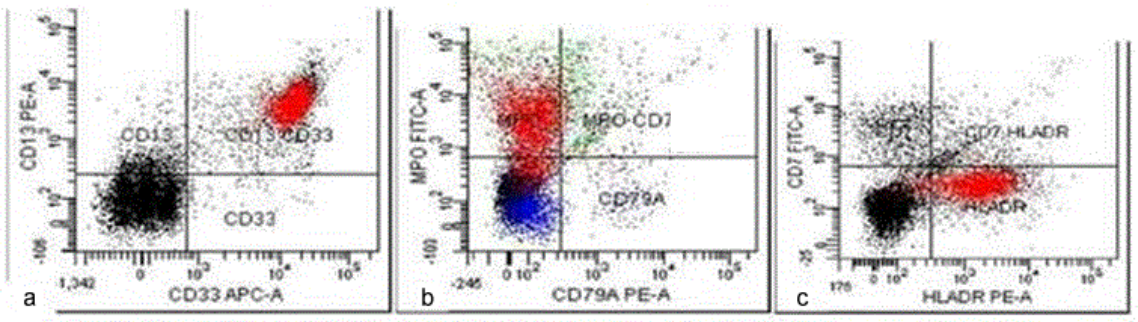

Figure 2: (a-c) Flow cytometery showing myeloblasts positive for: CD 13, 33, MPO and HLA-DR.

Case 2

A two and a half month old female infant, first product of non-consanguineous marriage was admitted in our hospital with short history of fever associated with poor feeding of 6 days duration. Fever was high grade, continuous associated with lethargy and refusal of feeds. She was full term normal delivery with birth weight of 2.7 kg. Antenatal and postnatal period was uneventful. TORCH titres were negative for IgM and IgG. There was no history of in-utero radiation exposure. At the time of admission the infant was febrile and lethargic and weighed 4.8 kg. She had no features suggestive of chromosomal

anomalies. Liver and spleen were palpable. There were no petechiae, skin nodules, rashes or lymphadenopathy. Investigations done revealed Hb of 6.3 g/dl with total leucocyte count of 1,45,000 cu mm and platelet count of 55,000 cu mm. PBS examination revealed normocytic normochromic red cells, leucocytosis with preponderance of blasts which constituted nearly 90% of all white blood cells. The serum LDH was 1203 U/L. Bone marrow aspirate showed replacement of normal hematopoietic elements by blasts constituting 90% of all nucleated cells (Figures 3a and 3b). The blasts were negative for MPO and Periodic acid-Schiff (PAS). Immunophenotyping done by flow cytometry on marrow aspirate revealed blast cells positive for CD 45, CD10, CD79a, HLA-DR, terminal deoxynucleotidyl (Tdt) and negative for myeloid and T cell markers (Figures 4a-4c). The diagnosis of calla-positive B cell ALL was given and the patient was started on Interfant collaborative group protocol which is a hybrid regime combining ALL standard treatment with elements for treatment of AML. The induction phase consisted of standard four drug induction with dexamethasone (10 mg/m^2/day), intravenous (IV) vincristine (1.5 mg/m^2 on day 0, 7 and 14), IV daunorubicin (25 mg/m^2/weeks) and intramuscular (IM) L-asparaginase (6000 U/m2 thrice a week for 9 doses starting on day 3). However despite aggressive management the patient succumbed to her illness within two weeks of starting treatment.

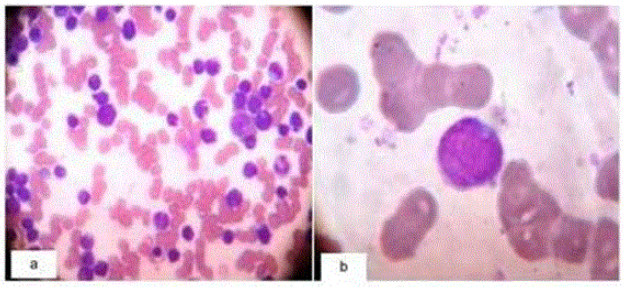

Figure 3: (a and b) Bone marrow aspirate showing diffuse infiltration by lymphoblasts (stained with Leishman's and magnified at x10 and x40, respectively).

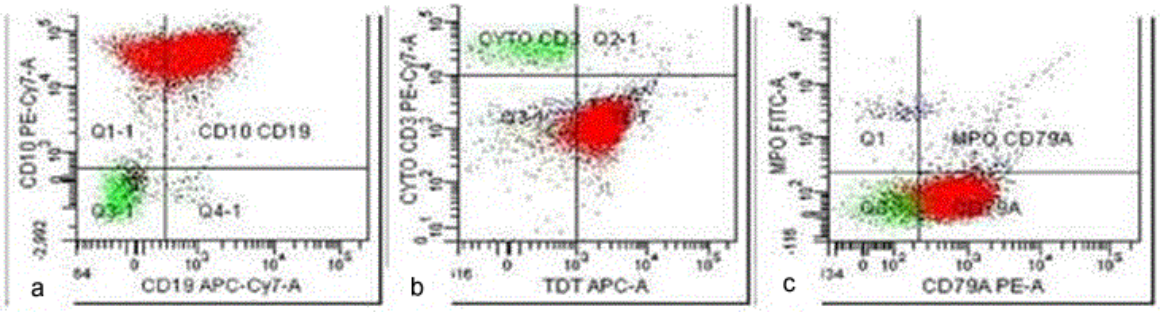

Figure 4: (a-c) Flow cytometery showing lymphoblasts positive for: CD 10,19,Tdt, 79a and negative for MPO.

Discussion

Acute leukemia in the neonate and young infant is categorized as congenital leukemia (present at birth or within few days of life) or neonatal leukemia (diagnosed in first 4-6 weeks of life) [5]. Several etiological risk factors have been associated with acute congenital leukemia which includes maternal exposure to occupational or environmental toxins and radiation. The role of maternal abuse of tobacco, alcohol and illicit drugs is hypothesized but not proven [6,7,8]. Acute leukemia is postulated to start in utero. Maternal infections like rubella, CMV, herpes and toxoplasmosis are known to be associated with CL. Chromosomal anomalies and syndromes associated with CL are Turner syndrome, Klippel Feil syndrome, Ellis-van Crevald syndrome and commonest being the Down syndrome [9]. The diagnostic criteria of CL includes disease presentation at or shortly after birth (less than 4-6 weeks), presence of leukemia blasts in the peripheral blood smear and in bone marrow, infiltration of immature cells into extra hematopoietic tissue and absence of any other condition that mimics congenital leukemia [10]. Congenital leukemias are always a diagnostic challenge as the presentation is highly variable and mimics other diseases like leukemoid reaction, sepsis, haemolytic disease of newborn and transient abnormal myelopoiesis (TAM) [11]. About 20-30% of the newborns present with leukemic skin infiltration (blue berry spots) which can involve any part of the body. Presentation may vary from pallor, lethargy, fever, failure to thrive, poor feeding, anemia, thrombocytopenia, bleeding from mucosal sites and diarrhea. Extramedullary infiltration causing hepatosplenomegaly and central nervous system involvement are also seen. Unlike acute leukemia presentation in older children, lymphadenopathy is less frequent in neonates. In infants who present with leukemia after few weeks of birth symptoms are ill-defined in form of fever, diarrhea, failure to thrive with leukemia cutis seen less commonly in them as compared to the neonate with leukemia at birth where they present with leukemia cutis and respiratory distress [8]. Diagnosis of CL is supported by cellular morphology, cytochemistry, IPT by flow cytometry and chromosomal studies. Both our cases showed leucocytosis with more than 20% blasts on the PBS and bone marrow. Bone marrow aspirate revealed replacement of normal hematopoietic elements by sheets of blasts. Further subtyping and categorization was carried out by flow cytometric analysis. In one of our cases the blasts were bright positive for CD45, CD13, CD33, CD117, HLA-DR, anti-MPO and was diagnosed as AML. Second case showed positivity for CD10, CD19, CD79a, HLA-DR and was diagnosed as calla-positive B cell ALL. Congenital AML is most commonly of AML-M4, AML-M5 of French American British (FAB) classification and typically presents with leukemia cutis and leucocytosis. Central nervous system involvement is seen more commonly in infants with AML as the leptomeninges are more vascular in infants as compared to adults and monoblasts can traverse endothelial cell lining and can enter the central nervous system. Acute lymphoblastic leukemia though common in older

children is rare in neonates with incidence of about 10%. In cases of Down syndrome, TAM is a well-recognized entity which shows spontaneous regression and is also associated with chromosome 21 mosaicism or translocation involving chromosome 21 with an otherwise normal karyotype with no features of Down syndrome [8,11]. Acute leukemia in infants differs significantly from the leukemia in older children. Infants have higher tumor burden with rearrangement in the mixed lineage leukemia (MLL) gene and hence are more resistant to standard chemotherapeutic agents. The mainstay of treatment is administration of combination chemotherapy. Treatment of acute leukemia is divided into induction phase targeting to attain remission and post remission consolidation/intensification. Maintenance therapy is generally not used in AML except in acute promyelocytic leukemia [12]. Infants diagnosed with congenital ALL leukemia are treated with hybrid therapeutic regime i.e. combining ALL standard treatment and AML treatment protocol consisting of multi-agent phases of induction and consolidation chemotherapy followed by maintenance treatment with antimetabolites [13]. Treatment of AML in infants does not differ significantly from older patients. Infants with AML are treated with BFM protocol. Prognosis of CL is very poor and carries a high mortality rate even with recent chemotherapeutic regimes [14]. Large number of chemotherapeutic agents have been used for treatment of CL with limited success. Improvement of outcome for acute leukemia in infants is still urgently needed. Most of these cases are unable to tolerate the effects of induction therapy as was seen in our second case. Remission was confirmed on post induction bone marrow study in the first case and presently the child is in remission and is under regular follow up.

Conclusion

Congenital acute leukemia is a rare disorder with diagnostic and management challenges characterized by rapidly progressive nature of the illness, greater achievement of remission in congenital AML as compared to congenital ALL, higher relapse rate, poor prognosis and difficulty in instituting and poor tolerance to combination chemotherapy by neonates and young infants. We report two infants diagnosed with AML- M2 and calla-positive B cell ALL based on bone marrow morphology, cytochemistry and immunophenotyping by flow cytometry. Because of very few cases being reported, there is lack of understanding about the biological nature of the disease, its progression and hence the definitive treatment. Resistance of the leukemic clone in congenital ALL to standard chemotherapeutic drugs entails using hybrid treatment regimens. Management of congenital AML-M2 with the BFM protocol and congenital ALL with a hybrid treatment protocol such as the Interfant collaborative group protocol along with intensive supportive care provides acceptable survival.

Declaration

Ethics approval

Approval of the Army Hospital (Referral & Research) Institutional Ethics Committee was taken prior to submitting the paper for publication.

Consent

Written informed consent was taken from the parents of both the cases for publication purpose.

Competing interests

The authors declare they have no competing interests

Author's Contribution

VVT and RM have contributed in conception and preparing the draft manuscript of this article. RM carried out the bone marrow studies and the flow cytometric analysis. KT contributed by providing the clinical intensive care and helped prepare the draft manuscript. All authors contributed towards providing intellectual content for this article and have approved the final manuscript. VVT was responsible for overall supervision and is the guarantor of the article.

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