

Acute Erythroleukemia (AML-M6) in one-year-old boy: a case report



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ABSTRACT

Background: Acute Erythroleukemia (AML-M6) is a rare case with approximately 3-4% of all Acute Myeloid Leukemia (AML) cases. AML-M6 is less common in the pediatric population, with an incidence of <1% of all pediatric leukemia cases. This case study aims to evaluate Acute Erythroleukemia (AML-M6) in a one-year-old boy at Prof. dr. IGNG Ngoerah Denpasar.

Case Presentation: A one-year-old boy with clinical manifestations of fluctuating fever for a month, paleness, bleeding gums, bruising all over his body, swelling of both eyelids and splenomegaly. Peripheral Blood Smear (PBS) examination revealed bicytopenia with moderate normochromic normocytic anemia, severe thrombocytopenia and leukocytosis. A hypercellular picture was obtained from the examination of Bone Marrow Aspiration (BMA) with an increase in erythroblast activity of 74%, proerythroblast at 50% and normal myeloblasts activity at 10%. The patient was diagnosed with Acute Erythroleukemia (AML-M6). The patient died on day 16 of treatment.

Conclusion: Based on the examination results, it was concluded that the patient was diagnosed with AML-M6 according to the PBS and BMA evaluation.

Keywords: Acute Erythroleukemia, Bone Marrow Aspiration, Pediatric, AML-M6.

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INTRODUCTION

Acute Erythroleukemia is a rare type of Acute Myeloid Leukemia-M6 (AML-M6), characterized by abnormal expansion of malignant erythroid cells in the spinal cord.^{1,2} Based on the French American British (FAB) classification for AML, acute Erythroleukemia is classified into AML-M6 with a definition of more than 50% of erythroid precursors in the entire cell population and > 20% myeloblasts in non-erythroid cells in the bone marrow.³ AML-M6 cases are rare, only about 3-5% of all AML cases, with an annual incidence of 0.0077 cases per 100,000 patients worldwide.² AML-M6 was more common in male and elderly patients with a median age of 65 years old. In the pediatric population, cases of AML-M6 are even less common. Data from the Children's Oncology Group states that AML-M6 cases are only about 2.3% of all pediatric patients with AML.² Other studies also indicate that AML-M6 cases were found in less than 1% of all leukemia cases in pediatrics.⁴

AML-M6 was associated with lower

leukocyte levels, abnormalities on chromosome 7, response to therapy and poorer survival rates than other AML subtypes based on the FAB classification.^{2,3} The clinical manifestations of AML-M6 include pallor, weakness, fever and the presence of bleeding. Physical examination revealed hepatosplenomegaly.⁵ In almost all cases, normocytic normochromic anemia and thrombocytopenia were found.⁶ The prognosis for AML-M6 is very poor, with a median survival rate of 3-14 months from diagnosis. Meanwhile, if intensive chemotherapy is carried out, the median survival rate of patients can reach 7.6 to 9 months.^{7,8}

Since AML-M6 in children are very rare, this case study aims to evaluate the clinical characteristics and the course of AML-M6 disease in a 1-year-old, especially in laboratory examination.

CASE PRESENTATION

A one-year-old boy was admitted to the hospital with a fever 1 month ago. Fever occurred throughout the day with a high temperature of 39°C and decreased

with fever-reducing medication. The patient also complained of paleness and nosebleeds one week before being admitted to the hospital. Another complaint is black defecation once a week, but currently, there are no complaints of black defecation. The patient also experienced swelling of the right and left eyelids two weeks before admission to the hospital. The swelling is bluish-red and is felt to be getting bigger. There are no complaints of cough, runny nose, vomiting and decreased consciousness. No weight loss was found in the patient.

The patient has received a Packed Red Cell (PRC) and Thrombocyte Concentrate (TC) transfusion of 4 bags each. At the time of the blood transfusion, there was no transfusion reaction in the patient. There was no history of allergies or surgery history in the patient. The patient had a history of spontaneous vaginal birth, assisted by a midwife, with a birth weight of 2,100 grams and received exclusive breastfeeding for six months. On physical examination, the general status was within normal limits. However, there was subconjunctival bleeding in the right eye,

Table 1. Hematology parameter evaluation.

Parameters	16/03	17/03	19/03	21/03	21/03	23/03	25/03	26/03	29/03	References
WBC (10 ³ /μL)	20.83	20.79	15.86	16.09	16.34	13.37	16.59	12.90	17.52	6.10-14.00
%Neu	17.50	23.30	32.70	20.90	21.10	24.10	27.90	24.70	14.50	18.30-47.10
%Lym	80.90	66.80	64.40	75.90	76.90	65.10	70.30	65.50	84.00	30.00-64.30
%Mon	1.40	9.80	2.40	2.50	1.50	10.50	1.70	9.50	1.30	0.00-7.10
%Eos	0.00	0.00	0.10	0.10	0.10	0.00	0.00	0.00	0.00	0.00-5.00
%Bas	0.20	0.10	0.40	0.60	0.40	0.30	0.10	0.30	0.20	0.00-0.70
#Neu (10 ³ /μL)	3.62	4.84	5.19	3.37	3.46	3.22	4.62	3.19	2.53	1.10-6.60
#Lym (10 ³ /μL)	16.86	13.89	10.22	12.21	12.56	8.70	11.66	8.45	14.72	1.80-9.00
#Mon (10 ³ /μL)	0.29	2.03	0.38	0.41	0.24	1.41	0.29	1.22	0.23	0.00-1.00
#Eos (10 ³ /μL)	0.01	0.00	0.01	0.01	0.01	0.00	0.00	0.00	0.00	0.00-0.70
#Bas (10 ³ /μL)	0.05	0.03	0.06	0.09	0.07	0.04	0.02	0.04	0.04	0.00-0.10
RBC (10 ⁶ /μL)	3.13	2.17	4.34	3.98	3.67	3.26	2.71	3.96	2.63	4.10-5.3
HGB (g/dL)	8.20	5.60	12.40	10.90	10.10	9.10	7.80	11.90	7.10	12.0-16.0
HCT (%)	25.70	18.00	36.10	34.50	31.10	27.60	22.60	32.70	22.50	36.0-49.0
MCV (fL)	82.10	82.90	83.20	86.70	84.70	84.70	83.40	82.60	85.60	78.0-102.0
MCH (pg)	26.20	25.80	28.60	27.40	27.50	27.90	28.80	30.10	27.00	25.0-35.0
MCHC (g/dL)	31.90	31.10	34.30	31.60	32.50	33.00	34.50	36.40	31.60	31-36
RDW (%)	18.80	18.80	13.80	14.60	14.60	14.80	15.20	14.20	15.00	11.6-18.7
PLT (10 ³ /μL)	8.00	75.00	28.00	7.00	50.00	30.00	63.00	34.00	13.00	140-440
NLR	0.22	0.35	0.51	0.28	0.27	0.37	0.40	0.38	0.17	≤3.13
MPV (fL)	-	-	-	-	10.20	9.10	-	-	-	6.80-10.0
%Retic	0.38	-	-	-	-	-	-	-	-	0.90-2.22
#Retic (10 ⁶ /μL)	0.01	-	-	-	-	-	-	-	-	0.05-0.12

WBC: White Blood Cells; Neu: Neutrophils; Lym: Lymphocytes; Mon: Monocytes; Eos: Eosinophils; Bas: Basophils; RBC: Red Blood Cells; HGB: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; RDW: Red Cell Distribution Width; PLT: Platelet; NLR: Neutrophils-to-Lymphocytes Ratio; MPV: Mean Platelet Volume; Retic: Reticulocytes.

Red: Higher than references;

Blue: Below than references

Table 2. Clinical chemistry evaluation.

Parameter	16/03	17/03	21/03	26/03	29/03	References
AST (U/L)	97.1	-	64.2	-	59.0	5-34
ALT (U/L)	16.00	-	12.90	-	8.80	11.00-50.00
BUN (mg/dL)	6.80	-	-	-	7.40	8.00-23.00
Creatinine (mg/dL)	0.44	-	-	-	0.38	0.72-1.25
Ferritin (ng/mL)	708.02	-	-	-	-	21.81-274.66
Serum Iron (ug/dL)	85.80	-	-	-	-	65-175
Procalcitonin (ng/mL)	-	0.26	-	-	-	<0.15
Albumin (g/dL)	-	-	-	3.55	-	3.50-5.20

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; BUN: Blood Urea Nitrogen.

Red: Higher than references;

Blue: Below than references

the liver was palpated 1 cm below the costal arch, Schuffner VII palpated the spleen, and petechiae in the right left-hand regions.

Based on the supporting examination, it was found that the patient had a history of leukocytosis with a dominant lymphocytosis accompanied by anemia and thrombocytopenia since the first complete blood count was performed

(16/03/22) until the last day of examination (29/03/22) (Table 1). There was also a decrease in the percentage and absolute values of reticulocytes (Table 1).

On the first day (16/03/22) of clinical chemistry examination, the patient was found to have high levels of AST (97.1 U/L) and Ferritin (708.02 ng/mL), followed by BUN levels (6.80 mg/dL) and Creatinine (0.44) mg/dL were low (Table 2). The

evaluation of peripheral blood smears showed the interpretation of Normocytic normochromic anemia, atypical lymphocytes, and thrombocytopenia results on 16/03/22. In addition, there was also erythroblast predominance on peripheral blood smear and an atypical picture of lymphocytosis or cell blast on WDF scattergram using Sysmex XN-3000 (Table 3 and Figure 1).

Table 3. Peripheral Blood Smear (PBS) evaluation.

Parameter	Results (16/03/22)
Erythrocytes	Most cell populations have normochromic normocytic, anisopoikilocytosis (positive ovalocyte, positive teardrop cell), negative polychromasia, and negative normoblast.
Leukocytes	Slightly increased number, lymphocytosis differential count, positive atypical lymphocytes, negative toxic granules, and negative vacuolization.
Platelet	Slightly decreased number, negative giant platelets, negative clumping.
Interpretation	Normocytic normochromic anemia, atypical lymphocytes, and thrombocytopenia.

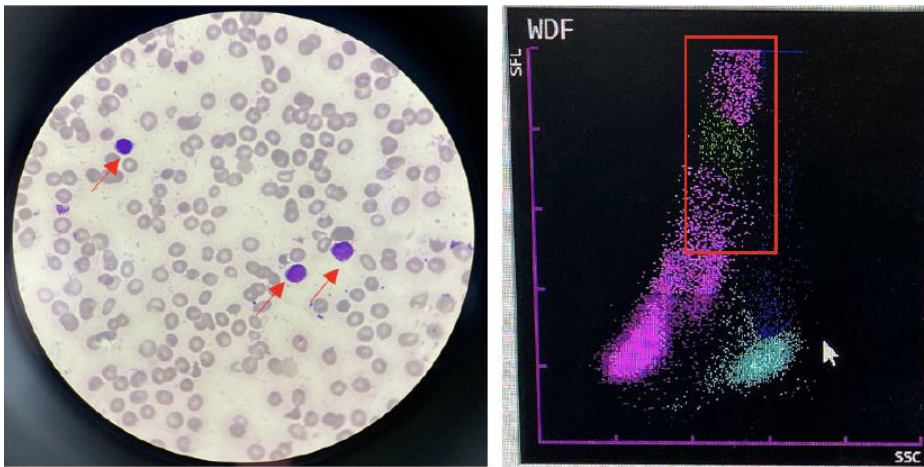


Figure 1. Peripheral Blood Smear (PBS) evaluation. (A) Normochromic normocytic anemia, erythroblast predominance (red arrow), and thrombocytopenia. (B) The results of the WDF scattergram using Sysmex XN-3000 showed an atypical picture of lymphocytosis or cell blast (red square).

Table 4. Urinalysis evaluation.

Parameter	19/03/22	References
Specific gravity	1.012	1.003-1.035
Turbidity	Clear	-
pH	5.50	4.50-8.0
Leukocytes (leuco/uL)	Negative	Negative
Nitrite (mg/dL)	Negative	Negative
Protein (mg/dL)	Negative	Negative
Glucose (mg/dL)	Negative	Negative
Ketone (mg/dL)	(1+)	Negative
Erythrocytes (ery/uL)	Negative	Negative
Urobilinogen (mg/dL)	2.0	Negative
Bilirubin (mg/dL)	Negative	Negative
Colour	Yellow	p.yellow-yellow
Leukocytes sediment (/LPB)	1.6	<2
Erythrocytes sediment (/LPB)	1.6	<2
Yeast cell (/LPB)	2.2	-
Epithelial Sedimen (/LPB)	1	<1
Silinder (/uL)	0.09	<2.25
Bacteria (/uL)	58.80	<26.4

Red: Higher than references;

According to the urinalysis evaluation, there was a positive ketone (+1), urobilinogen (2.0 mg/dL), and bacteria (58.80/uL) (Table 4). There was a decreased APTT (22.3 and 21.7 seconds)

during the study period (Table 5). Based on the bone marrow aspiration, the patient had increased activity in the erythroid system which consists of 74% erythroblast, 50% proerythroblast, decreased activity

of megakaryocytes system, and positive dysplasia signs (megaloblastic, blebs, multinucleated) (Table 6 and Figure 2). Those findings indicated Acute Erythroleukemia (AML-M6) dd/ Pure Erythroleukemia.

At the time of admission to the hospital (16/03/22), the patient received two bags of Thrombocyte Concentrates (TC) transfusions. On day 2 (17/03/22), the patient had melena and the hemoglobin level dropped to 5.60 g/dL, so the patient received a 150 ml Packed Red Cells (PRC) transfusion. After the transfusion, the patient's hemoglobin level increased to 12.40 g/dL on the 4th day of hospitalization (19/03/22). On day 8 (23/03/22), the patient again experienced fever and shortness of breath; suspected of having an infection, the patient was given antibiotics (Cefotaxim 50 mg/kgBW/time). On the 9th day of hospitalization (24/03/22), the patient was experienced facial swelling and also examined for Bone Marrow Aspiration (BMA) (Figure 2). The patient was given additional therapy with methylprednisolone 1.6 mg/kgBW/day and a 2-bag TC transfusion. On the 16th day of hospitalization (31/03/22), the patient experienced decreased consciousness due to suspected intracranial bleeding. The patient's condition worsened and experienced shortness of breath due to superior vena cava syndrome. The patient then developed bradycardia (120 beats/min, palpable weakness) and desaturated up to 85% with mask oxygen 8 lpm. Furthermore, the patient was unconscious and the pulse was not palpable. Cardiopulmonary resuscitation and epinephrine were administered, but the patient did not survive.

DISCUSSION

Based on the FAB classification, Acute Erythroleukemia is included in the Acute Myeloid Leukemia M6 (AML-M6) group,

a rare type of acute leukemia.⁹ This disease is characterized by increased components of the erythroid system with varying and increasing blast percentages.¹⁰ Cases of AML-M6 in the pediatric population are less common, with an incidence of only around 2.3% of all pediatric patients with AML based on data from the Children's Oncology Group.^{2,7} Other studies suggest that AML-M6 cases were found in less than 1% of all leukemia cases in pediatrics.^{4,11}

In the adult population, AML-M6 occurs in three phases: (1) the dominant erythroid phase in the form of extreme erythroid hyperplasia and megaloblastoid

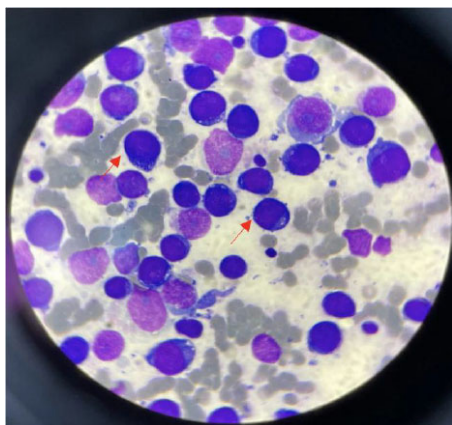


Figure 2. The Bone Marrow Aspiration (BMA) examination showed increased activity in the erythroid system with erythroblasts (red arrows) of 74% as the hallmark of Acute Erythroleukemia/Acute Myeloid Leukemia-M6 (AML-M6).

changes; (2) refractory preleukemic anemia phase characterized by the presence of ring sideroblasts or rapid changes to Erythroleukemia with an increase in the number of myeloblasts and cessation of granulocyte maturation and (3) the final phase in the form of AML conditions characterized by myeloblast proliferation.^{12,13} Meanwhile, cases of AML-M6 in the pediatric patient population usually do not go through the same evolutionary phase as chronic anemia in the adult population and have slightly different characteristics. Most cases of AML-M6 in the adult population are secondary, may occur after radiotherapy or chemotherapy after other primary malignancies, and have a history of myelodysplastic syndrome or the presence of AML with genetic abnormalities. Meanwhile, in the pediatric group, most reported AML-M6 cases occurred de novo.^{4,11,14} Based on the AML-M6 case series in the pediatric group, the mean age at initial diagnosis of AML-M6 in children was 4.7 years, with an age range of 2.5 months to 15 years. However, the mean age of 4.7 years shows the dominance of younger children in that age range.¹¹ In this case report, the patient's age when AML-M6 was diagnosed was one year which was still in the age range as in previous cases.

Overall, the clinical symptoms of AML-M6 in the pediatric and adult population are almost similar to the focus of symptoms associated with anemia.¹⁵ However, the clinical course of anemia

in the adult population is chronic which then turns into leukemia. While in the group of children, the symptoms of anemia experienced were similar to acute leukemia in other children, such as myeloid and lymphoid leukemia. Clinical signs and symptoms in the pediatric population occur due to the suppression of the normal process of hematopoiesis by malignant cells.^{11,15} Based on case reports and literature review, a consistent clinical manifestation was found to be pallor, identified in 100% of case reports regarding AML-M6 in children. Other manifestations are the presence of anemia, flu-like symptoms, hepatomegaly and splenomegaly, found in 54% and 50% of the previous reports, respectively. Santos FP et al. mentioned that the general clinical symptoms of AML-M6 are symptoms due to pancytopenias such as weakness, mucocutaneous bleeding and the presence of infection.² As many as 46% of patients experienced tumoral syndromes such as weight loss, cold sweats at night and fever.² The patient in the case report complained of fluctuating fever for about one month, paleness, nosebleeds, melena and swelling of both eyelids. The patient was also found to have Schuffner VII splenomegaly on physical examination. Extramedullary involvement, such as enlarged lymph nodes, hemangioma, and proptosis, is rare. However, a study conducted by Kesamneni et al. reported a three-year-old pediatric patient diagnosed with AML-M6 with the main symptom of protruding eyeballs or bilateral proptosis without visual impairment. The patient also had splenomegaly. In our case report, the patient was also found to have bilateral palpebral hematoma and Schuffner VII splenomegaly, where the clinical manifestations were in accordance with the previous study conducted by a previous study.¹⁶ Mandal PK et al. mentioned that in cases of AML-M6 in

Table 5. Coagulation test.

Parameter	21/03	23/03	References
PT (seconds)	12.3	13.4	10.8-14.4
INR	1.08	1.19	0.9-1.1
APTT (seconds)	22.3	21.7	24-36

PT: Prothrombin Time; INR: International Normalized Ratio; APTT: activated partial thromboplastin time.

Blue: Below than references.

Table 6. Bone Marrow Aspiration (BMA).

Parameter	Results (24/03/2022)
Cellularity	Hypercellular, M:E ratio 1:4
Erythroid system	Increased activity, 74% erythroblast with 50% proerythroblast, dysplasia (+) (megaloblastic, blebs, multinucleated).
Myeloid system	Normal activity (Myeloblast 10%)
Megakaryocytes system	Decreased activity
Other cells	There is no non-hematopoietic cell infiltration found
Interpretation	Bone marrow aspiration corresponds to Acute Erythroleukemia (AML-M6) dd/ Pure Erythroleukemia.

the pediatric population, hepatic failure was also often found, characterized by an increase in liver function.⁴ Our patient also found an increase in liver function or transaminitis in the form of an increase in AST to 97.1 U/L; therefore, the patient received ursodeoxycholic acid therapy given by the clinician.

Consistent laboratory findings found in cases of AML-M6 in the pediatric population are the presence of thrombocytopenia and anemia. Santos et al. said that anemia was very common, with 77% of cases having a hemoglobin level of less than 10 g/dL. In addition to anemia, thrombocytopenia is often found in 78-100% of cases. Neutropenia is also found in 70-77% of cases based on a previous study.² Tedja AT et al. stated that the results of peripheral blood smears of patients with AML-M6 would mostly find normochromic normocytic anemia and thrombocytopenia.⁶ The presence of erythrocyte abnormalities such as anisopoikilocytosis, anisochromia, and basophil stippling is not a typical finding. The neutrophil count can vary from normal to low, where Pseudo Pelger-Huet abnormalities can be found.⁶ The patient in this case report is known to have severe normochromic normocytic anemia with a hemoglobin level of 8.20 g/dL and thrombocytopenia with a platelet count of $8 \times 10^3/\mu\text{L}$. At the beginning of the MRS, the patient was also neutropenic, with a neutrophil percentage of 17.5%. After the TC and PRC transfusion, the patient's platelets had increased to $75 \times 10^3/\mu\text{L}$, and the patient's hemoglobin became normal at 12.40 g/dL but dropped again on the 6th day of hospitalization.

The gold standard for diagnosing AML-M6 is Bone Marrow Aspiration (BMA). BMA examination results in AML-M6 are characterized by erythroblast dominance, where erythroblasts are nucleated erythrocytes found in the spinal cord. Erythroblasts can appear as megaloblastoids and gigantoblastoids.^{4,11} The results of BMA in AML-M6 patients have characteristics in the form of hypercellularity with an increase in the number of erythroid cell systems accompanied by granulocyte depletion. Dysplasia can also be found in 34-50% of cases. About 71-89% of patients found

dysplasia of megakaryocytes, with the most common morphology in the form of micro-megakaryocytes and mononuclear megakaryocytes.⁴ The results of the BMA examination in our patient found hypercellularity with increased activity of the erythroid system with erythroblasts of 74% and proerythroblasts of 50%, dysplasia with megaloblastic, cytoplasmic, blebs and multinucleated morphology were also found. Meanwhile, the myeloid system was normal, with 10% myeloblasts. For the megakaryocyte system, decreased activity was found, and non-hematopoietic cell infiltration was not found in other cells.

Treatment of AML-M6 is essentially the same as therapy for other subtypes of AML, namely induction chemotherapy and post-remission therapy. However, the main therapy for AML-M6 is bone marrow transplantation. Allogeneic stem cell transplantation can assist some patients with poor karyotypes.^{4,16} A study conducted by the European Group of Blood and Marrow Transplantation on 203 patients with de novo AML-M6 found that 103 underwent autologous stem cell transplantation and 104 underwent allogeneic stem cell transplantation.¹⁷ In patients with autologous stem cell transplantation, the incidence of recurrence after 5 years was 70% and disease-free survival (DFS) was 26%.^{4,7,18} In a case report by Day DS et al., it was reported that a 4-month-old AML-M6 patient was treated with arabinosyl cytosine (Ara-C) and daunorubicin with improvement in clinical condition for four months.¹¹ However, the patient then relapsed due to pancytopenia and karyotypic instability. Another patient, aged 4 years also with AML-M6, was given therapy in the form of induction chemotherapy but failed due to kidney failure, respiratory failure and Ventilator-Associated Pneumonia (VAP), the patient died one month after treatment.¹¹ The patient in this case report has just received therapy in the form of TC and PRC transfusion, induction chemotherapy or a bone marrow transplant is planned to be given after the results of the BMA are out. When the results of the BMA analysis were completed, the patient worsened in the form of decreased consciousness due

to intracranial bleeding and respiratory failure due to superior vena cava syndrome and finally died on day 16 of treatment before chemotherapy or bone marrow transplantation could be performed.

AML-M6 is known to have a poor prognosis with a median Overall Survival (OS) of 3-9 months from diagnosis. During intensive chemotherapy, the median OS ranged from 7.6 to 9 months.⁸ The presence of a poor karyotype is associated with a worse prognosis. The results of multivariate analysis showed that morphological diagnosis was not an independent risk factor for determining OS and Disease-Free Survival (DFS).⁸ Meanwhile, age, hemoglobin level, karyotype, history of myelodysplastic syndrome, and chemotherapy-related diseases can significantly affect the survival rate of both OS and DFS patients. The most important risk factor is the presence of cytogenetic abnormalities, patients with complex and poor karyotypes are associated with a poorer prognosis.^{4,18} Based on those mentioned above, laboratory evaluations have a crucial part in determining the diagnosis and follow-up treatment regarding the AML-M6 cases.

CONCLUSION

In this case, we report a one-year-old boy diagnosed with acute erythroleukemia/acute myeloid leukemia M6 (AML-M6) from a Bone Marrow Aspiration (BMA) examination. The patient had clinical symptoms of fluctuating fever, pallor, severe anemia, thrombocytopenia, melena, palpebral hematoma and subconjunctival bleeding. The patient underwent TC and PRC transfusion, but the patient's condition continued to deteriorate and finally died on the 16th day of treatment.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

ETHICS CONSIDERATION

This case study has followed the COPE and ICMJE protocols according to the ethics publication guidelines. Informed consent has been obtained prior to the case study being conducted.

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The authors are responsible for the funding of this case study.

AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data acquisition, data analysis, until reporting the case study through publication.

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