

Infant Leukemia

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An eleven-month-old Bahraini infant girl, born full-term, vaccinated up-to-age, with normal milestone development; she was referred from King Hamad University Hospital (KHUH) with one-month history of high grade on and off fever associated with cough; her CBC showed anemia (7.4g/dl) and thrombocytopenia (30x10⁹/L). On examination, multiple bruises and small cervical lymph nodes were observed. CBC showed blasts (30%). Bone marrow aspiration, flow cytometry and cytogenetic were sent for Mixed Lineage Leukemia (MLL) rearrangement. She was low risk; she received chemotherapy.

This case was reported because of its rarity and up-to-date chemotherapy modalities which is linked to specific cytogenetic abnormality.

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The term “infant leukemia” generally refers to Acute Lymphoblastic Leukemia (ALL) or Acute Myeloid Leukemia (AML) diagnosed in a child before one year of age. The estimated incidence of acute leukemia in infants is 41 cases per million in the United States, which equates to 160 cases of infant leukemia per year, 90 of the cases are ALL and 70 are AML¹.

A high proportion of acute leukemias occurring in infants are characterized cytogenetically by balanced chromosomal translocations involving the MLL gene at chromosome 11q23. MLL rearrangements (MLL-r) occur in 5% of childhood ALL cases, but in 70% to 80% of ALL in infants¹.

The aim of this report is to present a case of a rare infant leukemia in an eleven-month-old Bahraini infant girl, with negative MLL rearrangement.

THE CASE

An eleven-month-old Bahraini infant girl was referred from KHUH with history of high-grade fever, on and off for the one month, cough, anemia and thrombocytopenia. She was treated as bronchopneumonia with antibiotic (Augmentin), after which her condition improved; however, she relapsed two days later. She was sent to Salmaniya Medical Complex (SMC) for further work-up. She was found to have multiple bruises and bilateral palpable small cervical lymph nodes of different sizes, the liver was 3 cm below the costal margin and the spleen 2 cm below costal margin; the rest of examination was normal.

Laboratory evaluation revealed hemoglobin of 7.4g/dl, platelets 35x10⁹/L, lymphocytes 46%, neutrophils 30% and blasts in the peripheral blood film. Bone marrow aspiration showed hypercellular trails, markedly reduced erythropoiesis, megakaryocytopenia and granulopoiesis with infiltration by 80% lymphoblasts, variable in sizes, with high nuclear

cytoplasmic ratio and inconspicuous nucleoli, see figure 1. Cytochemistry showed Negativity for Sudan Black, see figure 2. Morphologically diagnosed as Acute Lymphoblastic Leukemia, FAB classification L2.

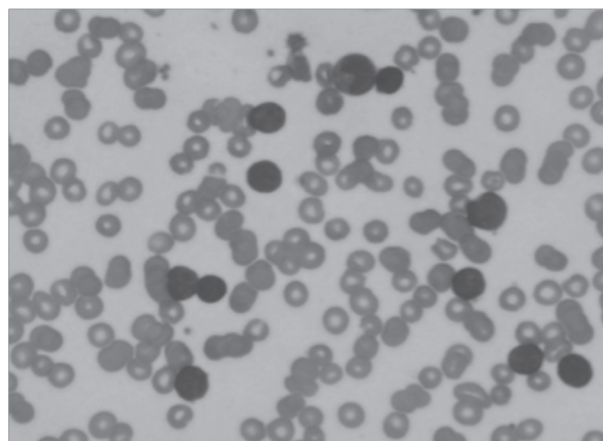


Figure 1: Bone Marrow Aspirate Showing Lymphoblast

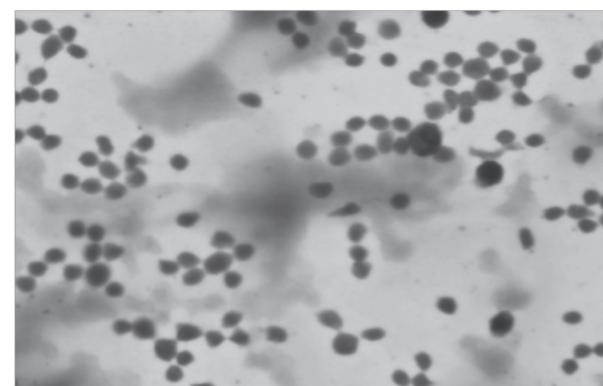


Figure 2: Negative Sudan Black in Lymphoblast

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Cytogenetic sent for chromosome analysis showed Karyotype: 46, xx. Fluorescence in-situ hybridization (FISH) analysis showed 12p rearrangement (deletion of ETV6-locus).

Monoclonal rearrangement pattern of the T cell receptor gene was detected by Polymerase Chain Reaction (PCR).

Immunophenotyping of the bone marrow aspirate showed blasts positive for CD10 (37%), CD 19 (45%), and cytoplasmic 79a (55%). Negative for CD34 and HLA-DR. Negative for myeloid markers (CD13, CD33 and cytoplasmic MPO) and the blasts expressing cytoplasmic CD3 (55 %). Negative for CD4 and CD8. The patient was diagnosed as infant mixed phenotype acute leukemia (MPAL B/T).

The patient was treated with Interfant-06, which includes: induction phase then IB followed by consolidation and maintenance with intrathecal chemotherapy during different phases.

DISCUSSION

At our institution, since the year 2005 up until now, there have been only 6 diagnosed infant leukemia cases, four died; two due to the disease, both were Pre-B ALL; one died with disease and pseudomonas sepsis which is M7 and the fourth died secondary to sever sepsis secondary to bone marrow suppression post induction course, see table 1.

Table 1: Six Cases Diagnosed as Infant Leukemia since 2005 in SMC

Sex	DOB	Age at Diagnosis	Diagnosis	Date of Diagnosis	Current Status
Female	24/3/2004	12.5 M	Pre-B ALL	17/4/2005	Died with disease
	7/2/2005	7 M	Pre-B ALL	27/9/2005	Died with disease
	5/3/2008	5 M	CML	2/8/2008	Alive in remission
	16/4/2009	6 M	AML M7	1/10/2009	Died with disease and sepsis due to Pseudomonas
Male	21/3/2009	9 M	AML M4	2/12/2009	Died secondary to severe sepsis Fungal secondary to severe BM suppression post induction course.
*Female	1/5/2013	11 M	MPAL	30/4/2014	Alive in remission

Total cases at SMC diagnosed since 2005, in addition to the case presented*

Only two cases are alive, a female with Chronic Myeloid Leukemia (CML) case, in addition to the case presented in this report.

Infant leukemia is among the most complicated clinical conditions in pediatric hematology/oncology. Many centers would rarely diagnose it¹.

The challenging aspect of the treatment of infant leukemia is patient's unique vulnerability to complications and toxicities. Many complex physiologic processes that undergo rapid changes during the first year of life, very limited data to differentiate the physiology of infants.

Currently, there are specific clinical trials for infant ALL in which all have the same induction with Interfant-99.4 and with

the same MLL based risk factors. These trails are conducted by three groups: Interfant (Interfant-06), COG (AALL0631) and JPLSG (MLL-10)¹.

Poor outcome was associated with MLL rearrangement (Mixed Lineage Leukemia), CD10 antigen negative, high WBC count and the diagnosis at the age of 6 months, in addition to the poor response to initial prednisolone therapy². The etiology of congenital and infant leukemia is usually overlapping³.

The etiology of infant leukemia is unknown; however, there are factors which predispose to the development of infant ALL, such as maternal smoking and alcohol consumption during pregnancy. Malignant transformation factors in utero have been suggested. Exposure of the mother during pregnancy with even a low radiation dose from Chernobyl is believed to be the cause of infant ALL in contaminated areas⁴.

Moreover, history of fetal loss and high birth weight are linked with risk for infant ALL⁵⁻⁷. High-birth-weight (more than 4000g) in the first year of life has shown to be an important risk factor for the development of infant ALL⁸. It is postulated that maternal consumption of dietary bioflavonoids may potentially lead to MLL translocations in utero and contribute to the development of infant MLL⁹.

CONCLUSION

This case was the sixth reported infant leukemia at our institution; it is presented due to its rarity and an update on therapy modalities of leukemia in infancy.

Optimizing management of leukemia in infancy needs cytogenetic analysis for specific genetic abnormality, which would guide the treatment option.

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