



CONGENITAL ACUTE MYELOID LEUKEMIA ALONGSIDE WITH DOWN'S SYNDROME: A RARE IRANIAN CASE REPORT

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Abstract – Objective: Congenital Leukemia (CL) is an extremely rare malignant condition with an incidence rate of fewer than five cases per 1 million live births in neonate mostly non-lymphoblastic leukemia in contrast to predominance of ALL found in later childhood. CL may be associated with syndromic conditions including Down's syndrome.

Case presentation: A 29-day-old male neonate will be presented with lethargy, poor feeding and mild hepatosplenomegaly, manifestations suggestive of sepsis and negative sepsis work-up. Physical examination showed that the patient was febrile and pale, with facial syndromic appearance suggestive for Down's syndrome. His peripheral blood smear showed severe leukocytosis, thrombocytopenia and atypical cells. Bone marrow examination revealed increased myeloblasts but no nucleated-RBC; confirmatory investigations finalized diagnosis of congenital leukemia. Karyotyping indicated chromosome 21-trisomy pattern.

Conclusions: Leukemia needs to be approached in such conditions with clinical features of sepsis and leukocytosis besides an oriented look for co-incident abnormalities.

KEYWORDS: Acute myeloblastic leukemia, Congenital, Chromosome 21, Down's syndrome.

INTRODUCTION

Congenital Leukemia (CL) is an extraordinarily rare condition in newborns, which is typically diagnosed at birth or within the first month of life¹. It makes a medical diagnostic challenge, as its clinical features are similar to prenatal/or natal sepsis. Most CLs are myeloid contrasting pediatric leukemia, which is frequently lymphoid in origin; prognosis is evenly poor^{1,2}. The course of congenital leukemia ordinarily leads to rapid deterioration and expiry due to infection or hemorrhagic events. We

introduce a neonate presenting with clinical manifestations of the sepsis; however, the patient was then confirmed as CL.

CASE PRESENTATION

A 29-day-old male neonate was transported to our Taleghani Pediatric Center due to increased leukocytosis. The patient was admitted at the referring hospital because of preterm birth and abnormal cardiac auscultation as well. He was a preterm neonate,



Fig. 1. A-B, Dysmorphic facial manifestations.

34 wks with birthweight of 2830 g born by caesarian section due to breech presentation as third child from a non-consanguineous marriage. His mother had unremarkable pregnancy with regular prenatal care. On physical examination, the newborn was lethargic and febrile, had pallor, with facial syndromic manifestations indicative of Down's syndrome including eye epicanthus, flat nasal bridge, low set ear and neck webbing (Figure 1 a, b). He had a respiratory rate of 65 beats/min and heart rate of 127 beats/min. The anterior fontanelle was 2*2 cm at flat level. His lungs were clear; a 2/6 systolic soufflé heard at left sternal border. The abdomen was soft with liver and spleen palpable 4 cm and 1.5 cm below the costal margins. No skin petechial nor purpura lesions were detected. The rest systemic examinations were clinically unremarkable. Our case was investigated for suspicion of early sepsis, showing $45 \times 10^3/\mu\text{L}$ leukocytosis, Hb of 14 g/dL, Red Blood cell count of $5000 \times 10^3/\mu\text{L}$ and platelet count of $50 \times 10^3/\mu\text{L}$. The peripheral smear showed 12% neutrophils, 8% lymphocytes, 2% monocytes and 78% blast cells (Figure 2).

There were no nucleated RBCs in the smear. C-reactive protein was 0.1 mg/l with lactate dehydrogenase of 1671U/L. Evaluation for congenital



Fig. 2. Peripheral smear illustrating blasts and neutrophils (x 400).

TORCH infections was negative and blood culture detected was sterile after 72 hrs. The mother's VDRL and HIV tests were negative as well as other hematologic investigations. Neonate received supportive care comprising IV fluids hydration, alkaline diuresis, IV antibiotics and platelet transfusions, bone marrow aspiration (35%myeloblasts), which was morphologically non-M3, negative for myeloperoxidase, sudan black and periodic acid schiff. Flow-cytometry exhibited positive CD 4, CD7, CD15, CD33, CD34 CD71, CD117, CD38, HLA-DR and negative for B and T lymphoid markers. Karyotyping indicated 47 XXY- chromosome 21 pattern; the diagnosis was confirmed as acute myeloid leukemia AML-non-M3.

Our newborn discharged after completing necessary standard supportive care and introduced for hematologic follow up.

DISCUSSION

Congenital leukemia (CL) is a rare entity with the incidence of 4.3 - 8.6 per million live births. It is characterized with the following criteria: 1) disease presentation in 30 days after birth; 2) proliferation of immature white cells, 3) infiltration of the cells into extra-hematopoietic tissues, 4) absence of any other condition, like sepsis, mimicking congenital leukemia^{2,3}. CL etiologies comprise intrauterine environmental insults, infections and exposure to radiation during pregnancy as well as chromosomal derangements. CL might be associated with Down's syndrome, Turner syndrome, Klippel Feil syndrome and Ellis-van Creveld syndrome as well^{4,5}; in our current case, CL was accompanied by Down's syndrome with dysmorphic clinical presentations. Clinical features of leukemia might be apparent at birth with hepatosplenomegaly, ecchymosis and petechial lesions. About 25-30% of newborns suffering from CL

present specific cutaneous infiltrates named leukemia cutis looking as firm red or blue nodules 'Blueberry Muffin'^{6,7} unlike the current case. In a previous study of six CL AML cases, autopsy revealed that leukemic infiltrates in them some organs including lungs⁸⁻¹⁰. A large ratio of CLs are of myeloid lineage, unlike pediatric leukemia, which are usually lymphoid in origin (1-3, and 11). About half of congenital AML are of M4 or M5 in terms of morphology; there is translocation of MLL gene at band 11q23 and positive CD14 in these cases. The t (9; 11) translocation is the next common genetic defect detected followed by the t (11; 19) translocation⁹. The differential diagnosis of CL comprises mainly sepsis and intra-uterine infections termed as TORCH; other possible reasons consist of hemolytic disease of the newborn (HDN) and transient myeloproliferative disease (TMD)¹⁻³. Infections were excluded through serology and culture in our present case; however, HDN numerous erythrocyte precursors were not detected in the peripheral smear in this current case. TMD of neonates is seen typically linked with Down's syndrome. They often have associated transient polycythemia and/or thrombocytosis, but were not perceived in our child. Spontaneous resolution of hematologic and bone marrow derangement happens within three months¹⁰. The prognosis for CL would be poor, with merely 23% of cases surviving at 24 months^{11, 12} but there was a CL case described to be living beyond 14 years⁴. Though rare cases of CL with spontaneous remission have been described, most were associated with Down's Syndrome or mosaicism for trisomy 21⁸ and also Noonan's syndrome¹³ as our introduced neonate. To the best of our knowledge the current case with mentioned exclusive features was not previously reported in the literature, especially in Iran.

CONCLUSIONS

We reported a rare 29-day-old newborn suffering CL-AML. Leukemia should be considered in such conditions presenting clinical features of sepsis and leukocytosis besides having an alert look for associating abnormalities, especially karyotyping. Patients with congenital leukemia are quite different in the way they present, their clinical behavior, chromosomal abnormalities, and the immunophenotyping characteristics. Further studies are necessary to simplify the nature of such a rare type of leukemia.

INFORMED CONSENT:

The paper has been written with supervision of Local Ethics Committee of the University; a written informed consent was obtained from the family.

ACKNOWLEDGMENT:

The authors would like to give special thanks to the parents of our case for their sincere cooperation.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

REFERENCES

- Perkins SL. Hematopoietic system. In: Gilbert Barnes E (Ed). Potter's pathology of the fetus, infant and child. 2nd ed. Elsevier 2007; pp. 1453-1514.
- Bajwa RP, Skinner R, Windebank KP, Reid MM. Demographic study of leukaemia presenting within the first three months of life in the northern health region of England. *J Clin Pathol* 2004; 57: 186-188.
- McCoy JP Jr, Overton WR. Immunophenotyping of congenital leukemia. *Cytometry* 1995; 22: 85-88.
- Warrier RP, Emami A, Ravindranath Y, Inoue S, Kaplan J. Perinatal leukemia: the surface antigens, cytochemistry and cytogenetic features. *Indian Pediatr* 1983; 20: 325-333.
- Duru C, Pughikumo C, Adeyemi O. Acute myeloblastic leukaemia in a patient with down's syndrome and sickle cell anaemia: a case report. *Pediatr Ther* 2013; 3: 167.
- Pui CH, Kalwinsky DK, Schell MJ, Mason CA, Mirro J, Dahl GV. Acute nonlymphoblastic leukemia in infants: clinical presentation and outcome. *J Clin Oncol* 1988; 6: 1008-1013.
- Resnick KS, Brod BB. Leukemia cutis in congenital leukemia: analysis and review of the world literature with report of an additional case. *Arch Dermatol* 1993; 129: 1301-1306.
- Badhe PB, Sane SY. Congenital leukemia – Organ involvement in six autopsy cases. *J Postgrad Med* 1992; 38: 127.
- Felix CA, Lange BJ. Leukemia in infants. *Oncologist* 1999; 4: 225-240.
- Zipursky A. Transient leukaemia-a benign form of leukaemia in newborn infants with trisomy 21. *Br J Haematol* 2003; 120: 930-938.
- Bresters D, Reus AC, Veerman AJ, van Wering ER, van der Does-van den Berg A, Kaspers GJ. Congenital leukaemia-the Dutch experience and review of the literature. *Br J Haematol* 2002; 117: 513-524.
- Isaacs H Jr. Fetal and neonatal leukemia. *J Pediatr Hematol Oncol* 2003; 25: 348-361.
- Bader-Meunier B, Tchernia G, Mielot F, Fontaine JL, Thomas C, Lyonnet S, Lavergne JM, Dommergues JP. Occurrence of myeloproliferative disorder in patients with Noonan syndrome. *J Pediatr* 1997; 130: 885-889.