

# Acute myeloblastic leukemia in neonate

Bagus Ngurah Mahakrishna, Ketut Ariawati

## ABSTRACT

**Introduction:** Congenital leukemia is defined as leukemia that develops intra uterine. It is an extremely rare malignancy associated with poor prognosis and a poorly understood natural history. Incidence reported to be 1 per-5 million neonates. Acute myeloblastic leukemia is more common than acute lymphoblastic leukemia in neonate. Clinical signs of neonatal leukemia among various patients such as hepatosplenomegaly, enlarged lymph nodes, leukemia cutis, and hyperleukocytosis. **Case Report:** We present a 6-days-old female neonate, referred to Sanglah Hospital with respiratory distress and lethargy. We found her with high breathing effort and fever. Physical examination found hepatomegaly. Laboratory examinations showed hyperleukocytosis (leucocyte count 140.000/mm<sup>3</sup>), anemia (hemoglobin 12.56 g/dL), normal thrombocytes count (245.400/mm<sup>3</sup>), and other laboratories within normal limits. Peripheral blood smear showed erythrocyte with normocytic normochromic, normoblastemia, leucocytes with elevated white blood cell count, immature white blood cells (blasts) as appeared in acute leukemia. Leukemia phenotyping showed myeloid lineage with aberrant expression CD 7 appropriate to acute myeloblastic leukemia. We diagnosed the patient with acute myeloblastic leukemia. Patient got hydration intravenously in order to prevent leukostasis syndrome. We planned

a chemotherapy protocol. **Conclusion:** Acute myeloblastic leukemia in neonate is a rare case. It was fetal form of malignant diseases with various clinical presentation such as high breathing effort and hyperleukocytosis. Its exact cause is still not fully understood. Congenital leukemia has a poor prognosis with an overall survival rate only 20% at 2 years of age.

**Keywords:** Acute myeloblastic leukemia, Hyperleukocytosis, Malignancy, Neonate

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## INTRODUCTION

Congenital leukemia is defined as leukemia that develops intra uterine, and occurs within 4 to 6 weeks of birth [1]. It is an extremely rare malignancy associated with poor prognosis and a poorly understood natural history. The term leukemia generally refers to acute lymphoblastic leukemia (ALL) or acute myeloblastic leukemia (AML) [2]. Incidence is reported to be 1 per-5 million neonates [3]. AML is more common than ALL in the neonate [4].

The etiology of congenital leukemia is still unknown. Several risk factors are known to be associated with the development of congenital leukemia. History of maternal alcohol consumption, tobacco smoking, maternal exposures to radiation, high birth weight, high levels of insulin like growth factors, being a later born child, congenital infection are suspected as a risk factor [5, 6].

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The clinical characteristics of neonatal leukemia differ significantly from those of leukemia in older children. The characteristic presentation of congenital leukemia are hepatosplenomegaly, enlarged lymph nodes, leukemia cutis, and hyperleukocytosis. Enlargement of the liver is found more often than an enlarged spleen. Enlarged lymph nodes are found in only one out of four patients.

The diagnostic criteria for congenital leukemia: presentation in the first 4 weeks of life; proliferation of immature myeloid, lymphoid or erythroid cells; infiltration of these cells into nonhematopoietic tissues and; the absence of other diseases which might cause this proliferation [7].

Definite diagnosis can be made based on peripheral blood smear and bone marrow aspirate. When the diagnosis leukemia is established, an intensive multi-agent chemotherapeutic regimen should be started. There is no specific treatment protocol for the treatment of either neonatal ALL or neonatal AML. Congenital leukemia has a poor prognosis with an overall survival rate of only 20% at two years of age.

## CASE REPORT

A 6-days-old female was referred to Neonatal Intensive Care Unit Sanglah Hospital with respiratory distress and lethargy. Respiratory distress started within 30 minutes after birth. It accompanied by chest retractions especially in subcostal and intercostal. There was no central cyanotic appeared. Patient was treated in Neonatal Intensive Care Unit Private Hospital for six days of antibiotic therapy and continues positive airway pressure (CPAP) support. Patient did not show any improvement and was decided to be referred to Sanglah Hospital.

In Emergency Room Sanglah Hospital, we found her with high breathing effort, fever, and grunting. Downes score total was 5, and we decided to treat her in Neonatal Intensive Care Unit with CPAP support.

She was born preterm by caesarean section with birth weight 2100 gram, birth length 40 cm, head circumference 27 cm, and spontaneously crying.

The patient had no familial history of tumor or cancer. She was the third child of three children. History of maternal alcohol consumption, tobacco smoking, exposure to chemicals, pesticides, X-ray radiation, the use of insect repellent, and stay near high voltage power was denied.

On physical examination the baby looked unwell, lethargy and grunting. Activity, tone, and reflex were weak with heart rate 140 beats/minute, respiratory rate 72 breaths/minute, axillary temperature was 38.2°C. Nasal flaring clearly seen. No anemia and spontaneous bleeding found. There were subcostal and intercostal retractions, breathing sound was normal. In cardiac examination, systolic heart murmur heard at the intercostal space II parasternal line sinistra. Abdominal examination found hepatomegaly with liver was palpable in 4 cm below right costal margin, 4 cm below processus xiphoideus, sharp and regular edge, tender in consistency.

We did serial blood values in this case. The serial blood values as seen in Table 1.

Peripheral blood smear showed erythrocytes with normocytic normochromic, anisocytosis, normoblastemia; leucocytes with an elevated white blood cell count, immature white blood cells (blasts); thrombocytes in normal limit; impressed an acute leukemia (Figure 1). In summary, the patient had hyperleukocytosis, anemia, and other blood values in normal limit. Blood culture result was still waited to be

Table 1: Blood values trend

Blood values	Day 1st	Day 10th	Day 19th
Hemoglobin (Hb)	12.56 g/dL	11.48 g/dL	9.70 g/dL
Hematocrit (Ht)	41.16%	37.86%	30.08%
Leukocytes	<b>140.100/mm<sup>3</sup></b>	<b>16.660/mm<sup>3</sup></b>	<b>6.800/mm<sup>3</sup></b>
Neutrophil	11.82 (8.44%)	2.60 (15.60%)	1.20 (17.59%)
Lymphocyte	61.38 (43.81%)	11.69 (70.21%)	4.68 (68.80%)
Thrombocytes	245.400/mm <sup>3</sup>	136.400/mm <sup>3</sup>	114.900/mm <sup>3</sup>
Immature to total neutrophil (IT) ratio	0.70	0.02	0.02
C-Reactive Protein (CRP)	11.89 mg/dL	0.83 mg/dL	0.83 mg/dL
<b>Electrolyte</b>			
Sodium	136 mmol/L	142 mmol/L	137 mmol/L
Chloride	99.9 mmol/L	109.90 mmol/L	95.6 mmol/L
Potassium	3.8 mmol/L	4.88 mmol/L	4.2 mmol/L
Calcium	9.2 mg/dL	9.0 mg/dL	8.2 mg/dL
<b>Kidney function test</b>			
BUN	11.0 mg/dL		
Creatinin serum	0.91 mg/dL		
Uric acid	5.40 mg/dL	1.30 mg/dL	

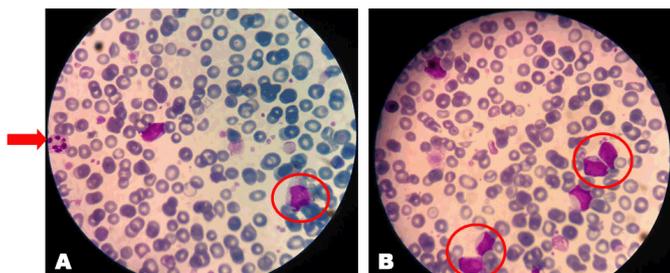


Figure 1(A and B): Peripheral blood smear showed blasts (red circle) and neutrophil (red arrow).

confirmed. Chest X-ray revealed a consolidation on the right and left paracardial region suspected neonatal pneumonia. Echocardiography showed large patent ductus arteriosus, and patent foramen ovale.

We diagnosed patient with suspected neonatal leukemia (AML differential diagnosis ALL), neonatal pneumonia, suspected early onset sepsis, large patent ductus arteriosus, and patent foramen ovale. Patient was treated in the incubator with CPAP support. Patient had intravenous fluid hydration with D5 1/4 NS fluid as much as 1.5 times of the total daily fluid maintenance requirement which was 380 ml/day ~ 16 ml/hour. Sodium bicarbonate 25 meq in 500 ml D5 1/4 NS (to alkalinize urine keeping pH urine 7.5), and allopurinol 10 mg/kg/day equal to 50 mg over 8 hours (oral). Patient got paracetamol 15mg/kg/dose over 6 hours intravenous and anti-failure furosemide 2 mg over 12 hours intravenous and spironolactone 3.125 mg over 24 hour oral. Antibiotics therapy were started with ampicillin 50 mg/kg/dose over 12 hours and amikacin 7.5 mg/kg/dose over 12 hours intravenously.

Evaluation during treatment (day 10th of treatment), patient had less effort of breathing, no temperature instability. Activity, tone, and reflex were normal with heart rate 140 beats/minute, respiratory rate 48 breaths/minute, axillary temperature was 36.9°C. Nasal flaring clearly seen. There were minimal chest retraction appeared, breathing sound was normal. In cardiac examination, systolic heart murmur heard at the intercostal space II parasternal line sinistra. Abdominal examination found hepatomegaly with liver was palpable in 4 cm below right costal margin, 4 cm below processus xiphoideus, sharp and regular edge, tender in consistency. Blood values evaluation showed that leukocytes level and IT ratio was decreased, whilst other laboratories values within normal limits as seen in Table 1. Blood culture result showed that there was no bacterial growth. Immunophenotyping resulted myeloid lineage with aberrant expression CD 7 that appropriate to acute myeloblastic leukemia.

We diagnosed patient with acute myeloblastic leukemia, neonatal pneumonia, large patent ductus arteriosus, patent foramen ovale, and clinically early onset sepsis. Patient was treated in the incubator with CPAP support, anti-failure furosemide 2 mg over 12

hours intravenous and spironolactone 3.125 mg over 24 hour oral. Intravenous fluid hydration and antibiotics was stopped due to normal septic marker result and no bacterial was found in blood culture. We planned a chemotherapy protocol.

Evaluation during treatment (day 19th of treatment), there was no respiratory distress, no temperature instability. Activity, tone, and reflex were normal with heart rate 140 beats/minute, respiratory rate 48 breaths/minute, axillary temperature was 36.9°C. There were no retractions, breathing sound was normal. In cardiac examination, systolic heart murmur heard at the intercostal space II parasternal line sinistra. Abdominal examination found hepatomegaly with liver was palpable in 4 cm below right costal margin, 4 cm below processus xiphoideus, sharp and regular edge, tender in consistency. Blood values evaluation showed that leukocytes level was decreased, whilst other laboratories values within normal limits as seen in Table 1. Re-echocardiography showed spontaneous patent ductus arteriosus closure, and patent foramen ovale, mild tricuspid regurgitation, trivial pulmonary regurgitation. We diagnosed the patient with acute myeloblastic leukemia, neonatal pneumonia, patent foramen ovale, mild tricuspid regurgitation, trivial pulmonary regurgitation, and clinically early onset sepsis. There was no specific management. We planned a chemotherapy protocol.

## DISCUSSION

Neonatal leukemia is diagnosed in the first 30 days after birth. Estimated incidence of neonatal leukemia ranges from 1 to 5 per-million live births. Less than 1% of all childhood leukemia is diagnosed in neonates [5]. Clinical signs of neonatal leukemia various among patients such as hepatosplenomegaly, a very frequently occurring symptom and can be found in around 80% of the patients. Enlargement of the liver is found more often than an enlarged spleen. Enlarged lymph nodes are found in only one out of four patients. Leukemia cutis (nodular cutaneous infiltrates), which is described in around 60% of all patients, are specific cutaneous leukaemic infiltrates and usually appear as firm blue, red, or purple nodules in a generalised distribution. Leukemia cutis is reported to be the initial presenting sign in about half of the neonatal cases. The third clinical feature, hyperleukocytosis, is present in the majority of the patients [5, 6]. In this case, hepatomegaly was found in abdominal examination with liver was palpable in 4 cm below right costal margin, 4 cm below processus xiphoideus, sharp and regular edge, tender in consistency. There were no enlarged lymph nodes and leukemia cutis. Laboratory investigation showed hyperleukocytosis with leucocytes count 140.100/mm<sup>3</sup>.

Immunophenotyping is a convenient method for quick and reproducible diagnosis of the majority of hematological malignancies. Immunophenotyping

become a widely used method to diagnose and classify acute leukemia, first in distinction of acute leukemia from other neoplastic diseases and reactive disorders, second in distinction of AML and ALL, and third in classification of AML and ALL into their subsets. It improves accuracy of acute leukemia classification and is considered particularly useful for identifying aberrant lineage association of acute leukemia. Aberrant phenotype in AML is known as a poor prognostic indicator. Aberrant phenotype is a phenomenon in which lymphoid associated and other myeloid lineage markers expressed in myeloblasts or myeloid associated markers expressed in lymphoblasts. Aberrant phenotype incidence has been reported in both ALL and AML with varying frequencies as high as 88%. Up to 48% of AML cases were reported to have aberrant expression of a single antigen associated with lymphoid cell lineage. Most frequently expressed lymphoid antigens were CD7 (31%) and CD2 (29%). Other marker was expressed as CD3 (15.7%), CD19 (12.2%) CD22 (12.2%), CD20 (6.1%) [8]. Aberrant CD56 and CD7 expression is associated with low remission rates in patient with acute leukemia [9]. In this case, leukemia phenotyping resulted myeloid lineage with aberrant expression CD 7 as in acute myeloblastic leukemia.

Antibodies to cell surface proteins are useful in the diagnosis of AML and can be correlated with the FAB subtypes (Table 2) [10].

Aberrant antigen expression in AML is associated with relapse and poor prognostic. A journal searching was done to know the prognosis of acute leukemia according to immunophenotyping result "Aberrant expression of CD7, CD56, and CD79a antigens in acute myeloid leukemias" [11]. The conclusion of this journal that AML with aberrant antigen expression can be distinguished from biphenotypic leukemia, which may manifest as both myeloid and lymphoid phenotype. The aberrant expression of CD7, CD56, and CD79a, represent the capacity of these leukemias for trilineal expression from leukocyte differentiation antigens, portends a poor prognosis [11]. In this case, leukemia phenotyping resulted aberrant expression CD 7, so that the patient had a poor prognosis.

An emergency condition in oncology that can be found is hyperleukocytosis, characterized by an increased number of peripheral white blood cell count >100,000/ $\mu$ L. Only a small proportion of AML patients present with hyperleukocytosis, but these patients have a particularly dismal prognosis due to a higher risk of early death resulting from hyper leukocytosis complications and higher probability of relapse and death in the long term period. Two main pathogenesis factors are responsible for the development of hyper leukocytosis were a rapid blast proliferation leading to a high leukemic tumor burden, and disruption in normal hematopoietic cell adhesion leading to a reduced affinity to the bone marrow. The three main complications of hyperleukocytosis were disseminated intravascular coagulation (DIC), tumor lysis syndrome and leukostasis. DIC is caused by high cell turnover and associated high levels of released tissue factor which then triggers the extrinsic pathway via factor VII. Tumor lysis syndrome may occur as a result of spontaneous or treatment induced cell death. The fact that myeloid blasts are larger than immature lymphocytes or mature granulocytes and that leukemic blasts were considerably less deformable than mature leukocytes explains the higher incidence of leukostatis complications in AML as opposed to acute lymphoblastic leukemia, chronic myeloid leukemia or chronic lymphocytic leukemia [12]. In this case, laboratory investigation showed complete blood count with hyperleukocytosis 140.100/mm<sup>3</sup>. There were no DIC, tumor lysis syndrome and leukostasis occurred in this patient.

Hyperleukocytosis hydration with intravenous fluids 5% glucose in ¼ normal saline, as much as 2–3 times needs maintenance fluids or 2–3 liters/m<sup>2</sup>/day to get minimal diuresis of 2–3 ml /kg/hour. Urine alkalinize was kept by giving bicarbonate sodium into an intravenous fluid around 40-60 meq/L in order to keep urine pH between 7.0–7.5. Allopurinol was given 10 mg/kg/day to decrease the concentrate of uric acid. In this case, patient got intravenous fluid hydration with D5 ¼ NS fluid as much as 1.5 times of the total daily fluid maintenance requirement which was 380 ml/day ~ 16 ml/hour. Bicarbonate natrium 25 meq in 500 ml D5¼NS (to alkalinize to keep urine pH 7.5), and

Table 2: Relationship among Immunologic Surface Markers with FAB Subtypes of Acute Myeloblastic Leukemia [10]

FAB Subtype of AML	Immunologic Surface Marker										
	HLA-DR	CD11b	CD13	CD14	CD15	CD33	CD34	Glycophorin	CD41	CD42	CD61
M1/M2	+				+	+	+				
M3/M3V		+	+		+	+	+				
M4/M5	+	+	+	+	+	+	+				
M6	+		+			+	+	+			
M7	+		+			+	+		+	+	+
Mo			+			+	+				

In this case, HLA-DR, CD 36, CD 117, CD 34, CD 7, and CD 33 was found in blast immunophenotyping associated with acute myeloblastic M1/M2.

allopurinol 10 mg/kg/day equal to 50 mg over 8 hour (oral).

Patent ductus arteriosus (PDA) is one of the most common congenital heart defects. PDA is defined as failure of the ductus arteriosus to close within 72 hours after birth. The incidence of PDA in term neonates is 1 in 2000 births, accounting for 5–10% of all congenital heart disease. In preterm neonates, the incidence is far greater, with reports ranging from 20–60%. Approximately 80% of preterm infants presenting with respiratory distress syndrome (RDS) also have a PDA, which may be due to the increased circulating prostaglandins (PGE<sub>2</sub>) associated with respiratory distress. The most common complication of a persistent PDA after birth is heart failure [13]. In this case, patient was born preterm with respiratory distress started within 30 minutes after birth. Echocardiography showed large patent ductus arteriosus. Patient got paracetamol 15 mg/kg/dose over 6 hours intravenous, anti-failure furosemide 2 mg over 12 hours intravenous and spironolactone 3.125 mg over 24 hour oral to prevent the existence of heart failure.

When the diagnosis leukemia is established, an intensive multi-agent chemotherapeutic regimen should be started. There is no specific treatment protocol for the treatment of either neonatal ALL or neonatal AML. Neonatal AML patients are treated similarly to older AML patients with a chemotherapeutic according the AIEOP AML2002/01 Protocol [5,14]. Treatment protocols include 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 chemotherapeutic regimen mainly based on cytarabine and anthracyclines. In this case, we planned a chemotherapy protocol.

## CONCLUSION

Acute myeloblastic leukemia in neonate is a rare case. It was a fetal form of malignant diseases with various clinical presentation such as respiratory distress, hepatosplenomegaly, and hyperleukocytosis. Its exact cause is still not fully understood. When the diagnosis leukemia is established, an intensive multi-agent chemotherapeutic regimen should be started. Congenital leukemia has a poor prognosis with an overall survival rate of only 20% at 2 years of age.

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## Author Contributions

Bagus Ngurah Mahakrishna – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Ketut Ariawati – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

## Guarantor of Submission

The corresponding author is the guarantor of submission.

## Source of Support

None.

## Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

## Conflict of Interest

Authors declare no conflict of interest.

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