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Congenital Leukemia With AML-M4 And Leukemia Cutis : A Case Report

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ABSTRACT

Introduction: Congenital leukemia is defined as the manifestation of leukemia that occurs in the first 4 weeks of life. Estimated incidence varies between 1–5 cases per million live births. Which is the main cause of death of all malignancies in newborns. Acute myeloid leukemia (AML) (56–64%) is more common than acute lymphoblastic leukemia (ALL) (21–38%). The predominant subtypes of AML in neonates are myelomonocytic, monocytic and megakaryotic leukemia (M4, M5, and M7). Leukemia cutis is a proliferation of leukemic cells in the skin that occurs in 25-64% of patients with neonatal acute leukemia.

Case presentation: A baby girl was born with characteristic and widespread skin lesions on the face in the form of erythematous patches partially violaceus/purplish in colour, multiple, well-defined, irregular edges, varying in shape and size, petechiae on the face and body that do not disappear with pressure and there is oedema on the nose and labia majora. Laboratory results showed hyperleukocytosis and thrombocytopenia. From the results of the examination of the peripheral blood smear, it showed normochromic anisopoikilocytosis, macrocytic, burr cell (+), normoblastemia, extremely increased leukocyte count, myeloblasts (+), monoblasts (+) and from bone marrow smears, it was found that there was an increase in erythropoiesis and granulopoiesis activity, myeloblasts 45 %, monoblast 15%. We diagnosed patients with congenital leukemia with AML-M4 and leukemia cutis.

Conclusion: Congenital leukemia with AML-M4 is rare in neonates. It has a typical manifestation that there is hyperleukocytosis, leukemiacutis and there is proliferation of myeloblasts and monoblasts. Congenital leukemia has a poor prognosis, namely 23% (1975-2000) and an increase of 44.2% (2001-2016).

Keywords: congenital leukemia, neonatal leukemia, AML-M4, leukemia cutis

INTRODUCTION

Leukemia is a rare cancer in the neonatal period. Das (2017) Congenital leukemia (CL) is leukemia that develops in the uterus.(Tewari et al., 2017) CL or also known as neonatal leukemia. Utami & Hospital, (2019) defined as a manifestation of leukemia that occurs in the first 4 weeks of life.(Pallavi et al., 2017; Rozen et al., 2013; Tewari et al., 2017; Utami & Hospital, 2019; Zhang et al., 2019) CL is one of the most common cancers in neonates, after teratoma and neuroblastoma, but it remains rare and almost always fatal without chemotherapy. Zhang et al., (2019) CL accounts for less than 1% of all childhood leukemias.(Das, 2017; Handler & Schwartz, 2015; Roberts et al., 2018; Tewari et al., 2017) In the Dutch study, the authors identified 15 cases over a 25 year period from 1975 to 1999 (ie less than 1 case per year).(Roberts et al., 2018) A study from Brazil identified 35 cases of non-DS leukemia in neonates over a 25 year period (1990-2013).(Roberts et al., 2018) Estimates of the incidence vary between 1–5 cases per million live births.(Das, 2017; Dosedla et al., 2019; Shrivastava et al., 2016; Tewari et al., 2017) Which is the main cause of death of all malignancies in newborns (Das, 2017)

Acute myeloid leukemia (AML) (56–64%) is more common in neonates with congenital leukemia than acute lymphoblastic leukemia (ALL) (21–38%), (Das, 2017; Dosedla et al., 2019; Roberts et al., 2018; Shrivastava et al., 2016; Tewari et al., 2017; Utami & Hospital, 2019), this is different from the prevalence of leukemia in children (childhood leukemia) which mainly consists of acute lymphoblastic leukemia (ALL).(Dosedla et al., 2019; Shrivastava et al., 2016; Tewari et al., 2017; Utami & Hospital, 2019) The predominant subtypes of AML in neonates are myelomonocytic, monocytic and megakaryotic leukemia (classification M4, M5 and M7 according to French-American-British [FAB]) (Handler & Schwartz, 2015)

Tumor syndrome with hepatosplenomegaly and skin nodules (leukemia cutis) is more common in CL.(Das, 2017) Leukemia cutis is a proliferation of leukemic cells in the skin that occurs in 25-64% of patients with acute neonatal leukemia. In fifty percent of cases, violaceous/purple nodules are an early manifestation of both AML and ALL.(Handler & Schwartz, 2015) Leukemia cutis sometimes precedes haematological findings by several weeks. The typical clinical picture includes multiple papules, macules, and nodules that are red to purple in color due to direct infiltration of the skin by malignant cells (Picone et al., 2014), The high total leukocyte count is identified by another unique feature.

The pathophysiology and prognosis of leukemia in this age group differ from cases occurring later in life. Although the etiology is unknown, the presence of leukemia at birth suggests possible intrauterine exposure to other drugs or toxins or the presence of genetic abnormalities and rearrangement of KMT2A which has been reported in 25% - 40% of cases. The prognosis for CL remains very poor, with 2-year survival of only 23% before 2000^{2} and 44.2% from 2001-2016.(Das, 2017) The overall prognosis in this age group remains poor despite intensive therapy.(Das, 2017) Diagnosis can be made based on the results of peripheral blood smears and bone marrow aspiration. Once the diagnosis is

established, an intensive chemotherapy regimen should be initiated. There is no specific treatment protocol for either ALL or neonatal AML(Mahakrishna & Ariawati, 2018)

We report the findings of a case of congenital leukemia with AML-M4 and leukemia cutis in a newborn baby girl.

CASE

A baby girl was born on 06/10/2020 spontaneously from a G3P2A0 mother at 39-40 weeks of gestation with an indication of the amniotic fluid leaking, the amniotic fluid looks clear and there is hist. Babies born immediately cry with an APGAR score of 7-9.

The mother performs ANC regularly and there is a history of untreated vaginal discharge in the last trimester, no history of other diseases during pregnancy, no history of taking drugs during pregnancy and no family history of the same disease.

On physical examination, the body weight was 2900 g and body length was 48 cm, according to the gestation period. Respiratory rate 48 x / min, body temperature 37 ° C, pulse 142 x / min, and a flat major fontanel. On the face, typical and widespread skin lesions appear in the form of erythematous patches partially violaceous in color, multiple, well-defined, irregular edges, varying in shape and size, and petechiae on the face and body that do not disappear with pressure and there is oedema in the nose and labia majora. There are no features that suggest to Down syndrome. Other physical examinations were within normal limits.

Fig. 1. Patient Dermatological Status

This patient has undergone complete blood laboratory examination and clinical chemistry which can be seen in table 1.

The results of a complete blood count showed hyperleukocytosis (WBC: 187.05 x 103 /µl), thrombocytopenia (Plt: 90 x 103/µl), an increase in IT ratio (0.23). An evaluation of peripheral blood smear and bone marrow puncture (BMP) have also been done with the results as shown in Tables 2 and 3.

On the first day of EHDT examination, there were myeloblasts 69%, promyelocytes 2%, rods 1%, segments 8%, lymphocytes 17%, monocytes 3% and nucleated erythrocytes

5/100 leukocytes, on the second day EHDT obtained myeloblasts 55%, monoblasts 15%, promyelocytes 1%, metamyelocytes 1%, rods 3%, segments 4%, lymphocytes 20%, monocytes 1% and nucleated erythrocytes 5/100 leukocytes. From the results of the BMP examination, it was found that myeloblasts 45%, promyelocytes 2%, other granulocyte series 9% and 15% monoblasts describe an Acute myelomonoblastic leukemia (AML-M4), Non-Down syndrome (?) neonatal leukemia.

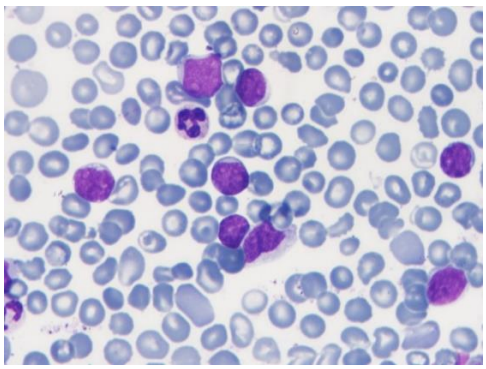

Fig. 2. Result of Peripheral Blood Smear

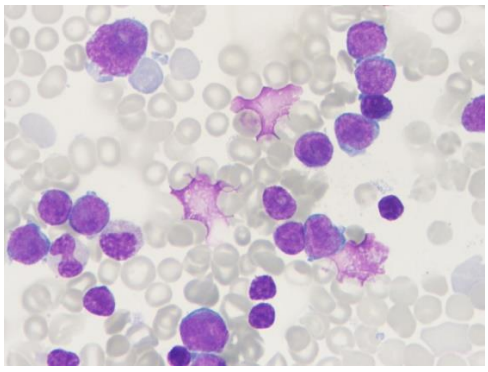

Fig. 3. Result of Bone Marrow Aspiration

We diagnosed this patient with Congenital Leukemia with AML-M4 and leukemia cutis. The patient was given injection of Vitamin K, IV Bactesyn 2 x 300 mg, IV Mikacin 1 x 50 mg.

DISCUSSION

The term "neonatal leukemia" is often known as "congenital leukemia".(Das, 2017) Congenital leukemia (CL) is the term used for leukemia that is diagnosed at birth or the first month of life. This is a rare occurrence,(Handler & Schwartz, 2015) with an incidence of approximately 1 – 8.6 per 10^3 live births.(Handler & Schwartz, 2015) In neonates with leukemia, AML is more common than ALL.(Handler & Schwartz, 2015) Acute myeloid leukemia accounts for 75% of acute leukemia in neonates.(Das, 2017) The predominant subtypes of AML in neonates are myelomonocytic, monocytic and megakaryotic leukemia (classification M4, M5 and M7 according to French-American-British [FAB]).(Handler & Schwartz, 2015)

The following are the diagnostic criteria for CL:(Das, 2017; Dosedla et al., 2019; Shrivastava et al., 2016)

a) Presentation of disease in the first 4 weeks of life,
b) Myeloid, lymphoid or erythroid cell proliferation,
c) Infiltration of cells into nonhematopoietic tissue and,
d) Absence of other diseases that can cause a leukemia-like leukemoid reaction.

CL is leukemia that develops in the uterus.(Tewari et al., 2017) In CL, all mutations occur in the uterus and the baby is born with a clear clinical and hematological manifestation of leukemia.(Roberts et al., 2018)

Clinical signs of leukemia may be clearly found at birth with hepatosplenomegaly, cuticle-petechial leukemia and ecchymosis.(Dosedla et al., 2019; Roberts et al., 2018; Shrivastava et al., 2016) The unique presentation of CL is the presence of nodular skin tissue infiltration (leukemia cutis) described as "blueberry muffin baby",(Das, 2017; Roberts et al., 2018) single or multiple 1–2.5 cm in diameter, firm, violaceous nodules.(Handler & Schwartz, 2015) which occurs in 25-64% of patients.(Das, 2017; Handler & Schwartz, 2015) In a cohort of neonates in the Netherlands with CL, the prevalence of skin infiltration by leukemic cells was 63.5%.(Handler & Schwartz, 2015) In 50% of cases, violaceous nodules are an early manifestation of both AML and ALL.(Handler & Schwartz, 2015)

Anemia, thrombocytopenia, leukocytosis or leukopenia with neutropenia and the presence of blasts on the peripheral blood smear confirm the diagnosis.(Das, 2017) Hyperleukocytosis, with a white blood cell count greater than > 50 x 10^9/L, is seen at 65% of ALL patients and 49% of AML patients with neonatal leukemia.(Handler & Schwartz, 2015) The mean leukocyte count was 10^4 × 109/L. Hyperviscosity and leukostasis can be fatal to the function of the central nervous system, heart and lungs.(Das, 2017)

Bone marrow aspiration and biopsy are necessary however, expertise is required when performing the procedure on a neonate. Immunopenotyping from bone marrow or even peripheral blood samples helps differentiate AML from ALL. Cytogenetic studies help characterize leukemia. Fluorescent in situ hybridization (FISH) helps in the rapid diagnosis of MLL rearrangements.(Das, 2017)

The etiology of CL is still unknown. There are several known risk factors associated with the development of congenital leukemia.(Mahakrishna & Ariawati, 2018) (Table 4).

The differential diagnosis of CL includes a leukemoid reaction (most commonly seen in very preterm neonates, especially when there is maternal chorioamnionitis or neonatal sepsis, stage IVS neuroblastoma,(Roberts et al., 2018) hemolysis, hypoxia and transient abnormal myelopoiesis (TAM).(Roberts et al., 2018) The list of differential diagnoses is shown in table 5.(Das, 2017)

Leukemoid reaction is a hematological disorder characterized by an increase in leukocytes of more than 50,000/uL, mainly consisting of mature neutrophils, as a result of abnormalities outside the bone marrow, or known as reactive.[3] The most common causes of leukemoid reaction are infections in neonates such as congenital infection cytomegalovirus, Syphilis, Toxoplasmosis, Rubella, Listeria monocytogenes, Herpes, or sepsis.(Das, 2017; Dosedla et al., 2019; Utami & Hospital, 2019) In addition, leukemoid reactions in neonates can also occur in hemolytic diseases such as blood group incompatibility,(Dosedla et al., 2019; Utami & Hospital, 2019) and birth-related hypoxia, or severe bleeding. Another factor that can cause a leukemoid reaction is malignancy (Dosedla et al., 2019; Utami & Hospital, 2019) and administration of drugs such as corticosteroids.(Utami & Hospital, 2019) In practice, CL is usually easily distinguished from the reactive changes seen in association with maternal chorioamnionitis and in infants with severe infection, particularly those who are very premature (gestational age <26 weeks at birth). In contrast to CL, there is a predominance of myelocytes, metamyelocytes and neutrophils and circulating blast cells rarely exceed 8%. These changes usually end within 3-4 days of birth. Roberts et al., (2018) In addition, patients with leukemoid reactions due to infection are usually characterized by intrauterine growth retardation and/or microcephaly (Utami & Hospital, 2019)

Hemolytic disease of the newborn characterized by increasing of the number of erythrocyte precursors in the peripheral blood can occur due to the presence of blast cells in the circulation. Often accompanied by hepatosplenomegaly due to extramedullary hematopoiesis and the presence of skin nodules.(Utami & Hospital, 2019) In TAM the percentage of blast cells varies widely, from about 10% to >80%. Circulating blast cells in TAM are pleomorphic and sometimes, but not always, have the characteristic cytoplasmic blebbing characteristic of megakaryoblasts. Another clue to the diagnosis of TAM is the presence of giant platelets and megakaryocyte fragments; most neonates with TAM are not anemic but platelet counts and white cell counts are highly variable. This finding should be considered in the presence of Down syndrome mosaicism if the typical clinical features of constitutional trisomy 21 are not present. In contrast, in non-DS cases, except those associated with t(1;22), differentiation was very often monocytic/monoblastic, anemia and thrombocytopenia. Typical skin nodules are quite common in non-DS leukemia, but are very unusual in TAM and are not seen in leukemoid reactions.(Roberts et al., 2018)

Violaceous nodules may be difficult to distinguish from other similar 'blueberry muffin baby' causes such as intrauterine infection, hemolytic disease of the newborn, juvenile xanthogranuloma, Langerhans cell histiocytosis, cutaneous neuroblastoma, neonatal lupus erythematosus and certain tumors. This condition can be differentiated based on serological and histological examination. Various infections, notably rubella and toxoplasmosis, in which extramedullary hematopoiesis results in skin tissue nodules. Serological evaluation in the absence of antibodies in the neonate's bloodstream with an

enzyme link immunosorbent assay (ELISA) can rule out causes of extramedullary hematopoiesis, including congenital infections such as rubella, syphilis, toxoplasmosis, listeriosis, herpes simplex, parvovirus B19, and cytomegalovirus. Also if the neonate is caused by congenital infection, there must be another manifestations such as hearing problem, choreoretinitis and small for gestational age.(Handler & Schwartz, 2015)

In hereditary sperocytosis and hemolytic disease of the newborn (ABO or RH incompatibility), the neonate will have a positive Coomb test and elevated indirect bilirubin. In twin-to-twin transfusion syndrome, in which one fetus receives blood from its twin fetuses, the condition in its severe form can cause anemia with a blueberry muffin appearance. Extensive neuroblastomas tend to have ecchymosis and periorbital bluish, firm nodules that redden upon compression; Rhabdomyosarcomas usually have normal result of bone marrow aspirates and peripheral blood smears but stained histologically with desmin and muscle-specific actin. Juvenile xanthogranulomas have Touton giant cells in 85% of cases and staining is negative for protein S-100 and CD1a, but positive for CD68 and factor XIIIa. Langerhans histiocytosis is generally diffuse, with small umbilical vesicles and pustules that rupture easily. Langerhans histiocytosis can be confirmed using CD1a, CD45 and/or S100 immunostaining on histology or identification of Birbeck granules on electron microscopy. In leukemia cutis, the diagnosis of rearrangement in the MLL gene can be made by fluorescence in situ hybridization (FISH) or reverse-transcriptase (RT) PCR analysis. Histological examination will show the dermis is diffusely replaced by pleomorphic mononuclear cells with a high nuclear-to-cytoplasmic ratio. In leukemia cutis, the diagnosis of rearrangement in the MLL gene can be made by fluorescence in situ hybridization (FISH) or reverse-transcriptase (RT) PCR analysis. Histological examination will show the dermis is diffusely replaced by pleomorphic mononuclear cells with a high nuclear-to-cytoplasmic ratio. In leukemia cutis, the diagnosis of rearrangement in the MLL gene can be made by fluorescence in situ hybridization (FISH) or reverse-transcriptase (RT) PCR analysis. Histological examination will show the dermis is diffusely replaced by pleomorphic mononuclear cells with a high nuclear-to-cytoplasmic ratio.(Handler & Schwartz, 2015)

The diagnosis of congenital leukemia in this patient was based on the presence of hyperlecocytosis (187.05 x 10^3/µl), thrombocytopenia (90 x 10^3/µl), myeloblasts and monoblasts in peripheral blood and bone marrow and the presence of leukemia cutis immediately at birth. From the physical examination, there was no hepatosplenomegaly which based on the theory of hepatosplenomegaly is a sign that is often found in congenital leukemia, therefore it is necessary to suggest an abdominal ultrasound examination in this patient. Other possible diagnoses can be ruled out such as leukemoid reaction excluded based on peripheral and bone marrow counts dominated by myeloblasts and monoblasts, clear amniotic fluid, normal temperature and a CRP that is not too high does not support the presence of a severe infection. Physical examination also did not reveal any organ abnormalities caused by congenital infections such as

microcephaly, choreoretinitis and small for gestational age. However, the possibility of congenital infection has not been completely ruled out because serological tests for the diagnosis of syphilis and TORCH have not been performed. The diagnosis of TAM can be ruled out where TAM is more common in Down syndrome and there is rarely leukemia cutis. In this patient, the physical examination did not show a Down syndrome picture and in this patient there was leukemia cutis but it was still recommended for cytogenetic examination. Peripheral blood examination shows many macrocytic erythrocytes and an increase in erythrocyte precursors, but this can also be seen in congenital AML. From the peripheral blood smears and bone marrow aspiration, the morphology of the blasts leads to the myeloid series, namely myeloblasts and monoblasts, which can lead to an Acute Myelomonocytic Leukemia (AML-M4). This is in accordance with the literature which states that AML is more common in congenital leukemia than ALL.

This is also has similar result with a study analyzing 59 cases of congenital leukemia from 2001-2016 which showed that AML was significantly more common in congenital leukemia than ALL ($p<0.001$), consisting of 66.1% women and 33.9% men. Aroud 67.8% of patients had skin infiltration. Hyperlecocytosis was present in 62.7% of patients (37/59) with a mean white blood cell count of 68.5 x 10^9/L (normal range 4-10^9 x 10^9/L), but anemia was less common (15/42, 35 ,7%) and the average platelet count was 78 x 10^9/L (normal range 100-300 x 10^9/L). Blast cells were present in peripheral blood and bone marrow (32/44, 72.7%).[2] The median age was 210 days and the 2-year survival rate was 44.2%, which was significantly higher than the average survival rate equivalent to 23% in patients from 1975–2000 (P=0.008). Amount of 57,6% patients treated with chemotherapy and had median age 734 days, compared to those who did not treated with chemotherapy had median age 646 days (P=0,12), with the 2-year survival rate was 47% and 41.(Das, 2017)

Once the diagnosis of leukemia is established, an intensive multi-agent chemotherapy regimen should be initiated. There is no specific treatment protocol for the treatment of neonatal ALL or AML. Neonatal AML patients were treated similarly to older AML patients with chemotherapy according to the AIEOP 2002/01 AML Protocol. The treatment protocol included steroids, vincristine, L-asparaginase, 6-mercaptopurine and methotrexate together with anthracyclines and cytarabine. Neonatal AML patients are treated similarly to older AML patients with a chemotherapy regimen based primarily on cytarabine and anthracyclines Mahakrishna & Ariawati (2018), Treatment of neonatal AML with anthracyclines and cytarabine has an overall survival (OS) of 30%. High recurrence rate (50%).(Das, 2017)

CONCLUSION

Had been reported case of acute leukemia in newborn neonates with AML-M4 and leukemia cutis have been reported. Congenital leukemia with AML-M4 is rare in neonates. It has a typical manifestation that there is hyperleukocytosis, leukemia cutis and there is

proliferation of myeloblasts and monoblasts. Congenital leukemia has a poor prognosis, namely 23% (1975-2000) and an increase of 44.2% (2001-2016). In establishing the diagnosis of this malignancy, it is necessary to distinguish it from other disorders such as leukemoid reactions, TAM, and neuroblastoma, which require good cooperation and communication between the fields of Fetomaternal, Perinatology, and Clinical Pathology. Bone marrow aspiration examination is very important to determine the type of leukemia, which will greatly affect the type of therapy.

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Table 1. Laboratory Examination Results

Inspection	Results		Referral Value
Hematology	**06/10/20**	**07/10/20**	
Hemoglobin	14.3	14.1	12.7 – 16.4 g/dl
Hematocrit	42.6	41.4	36 – 47%
Leukocytes	**187.05**	**195.31**	7.5 – 15.8 x 10^3/µl
Platelets	**102** **Correction: 90**	**90**	133 – 255 x 10^3/µl
Erythrocytes	3.94	3.84	3.7 – 4.7 10^{12}/µl
MCV	108.1	107.8	90 – 105 fl
MCH	36.3	36.5	32-36 pg
MCHC	33.6	33.8	34 – 35 g/dL
RDW	26.2	26.6	15.8 – 17.8%
Count Type	-/-/-/7/66/27	-/-/-/7/66/27	2-4/<1/<8/21-55/11-40/5-11
Ret-He	38.5		31.5-37.7 pg
Ret %	4.73(4,8)		2.1-3.7%
IT Ratio	**0.23**		<0.2
Clinical Chemistry			
GDS	**65**		36-99 mg/dL
Albumin		3.9	2.8-4.4g/dL
CRP	Positive (titer: 12)		Negative (-) Positive (titer = 12) Positive (titer = 24) Positive (titer = 48) Positive (titer = 96)

Table 2. Results of Evaluation of Peripheral Blood Smear

Inspection	Results	
EHDT	**06/10/20**	**08/10/20**
Erythrocytes	Normochromic, anisopoikilocytosis, macrocytic, burr cells +, normoblasts + (5/100 leukocytes)	Normochromic anisopoikilocytosis, macrocytic, burr cells +, normoblasts + (5/100 leukocytes)
Leukocytes	Greatly increased, myeloblasts +	Greatly increased, myeloblasts +, monoblasts +
Count Type	-/-/1/8/17/3, Myeloblasts 69%, promyelocytes 2%	-/-/3/4/20/1, myeloblasts 55%, monoblasts 15%, promyelocytes 1%, metamyelocytes 1%
Platelets	Decreased (correction: 90 x103/µl)	Decreased

Table 3. Results of Examination of Bone Marrow Aspiration

Inspection	Results
BMP	**08/10/20**
Cellularity	Hypercellular
Ratio M : E	4.5 : 1
Erythropoiesis	Activity increased, 20% ANC
granulopoiesis	Increased activity, 45% myeloblasts, 2% promyelocytes, other granulocyte series 9%
Megakaryopoiesis	Activity decreased
Etc	There is proliferation of monoblasts (15%)
Conclusion	Acute myelomonoblastic leukemia (AML-M4), Non-Down syndrome (?) neonatal leukemia.

Table 4. Putative Relationship Occurrence of Congenital Leukemia.(Das, 2017; Handler & Schwartz, 2015)

Putative Relationship Occurrence of Congenital Leukemia
Chromosomal aberrations: Trisomy 21 and others (1,8,9,13 and 19)

Congenital syndromes: Ellis-van Creveld, Klippel-Feil
Identical twins with leukemia
Large-for-date babies
Prelabor elective caesarean section
Alcohol consumption during pregnancy
Marijuana consumption during pregnancy
Mother exposed to topoisomerase II inhibitors (flavonoids)

Table 5. Differential Diagnosis of Congenital Leukemia.(Das, 2017)

Differential Diagnosis of Congenital Leukemia
Intrauterine infections: Toxoplasmosis, cytomegalovirus, rubella, herpes, syphilis and HIV
Postnatal infection: Severe bacterial sepsis
Hematologic disorders: Blood group incompatibilities, twin-to-twin transfusion syndrome, alpha thalassemia, Diamond-Blackfan anemia, congenital dyserythropoiesis anemia
Other malignancies: Neuroblastoma, congenital rhabdomyosarcoma
Histiocytic disorders: Langerhans cell histiocytosis, juvenile xanthogranuloma, hemophagocytic lymphohistiocytosis