

Congenital acute myeloid leukemia: A rare diagnostic enigma case report with review of literature

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Dear Editor,

Congenital leukemia (CL) is leukemia that develops in utero.^[1] CL is extremely rare usually diagnosed at birth or within 1-month of life.^[1-3] Incidence is reported to be 1 in 5 million.^[1] The doubling time of leukemic cells leads to clinically evident disease after birth or shortly thereafter.^[1] An estimated 175–200 cases are reported in the literature.^[3] Most CL are Myeloid in origin unlike pediatric leukemias which are Lymphoid.^[1,2] There is a 20 fold increased risk of leukemia in individuals with Down syndrome (DS) (Brewster and Cannon, 1930).^[4] All cytogenetic types of DS predispose to leukemia (megakaryocytic or acute myeloid leukemia [AML]-M0)^[1] DS is known to be associated with transient myeloproliferative disorder (TMD) in about 10% newborn cases with spontaneous remission.^[1,5] CL has a poor prognosis.^[1,2,4,5]

A day old premature female child weighing 1.8 kg was born to the elderly female of nonconsanguineous marriage. It was a normal vaginal delivery and third in birth order. No

history of addiction, cytotoxic drug or exposure to radiation during the antenatal period. No history of maternal fever, rash or lymphadenopathy in the first trimester. Regular antenatal visits for growth retardation. At birth the baby had cyanosis, delayed cry, lethargy, and difficulty in breathing with feature of DS (mongoloid facies, epicanthic folds, low set ears, flattened nasal bridge, hypotonia, simian crease), pallor, and respiratory distress. Liver just palpable, spleen 2 cm below the costal margin. No palpable lymph nodes or skin lesions seen. Clinical diagnosis was DS with sepsis. Baby was shifted to Special Neonatal Care Unit.

Complete blood count and peripheral smear (PS) revealed Hb 8.6 g%, macrocytes, nucleated red blood cell: 10/100 white blood cells (WBC's), total leukocyte count - 1,47,000/cmm, myeloblasts 75% [Figure 1], platelets 80,000/ μ l. Cytochemical stain: Myeloperoxidase (MPO) positive. Diagnosis of AML-M2 by FAB classification. Flow cytometry of peripheral blood (PB)-blasts positive for cyMPO (~75.7%), CD34 (~86.5%), CD7 (~94.2%), CD13 (~16.0%), CD33 (83.9%), CD117 (~97.8%), HLA DR (~15.0%). Lymphoid markers and septic workup was negative.

Final diagnosis congenital AML-M2 with DS.

Table 1: Points to differentiate CL from TMD

| CL | TMD |
|---|---|
| Presentation at birth with marked symptoms | At birth or later, clinically silent |
| Cytopenia (low platelet and hematocrit) | Normal hematocrit and platelet count. Platelet of variable sizes |
| Frank acute myeloid leukemia | Acute megakaryoblastic leukemia |
| Rapidly progressive, mostly fatal | Transient with spontaneous regression |
| Blast count in PS very high (75%) | Low blast count |
| Myeloblast on PS-large oval nucleus, fine chromatin, 3 or more nucleoli, basophilic cytoplasm | Megakaryoblast-large cells, pale blue cytoplasm, cytoplasmic blebbings, nucleus with condensed chromatin, 1 to many distinct nucleoli |
| MPO positive | MPO negative |
| Myeloid markers : CD7, CD13, CD117. positive lymphoid, and megakaryoblastic marker negative | Megakaryoblastic markers: CD41, CD61, HLA-DR. Myeloid markers weak or negative |
| No other condition mimicking leukemia | Myelodysplasia, transient leukemia |
| Rapid downhill course, death on 2 nd day | Favorable outcome mostly, without intervention |

CL=Congenital leukemia, TMD=Transient myeloproliferative disorder, PS=Peripheral smear, MPO=Myeloperoxidase, HLA=Human leukocyte antigen

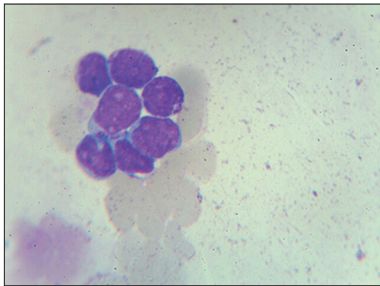


Figure 1: Peripheral Smear shows a collection of blasts with large oval nucleus composed of very fine nonaggregated chromatin and three or more inconspicuous nucleoli. The cytoplasm is scant with basophilic character devoid of granules (Leishman, x100)

Congenital leukemia is diagnosed at birth or within few days of birth.^[1-3] Incidence is 1 in 5 million.^[1] The Children's Oncology Group show the fourfold higher incidence of AML to ALL in DS children (Zipursky *et al.* 1992).^[1,4] Advanced maternal age is the risk factor for DS and CL (Ross *et al.*)^[4] The Criteria for CL diagnosis (1) disease presentation at or shortly after birth (30 days), (2) increased immature WBC's, (3) infiltration of cells into extra hemopoietic tissues, (4) absence of any condition causing leukemoid reaction mimicking CL. That is, congenital syphilis, blood group incompatibility, and TORCH.^[2,5] AML-M2 and trisomy 21 show translocation (8;21).^[6] Multiple studies show a higher incidence of leukemia in DS patients (Robison *et al.* 1984)^[1,6,7] and the role of trisomy 21 in leukemogenesis.^[6] About 2% of pediatric leukemia patients have DS.^[7] Disrupted hemostasis, ineffective granulopoiesis regulation, immune deficiency, abnormal cell kinetics, susceptibility to viral transformation, predisposition to nondysjunction, chromosomal fragility, impaired DNA repair are factors predisposing to leukemia in DS (Fong and Brodeur 1987).^[5,7] Characteristic hematopoietic manifestation of DS in 10% cases is transient leukemia or TMD, Schunk and Lehman (1954).^[4,5] TMD is distinguished from CL by spontaneous remission within first 3 months, no evidence of underlying infective pathology/hemolysis, lower blast percentage in PB. Difference between CL and TMD is presented in Table 1. Clonal/cytogenetic abnormality in AML is not seen in DS.^[1] In our case presentation was at birth, blasts very high (75% in PB), typical Down phenotype, no other disorder mimicking leukemia, CL (AML) diagnosis confirmed by immunophenotyping with rapid downhill course and death on the 2nd day. A study suggests that targeted gating for blasts along with a suitable panel of monoclonal antibodies show similar immunophenotyping

pattern in PB and bone marrow (BM). This minimizes necessity of BM aspiration in leukemia.^[8] Majority cases of AML are diagnosed on morphology alone. In our cases PS morphology, cytochemical stain, and immunophenotyping was done on PB, which correlated well with clinical symptoms and PS examination. Unfortunately, BM and karyotyping was not done as baby expired on 2nd day. CL has poor prognosis^[1,2,4,5] with 23% survival at 24 months.^[1]

We present this rare case to generate awareness about CL with DS in a newborn and differentiation from other conditions mimicking leukemia.

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Conflicts of interest

There are no conflicts of interest.

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