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Dewan Redaksi Majalah IJCP

NEONATAL ACUTE MYELOID LEUKAEMIA

(Leukemia Mielosistik Akut Pada Neonatus)

Luh Putu Rihayani Budi[1], Ketut Ariawati[1], Sianny Herawati[2]

ABSTRACT

Acute myeloid leukaemia (AML) is a. malignant, clonally disease that involves proliferation of blasts in bone marrow, blood, or other tissue. The blasts most often show myeloid or monocytic differentiation. The incidence of AML increases with age, but when neonatal leukaemia does occur, it is paradoxically AML rather than ALL. All the signs and symptoms that present on patient with AML are caused by the infiltration of the bone marrow with leukaemic cells and resulting failure of normal haematopoiesis. Without the normal haematopoietic elements, the patient is at risk for developing life-threatening complications of anaemia, infection due to functional neutropenia, and haemorrhage due to thrombocytopenia. Organomegaly is seen in approximately half of patient with AML due to hepatic and sphlanic infiltration with leukaemic blasts. Prognosis of neonatal leukaemia is poor with the 6-month survival rate is only one third despite aggressive chemotherapy. It has higher mortality rate than any other congenital cancer. The researchers reported two of AML diagnosed cases in neonatal period. The first case, a one-day-old male was referred with respiratory distress and suspect Down syndrome with spontaneous petechiae. The second case, a 17-day-old female presented with bloody diarrhoea and history of hypothyroid. Dysmorphic face and hepatosplenomegalia were found in both of the physical examination. Their complete blood count revealed leukocytosis and thrombocytopenia. Peripheral blood smear revealed myeloblast 30% on the first case and 23% on the second case. Both immunophenotyping revealed the population of blast expressing myeloid lineage (CD33 and CD34).

Key words: *Neonatal, acute myeloid leukaemia*

ABSTRAK

Leukemia mielositik akut (LMA) adalah keganasan sel darah yang ditandai dengan ploriferasi sel blast dengan diferensiasi mieloid atau monositik di sumsum tulang, darah tepi, dan jaringan lainnya. Angka kejadian LMA meningkat dengan bertambahnya usia, namun pada masa neonatus angka kejadian LMA lebih tinggi dibandingkan LLA. Gejala yang muncul pada pasien dengan leukemia diakibatkan oleh infiltrasi sumsum tulang oleh sel-sel leukemia yang mengakibatkan gagalnya hematopoiesis normal. Gagalnya hematopoiesis menyebabkan pasien menjadi berisiko untuk mengalami anemia, infeksi berat akibat neutropenia, dan perdarahan akibat trombositopenia. Infiltrasi sel-sel blast pada hati dan lien menyebabkan terjadinya organomegali pada organ-organ tersebut (hepatosplenomegali). Neonatus dengan leukemia memiliki perjanana penyakit yang buruk dengan angka keselamatan selama 6 bulan hanya sepertiga walaupun dengan menjalani kemoterapi. Leukemia pada masa neonatus memiliki angka kematian yang lebih tinggi dibandingkan dengan keganasan kongenital lainnya. Kami melaporkan dua kasus LMA pada masa neonatus. Kasus pertama adalah laki-laki usia satu hari yang dirujuk dengan distress napas dan kecurigaan Sindrom Down dengan petekiae spontan. Kasus ke dua adalah perempuan berusia 17 hari yang datang dengan keluhan diare berdarah dengan riwayat hipotiroid sebelumnya. Wajah yang dismorfik dan hepatosplenomegali ditemukan pada kedua neonatus tersebut. Pemeriksaan darah tepi pada keduanya menunjukkan leukositosis dan trombositopenia, sedangkan hapusan darah tepi menunjukkan mieloblast sebanyak 30% pada kasus pertama dan 23% pada kasus ke dua. Pemeriksaan fenotip imonologis yang dilakukan pada kedua neonatus tersebut menunjukkan populasi sel blast yang mengekspresikan petanda mieloid (CD33 dan CD 34).

Kata kunci: Neonatus, leukemia mielositik akut

INTRODUCTION

Acute myeloid leukaemia (AML) is a clonally expansion of any one of several non lymphoid haematopoietic progenitors that retain the capacity of self-renewal, but are severely limited in their ability to differentiate into functional mature cells. These various progenitors include cells of granulocyte, monocyte/macrophage, erythroid, and megakaryocytic lineage.[1]

AML is the major subtype of acute leukaemia in adults, but only represents 15% of newly diagnosed cases of acute leukaemia in children.[2] While 2.5% to 5% of paediatric ALL occurs in infants, AML in infants comprises 6% to 14% of paediatric AML. The peak

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annual incidence of paediatric AML of 10.6 per million occurs during the first year of life. Both ALL and AML occur more frequently in female than male infants.[3]

Almost 80% of patients with AML will demonstrate chromosome abnormalities, usually a mutation resulting from a chromosomal translocation. The translocation causes abnormal oncogene of tumour suppression gene expression, and this result in unregulated cellular proliferation. [4]

There is a large range of presenting signs and symptoms for paediatric AML. Organomegaly is seen in approximately half of patients with AML due to hepatic and sphlanic infiltration with leukaemic blasts.[2] Hyperleucocytosis in AML can result in life-threatening complications due to the large size of AML blasts and their adhesion properties. When the peripheral WBC is >100× $10^9/\mu$L, AML blasts can begin to clump resulting in leucostasis and slugging of blasts in small vessels. This in turn leads to cellular hypoxia, tissue infarction, and ultimately tissue haemorrhage. Rapid lowering of WBC is necessary, often using leukapheresis along with aggressive hydration.[2]

The factors that influence outcome in infants with AML remains generally obscure.[5] In infants with congenital leukaemia under the age of 1 month, the 6-month survival rate is only one third despite of aggressive chemotherapy. It has higher mortality rate than any other congenital cancer, but recently some reports showed spontaneous remission.[6]

First Case

A near term male neonate weighing 2,560 gram age 1-day-old was referred to Sanglah hospital with diagnosed as preterm baby suffering respiratory distress and suspect of Down syndrome. The baby was delivered by a caesarean section due to placenta previa. His mother suffered from tuberculosis infection and already completed her tuberculosis treatment before the pregnancy. No diseases during the pregnancy period were noted, nor were consuming any traditional medicine.

Gross examination of the infant noted at birth to have petechiae and ecchymosis on his whole body and suffered respiratory distress approximately 10 minutes after the delivery. Physical examination showed dysmorphic features (figure 1.), hepatomegaly, and no limphadenopaty. Thorax examination revealed retraction in the chest wall without rhales or wheezing and murmur grade III/VI on ICS II left parastrelnal line.

The initial complete blood count revealed leukocytosis (WBC 63.88× $10^3/\mu$L) with monocyte 51.9%, neutrophils 36.30%, lymphocyte 8.30%, eosinophil 0.06%, and basophile 3.84%. The haemoglobin was 12.7 g/dL, platelets count 109.4× $10^3/\mu$L, and reticulocyte 0.6%. First CRP was not elevated and first blood culture revealed *Acinetobacter iwoffii*. Thorax x-ray showed infiltrate in both paracardial sinister and dextral and echocardiography revealed small secundum ASD with mild LPA stenosis. We diagnosed him as preterm baby with respiratory distress syndrome, severe sepsis, and small secundum ASD. We treated the patient with empiric antibiotics, CPAP support, no cardiac treatment, and planned to evaluate echocardiography at six-month-old.

Second complete blood count revealed hyperleukocytosis 111.0× $10^3/\mu$L, with monocyte 3.20%, neutrophils 43.20%, lymphocyte 8.30%, eosinophil 0.70%, and basophile 6.30%. The haemoglobin was 13 g/dL and platelets count 137 x $10^3/\mu$L. No elevation on CRP and the IT ratio was difficult to evaluate. The peripheral blood smear showed normochromic normocytic anaemia with slight anisocytosis,

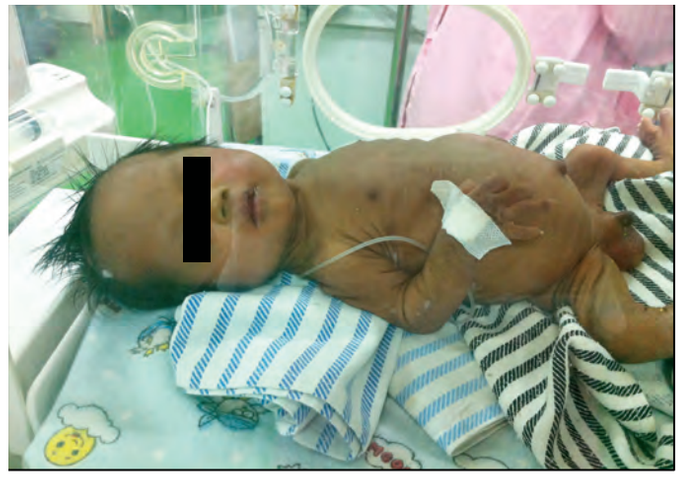

Figure 1. A one-day-old male neonate with dysmorphic feature (Picture was taken under parent permission)

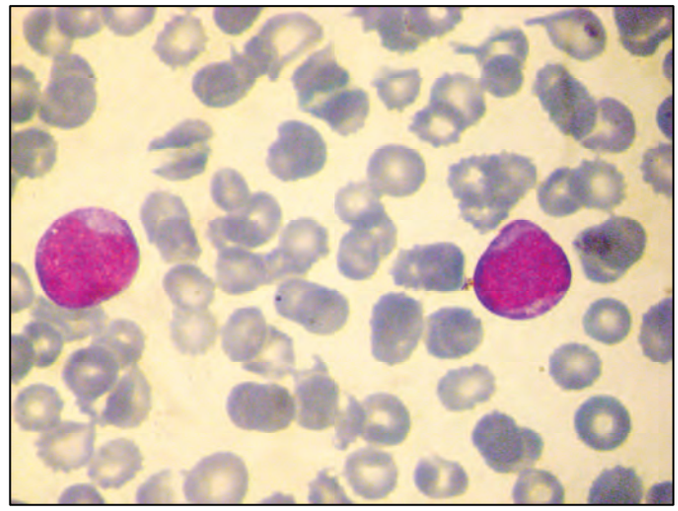

Figure 2. The peripheral blood smear on the first case revealed myeloblast

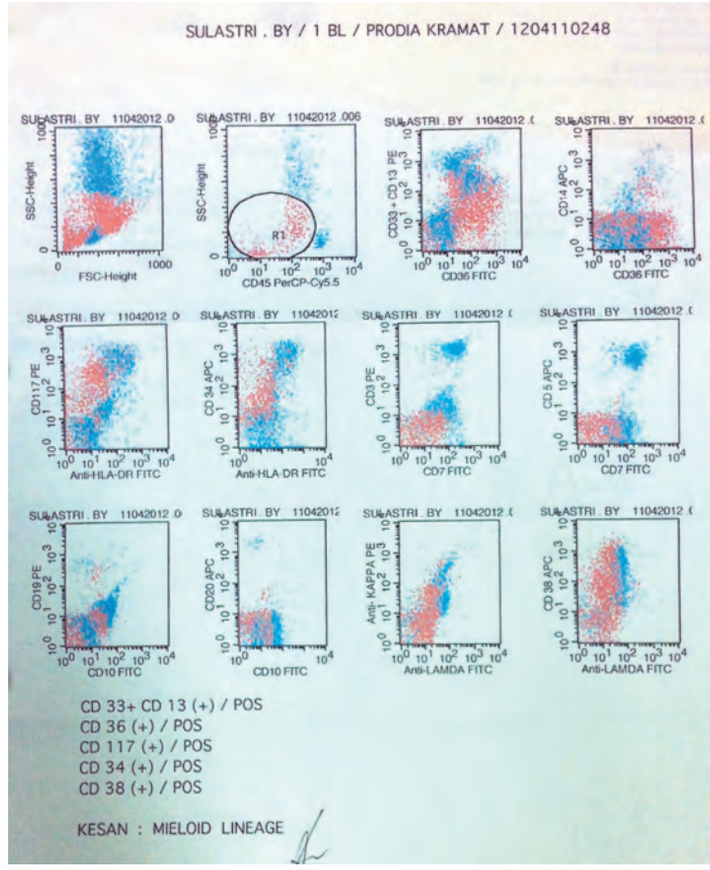

Figure 3. Immunophenotyping appropriate to myeloid lineage

thrombocytopenia with no giant thrombocyte, and leukocytosis with 10% myeloblast. The researchers suspected the baby with AML. Aggressive hydration was performed due to hyperleukocytosis. Complete blood count, urinalysis, uric acid, electrolyte, and renal function were evaluated every day.

Second blood smear showed normochromic normocytic anaemia with slight anisocytosis, thrombocytopenia with no giant thrombocyte, and leukocytosis with 30% myeloblast. No bone marrow aspiration was performed and by immunophenotyping revealed the population of blasts expressing CD13 positive, CD33 positive, CD36 positive, CD117 positive, CD34 positive, and CD38 positive (figure 6). A diagnosis of acute myeloid leukaemia was made. The

parents refused of chemotherapy treatment, they only want conservative one.

Second Case

The examined second case was a 17-day-old female neonate presented with bloody diarrhoea and history of hypothyroid. No fever present, as well as respiratory distress noted, and other bleeding manifestation. She was born on March 9th 2012, near preterm (35-36 weeks) by normal vaginal delivery (birth weight 2680 g and length 48 cm). The mother had regular prenatal care with no history of antenatal medical illness.

Physical examination showed dysmorphic feature noted since she was born and suspected with Down syndrome. The thorax examination revealed systolic murmur grade II/VI without precordial bulging, there is no ictus cord's, as well as retraction. On the abdomen region were found hepatosplenomegalia. No petechiae or echimosis were found on skin.

The initial complete blood count revealed leukocytosis (WBC 23.29× $10^3/\mu$L) with monocyte 14.1%, neutrophils 39.0%, lymphocyte 45.7%, eosinophil 0.1%, and basophile 1.1%. The haemoglobin was 14.9 g/dL, platelets count 27 x $10^3/\mu$L, and reticulocyte 3.6%. The faeces analysis was within normal limit. On the peripheral blood smear showed hypochromic anisopoikilocytosis erythrocyte, leukocytosis with predominantly myeloid, monoblast, and myeloblast 23%, and thrombocytopenia (figure 4). Echocardiography revealed patent foramen ovale or small ASD secundum with mild tricuspid regurgitation and doesn't need any therapy. In this case the chromosome analysis established Down syndrome.

Antibiotic treatment was given, continuing hypothyroid therapy, and transfusion packed red cells and platelets. No bone marrow aspiration was performed and by leukaemia phenotyping was revealed the population of blasts expressing HLA-DR positive, CD33 positive, CD34 positive, CD117 positive (figure 5). A diagnosis of acute myeloid leukaemia was made. The parent refused chemotherapy treatment except only the conservative one.

DISCUSSION

The term infant acute leukaemia is usually applied when the diagnosis is made within the first twelve months after birth.[7] The incidence of AML increases with age. However, when congenital leukaemia (occurring during the neonatal period) dose rarely occurs, it is paradoxically AML rather than ALL and is often monocytic. The rate of AML is higher in males than females, and there is increased incidence in the developing country but in the more industrialized one. Congenital defects such as Down syndrome and bone marrow failure syndrome such as Fanconi's anaemia has demonstrated that these factors are often implicated in the pathogenesis of AML.[4]

The WBC may be normal, increased, or decreased in patient with AML. It is markedly elevated over 100 x $10^9/\mu$L cells in less than 20% of cases. Conversely, the WBC is less than 5.0 x $10^9/\mu$L in about half the patients at the time of diagnosis. Blasts are usually seen on the peripheral smear examination, but in leukopenic patients, the numbers maybe few and require a diligent search to uncover. The cytoplasm inclusion known as Auer Rods often present in a small percentage of the myeloblast, monoblast, or promyelocytes in the various subtype of AML.[4]

Anaemia is a very common feature due to inadequate production of normal red cells. The reticulocyte count is usually normal or decreased.[4] Coagulopathy is a common presenting complication of AML, particularly in acute promyelocytes leukaemia. Coagulopathy may result from thrombocytopenia as well as from disseminated intravascular coagulation

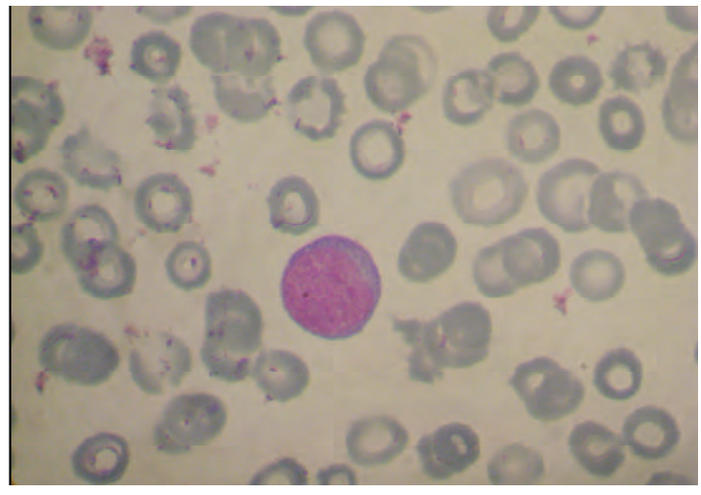

Figure 4. The peripheral blood smear on the second case revealed myeloblast

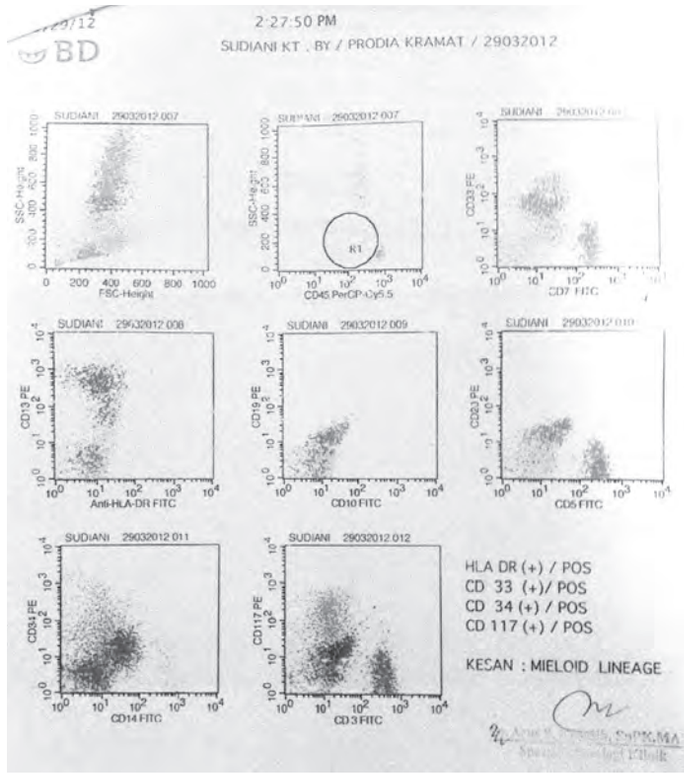

Figure 5. The immunophenotyping in the second case appropriate with myeloid lineage

(DIC) due either to infection or to the release of coagulant activity associated with the cytoplasm activity of some AML blast.[2]

Immunophenotyping can help to classify the clone of leukaemic blasts by using monoclonal antibodies directed against cell surface markers. The specific lineage and stage of maturation can be tagged, and this information then is used to indicate the appropriate therapy and can be correlated to the prognosis. Immunophenotyping can be done by flow cytometry or by immunohistochemistry methods. Multiple antigens can be detected simultaneously on a single cell using flow cytometry. Table 1 presents a selected panel of monoclonal antibodies.[4]

Table1. Selected panel of monoclonal antibodies

Lineage	Marker
Haematopoietic precursor	CD117 (HLA-DR), CD34
Myeloid	CD11b, CD13, CD33, CD15
T-lineage	CD1, CD2, CD3, CD4, CD5, CD7, CD8, TdT
B- lineage	CD10, CD19, CD20, CD21A, CD22, CD23, CD24, CD79a, TdT
Erythroid	Glycophorin A
Monocytic	CD14, CD4, CD11b, CD11c, CD36, CD64
Megakaryocytic	CD41, CD42, CD61

From Caldwell B, 2007

In 1976, the FAB (French-American-British) group proposed a system of classification of AML based on morphologic and cytochemical features.[8]

The FAB M4 subtypes commonly expresses CD14 (73%), CD15 (100%), CD13 (57%), and CD33 (92%). The M5 subtype shows a similar pattern of antigen expression but rarely expresses CD13. M1 and M2 blasts expresses CD14 (14% of M1 and 19% of M2), CD15 (34% of M1 and 44% of M2), they often express CD13 (80% of M1 or M2). AML blasts also frequently express lymphoid surface antigens. In a retrospective study by the Children's Cancer Group (CCG), 24% of AML cases express the B-lineage marker CD19 and 48% expresses one or more T-lineage cell surface antigens.[2]

Table 2. FAB Classification (From Clark JJ, *et al.,* 2009)[8]

M0	AML with minimal differentiation
M1	Myeloblast leukaemia without maturation
M2	Myeloblastic leukaemia with maturation
M3	Acute promyelocytic leukaemia
M4	Acute myelomonocytic leukaemia
M5	Acute monoblastic leukaemia
M6	Acute erythroblastic leukaemia
M7	Acute megakaryoblastic leukaemia

Because of the rarity of this disease, there is no standard protocol of chemotherapy. Although there had been reported cases of prolonged periods of remission, rapidly downhill course were also noted in some cases and some of them died after relapse during the course of chemotherapy. While some cases remitted spontaneously without treatment, paradoxically, those who had chromosomal abnormalities died after initiation of chemotherapy.[6] AML therapy is an intensive and nearly myeloablative, supportive care measures have a large impact on overall survival mortality and morbidity. Current standards of care include mandatory hospitalization for the duration of pancytopenia, with prompt initiation of an empiric antibiotics regiment for fever (includes initial use of vancomycin for α-streptococcal coverage and antifungal for prolonged fever without a source). Nutritional support is important, in addition to routine transfusion support with both platelets and packed red blood cells.[2]

Leukocytosis refers to an increase in the total number of white blood cells due to various physiologic, infectious, inflammatory or malignant processes. The normal leukocyte count in a neonate ranges from 9000 to 30000/mm^3 due to a surge in cytokine secretion (Granulocyte Colony Stimulating Factor and Granulocyte Macrophage Colony Stimulating Factor) in the immediate postpartum period. Leukaemoid reaction is a moderate, advance, or sometime extreme degree of leukocytosis, which is similar to that occurring in leukaemia but is due to some other cause. A leukocytosis exceeding 50.000 WBC/mm^3 with a significant increase in early neutrophils precursors is referred to as leukaemoid reaction. There is a mix of early mature neutrophils precursors, in contrast to the immature forms typically seen in leukaemia.

Hyperleucocytosis is defined as WBC counts >100.000/mm^3 and most cases encountered are due to either congenital leukaemia or a transient myeloproliferative disorder occurring in association with Down syndrome, both of which are relatively rare entities.[9] Hyperleucocytosis can result in life-threatening complication due to the large size of AML blasts and their adhesion properties. When the peripheral WBC is >100.000 x $10^9/\mu$L, AML blasts can begin to clump, resulting in leucostasis and slugging of the blasts in small vessels. This in turn leads to cellular hypoxia, tissue infarction, and ultimately tissue haemorrhage. When this occurs in the central nervous system (CNS), the patient is at a greatly increased risk for stroke and a somnolence syndrome that may progress to coma. The manifestations of hyperleukocytosis in the lungs include parenchymal infiltrates, pulmonary oedema, respiratory failure and occasionally hemorrhage.[2]

The primary management goals of hyperleukocytosis are to reduce the number of WBCs and to prevent complications. These goals are accomplished through leukapheresis, exchange transfusion and chemotherapy. Aggressive intravenous hydration (3000 mL/m^2 daily) and other measures to reduce the risk of tumour lyses are also implemented. Other essentials management measures include maintenance of adequate urinary output (1-2 mL/kg per hour), correction of metabolic abnormalities and blood product support.[9]

Some studies have shown an unfavourable outcome in very young patients, others have found comparable survival rates between the two age groups, while still others indicated a better prognosis for infants.[5] In approximately 10% of children with Down syndrome will developed transient myeloproliferative disorder, which is distinguish from AML by the fact that the majority of these patient undergo spontaneous regression. Children with Down syndrome have a superior response to AML therapy compared with other children.[5]

CONCLUSION

Our first case is a one-day-old male neonate referred with diagnosed preterm baby with respiratory distress and suspect Down syndrome. No diseases during the pregnancy period were noted, nor were consuming any traditional medicine. Physical examination showed dysmorphic features, petechiae and echimosis, hepatomegaly, and no lymphadenopaty. Thorax examination revealed retraction in the chest wall without rhales or wheezing and murmur grade III/VI on ICS II left parasternal line. The complete blood count revealed anaemia, hyperleukocytosis and thrombocytopenia. Blood smear revealed full of blast. Thorax x-ray showed infiltrate both in paracardial sinister and dextral. Echocardiography revealed small secundum ASD with mild LPA stenosis. Aggressive hydration was performed due to hyperleukocytosis. Immunophenotyping revealed the population of blasts expressing CD13 positive, CD33 positive, CD36 positive, CD 117 positive, CD 34 positive, and CD 38 positive.

Our second case a 17-day-old female neonate established Down syndrome, presented with bloody diarrhoea with history of hypothyroid, no fever present as well as respiratory distress noted, and absent of other bleeding manifestation. On the physical examination researchers noted dysmorphic face, systolic murmur grade II/VI and hepatosplenomegaly. The initial complete blood count revealed leukocytosis and thrombocytopenia. Peripheral blood smear

showed myeloblast 23%. Echocardiography revealed patent foramen oval or small ASD secundum with mild tricuspid regurgitation. Leukaemia phenotyping revealed the population of blasts expressing HLA-DR, CD33, CD34, as well as CD117 positive. A diagnosis of acute myeloid leukaemia was made. Both of the studied cases refuse chemotherapy treatments except the conservative one.

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