CONGENITAL ACUTE LYMPHOBLASTIC LEUKAEMIA – A MOSAIC TRISOMY CHROMOSOME 22 AND t(5;15) (p15;q15) : A CASE REPORT

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ABSTRACT

Neonatal leukaemia is a rare blood cancer occurring in baby less than 30 days of life is characterized by proliferation of white cells without known and obvious reasons. We report a case of a 7-day-old girl diagnosed with congenital leukaemia. At the time of presentation, she was evaluated as early neonatal sepsis. However, her laboratory investigations were consistent with B cell acute lymphoblastic leukaemia. Her cytogenetic analysis showed 46 XX trisomy 22, t(5,15) (p15,q15) and del 7 (q33,q35). She was managed with standard Interfant 06 protocol and had achieved marrow remission during the course of chemotherapy. Our case highlights the differentiation between lymphocytic leukemoid reaction and lymphoblastic malignant cells and also congenital acute lymphoblastic leukaemia who had a good outcome from the chemotherapy.

Keywords: Congenital Leukaemia, Hematagones, Interfant-06 protocol
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Introduction

Leukaemia among neonates is a rare disease and to make it unusual, congenital leukaemia usually associated with syndromic child or other anomalies. Diagnosis of neonatal leukaemia is made in newborn presenting less than 30 days of life. It is classified into Down syndrome associated neonatal leukaemia and non-Down syndrome neonatal leukaemia (Non-DS Neonatal Leukaemia). Non-DS neonatal leukaemia is a very rare disease and it has to be differentiated with lymphocytic leukemoid reaction which is commonly associated with infection. The estimated incidence of neonatal leukaemia is 41 cases per million in United States and infantile B-Acute Lymphoblastic Leukaemia (ALL) is commoner than Acute Myeloid Leukaemia (AML) or T-ALL [1]. The prognostic significance differs between ALL and AML. In ALL, infants do worse than older children. The 4-year event-free survival (EFS) in Interfant-99, the largest trial of infant ALL to date, was 47% [2]. Sometimes patient usually succumb to death while ongoing initial induction of chemotherapy.

The youngest reported case, excluding cases presenting at birth, was a 19-day-old neonate [3]. Early diagnosis is important to ensure favorable outcome. The main clinical features of neonatal ALL include hepatosplenomegaly (80%), leukaemia cutis (60%), extramedullary infiltration and CNS infiltration which occurs in more than a third of patients. The diagnosis usually require bone marrow (BM) studies, cytochemistry and immunophenotyping as it has to be differentiated from various utero infections like TORCHES, sepsis and haemolytic disease of malformations.

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newborn. Here we report the earliest presentation to date a 7-day-old newborn with congenital acute lymphoblastic leukaemia.

Case presentation

A 7-day-old baby was referred from a local hospital for fever with leukocytosis and thrombocytopenia. She was born full term via spontaneous vaginal delivery with a birth weight of 2.84 kg from a 30-year-old mother with history of erythematous rash of unknown origin during her pregnancy. Her mother was not on any drug and never exposed to radiation. The patient was the product of non-consanguineous marriage and no history of any malignancy in their family. She appeared normal at birth and was discharged on the next day. On examination, patient was a normal looking girl without any apparent anomalies to suggest Down syndrome features. Her lungs were clear and heart sound showed normal rhythm without murmur. No skin lesions were noted. However, noted hepatosplenomegaly with no lymph node palpable. The baby was initially evaluated for early neonatal sepsis. Her blood investigations revealed haemoglobin level was 14.8 g/dL, leukocyte count of 97.78 x 10^9 and her platelet was 43 x 10^9. Her septic work up was all negative and unremarkable. Other biochemical and serological investigations including TORCH titres were within normal limits. Urine analysis was also normal. Peripheral blood film showed the presence of 82 % circulating blast cells with no evidence of gross haemolysis. Bone marrow aspirate smear was markedly haemodiluted however there were predominantly blast cells seen. Her trephine biopsy showed homogenous population of immature cells that were positive for Tdt, cd10 and cd79a. Marrow specimen was sent for immunophenotyping and chromosomal studies. The immunophenotyping revealed blast cells positive for CD79a, CD19, clygM, CD38, nTdt, cyCD22, majority were CD10 with minimal CD20 with negative for myeloid and T cell markers. Based on that, a diagnosis of B cell acute lymphoblastic leukaemia was made. Cytogenetic analysis revealed 46XX, t(5,15)(p15;q15) and 46XX, trisomy 22, t (5,15)(p15;q15) and del 7 (q33,q35).

Patient was then started on Interfant 06 protocol. The induction phase consisted of standard four drugs induction with dexamethasone (6 mg/m^2/day), intravenous (IV) vincristine (1.5 mg/m^2 on days 8, 15, 22 and 29), IV daunorubicin (1 hour infusion /20 mg/m^2 for day 8 and day 9), IV cytarabine ( 30 minutes infusion 75mg/m^2 for two weeks) and intramuscular (IM) L-asparaginase (1000 U/m^2 on day 15, day 18, day 22, day 25, day 29 and day 33). Currently she was in her maintenance phase.

Figure 1. Peripheral blood smear showed lymphoblast which was small in size, high nuclear cytoplasmic ratio and scanty cytoplasm with inconspicuous nucleoli. (Wright’s stain x20 HPF)

Figure 2. Bone marrow aspiration smear demonstrated sheets of lymphoblast cells similar morphology as in Figure 1. (May Grunwald-Giemsa (MGG) Stain X40 HPF)
Figure 3. Flow cytometry of the BMA; (A) Blasts showed negative expression of MPO and cyCD3 (red), (B) The blasts were positive for cyCD79a but negative for CD34(red) expression, (C) CD20 vs CD10 gated on the B cells (red and purple) shows abnormal maturation patterns of the immature B cells. (D) The blasts were positive for CD19 and CD38 expression (purple and red).

Discussion

Congenital leukaemia is a diagnosis made at first month of life and it is a rare disease. The incidence was fewer than 5 cases per 1 million live births. The most types of congenital leukaemia is AML and it is commonly associated with Down syndrome [4]. Advanced maternal age is one of the risk factor postulated to cause congenital leukaemia [5]. They are known to have a poor prognosis with 23% of them will not survived more than 24 months [2]. The criteria for diagnosis of congenital leukaemia include age of presentation which is after birth or within 30 days of life. In the peripheral blood film, there is marked proliferation of blast cells with evidence of infiltration to the extra haematopoietic tissue [6]. Based on these criteria, our patient has fulfilled the diagnostic criteria in which she presented at day 7 of life with 70% blast cells in her peripheral blood film. She also presented with hepatosplenomegaly. All her septic work-up and TORCHES were negatives.

The most common clinical manifestation of congenital leukaemia includes cutaneous manifestations such as petechiae, purpura or leukaemic skin nodules. The skin nodules are described as bluish to slate gray in colour, presented like a deep seated tumour in the dermis layer and may be visible in any sites of the body known as Blueberry muffin [4]. However, this type of lesion was not seen in this patient.
Hepatosplenomegaly is common but lymphadenopathy is not a frequent finding.

The diagnosis was very challenging in this patient because she presented at day 7 of life after uneventful hospital delivery and discharged well on day 2. The initial workup was towards leukemoid reaction secondary to infection, in view of hyperleukocytosis and thrombocytopenia. Based on patient’s peripheral blood morphology, there were 70% blast cells. Both haematogones and lymphoblast showed similar appearance based on morphology. They are described as round to oval, sometimes indented with fine chromatin pattern, scanty basophilic cytoplasm without vacuoles. Haematogones are hyperplasia benign B-lymphoid cells precursor that are present in higher amounts in the bone marrow (BM) of healthy infants and children and decline within minutes as age increase [7]. Haematogones are also present due to severe infection in newborn. Therefore, immunophenotyping can be used to discriminate these reactive cells from lymphoblasts. Immunophenotyping profiling for both reactive and blast cells might be similar as both may show expression of CD79a, CD19, CD10, CD20, TdT and CD38. However, the blasts might express aberrant markers such as CD58, CD123 and CD66c that can be used to differentiate the cells from haematogones. Both haematogones and lymphoblasts also expressed precursor CD10 and CD34, but the distinguishing feature is the continuity of the expression of CD20 and CD10 antigens in former indicating features of maturation. Haematogones consist of immature, intermedia and mature cells type hence, there is continuity of expression of these antigens. For example in immature type of haematogones, there would be positive of CD34 and Tdt with absent of CD19. In term of intermedia type, those young cells will acquire expression of CD19 and lose expression of CD10 and Tdt where as in mature phase of haematogones, those cells will have negative or low intensity of CD10 expression [7]. However, in our patient, the lymphoblasts permit high expression of CD10, Tdt, CD79a and CD19 positive cells thus exhibited incomplete maturation spectrum.

The aetiologies involved in congenital leukaemia include chromosomal defects, intrauterine environmental insults, viral infections and exposure to radiation in pregnancy [8]. The most common chromosomal aberration involved is the myeloid-lineage leukaemia gene at the translocation 11q23 breakpoint [9]. However, from her G banding cytogenetic study, there were multiple chromosomes abnormalities detected which were mosaic 46XX, t (5,15)(p15;q15) and del 7 (q33,q35). Cytogenetic abnormalities such as Monosomy 7, deletions of 7q and trisomy 22 are known to be associated with myeloid disorders with unknown significant in lymphoid leukaemia. Based on Sharif et al, involvement of chromosome 7 in lymphoid leukaemia may confer poor prognosis. It has been postulated that tumour suppressor gene is located on the loci of chromosome 7 which predispose to leukomogenesis [10]. A study by Corona-Rivera et al showed 7 infants with acute lymphoblastic leukaemia harbour t(5,15)(p15;q15) had good outcome following treatment [11]. However, a case reported by Lee SH et al stated their patient who manifested t(5,15)(p15;q15) showed unfavourable outcome [12]. Expanded cohort study would be essential to predict the prognostic significance of t(5;15)(p15;q11-q13).

In conclusion, this was the earliest presentation of congenital leukaemia reported to date mimicking leukemoid reaction in Malaysian cohort. Congenital acute lymphoblastic leukaemia is a rare type and mostly associated with a poor prognosis. However, up to this write up, this patient showed responded to chemotherapy and still on follow-up. The presence of t(5,15)(p15;q15) could be a good prognostic marker. Therefore, understanding on the biological nature of the disease might help in defining and stratifying the disease better.

Conflicts of interest

I do not believe that there is a conflict of interest that could potentially be construed to affect the material contained in the manuscript that is being submitted to the Journal.

References


