Congenital leukemia in a 2-month old boy
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Citation

Abstract
Acute leukemia is rare in infants. Only a few cases of congenital leukemia have been reported so far. Congenital leukemia occurs at the rate of 1 per 5 million births. It is characterized by non-specific symptoms requiring a high index of suspicion for further investigations and diagnosis. We report here a rare case of congenital lymphoblastic leukemia in a two-month-old boy.

CASE REPORT
A 2-month-old boy was admitted to a primary care hospital for two days. Details of management are as follows:

- Urinalysis: unremarkable
- Chest radiograph: Right mid zone and lower zone infiltrates
- Ultrasound scan of the abdomen: hepatosplenomegaly with minimal ascites and right pleural effusion.
- He was treated for acute bronchopneumonia.

He was urgently transferred to our unit in view of his deteriorating clinical status with increasing respiratory distress and low oxygen saturations (SpO2 ~ 70).

At admission, the child was sick, pale looking, febrile and tachypneic with signs of severe dehydration. There was no evidence of microcephaly, cataract, facial dysmorphism, lymphadenopathy or skin lesions. He was in severe respiratory distress with subcostal, intercostal recession and grunting. Auscultation of chest revealed bilateral crepitations. The abdomen was distended with a hepatomegaly of 5 cms and splenomegaly of 2 cms. External genitalia were normal. He had feeble peripheral pulses with prolonged capillary refill time. Heart sounds were normal. He was drowsy and irritable. There were no focal neurological deficits.

The history was reviewed with the parents. He had been irritable and crying excessively for 15 days. He had had an intermittent moderate fever for 5 days and cough and coryza for 4 days. The parents had noticed that the child developed abdominal distension and shortness of breath a day prior to admission. There was no history of jaundice or bleeding diathesis. The antenatal, birth and immediate postnatal history was uneventful. There was no history of maternal fever with rash & lymphadenopathy during the first trimester of pregnancy. He was delivered at full term by caesarian section. He cried immediately after birth and his birth weight was 2.5 kg. He was immunized up to date and had been breast-fed since birth. The child was gaining weight well; his weight at admission was 4.45 Kg (~ between 10th & 25th percentile for age & sex; birth percentile ~ 5th centile).
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Figure 1
Figure 1: Chest X-Ray: B/L Infiltrates – more in Rt. Upper zone.

Figure 2
Figure 2: Post Mortem Liver Biopsy; HE Stain: 10 X

Figure 3
Figure 3: Post Mortem Liver Biopsy; HE Stain: 40 X

Figure 4
Figure 4: Post Mortem Lung Biopsy
LAB INVESTIGATIONS

Initial hematological investigations demonstrated a hemoglobin level of 5.4 gm/dl, a total leukocyte count of 26,200/ mm3 and platelet count of 29,000/ mm3. The peripheral blood smear was reported as showing normocytic normochromic red cells with a marked leukocytosis and a shift to the left, and lymphocytosis with reactive lymphocytes. The serum creatinine level was 0.87 mg/dL. Serum electrolytes revealed hyponatremia (sodium: 122.6 meq/l) and hyperkalemia (potassium: 5.97mg/dl). CRP was positive (7.06 mg/l) and an arterial blood gas analysis was suggestive of severe metaboloc acidosis (pH: 7.00, PCO₂: 20.3, PO₂: 8.6, HCO₃: 4.9, BE: -26.3 SpO₂: 90.9%). Chest x-ray revealed extensive infiltrates bilaterally, more in the upper zone (see figure). HbsAg and HIV-1 & HIV-2 by were negative by ELISA.

CLINICAL COURSE

He was electively intubated and placed on pressure-control mode mechanical ventilation. Management was initiated as for fulminant sepsis with shock. Measures included fluid resuscitation, intravenous antibiotics (Piperacillin + Tazobactum & Tobramycin), inotropic support (dopamine ~ 5 gm/kg/min & dobutamine ~ 10 gm/kg/min). Supportive therapy also included packed cell transfusion (20 ml/kg), correction of electrolytes and metabolic acidosis. Subsequent to admission, he was successfully resuscitated twice from cardiac arrest. There was a progressive downhill course after that point. Despite aggressive intensive care support he continued to deteriorate and died within 6 hours of admission.

In view of his age at presentation, bilateral lung infiltrates, hepatosplenomegaly, severe anemia with thrombocytopenia and lymphocytic leucocytosis and a severe metabolic acidosis resistant to alkali therapy, we considered differential diagnoses other than septic shock including:

1. Storage disorder: Gauchers disease.
2. Inborn errors of metabolism.
3. Hematological malignancy.

After much persuasion and time, parents agreed for a limited postmortem investigation, inclusive of liver and lung biopsy only. Parents refused special investigations for diagnosis of inborn errors of metabolism and a bone marrow study. A post mortem review of a peripheral blood smear was also carried out.

Liver biopsy (PM Specimen): Section shows linear fragments of normal hepatocytes with dilated sinuses containing few large lymphocytes. Periportal areas are infiltrated by nodular collections of large cells with round to cleaved nucleus and scanty cytoplasm. The nucleoli are very tiny. Some of these cells are seen infiltrating the bile ducts. These findings are suggestive of Leukemic infiltration of liver. See figures. Lung biopsy (PM Specimen): Sections of lung show aerated alveoli containing RBC’s. No infiltrates are seen. S/o Alveolar hemorrhages. Peripheral blood smear review: RBC: Normocytic, Normochromic. WBC: Leucocytosis. Neutrophilia with mild shift to left and lymphocytosis. Lymphoblasts constitute 21% of cells. Platelets: Markedly decreased. Morphology of Lymphoblasts: Cells are varying in size, having large cytoplasm with irregular and homogenous nuclei. Nucleoli are seen. Tdt and PAS special stains positive. Morphologically L-2 subtype. Comments: Acute lymphoblastic leukemia.

Final Diagnosis: Congenital Leukemia: All-L2 Sub Type (Fab Classification)

DISCUSSION

Congenital leukemia is a very rare disorder (1). Only 200 reports of congenital leukemia are published in literature (2). The majority are Non-Lymphocytic type (80%), while acute
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lymphoblastic leukemia (ALL) comprises only < 20%. Familial neonatal leukemia is extremely rare and no child born to a mother with leukemia has been found to have the disease during the neonatal period (\[1\]). Congenital leukemia is occasionally associated with number of congenital anomalies and with chromosomal disorders such as Down's syndrome, Edward's and Patau's syndrome and a number of nonspecific chromosomal abnormalities. Subtle cytogenetic abnormalities may occur more commonly in the affected infants and their parents, when studied with newer cytogenetic techniques (\[2\]).

The clinical signs of leukemia may be evident at birth with hepatosplenomegaly, petechiae and ecchymosis. Leukemic cell infiltration into the skin (leukemia cutis) is commonly found (\[3\]). In infants in whom the disease develops within the first month (not at birth), the symptoms are ill defined with low-grade fever, diarrhea, hepatomegaly and failure to gain weight. Leukemia cutis is less common (\[3\]).

Clinically, it is important to differentiate congenital leukemia from other leukoerythroblastic conditions, which are seen in response to bacterial infection, hypoxemia and severe hemolysis in the neonate (\[3\]). Other differential diagnosis includes congenital syphilis, intrauterine viral disease, neuroblastoma and the transient myeloproliferation syndrome associated with Down's syndrome (\[4\], \[5\], \[6\]).

Cellular morphology, immunophenotype and chromosomal studies differentiate acute lymphoblastic from acute non lymphoblastic leukemia found in newborns (\[3\]). FAB classification based on cell morphology reveals that the most common subtype in infantile and neonatal acute nonlymphocytic leukemia is the monocytic variety (\[7\]). The most common locus involved in translocation in infantile acute lymphoblastic leukemia is at 11q 23 – this is involved in at least 50% of infant leukemias and in many neonatal cases (\[8\]).

The course of congenital leukemia is one of rapid deterioration and death from hemorrhage and infection. Specifically, it is a more aggressive disease with increased incidence of leukocytosis, massive hepatosplenomegaly, CNS involvement, thrombocytopenia, hypogammaglobulinemia, disseminated intravascular coagulopathy (DIC) and less frequent remission induction by 14 days (\[9\]). The current improved success of remission induction with treatment of acute non-lymphocytic leukemia in infants younger than 1 year is similar to that in older children using combination chemotherapy. However, the experience with newborns is limited, but between 1984 to 1989, 5 of 12 newborns with acute non-lymphocytic leukemia sustained complete remission with chemotherapy, and all were in the myelomonocytic or monocytic category (\[10\]). However, in acute lymphoblastic leukemia, the treatment outcome is significantly poorer in infants younger than 1 year at diagnosis (23% disease-free survival compared with 70% for older children) and may be even lower in newborns. Only 10 to 20% survival for infants younger than 6 months of age at diagnosis has been reported as compared to 40% for those, older than 6 months (\[11\]). Fewer than 15% of newborns with acute lymphoblastic leukemia have remission lasting more than few months.

Bad prognostic indicators: (\[12\])

1. Leukocytosis
2. Massive hepatosplenomegaly
3. CNS involvement
4. Thrombocytopenia
5. Hypogammaglobulinemia
6. DIC
7. Remission induction not achieved by 14 days of age

In Acute lymphoblastic leukemia, the treatment outcome is (\[12\]):

< 6 months: 5-20 % survival.
> 6 months: 30-40 % survival
Older children: 70 % survival

Success of Remission induction in Congenital AML is almost similar to that in older children using combination chemotherapy.

INDICATIONS FOR POST MORTEM DIAGNOSIS

1. Overt major and multiple minor congenital anomalies with facial dysmorphism not indicative of commonly seen genetic disorders.
2. Suspected Inborn errors of metabolism.
3. Suspected hematological / oncological disorders
4. Diagnosis not confirmed during the life of the child.
INVESTIGATIONS IF DEATH IS INEVITABLE &
DIAGNOSIS NOT CONFIRMED DURING THE
LIFE OF THE CHILD()

1. Chromosomal Karyotype.

2. Lithium heparin sample of plasma separated and
   frozen (for Inborn errors of metabolism).

3. Whole blood for DNA analysis.

4. Urine for Microscopy, Biochemistry and metabolic
   screening.

5. Bone marrow study (aspiration & biopsy).

6. Biopsies: Liver, Lung, Skin, Kidney etc.

7. Skeletal survey.

CONCLUSION

We hereby report a case of congenital leukemia confirmed
by a limited post-mortem investigation.

Limited post-mortem investigations can be useful in lieu of a
full autopsy, if the diagnosis is not confirmed during the life
of the child.

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