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*Case History*

# A rare case of congenital acute lymphoblastic leukemia presenting as Leukemia Cutis and generalized lymphadenopathy

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**Key Words - Congenital leukemia, Leukemia cutis, pancreatic infiltration**
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## Abstract

Congenital leukemia is rare and possesses much poor prognosis with higher relapse rate even with intensive chemotherapy. Acute lymphoblastic leukemia (ALL) is even rarer with poorer outcome.

This is a case of congenital leukemia detected at birth in a non-syndromic term baby with petechiae, ecchymoses, and splenomegaly. There was leukemia cutis and generalized lymphadenopathy which are considered as uncommon manifestations in congenital ALL. Diagnosis was made with peripheral blood having hyperleukocytosis with 95% lymphoblasts, thrombocytopenia and anaemia with flowcytometry findings suggestive of B type ALL. There was significant pancreatic enlargement detected ultrasonically with normal enzyme levels which is an unusual association in congenital ALL.

Despite having extremely high leucocyte count, high Lactate Dehydrogenase with some biochemical features such as hypocalcemia, hyper-phosphatemia and hyperuricemia to suggest tumour lysis, baby was managed successfully with hyperhydration, intravenous steroids and oral Allopurinol during the first 02 weeks of life until baby became stable for initiation of chemotherapy.

There was early response to steroid treatment indicating better prognosis while having early age at diagnosis, significant leukocytosis at presentation and CD10 negativity as predictors of poor outcome.

## Introduction

Congenital leukemia is rare. Non lymphoblastic leukemia accounts for over2/3$^{rd}$ among reported cases[1], making congenital lymphoblastic leukemia (ALL) an exceedingly rare occurrence. It is characterized bymarked leukocytosis, thrombocytopenia and anemia and generally has a poor prognosis even with modern chemotherapeutic regimens.

We report a case of congenital B type- ALL diagnosed at birth with leukemia cutis, generalized lymphadenopathy and asymptomatic pancreatic enlargement which are unusual associations of ALL in neonates.

## Case

A baby girl was born at 37 weeks of gestation via elective caesarian section with an APGAR of $1^{10}$, $5^{10}$, $10^{10}$. Her birth weight was 3kg.

There was no respiratory distress although oxygen requirement of 0.5L/min nasal prongs and a pre- post ductal difference raised the clinical suspicion of persistent pulmonary hypertension. Her haemodynamic parameters were stable throughout. No dysmorphic features were present, and all limbs had developed normally.

Most striking features that caught immediate attention however were petechiae and echymotic patchesspread over the body including face and oral mucosa.

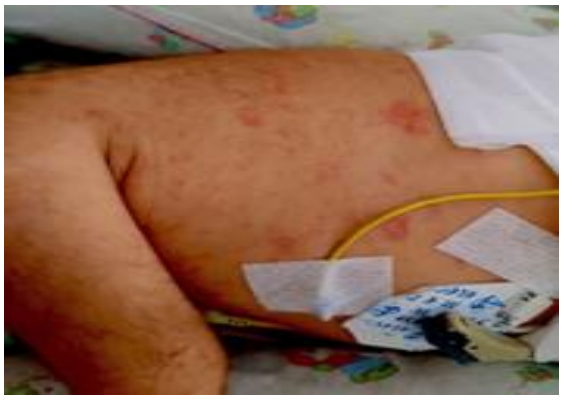

***Figure1: Petechiae and Echymosis***

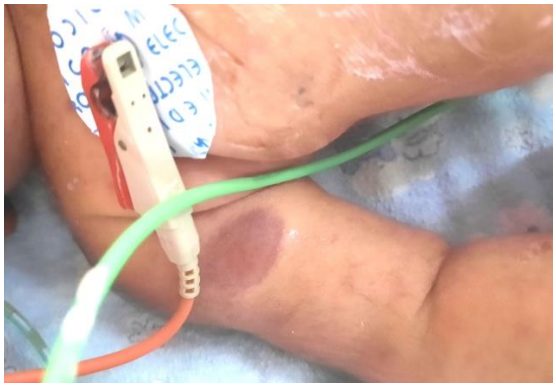

***Figure2: Leukemia Cutis over right forearm***

There were few palpable subcutaneous lesions over the forearm, abdomen, and the back of the chest, largest being 2.5cm×1.0cm in size. They were suggestive of subcutaneous deposits (Leukemia Cutis). Scattered lymphadenopathy was noted involving bilateral axillary and inguinal areas. Abdominal examination revealed moderate splenomegaly without hepatomegaly.

She was the second child of non-consanguineous parents, and their first baby was healthy at 03 years of age. Antenatal history of this pregnancy was uneventful without features supportive of sepsis, congenital infection, or maternal medical diseases. Antenatal scans were normal. There was no family history for haematological malignancies or bleeding disorders.

Day 01 investigations showed a white cell count of 1128 × $10^9$/L with 80% blast cells, haemoglobin of 12.1g/dL (haematocrit-62.6%) and platelet count of 28000×$10^6$/L. Blood groups of mother and baby were ‘A positive’ and ‘O positive’ respectively. Direct antibody test was negative. Screening for congenital infections was found to be negative along with negative septic screening.

There was direct hyperbilirubinemia (50% of total bilirubin) with mild elevation of total bilirubin of 50.3µmol/L(<50µmol/L) at birth. Liver enzymes including Gamma Glutamyl Transferase (ɤGT) were also elevated [day 01- Aspartate Trasaminase (AST)-244U/L(10-31U/L), Alanine Transaminase (ALT)-81U/L (7-40 U/L), ɤGT- 90.8U/L (2-30U/L)].

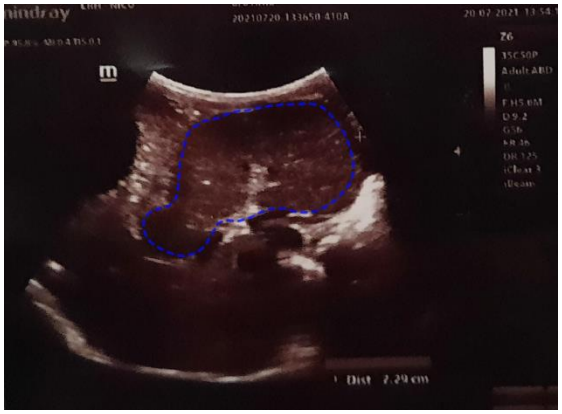

***Figure3: Splenomegaly in USS***

Ultrasound scan (USS) abdomen showed an enlarged spleen (cranio-caudal length- 7.2cm, Normal 3.2-5.5cm) with normal echogenicity, without hepatomegaly.

Gall bladder and the biliary tract were normally visualized. The striking feature was enlarged pancreas (maximum diameter Neck-1.9cm, Head- 2.0cm, Tail- 2.5cm) without focal lesions. Renal tissue was normal and there was no ascites. Serum Amylase was normal for age (Serum Amylase- 03U/L normal <30U/L).

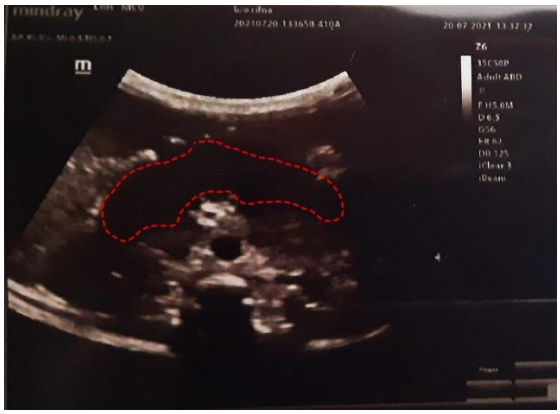

***Figure4: Enlarged Pancreas in USS***

By 16th hour of life baby had focal convulsions involving oro-facial region raising the possibility of either intracranial bleeding or electrolyte abnormalities. Convulsions were managed with IV phenobarbitone, followed by Midazolam infusion. Serum calcium was also corrected with intravenous calcium. Baby was intubated and ventilated due to poor respiratory effort and desaturation. Ultrasound of brain revealed a Grade-I caudo-thalamic groove haemorrhage of left side and a prominent right ventricle measuring 5mm in size without a midline shift.

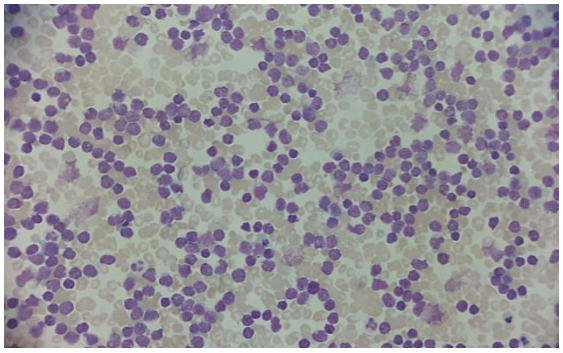

***Figure5:Peripheral smear illustrating blasts. (Leishman x400)***

Blood picture showed marked leukocytosis with severe neutropenia and 95% lymphoblasts. Anaemia and thrombocytopenia were also evident.

***Table 1: Flowcytometry with a diagnosis of B-ALL***

| **Percentage of total nucleated cells gated in the moderate CD45 region(Blasts gate)- 94%** | | | | |
|---|---|---|---|---|
| **Immuno-phenotyping of above population as follows** | | | | |
| Immature markers | Myeloid markers | B markers | T markers | Other |
| CD34- Positive | CD33- Negative | CD19- Positive | CyCD3-Negative | CD41- Negative |
| TdT- Negative | CD13- Negative | CD20- Negative | SmCD3-Negative | CD71- Negative |
| HLADR-Positive | MPO- Negative | CD10- Negative | CD5- Negative | |
| CD117-Negative | CD14- Negative | CD79a-subset positive | CD7- Negative | |
| | CD64-Negative | | | |

Flowcytometry confirmed a diagnosis of acute B-Lymphoblastic Leukemia (B-ALL).
Following multidisciplinary discussion with Neonatologist, Paediatric Oncologist, Hematologist and transfusion specialist, decision was made to start on hyper-hydration (125ml/$m^2$/day) with simultaneous management of hyper-uricemia (Oral Allopurinol 100mg/$m^2$/8hourly) followed by initial treatment with intravenous steroid-Dexamethazone 1.5mg/$m^2$ 12 hourly. Leukocyte count was monitored twice a day as shown in Table2.

Aggressive antibiotic treatment was implemented due to severe neutropenia. Abscess formation was noted over left pinna with rising inflammatory markers. It was surgically drained.

There was severe persistent pulmonary hypertension (PPHN) and a large patent ductus arteriosus (PDA) with bidirectional shunting in the echocardiography. Following management of hyper-viscosity of blood, PPHN had resolved with resultant closure of the PDA. Hyper-hydration was reduced to maintenance fluid by day 09 of life after white cell count has been normalized.

## Discussion

Diagnosing Leukemia within first 28 days of life is defined as congenital/ neonatal leukemia. The term 'congenital' is mostly used when it is diagnosed at birth or within first few days after birth. It is an extremely rare occurrence with incidence of 1-5 cases per one million live births[1]. Yet it is the third common malignancy among neonates after Teratoma and Neuroblastoma due to rarity of malignancies in this age group[1]. More than 2/3rd of cases with neonatal leukemia are non-lymphoblastic leukemia while acute lymphoblastic leukemia (ALL) as in this case accounts only for 10-20%[2].

Diagnosis of congenital leukemia is supported by features of extra-haematopoetic tissue infiltration, absence of any other disease causing leukemoid reaction such as congenital infections/ feto-maternal blood group discrepancies and absence of syndromic features in the baby.

***Table 2: Resolution of cell counts with treatment over first 09 days of life***

| | 19/7 11am | 19/7 11pm | 20/7 11pm | 21/7 9am | 21/7 9pm | 22/7 9am | 22/7 9pm | 23/7 9am | 23/7 9pm | 24/7 9am | 24/7 9pm | 25/7 9am | 26/7 9am | 27/7 9am |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WBC($\times10^9$/L)** | 1128 | 946.5 | 854.2 | 710.7 | 372 | 285.7 | 224.1 | 121.5 | 79.6 | 50.0 | 33.8 | 24.3 | 16.2 | 11.8 |
| **Ne %** | 1 | 4 | 0 | 0 | 1.2 | 2.1 | 3.3 | 5.6 | 4.7 | 8.2 | 10.4 | 10.3 | 12.5 | 21.4 |
| **Ly %** | 98 | 96 | 92.1 | 92.8 | 87.8 | 92.1 | 91.1 | 88.6 | 84.4 | 85.2 | 81.2 | 81.0 | 74.4 | 67.1 |
| **Hb (g/dL)** | 12.1 | 8.4 | 8.6 | 9.1 | 9.9 | 8.0 | 8.0 | 7.9 | 7.9 | 8.2 | 10.4 | 10.0 | 9.0 | 7.6 |
| **Hct %** | 62.6 | 39.9 | 39.5 | 39.1 | 33.4 | 29.1 | 29.1 | 26.9 | 25.9 | 28.2 | 33.3 | 34.0 | 29.6 | 23.5 |
| **Platelets($\times10^9$/L)** | 28 | 13 | 111 | 47 | 38 | 28 | 19 | 16 | 43 | 24 | 15 | 11 | 39 | 39 |

***Table 3: Table 2: Electrolytes, Renal function, and Uric acid concentration of the baby since birth up to day09***

| | Day1 | Day2 | Day3 | Day4 | Day5 | Day6 | Day7 | Day8 | Day9 |
|---|---|---|---|---|---|---|---|---|---|
| **$K^+$ mmol/L** | 4.1 | 5.46 | 5.6 | 4.6 | 5.7 | 5.4 | 5.3 | 4.1 | 3.8 |
| **$Ca^{2+}$ mmol/L** | 1.6 | 1.55 | 1.9 | 2.24 | 2.46 | 3.0 | 2.6 | 2.5 | 2.3 |
| **$PO_4^{3-}$ mmol/L** | 3.4 | | 3.36 | 2.85 | 2.5 | 1.56 | 1.41 | 1.44 | |
| **S.Cr µmol/L** | 63 | 99 | 74 | | 51 | 38 | 37 | 25 | 35 |
| **BU mmol/L** | 6.3 | 8.9 | 9.4 | | 18.1 | 14.6 | 12.9 | 10.7 | 9.8 |
| **UricAcid µmol/L** | 521 | - | - | - | 182 | 159 | 118 | 92 | 55 |

Congenital leukemia manifests as petechiae, echymosis, hepatosplenomegaly, intracranial haemorrhages or otherill-defined symptoms such as poor feeding, fever and failure to thrive. 25% -30% of cases will have leukemia cutis/chloroma (blue/purple to brown skin nodules) due to leukemic infiltrates[3] especially when the disease occurred in-utero. This phenomenon is common in acute myeloid leukemia (AML) and occurs only in 1% of paediatric ALL cases. There is only one case reported in literature with neonatal ALL and leukemia cutis[4] similar to our baby.

Jaundice, ascites, and pleural effusions are common, while generalized lymphadenopathy is a rare phenomenon in neonates[13]. In our baby there was prominent generalized lymphadenopathy, but no jaundice or effusions.

Most consistent haematological feature in neonatal leukemia is hyper-leukocytosis with a median leukocyte count of 68× $10^9$/L[13.] Anemia was less common than thrombocytopenia[5]. This case had markedly high initial leukocytes of 1128 × $10^9$/L. There were both thrombocytopenia and anemia since birth needing transfusion.

Common sites of leukemic infiltration in children are testicles, mediastinum, lungs, liver, central nervous system, and kidneys, with renal infiltration being the commonest[6-9]. Massive diffuse enlargement of the pancreas is unusual in children due to leukemic infiltration[8]. The reported few paediatric cases have had clinical and biochemical features suggestive of pancreatitis and cholestasis[8-10]. Another study reporting autopsies of six cases of congenital leukemia revealed only one case with pancreatic involvement[11]. Our baby had a massive pancreatic enlargement without significant cholestasis or clinical or biochemical evidence of pancreatitis. There is only one paediatric case reported to have significant asymptomatic leukemic infiltration of pancreas and there are no reported cases in neonates[12].

Although there was no hepatomegaly, or biliary obstruction, elevated liver enzymes and direct hyperbilirubinemia would suggest some hepatic infiltration. Hepatic failure has been reported in some neonatal cases leading to death[13].

There was persistent pulmonary hypertension in the index baby with a pressure gradient of 53mmHg over Tricuspid valve. Although it has not been described in cases of congenital leukemia, development of pulmonary hypertension is a known entity in haematological disorders due to massive cell-lysis and chemically mediated vascular remodelling[14].

Diagnosis of tumour lysis syndrome (TLS) needs to fulfill two or more of laboratory criteria (i.e. hyperkalemia, hyperuricemia, hyperphosphatemia or hypocalcemia) along with one of the clinical criteria (i.e. Serum creatinine >1.5×normal for the age or cardiac dysrhythmia/ death or seizures or neuromuscular instability). These features should present over 24 hours during 3days prior to or 7 days after initiation of chemotherapy[15-16].

There are no neonatal cases reported with spontaneous tumor-lysis in literature. In this case, elevated Uric acid, Phosphate, and hypocalcemia were noted on day 01 of life as biochemical criteria. But clinical criteria were not clear enough to diagnose tumor lysis syndrome.
Lactate Dehydrogenase (LDH)> 1000 IU/L is an indicator of high tumor burden and LDH could be considered as an early predictor of tumor lysis syndrome[17]. Although this baby had LDH of 1889 U/L on day 02, we believe that early initiation of prompt management resulted in resolution of LDH and other suggestive parameters of tumor lysis syndrome.

Management of neonatal lymphoblastic leukemia is a clinical challenge as it differs significantly from leukemia in older children. They tend to have higher tumor burden with rearrangements of mixed lineage leukemia (MLL) gene making them highly resistant to standard chemotherapeutic agents[23]. Neonatal ALL is treated with hybrid therapeutic regimen[23]. This consists of ALL standard treatment and AML multi-agent phases of induction and consolidation followed by maintenance with antimetabolites[23]. IV Steroids were started on this baby as a bridging therapy with frequent monitoring for occurrence of TLS aiming to start chemotherapy once the baby became stable.

Prognosis of congenital leukemia is worse than paediatric non congenital cases. In a series of 30 neonates with congenital ALL, 2-year overall survival was only 20% following intensive chemotherapy of 02 yearscompared to 66.4% in older infants[21-22]. The 2-yearevent free survival (EFS) was also 20% in congenital leukemia which is significantly lower than the reported EFS among older children of >80%[18-19].

Outcomes assessed among infants with ALL had differed depending on the status of MLL gene, CD10 expression, leukocyte count at presentation, age at diagnosis, co-expression of myeloid markers and response to steroids[18-19]. Patients who had a poor response to steroids had EFS 15%, while the better response group had 53% of EFS[20].Babies who had a leukocyte count< 50 × $10^9$/L had a significant favorable prognosis in a small group of infants studied with intensive multi-agent chemotherapy[24]. CD10 negativity has also been a poor prognostic indicator[22]. Out of above mentioned six prognostic indicators, 03 poor prognostic factors were noted in this case (i.e. early age at diagnosis, markedly high leukocytosis at presentation, CD10 negativity) while early response to steroids can be considered as a good prognostic marker.

## Conclusion

We report a rare presentation of congenital acute lymphoblastic leukemia with unusual clinical manifestations. Scarcity of reported cases have made understanding of pattern of presentation, pathophysiology, prognostic factors with immuno-histochemical characteristics extremely poor. This has resulted in lack of adequate clinical guidelines and chemo therapeutic protocols in treating this condition which contributes in part to the poor prognosis observed.

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