

ACUTE PROMYELOCYTIC LEUKEMIA

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ABSTRACT

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML). The disease is very uncommon in children less than 10 years of age. Every sign and symptom that present on patient with APL are caused by the infiltration of the bone marrow with leukemic cells and resulting failure of normal hematopoiesis. Without the normal hematopoietic elements, the patient is at risk for developing life-threatening complications of anemia, infection due to neutropenia, and hemorrhage due to thrombocytopenia, disseminated intravascular coagulation, fibrinolysis, and proteolysis of mature cells. We reported one case of a nine-year-old girl with pale, limp, recurred fever, hematoma, and petechiae. Physical examination revealed pale in conjunctiva, gingival hypertrophy, and hepatomegaly. Complete blood count showed normochromic normocytic anemia, thrombocytopenia, and leukopenia, with neutropenia. Bone marrow aspiration revealed a bundle of auer rod, promyelocyte 60 %, myeloblast 2 %, concluded AML(M3). We provided chemotherapy with vitamin A, daunorubicin, and cytarabine, but the condition was decreased and finally died after the first cycle of chemotherapy. [MEDICINA 2015;46:178-83].

Keywords: acute promyelocytic leukemia, children

LEUKEMIA PROMIELOSITIK AKUT

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ABSTRAK

Leukemia promielositik akut (LPA) merupakan salah satu sub tipe dari leukemia mielositik akut (LMA). Penyakit ini sangat jarang pada anak-anak kurang dari 10 tahun. Semua tanda dan gejala klinis pada pasien dengan LPA disebabkan karena infiltrasi sumsum tulang oleh sel-sel leukemia dan mengakibatkan kegagalan hematopoiesis normal. Komplikasi LPA yang mengancam jiwa antara lain anemia, infeksi akibat netropenia, dan perdarahan akibat trombotopenia, *disseminated intravascular coagulation*, fibrinolisis, dan proteolisis. Kami melaporkan satu kasus anak sembilan tahun dengan keluhan pucat, lemas, demam berulang, hematoma, dan petekie. Pada pemeriksaan fisis didapatkan konjungtiva pucat, hipertrofi gingiva, dan hepatomegali. Pemeriksaan darah lengkap menunjukkan anemia normokronik normositik, trombotopenia, dan leukopenia, dengan neutropenia. Aspirasi sumsum tulang menunjukkan adanya *bundle of auer rod*, *promyelocyte* 60%, *myeloblast* 2%, disimpulkan sebagai AML (M3). Kami kemoterapi dengan vitamin A, daunorubisin, dan sitarabin, tapi kondisi anak kemudian menurun dan akhirnya meninggal setelah periode pertama kemoterapi. [MEDICINA 2015;46:178-83].

Kata kunci: leukemia promielositik akut, anak

INTRODUCTION

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) with distinctive biologic and clinical features that is now highly curable. Acute myeloid leukemia is a type of cancer caused by the malignant proliferation of bone marrow-derived cells that invade

the bloodstream, distance organs, and induce loss of normal bone marrow.^{1,2}

Acute promyelocytic leukemia is characterized by the t(15;17) (q22;q11 sampai 21) translocation. This translocation reflects the molecular rearrangement of the promyelocytic leukemia (PML) gene, located at 15q22, with the RARA gene, located at 17q21, and

is considered to be critical for the pathogenesis of the disease since it blocks differentiation during the promyelocytic stage of myeloid maturation. Promyelocytic leukemia has been shown to function as a tumor suppressor and RARA has differentiation-promoting and growth-suppressing activities, being essential for normal hematopoiesis.^{3,4}

Acute promyelocytic leukemia is relatively uncommon, the frequency being estimated as 10% of acute leukemias. The mean incidence in Europe is about 2-3 cases per million inhabitants per year.³ In the United States is estimated 600 to 800 new cases every year.^{3,5} The frequency seems to be higher in Southern Europe (Italy and Spain: 15% of AML). Both sexes are equally vulnerable to APL, and there is a wide range in age at first presentation.³ One of the most striking features of APL is its age-associated incidence rate. The disease is very uncommon in children less than 10 years of age. Its incidence increases steadily during the teen years, reaches a plateau during early adulthood, and remains constant until it decreases after age 60 years.⁵

The diagnosis of APL is made morphologically on bone marrow smears. The malignant cells bear numerous large granules and several Auer rods. Bone marrow aspirates (BMA) also taken at presentation for cytogenetic evaluation and for reverse transcriptase polymerase chain reaction (RT-PCR) assays in order to detect the t(15;17) translocation and the PML-RAR α mRNA respectively. Immunophenotyping confirms the myeloid lineage (CD13-CD33) with association in some cases with CD19 and/or CD2 antigens usually found in lymphoid lineages.³

Although 65 to 80 percent of patients with APL have a complete remission with standard chemotherapy, approximately 10 to 20 percent die either before or during chemotherapy of bleeding attributable to disseminated intravascular coagulation, fibrinolysis, and proteolysis into mature cells.¹ Standard chemotherapy and all-trans-retinoic acid (ATRA) as induction or maintenance treatment improves disease free and overall survival as compared with chemotherapy alone and should be included in the treatment of APL.^{1,6}

The purpose of this case report to determine APL in children.

CASE ILLUSTRATION

SP, a nine-year-old girl was referred to Sanglah Hospital with diagnosis of aplastic anemia and differential diagnosis myelodysplasia syndrome. She complained pale since two weeks, limp from 6 months, and recurred fever since 6 months before. Hematoma and petechie often appeared in her body since 6 months. She was in a generally satisfactory condition. Her respiratory rate was 22 times/minute, her heart rate was 94 beats/minute, her blood pressure was 100/70 mmHg, and O₂ saturation 98%.

Head examination revealed pale in conjunctiva and gingiva hypertrophy on the gums (**Figure 1**). Chest examination was within normal limit. Abdomen examination revealed no hepatosplenomegaly nor lymphadenopathy. Extremities examination revealed petechiae and hematoma. The complete blood count showed normochromic normocytic anemia (Hb=8.3g/L; Ht=20.50%; MCHC=40.30g/L, MCV=92.8fL) with elevated reticulocyte (4%) and thrombocytopenia (PLT=48x10⁹/

L). There was also leukopenia (WBC=0.85x10⁹/L) with neutropenia (Ne=0.46x10³/ μ L). Her first C-reactive protein (CRP) was elevated (3.605 mg/L) and first urine culture and blood culture revealed no growth. The hemostatic function was within normal limits with bleeding time was 1'30", clotting time 7'00", prothrombin time was 13.30 seconds (control 12.00 seconds), activated prothrombin time 35.10 seconds (control 39.40 seconds), and international normalized ratio was 1.15. The liver function test and kidneys function test were within normal limits. Abdominal ultrasonography showed mild hepatomegaly.

Blood smear revealed normochromic erythrocytes, anisopoikilocytosis (burr cell, tear drop cell), polichromasia, leukocytes leukopenia, differentiated neutropenia, toxic-granule, no blast, decreased platelet with no giant platelets, and pancytopenia. Bone marrow aspiration revealed hypercellularity, erythroid system activities decline, myeloid system activity was increased, a bundle of auer rod, promyelocyte 60 %, myeloblast 2 %, megakaryocyte system activities were declined, with conclusion AML(M3).



Figure 1. Gingival hypertrophy.

During hospitalization, the patient was suffered febrile neutropenia, anemia, and thrombocytopenia. Antibiotics and blood transfusion were given. One months later, general condition was improved, without fever, and she was planned to receive chemotherapy. On January 8th 2013 chemotherapy was started with high dose vitamin A 200.000 IU/day as a substitute of ATRA, followed by daunorubicine 60mg/m²/day for 3 days and cytarabine 200 mg/m²/day for 7 days that was given 3 days after free of vitamin A consumption. After first cycle of period of chemotherapy, the patient was clinically unstable. She was suffered from recurred febrile neutropenia, anemia, and trombocytopenia and got blood transfusion. Physical examination revealed gingival hypertrophy and hepatomegaly. The complete blood count on January 15th 2013 showed normochromic normocytic anemia (Hb=6.8g/L; Ht=19.3%; MCHC=34.9g/L, MCV=79fL), thrombocytopenia (PLT=5x10⁹/L). There was also leukopenia (WBC=0.36x10⁹/L) with neutrophenia (Ne=0.1x10³/μL). On Pebruary 16th 2013, the patient suddenly suffered hematemesis and melena. The hemostatic functions were prolonged, prothrombin time 32.10 seconds (control 12.4 seconds), activated partial thromboplastin time 96.8 seconds (control 36.8 seconds), and international normalized ratio 2.57. The liver function test, kidneys function test and electrolytes were within normal limits. She got blood transfusion such as packed red cell, platelet concentrate, fresh frozen plasma, and cryoprecipitate. However her condition was deteriorated and finally died on Pebruary 17th 2013.

DISCUSSION

Acute promyelocytic leukemia in children is rare. The disease is very uncommon in children less than 10 years of age. Its incidence increases steadily during teen

ages, reaches a plateau during early adulthood, and remains constant until it decreases after age of 60.⁵ In this case the symptoms of leukemia ocured at the age of nine years and eight months old.

There is large range of presenting signs and symptoms for pediatric AML. Life threatening complications occur due to decreased normal hematopoiesis secondary to leukemic infiltration of the bone marrow as well as to organ dysfunction and failure as a result of leukemic infiltration. The complete blood count and examination on peripheral blood smear are the first step in the laboratory diagnosis of leukemia. Blood cell counts are variable in patients with AML. White blood cell (WBC) count may be normal, increased, or decreased. It is markedly elevated over 100 x 10⁹/mL cells in less than 20% of cases. Conversely, the WBC is less than 5.0 x 10⁹/mL in about half of 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. Cytoplasmic inclusion known as auer Rods often present in a small percentage of the myeloblasts, monoblasts, or promyelocytes in the various subtype of AML.⁷ In our case the WBC was decreased (WBC = 0.85 x10⁹/L). On peripheral blood smear examination revealed leukopenia, differentiated neutropenia, no toxic granule, and no blast.

Anemia is a very common feature due to inadequate production of normal red cells. The reticulocyte count is usually normal or decreased. Red cell anisopoikilocytosis is mildly abnormal, with few poikilocytosis presents.⁷ In our case the complete blood count showed anemia, with increased reticulocyte count and anisopoikilocytosis on peripheral blood smear.

Coagulopathy is a common

presenting complication of AML particularly in acute promyelocytic leukemia but also in acute myelomonocytic leukemia and acute monocytic leukemia subtypes. The coagulopathy may result from thrombocytopenia as well as from disseminated intravascular coagulation (DIC) due either to infection or to the release of coagulant activity associated with the cytoplasmic activity of some AML blasts. Disseminated intravascular coagulation may worsen as therapy is initiated due to increased release of these coagulant proteins associated with tumor lysis and leading to factor depletion and bleeding.⁸ In our case, physical examination revealed bleeding manifestation, such as petechiae and hematome on skin. Thrombocytopenia was noted in our cases.

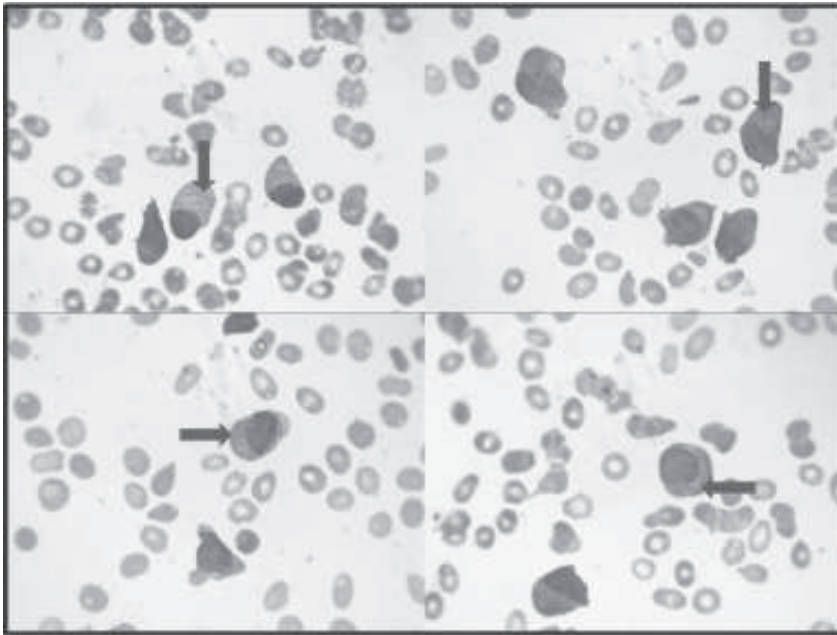
Organomegaly is seen in approximately half of patient of AML due to hepatic and splenic infiltration with leukemic blasts. Extramedullary leukemia is observed in 10-20% of patient with gingival hyperthrophy, lymphadenopathy, and leukemic cutis (palpable non tender nodules in the skin) being the most common.⁸ In our case, physical examination revealed ginggival hiperthrophy, without hepatomegaly and nor splenomegaly. Abdomen ultrasonography showed mild hepatomegaly.

In 1976, the French-American-British (FAB) group proposed a system of classification of AML based on morphologic and cytochemical features (**Table 1**). The system divides AML into seven subtypes, M1 through M7. An M0 subtype was later added to describe undifferentiated leukemia and since 1976 immunophenotypic data have also been included.⁹

The presumptive diagnosis of APL can usually be made by review of the peripheral blood smear alone or with the bone marrow aspirate and core biopsy by an experienced hematologist and hematopathologist in the presence of the

Table 1. FAB classification⁹

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

**Figure 2.** Bone marrow aspiration showed bundle of auer rod, promyelosit was 60 %, myeloblast 2 %.

characteristic clinical findings. The peripheral blood smear often shows leukopenia with circulating promyelocytes, which usually have abundant, often irregular-appearing primary azurophilic granules. Leukemic promyelocytes with multiple auer rods may be found and are identified only in APL. The bone marrow aspirate shows morphologically classic APL which is characterized by the presence of blasts promyelocytes hypergranulate > 20% with intracytoplasmic auer rods that in several cases, for their high number, form the so-called “fagot cells”.^{3,6} In our case bone marrow aspiration shows the description of hiperselularitas, eritroid system activities was increased, myeloid system activity increase, showed

bundle of auer rod, promyelosit was 60 %, myeloblast was 2 %, decline megakaryocyte system activities (**Figure 2**). The conclusion was AML(M3).

Stratified APL based on the WBC count and platelet count, as shown in **Table 2**. Chemotherapy in patients with APL depending on stratified of the disease based on the WBC count and platelet count. Chemotherapy regimen are widely used European APL regimen or PETHEMA regimen as shown in

Table 2. Stratified APL^{10,11}

	Low risk	Intermediete risk	High risk
WBC	< 10,000/ μ L	< 10,000/ μ L	> 10,000/ μ L
Platelet	> 40,000/ μ L	< 40,000/ μ L	

Table 3.

In our case, including low risk using European regimen. However because they have not availability of ATRA in Indonesia we used high doses of vitamin A derivates 200,000 IU as a substitute for ATRA. It was expected by administering combination of vitamin A and chemotherapy would give equal prognosis with ATRA and chemotherapy.

Acute promyelocytic leukemia therapy is intensive and nearly myeloblative, 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 regimen for fever. Antifungal prophylaxis is standard, as is prompt initiation of empiric antifungal treatment for prolonged fever without a source. Nutritional support is important, in addition to routine transfusion support with both platelets and packed red blood cells.¹² In our case we treated her with empiric antibiotic followed with definitive antibiotic according to blood culture. We gave nutritional support, oxygen therapy when needed, and transfusion of packed red cells and platelets.

Coagulopathies can also complicate the hemostatic defects associated with thrombocytopenia. Disseminated intravascular coagulation is most often seen in APL due to release of procoagulants from the abnormal primary granules, which activate cascade, leading to decreased factors II, V, VIII, and X, and fibrinogen, as well as rapid platelet

Table 3 . Protocol therapy APL¹⁰⁻¹³

	Induction therapy	Consolidation therapy	Maintenance therapy
European APL regimen	<ul style="list-style-type: none"> •Daunorubicin 60 mg/m²/day IV for three day •Cytarabine 200 mg/m²/day IV as 24hours continuous infusion on days 1-7 •ATRA 25 mg/m²/day in 2 divided doses 	Consist of two cycle First cycle <ul style="list-style-type: none"> • Daunorubicin 60 mg/m²/day IV on days 1-3 • Cytarabine 200 mg/m²/day IV as 24 hours infusion on days 1-7. Second cycle <ul style="list-style-type: none"> • Daunorubicin 45 mg/m²/day IV on days 1-3 • Cytarabine 1 g/m² every 12 hours on days 1-4 . • ATRA administered concurrently with cycles above: ATRA 25 mg/m²/day for patients in two divided doses for 15 days with each four weeks cycle of chemotherapy (especially for intermediate and high risk patients). 	Molecular remission. (PCR evaluation is negative) <ul style="list-style-type: none"> • ATRA 45 mg/m²/day for 15 days every three months • 6-MP 60 mg/m²/day orally • Methotrexate 20 mg/m² orally every week; Administered for 2 years
PETHEMA regimen	<ul style="list-style-type: none"> •Idarubicin 12 mg/m² IV bolus on days 2, 4, 6, and 8 •ATRA 25 mg/m²/day in two divided doses 	Consist of three cycles. First cycle <ul style="list-style-type: none"> •Idarubicin 5 mg/m² IV bolus on days 1-4. Second cycle <ul style="list-style-type: none"> •Mitoxantrone 10 mg/m² IV bolus on days 1-3. Third cycle <ul style="list-style-type: none"> •Idarubicin 12 mg/m² IV bolus for single dose. ATRA administered concurrently with cycles above: ATRA 25 mg/m ² /day for patients in two divided doses for 15 days with each 4 weeks cycle of chemotherapy (especially for intermediate and high risk patients). Arsenic trioxide 0.15 mg/kg/day IV for five days per week every other month for 4 cycles plus ATRA 25 mg/m ² /day orally in two divided doses for two weeks per month for seven cycles.	

Relapse therapy in European APL regimen or the PETHEMA regimen used arsenic trioxide induction and consolidation doses initially. If molecular remission is achieved with salvage therapy, the patient should be considered for autologous stem cell transplantation. If persistent molecular or hematologic disease is noted after salvage therapy, the patient should be considered for allogeneic stem cell transplantation with good performance status and a human leukocyte antigen (HLA) matched donor is available.

Prophylactic intrathecal chemotherapy constitute of cytarabine 50 mg plus methotrexate 15 mg plus hydrocortisone 30 mg weekly for 5 weeks

consumption.¹³ Disseminated intravascular coagulation may worsen as therapy is initiated due to increased release of these coagulant proteins associated with tumor lysis and leading to factor depletion and bleeding.⁸ In our case the patient suddenly was suffered from hematemesis and melena. The hemostatic function were prolonged, prothrombin time was

32.10 seconds (control 12.4 seconds), activated partial thromboplastin time was 96.8 seconds (control 36.8 seconds), and international normalized ratio was 2.57. She got blood transfusion such as packed red cell, platelet concentrate, fresh frozen plasma, and cryoprecipitate, However the condition was deteriorated and finally died.

SUMMARY

We reported a case of a 9 year old girl with APL, with chief complain were pale, limp, recurred fever, often appearing petechiae and hematoma in the skin. On physical examination we found gingiva hypertrophy. Complete blood count showed normochromic normocytic anemia, throm-

bocytopenia, and leukopenia with neutropenia. C-reactive protein was elevated and abdomen ultrasonography showed mild hepatomegaly. Bone marrow aspiration revealed increased myeloid system activity, a bundle of auer rod, promyelocyte was 60 %, myeloblast was 2 %, conclusion appropriate with AML(M3). We threat the patient using low risk European Regimen. However because they have not availability of ATRA in Indonesia we used high doses of vitamin A derivates 200,000 IU as a substitute for ATRA. It was expected by administering combination of vitamin A and chemotherapy would give equal prognosis with ATRA and chemotherapy. The patient suddenly was suffered from hematemesis and melena. The prothrombin time and activated partial thromboplastin time were prolonged. However the condition was deteriorated and finally died.

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