CASE REPORT

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Acute Myeloid Leukemia in a Three-Year-Old Girl Mimicking Chronic Myeloid Leukemia in Blast Crisis, Challenge in Diagnosis and Treatment in Limited-Resourced Health Care Facility: A Case Report

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ABSTRACT

Introduction: Acute myeloid leukemia (AML) is the second most common hematologic cancer in childhood. Clinically, AML has similar symptoms to other types of leukemias, and diagnosis remains a challenge due to limited access to pediatric hemato-oncology diagnostic examination. This study aims to report AML in a 3-year-old girl who was first suspected of Chronic Myeloid Leukemia (CML) in blast crisis, using a combination of clinical-hematology parameters and conventional morphology examination in a limited-resourced healthcare facility.

Case Presentation: A 3-year-old girl was referred from a rural Eastern Indonesia hospital with symptoms of prolonged fever, leucocytosis, severe anemia, and severe thrombocytopenia. In the previous hospital, the patient had a history of hyperleukocytosis and peripheral blood smear suspected of CML in blast crisis. A peripheral blood smear was repeated in our hospital and showed findings of Auer rod cells suggesting AML. Two bags of packed red cells and 2 thrombocyte concentrations were administered before referral for further diagnostic evaluation with bone marrow aspiration. Bone marrow aspiration revealed multiple nucleoli suggested for AML with FAB classification as M4 subtypes, and she received chemotherapy in a tertiary hospital.

Conclusions: With limited resources, suspicion based on persistent clinical symptoms, routine hematology tests, and peripheral blood smear examination are important to distinguish AML from CML in blast crisis. Understanding clinical hematology parameters and peripheral blood smears is the first step in AML diagnosis pathway and decision for further diagnostic referral. Supportive therapy and early recognition of oncologic emergency must be done before referral to a tertiary referral hospital.

INTRODUCTION

Childhood cancer is very rare, with hematologic malignancies as the highest epidemiology of cancer in the pediatric population, accounting for approximately one-third of all childhood cancers [1]. Although more common in adults, Acute Myeloid Leukemia (AML) is a clinically and genetically heterogeneous disease that accounts for 15–20% of all childhood leukemias [2]. AML includes varied disorders characterized by abnormal proliferation and differentiation of myeloid precursors in the bone marrow. AML is less common than Acute Lymphoid Leukemia (ALL), but it is responsible for most acute leukemia deaths in children. Children with AML may show a wide range of manifestations, from fever, anemia, or thrombocytopenia. Physical examination may associated with findings of fever, bleeding, bone pain, lymphadenopathy, splenomegaly, and hepatomegaly. In most cases, leucocytosis was accompanied by normocytic normochromic anemia and severe thrombocytopenia.

Laboratory examination, including routine hematology tests, peripheral blood smear, and bone marrow aspiration with morphologic analysis and flow cytometry, are necessary for diagnosis [3,4]. Over the past decades, recent advances in chemotherapy, hematopoietic stem cell transplantation, and supportive care have increased

the long-term survival rates of children with AML up to 65%. The increase in the 5-year probability of overall survival of pediatric AML in high-income countries (HICs) is primarily due to improved diagnostic techniques and higher-level treatment strategies. However, most pediatric AML in low-income countries (LMIC) have not benefited from these advances in diagnostic or therapeutic options and continue to have survival rates lower than 40% [5,6]

Chronic Myeloid Leukemia (CML) is also a stem cell disorder of uncontrolled proliferation of myeloid cells. CML has three clinical phases, including the chronic phase, accelerated phase, and blast phase. One of the phases of CML, which is the blast phase, has clinical, phenotypic, and genetic features identical to acute leukemia features such as AML. The most specific characteristic of CML is the presence of the Philadelphia (Ph1) chromosome [3.4]. Bone marrow aspiration is necessary to diagnose childhood leukemia and distinguish which cell line is affected [1].

Accurate diagnosis of suspected CML in the blast phase, including molecular analysis, is crucial for further management of this rare but serious condition [7,8]. However, a comprehensive diagnosis approach remains challenging in LMICs such as Indonesia. In limited health care resources, high suspicion based on persistent clinical symptoms with hematology parameters and peripheral blood if a sufficient number of blasts present can help make a diagnosis quickly and guide decisions for referral plan to prevent delay in further definitive diagnosis evaluation and treatment. Here, we report a case of a 3-year-old girl with AML who had an initial peripheral blood smear mimicking CML in a blast crisis. This case study aims to understand clinical-hematology parameters, peripheral blood smear interpretation, early recognition of oncologic emergencies, and supportive treatment before referral to differentiate AML and CML in blast crisis in a resourced healthcare facility.

CASE PRESENTATION

A three-years-eight-months-old girl came to the children's outpatient ward of Wangaya Hospital in Denpasar, Bali. The patient was referred from a rural Eastern Indonesia hospital with symptoms of prolonged fever. The patient had shown symptoms of fever since three weeks ago, accompanied by nose-bleeding and gum-bleeding for about one week and bruises on both hands and feet. When she arrived, she was found weak and pale. She also complained of body aches and abdominal pain since the onset of the fever. Her mother also noticed that the patient's stomach became bigger than before.

In the previous hospital, the initial complete blood count two weeks prior to the consultation showed the white blood count was 104.43x103/µL, a hemoglobin level of 7.5 g/dL, and a platelet count of 24 x103/µL. A peripheral blood smear was done in the previous hospital and showed hypochromic microcytic, poikilocytosis, increased number dominated by myeloid cells in all stages of maturation, with the proportion of myeloblast 23%, promyelocyte 18%, myelocytes 27%, metamyelocyte 18%, neutrophils stab 10%. She was diagnosed with Suspect CML in the blast crisis phase. She was admitted for eleven days to a rural hospital in Eastern Indonesia and received a blood transfusion of packed red cells. She was also given Hydroxyurea 500 mg once daily orally for two weeks. After improving her general condition, she was referred to Bali for further evaluation and management.

The patient was the only child in the family with no history of allergy or surgery. The patient had a history of spontaneous labor, assisted by a midwife, with a birth weight of 2,600 grams, no abnormality during delivery, and received exclusive breastfeeding for six months. Immunization records were complete, and growth and development were appropriate as per age. History of chronic medical disease, cancer, or blood problems in the family was denied.

Physical examination in the outpatient ward showed body temperature was 38.9 degrees Celsius and slightly tachycardia. Eye conjunctivas were pale, and gum bleeding was noted. The stomach was distended, the bowel sound was within normal limits, and hepatomegaly-splenomegaly with ascites was noted. The liver and spleen were palpable about three centimeters below the costal margins. Abdominal circumference was measured at 51 centimeters. No apparent bruise, rash, or cutis on the skin. There was no abnormality during the cardiac and respiratory examination. An anthropometry examination was done; her body weight was 12 kg with a height of 92 centimeters, arm circumference of 15.5 centimeters, and her nutritional status was normal as per age. Development examination is appropriate as per age.

Complete blood count, electrolyte, and uric acid tests were obtained upon admission to our hospital. Total white blood cell was 42.45x103/µL with severe anemia (hemoglobin 5.7 g/dL) and severe thrombocytopenia (platelet count 11 x103/µL) while electrolyte, as shown in **Table 4**, showed an imbalance of hyponatremia (atrium 128 mmol/L) and hypokalemia (potassium 3.0 mmol/L). She was diagnosed with Leukocytosis, observation of severe normochromic normocytic anemia, severe thrombocytopenia, and organomegaly, suspected of chronic myeloid leukemia in blast crisis with neoplasm-related pain and electrolyte imbalance. She was admitted to our hospital for stabilization before being referred to a pediatric oncologist in a higher-care hospital. She planned to receive two bags of packed red cells, two thrombocyte concentrations, symptomatic medication such as paracetamol for fever and pain, omeprazole as stomach protector, and potassium chloride supplementation.

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Table 1. Hematology parameter evaluation

Parameters	Date 03/02	Date 11/02	Date 16/02	Date 19/02	References
WBC (103/µL)	104.43	69.37	42.45	24.78	5.0-13.0
%Neu	4.9	4.8	3.7	4.3	32-52
%Lym	34.5	33.4	25.6	28.7	30-60
%Mon	62.2	59.9	70.0	66.3	2-8
%Eos	1.9	1.8	0.6	0.6	0-4
%Bas	0.1	0.1	0.1	0.1	0-1
#Neu(103/µL)	4.2	3.35	1.58	1.08	1.50-7.00
#Lym(103/µL)	24.1	23.17	10.85	7.12	1.00-3.70
#Mon(103/µL)	42.2	41.4	29.72	16.42	0.00-0.70
#Eos(103/µL)	1.3	1.27	0.27	0.14	0.00-0.40
#Bas(103/µL)	0.04	0.04	0.03	0.02	0-0.10
RBC (106/µL)	3.6	3.7	2.56	4.09	4.00-5.30
HGB (g/dL)	7.5	8.0	5.7	10.5	12.0-16.0
HCT (%)	25.6	27.2	19.1	32.2	35.0-45.0
MCV (fL)	72.3	73.3	74.6	78.8	75.0-91.0
MCH (pg)	21.3	21.6	22.3	25.7	25.0-33.0
MCHC (g/L)	29.3	29.4	29.8	32.6	31.0-37.0
RDW (%)	22.3	22.8	*00000	*00000	9.0-17.0
PLT	24	74	11	8	150-400

Table 2. Peripheral blood smear evaluation

Parameter	Date 03/02	Date 16/02
Erythrocytes	Hypochromic microcytic, poikilocytosis (tear drop cells, ovalocytes, fragmented red cells, burr cells)	Hypochromic microcytic, anisopoikilocytosis (pencil cells, tear drop cells, helmet cells) Polycromatophilic cells (-), normoblast cells (-).
Leucocytes	It seems to be increased in number, dominated by myeloid cells in all stages of maturation with proportions myeloblast 23%, promyelocyte 18%, myelocyte 27%, metamyelocyte 18%, neutrophils stab 10%, smudge cells (+)	Seems to be increased in number. There are mononuclear cells with bluish-purple cytoplasm, regular and irregular nuclei, 1 -3 nucleoli, Auer rod positive, suggesting to proportions monoblast 21%, promonocyte 28%, monocytes 24%, lymphocytes 15%, neutrophils stab 10%, eosinophils 2%.
Platelet	Seems to be decreased in number, giant platelet (-)	Seems to be decreased in number, giant platelet (-) clumbs platelet (-)
Interpretation	Chronic Myeloid Leukemia Juvenile - Blastic phase	The morphology of the peripheral blood smear showed a suspected acute myeloblastic leukemia with a differential diagnosis of chronic myeloid leukemia in blast crisis.

Table 3. Bone marrow aspiration result

Parameter	Result
Cellularity	Hypercellular
Erythroid System	Decrease in erythroid system activity
Myeloid System	Increase of myeloid system activity,Myeloblast 25%, monoblast 30%, Auer rods positive
Megakaryocyte System	Decrease of megakaryocyte activity
Other cells	No other non-hematopoietic cell infiltration in bone marrow
Conclusions	Manifestation of bone marrow with Acute Myeloblastic Leukemia (AML FAB M4 Subtype)

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Table 4. Other laboratory parameters

Parameters	Date 16/02	References
Natrium (mmol/L)	128	130–145
Potassium (mmol/L)	3.0	3.5–5.5
Chloride (mmol/L)	102	95–108
Uric acid (mg/dL)	5.7	3.4–7

During four days of hospitalization, she has shown bleeding symptoms more prominent, such as gum bleeding and nose bleeding, about twice a day. The morphology of the peripheral blood smear, detailed in **Table 2**, showed circulating myeloblasts (> 20%) and schistocytes with more abundant and prominent cytoplasm. After blood transfusion, another routine blood test was drawn upon referral. She was referred to a tertiary hospital with a Pediatric Hematology-Oncology Ward for further evaluation and management. Bone marrow aspiration was performed at a referral hospital, which is shown in **Table 3**, and an increase in myeloid cell lineage with blast was > 20%. Auer rods supported the findings of AML-M4. She started induction therapy according to tertiary hospital protocol for AML, which consists of Methotrexate, Dexamethasone, Vincristine, Cyclophosphamide, and Adriamycin. Treatment was reported to be well tolerated.

DISCUSSION

AML is a blood neoplastic disease characterized by the proliferation of myeloid cell lineage. The pathogenesis of AML is characterized by the mutation of genes in the hematopoiesis process. The mutations result in undifferentiated myeloid precursors in the peripheral blood and blood marrow, which causes ineffective erythropoiesis and bone marrow failure. Cellular characteristics of AML are the findings of > 20% blast cells, with features similar to those that characterize early differentiation of myeloid-monocyte-megakaryocyte series of blood cells in bone marrow aspiration [3,4]. Currently, flow cytometry to identify surface antigens, followed by chromosomal and molecular genetic methods, is required for precise diagnostic and therapeutic options. The World Health Organization (WHO) has classified AML by genetic, immune-phenotypic, biological, and clinical features, which provide biologic and prognostic information [4,10]. In comparison, The French-American-British (FAB) Cooperative Group developed a classification system based on morphologic and cytochemical characteristics [3].

AML is relatively rare in children but causes excessive mortality. The incidence of childhood cancer has been increasing over time with under-diagnosed and under-treated cases, especially in LMIC. Studies revealed challenges in LMIC to address childhood cancer cases include delayed diagnosis, limited healthcare access, treatment abandonment, and suboptimal supportive care [10,11]. In limited resources health care facility, where advanced diagnostic features such as bone marrow aspiration, flow cytometry, and chromosomal and molecular genetic techniques, it is very important for a pediatrician to understand the clinical manifestation and interpretation of complete blood count (CBC) and conventional peripheral blood smear as a measure of bone marrow function in a child suspected for AML.

Anamnesis and physical examination are important clinical skills that are needed as the first step in diagnosing AML in the pediatric population. Clinically, AML has a wide range of signs and symptoms. The initial presentation of AML, like most types of leukemia, is usually non-specific. As the disease progresses, signs of bone marrow failure become more obvious. Some common clinical features range from fever, anemia, or thrombocytopenia to life-threatening coagulopathy or extramedullary disease complications resulting in organ dysfunction [3,4]. In this study, the patient was brought to the hospital with a chief complaint of fever accompanied by nose bleeding, gum bleeding, and bruises on both hands and feet, which she had never had before. Along the days, she complained of severe bone pain throughout the day and night. Organ infiltration, which is hepatomegaly and splenomegaly, was found in physical examination. The finding of pallor, purpuric, and petechial skin lesions also reflect bone marrow failure in this patient. The extramedullary disease consists of a collection of immature myeloid cells outside the bone marrow, which happens in 10-20% of patients with AML. The most common presentations are gingival hypertrophy, lymphadenopathy, and leukemia cutis. In AML-M4, symptoms associated with CNS disease are often seen compared with other classifications of AML [3,9]. In this patient, no CNS manifestation was found.

CBC with a differential count and peripheral blood smear should be considered as the tools to help guide the diagnosis of suspected AML or leukemia cases in children [1,12]. In our hospital, CBC revealed leukocytosis with white blood cell 42.45x103/µL with severe anemia (hemoglobin 5.7 g/dL) and severe thrombocytopenia (platelet count 11 x103/µL). The degree of anemia, thrombocytopenia, and neutrophil count is highly variable in each child. Hematology parameters are shown in **Table 1** in this patient shown two weeks prior to our CBC evaluation in our hospital, and her first laboratory result showed hyperleukocytosis with white blood count of 104.43x103/µL, hemoglobin level 7.5 g/dL and platelet count 24 x103/µL. Hyperleukocytosis is a laboratory finding of white blood cell count equal to or more than 100 x103/µL and is presented in 5%–20% of patients with AML. Retrospective analyses show an association of monocytic AML subtypes (FAB

AML M4/5) with this complication. Two main pathogenetic factors of hyperleukocytosis include rapid blast proliferation and disruption in normal hematopoietic cell adhesion, leading to a reduced affinity to the bone marrow. Clinical manifestations of hyperleukocytosis are leukostasis, disseminated intravascular coagulation, and tumor lysis syndrome, which can cause life-threatening complications in children with AML. These patients have a higher early mortality rate of 8% in the first 24 hours to around 20% during the first week, so early recognition of hyperleukocytosis from CBC has a crucial advantage for the patient [13,14]. This patient received Hydroxyurea 500 mg orally once daily. Administration of hydroxyurea, a cytoreduction, to gradually lower the white blood cell count prior to intensive chemotherapy has become common practice in several centers [15].

Peripheral blood smear may assist in displaying the spectrum of cells at different stages of maturation and neutrophilic toxic changes [12]. There were two suspicions from this patient's peripheral blood smear. From a previous peripheral blood smear in a previous hospital, the patient was suspected of CML in blast crisis. In contrast, in our hospital, the morphological features support the diagnosis of AML. Diagnosis of leukemia sometimes can be differentiated using morphologic features alone, although not an accurate diagnostic tool [1,12].

CML is a clonal myeloproliferative disorder of granulocyte-macrophage progenitor cells and is characterized by the presence of the Philadelphia (Ph1) chromosome. CML in childhood is rarer than AML, with approximately 1–3% of childhood leukemia. CML has three phases, which are the chronic phase, the accelerated phase, and the blast crisis phase. Clinical symptoms of CML are similar to AML, which consists of non-specific complaints of fever, night sweats, weight loss, bone pain, abdominal pain, neurologic problems, hepatomegaly, splenomegaly, and pallor. One phase of CML, known as the CML blast crisis, can look very similar to AML, but some differences separate these two conditions [3,4].

Both AML and CML involve myeloid cells. Myeloid cells eventually develop into red blood cells, platelets, or white blood cells, such as neutrophils, eosinophils, and monocytes. However, AML and CML are classified differently. Findings of > 20% blast cells and Auer rods, clumps of azurophilic granules resembling elongated needles, in peripheral blood smear, and bone marrow aspiration are diagnostic of AML, as shown in this patient in **Table 2** and **Figure 1**. While in CML, the blast phase may have distinctive morphological features in peripheral blood. The blasts in CML in the blast phase can be mixed of myeloid, lymphoid, or mixed-lineage phenotypes [5,12]. In CML, the peripheral smear frequently shows immature granulocytes and absolute eosinophilia and basophilia. However, in some patients with white blood

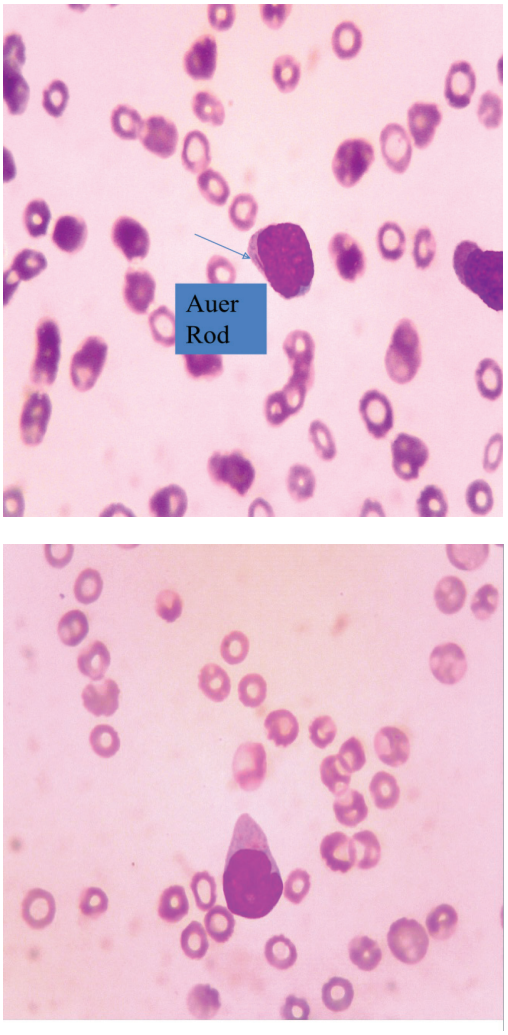

Figure 1. RBC hypochromic microcytic, Auer rod cells, and mononuclear cells with bluish-purple cytoplasm.

cell counts ≤ 50,000/mcL (≤ 50 × 109/L) and even in some with higher white blood cell counts, immature granulocytes may not be seen [16]. Bone marrow aspiration is still warranted to accurately diagnose childhood leukemia [1,12].

WHO laid down criteria for diagnosis when one or more of the following criteria are present: Blast > 20% of peripheral blood leukocytes or nucleated bone marrow cells, extramedullary blast proliferation, and large foci of clusters of the blast in the bone marrow biopsy [16]. Bone marrow examination will show 10% leukemic blasts but may be poorly defined in the accelerated phase, which is characterized by increasing leukemic blasts to 19%. CML in blast crisis might resemble AML or ALL where blast > 20% in blood or bone marrow. 80% of blast crises are myeloid blast crises, which may be myeloblastic or myelomonocytic [3,4]. This explains why one of the differential diagnoses of CML in blast crisis could be AML. Advanced diagnosis with cytogenetic evaluation is needed to find the presence of the Ph1 chromosome of the BCR ABL1 fusion gene to diagnose CML in children [3].

Aggressive chemotherapy is successful in remission in approximately 85–90% of patients with childhood AML [4]. General evaluation of electrolytes, creatinine, liver enzymes, uric acid, lactate dehydrogenase, coagulation studies, and blood cultures every 24 hours when febrile are needed before starting treatment [3]. Initial response to induction therapy is an essential predictor of the outcome in AML children. Failure to achieve clinical remission is a highly predictor of poor outcomes, even if subsequent therapy results in remission [17]. Supportive care is highly crucial in the treatment of children with AML because the therapy can be very toxic, causing long periods of transfusion and severe neutropenia. Death within the first two weeks of diagnosis is related to the complications of AML, such as leukostasis and bleeding, while infections are the main cause of death in children with AML later in the course of therapy [1,3]. Optimizing supportive care in children with AML is important to minimize morbidity and mortality of the disease and also to reduce therapy-related toxicity [17].

In contrast with HIC, where upfront therapy such as hematopoietic stem-cell transplant and molecular targeted therapies are beneficial for AML patients, pediatric oncology services are often perceived as too expensive in LMIC [10,17]. In HIC, stem cell transplantation from matched-sibling after remission has long-term disease-free survival in about 67% of patients, which is now recommended for relapse cases; however, in LMIC, with limited option therapy, survival rates range from 10% to 50% [4,8]. In our patient, the management of the patient is focusing on stabilization of the patient's clinical condition, which includes transfusion of 2 packed red cells due to severe anemia and two thrombocyte concentrations for severe thrombocytopenia along with other supportive management for her pain, hydration, and nutrition support. In limited healthcare facilities, the management mainly uses supportive therapy to optimize the patient's general condition for further referral and treatment.

CONCLUSIONS

Understanding clinical-hematological parameters and morphologic analysis of peripheral blood can help to differentiate AML and CML in blast crises in limited healthcare facilities for pediatric hemato-oncology cases. Although definitive diagnosis and treatment remain challenging in limited healthcare resources, the first step in diagnosis and early recognition of an oncologic emergency can be addressed faster. Stabilization of general condition, including supportive treatment, is necessary prior to transfer to the nearest pediatric oncology center.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by the ethical committee at Wangaya General Hospital Denpasar: 07/1353/RSUDW.

Competing interest

The author(s) declare no competing interest in this study.

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