A Rare Pediatric Case Report With Review of Literature for the Diagnosis of Acute Megakaryoblastic Leukemia (FAB M7)

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Received: Jun 04, 2021; Accepted: Aug 16, 2021

CITATION: Theyab A, Algahtani M, Dobie G, Hamali HA, Mobarki AA, Saboor M, *et al*. A rare pediatric case report with review of literature for the diagnosis of acute megakaryoblastic leukemia (FAB M7). Recent Adv Biol Med. 2021;7(3):1443014. https://doi.org/10.18639/RABM.2021.1443014

ABSTRACT

Acute megakaryoblastic leukemia (AMKL) is a subtype of acute myeloid leukemia (AML) accounting for 3%–10% of primary AML in childhood. Clinical manifestations of AML patients can include low grade of fever, diarrhea, easy bruising, failure to growth, and life-threatening clinical manifestations. Laboratory tests are very crucial to make a definitive diagnosis and treatment. We report here an uncommon case of AMKL in a 12-month-old boy who presented with general paleness and fatigue. Based on blood film investigation, bone marrow examination report, and immunophenotyping, he was diagnosed as a case of AMKL without Down syndrome.

KEYWORDS: Acute Myeloid Leukemia; Acute Megakaryocytic Leukemia; Immunophenotyping; Bone Marrow Examination.

1. INTRODUCTION

Acute myeloid leukemia (AML) is a type of varied (heterogeneous) hematological malignancies illustrated by uncontrolled proliferation of the bone marrow myeloid precursors with maturation arrest at blast stage that prevent myeloid differentiation into more mature blood cells [1]. Consequently, this causes accumulation of leukemic blast cells in the bone marrow and peripheral blood. Moreover, infiltration of the bone marrow with blast cells reduces the production of all blood cell lines including normal red blood cells, platelets, and mature white blood cells [2]. It is responsible for 80% of adult acute leukemias and for about 15%–20% of the acute leukemias in children [3].

Subtype classification of AML is performed on the basis of blood cells morphology in the French–American–British (FAB) classification system. However, additional investigations are required to make the diagnosis according to the WHO classification of myeloid neoplasms and acute leukemia. This includes cytochemical staining, molecular genetics, cytogenetics, and immunophenotyping data. Clinical presentations of AML patients vary depending on the disease phenotype and stage, but, however, may include fatigue, easy bruising, low-grade fever, weight loss, and hepatosplenomegaly. Bone tenderness and lymphadenopathy can also be seen in some subtypes such as acute megakaryoblastic leukemia (AMKL) (M7) [4].

The provisional diagnosis of AML can be made based on the clinical presentations, full blood examination results and morphology [4], whereas the confirmatory diagnosis usually requires further tests including bone marrow aspiration, immunophenotyping, and molecular genetics investigations [5]. Although these tests confirm the provisional diagnosis, they can also exclude the differential diagnosis.

Table 1: The confirmatory tests' results for common AML subtypes.

Subtypes	Bone marrow	Cytochemistry	Immunophenotyping	Cytogenetics & molecular tests
AML with minimal differentiation (FAB M0)	Markedly hypercellular with: - more than 90% blast cells - less than 10% promyelocytes	+ MPO + SBB + CAE	+ CD13 + CD 33, + CD 117 + CD 34	
AML without maturation (FAB M1) AML with maturation (FAB M2)	Hypercellular with: - 30% –89% blast cells - more than 10% promyelocytes or neutrophils	+ MPO + SBB + CAE	+ CD13 + CD 33, + CD 117 + CD 34	t(8:21) AML1/ETO
APL with the *PML-RARA* fusion gene	>30% blast cells	+ MPO + SBB + CAE	+ CD13 + CD 33 + CD 2 + CD 9	t(15:17) PML-RAR gene
Acute myelomonocytic leukemia (FAB M4)	>20% myeloblasts with >20% monoblasts	+ MPO + SBB + CAE + ANAE	+ CD13 + CD 33 + CD11b, 11c, + CD14 + CD 64	inv(16) & 11q23
Acute monoblastic/monocytic leukemia (FAB M5)	Monocytic cells are more than 80% of nonerythroid cells	+ ANAE	+ CD11b, 11c, + CD14 + CD 64	11q23 MLL/AF-9
Pure erythroid leukemia (FAB M6)	- Erythroid hyperplasia with megaloblastoid changes - dyserythropoietic and dysgranulopoietic changes - Erythroblasts in more than 50% of all nucleated cells - myeloblasts in more than 20% of nonerythroid cells	+ PAS (early erythrocytic precursors) + MPO and SBB (in > 5% in myeloblasts)	+ CD13 + CD 33, + CD 117 in myeloid component whereas + Glycophorin A (erythroid component)	
Acute megakaryoblastic leukemia (FAB M7)	>20% blasts with >50% megakaryocytic cells, high pleomorphic megakaryoblasts & increased reticulum fibrosis (often a dry tap)	+ PAS, + MPO + SBB, + platelet peroxidase + Nonspecific esterase (acetate) - Nonspecific esterase (butyrate)	+ CD41 + CD61 + CD42 + Platelet GPIIIa and + von Willebrand factor - CD34 & - CD45	t(1:22) in some cases

Abbreviations: Myeloperoxidase (MPO), Sudan black B (SBB), Chloroacetate esterase (CAE), alpha naphthyl acetate esterase (ANAE), Periodic Acid Schiff (PAS), positive (+), negative (-).

AMKL is a rare form of AML, developing from primitive megakaryoblasts and is correlated with poor prognosis. It is categorized by a proliferation of more than 20% of blasts with >50% megakaryocytic cells, high pleomorphic megakaryoblasts, and increased reticulum fibrosis, often a dry tap in the bone marrow. It can be identified by immunophenotyping via antibodies to glycoproteins (GPs) including GP Ib-V-IX complex (CD42), GP IIb/IIIa (integrin $\alpha_{IIb}\beta_3$) (CD41a), and GP IIIa (integrin β_3) (CD61) (Table 1). AMKL was shown to be an independent negative prognostic factor for survival with 4–10 months overall survival, and complete remission rate is reported to be ~50% and it is recommended to use allogeneic stem cell transplantation in the first remission [6].

Herein, we discuss a case report of a 12-month-old child diagnosed with acute megakaryoblastic leukemia without Down syndrome (non-DS-AMKL) having t(1;10) chromosomal abnormality and review of literatures.

2. CASE REPORT

A 12-month-old male child presented to a pediatrician at our clinic for a routine 12 months' check-up. On examination, he was pale with easy bruising. Full blood examination demonstrated that patient is anemic (Hgb 8.2 g/dL) and thrombocytopenic (platelets 21 × 10^3/μL).

In addition to the thrombocytopenia and normochromic normocytic anemia, the early evaluation integrated an extra examination of the peripheral blood, which verified leukoerythroblastic blood pictures with a rare circulating blast, infrequent nucleated RBCs, 9% atypical lymphocytes, and occasional smudge cells. Aspirate and a bone marrow biopsy demonstrated 3% blasts, reticulin fibrosis, normocellular bone marrow with tri-lineage hematopoiesis, and depletion of stores of iron. The child was discharged after he received a blood transfusion.

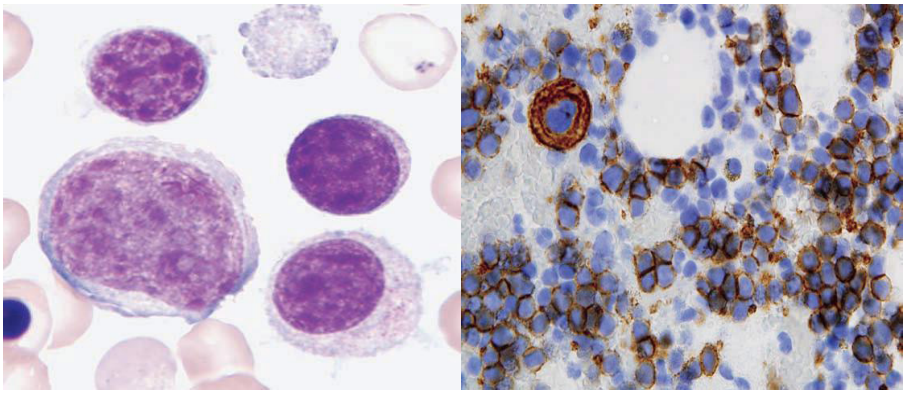
Following 15 days, the clinical status of the child deteriorated, and a second test of the peripheral blood verified noticeable anemia, RBC 2.4 × 10^6/μL (normal range: 3.70–5.30 × 10^6/μL), Hgb 7.0 g/dL (normal range: 10.5–13.5 g/dL), and Hct 19.6% (normal range: 33.0–39.0 g/dL) with dysplastic changes and leukoerythroblastosis (blasts 10%). The results of the bone marrow biopsy showed an atypical mononuclear cell infiltrate with clear fibrosis. Establishing the lineage of these cells by using comprehensive immunohistochemical evaluation was not supportive.

The studies of flow cytometric immunophenotyping observed that about 14% of overall cells expressing CD61 but not CD34 or CD117. Finally, a t(1; 10) translocation and hyperdiploid karyotype with 50 chromosomes were demonstrated by cytogenetic analysis. No legitimate trisomy 21 (Down syndrome) was observed.

3. DISCUSSION

Based on clinical presentations, bone marrow examination, complete blood count results, morphology, and flow cytometer results, this case is highly suggestive of acute megakaryocytic leukemia. As the patient had a normochromic normocytic anemia and thrombocytopenia, these symptoms/signs that are presented so suddenly in this child were caused by the accumulation of leukemic cells in the bone marrow which resulting failure of hematopoiesis. The peripheral blood also demonstrated leukoerthroblastic blood picture and nucleated red blood cells which were caused by the infiltration of the bone marrow [7]. However, according to Bennet *et al*., acute megakaryoblastic leukemia is defined by more than 30% of blast cells in the bone marrow aspirate or biopsy determined via immunophenotyping and morphology [8]. At the beginning, the patient was in the early stage of the disease and the percentage of blast cells was relatively normal. It is argued that the low percentage of blast cells could be due to the difficult aspiration of the bone marrow to enable the diagnosis as reticulin fibrosis leads to a false-negative result [8]. However, the presence of 9% atypical lymphocytes and smudge cells is likely to be the blast cells observed as small cells with large nuclei and dark blue cytoplasm. They appeared to resemble lymphoblast morphology (Figure 1) [8].

Figure 1: Acute megakaryocytic leukemia. A, Note heterogeneity of blasts, one small with scant cytoplasm, two with cytoplasmic blebbing, and one quite large (peripheral blood 31,000). B, Positive reaction for CD42b (bone marrow, 31,000) (Adapted from ref. [9]).



Differential diagnosis of this case to Myelodysplastic syndrome (MDS) is crucial because they share some clinical features and some cytogenetic abnormalities with AML-M7. MDS is characterized by bone marrow failure with peripheral cytopenia and at the risk of progression to AML [10]. Nevertheless, this disease can be excluded because it occurs mainly in patients over the age of 60. There was also no report of bruising or easy bleeding as this is common in about 55% of MDS patients [11].

A patient with MDS usually has a macrocytic anemia with increased iron stores [12], while the child came with normochromic normocytic anemia and absent of iron stores. Furthermore, the flow cytometric immunophenotypic studies demonstrated about 14% of cells expressing CD61 and this marker is not expressing in MDS. Absence of genetic abnormalities associated Myelodysplasia such as 5q del, result also can exclude MDS [13].

In infants, AML-M7 is associated with Down syndrome and the age of patients tends to be older with average age of 2 years [14, 15]. In this case, the patient was 12-month-old and had no report of trisomy 21; therefore, this child tends to be non-Down syndrome patient (non-DS-AMKL) and this kind of disease is restricted to t(1;22)(p13;q13) abnormality [16] but interestingly, the cytogenetic evaluation of the bone marrow aspirate confirmed presence of t(1;10) which is not common to be associated with AML-M7. Hyperdiploid karyotype with 50 chromosomes has been detected too. In addition, infants with trisomy 21 are at high risk of developing transient leukemia [17] which has been ruled out in this case.

Hence, based on the clinical presentation, the initial diagnosis was more suggestive of acute megakaryoblastic leukemia (AML-M7). As a result of these findings, the patient would need a further laboratory investigation before giving the final result.

On laboratory diagnosis, presence of leukopenia and neutrophilia with left shift was demonstrated in peripheral blood smear which indicate that the patient had been treated with G-CSF (neuogen therapy) that induces the generation of new granulocytes cells to exchange the damaged blast cells by intensive chemotherapy [18] and this in turn had led to immature form of neutrophil emerge in the peripheral blood. Roughly 8 weeks after initial presentation, the percentage of blasts increased to 16% with mixtures of circulating cells observed in the peripheral blood, including blast cells with cytoplasmic blebbing and some with convoluted nuclei. There were also hypogranular neutrophils and giant platelets which are sometimes present with megakaryoblastic fragments.

In the bone marrow, the percentage of blast cells has increased to 83% and they were mostly large with a high nuclear to cytoplasmic ratio and scant basophilic cytoplasm and distinct blebbing pseudopod formation. The presence of the blast cells with cytoplasm blebs may give a hallmark clue as to the blast's lineage [7]. Large and hyperlobate megakaryocytes were also seen with dysplastic forms.

However, morphology is not enough to confirm the final diagnosis. Immunocytochemistry performed on the bone marrow demonstrated the presence of CD 61 (glycoprotein IIIa) and this marker confirmed the lineage of megakaryocytic cells [19].

The flow cytometry is more sensitive and specific than surface staining to identify the latter markers. Flow cytometric immunophenotypic studies have verified approximately 8% of total cells in the bone marrow expression of CD13/33 and CD61, whereas CD117 and CD34 were not expressed. According to Ciesla (2007), CD61 is specific marker for megakaryoblasts, while CD13 and CD33 are specific myeloid markers for AML, and CD117 and CD34 are not often expressed on AMgeL (Table 1).

In addition, the cytogenetic analysis confirmed the presence of hyperdiploid karyotype (48–50 chromosomes) which were associated with heterogeneous cytogenetic subgroup of AML [20] and t(1; 10) abnormality.

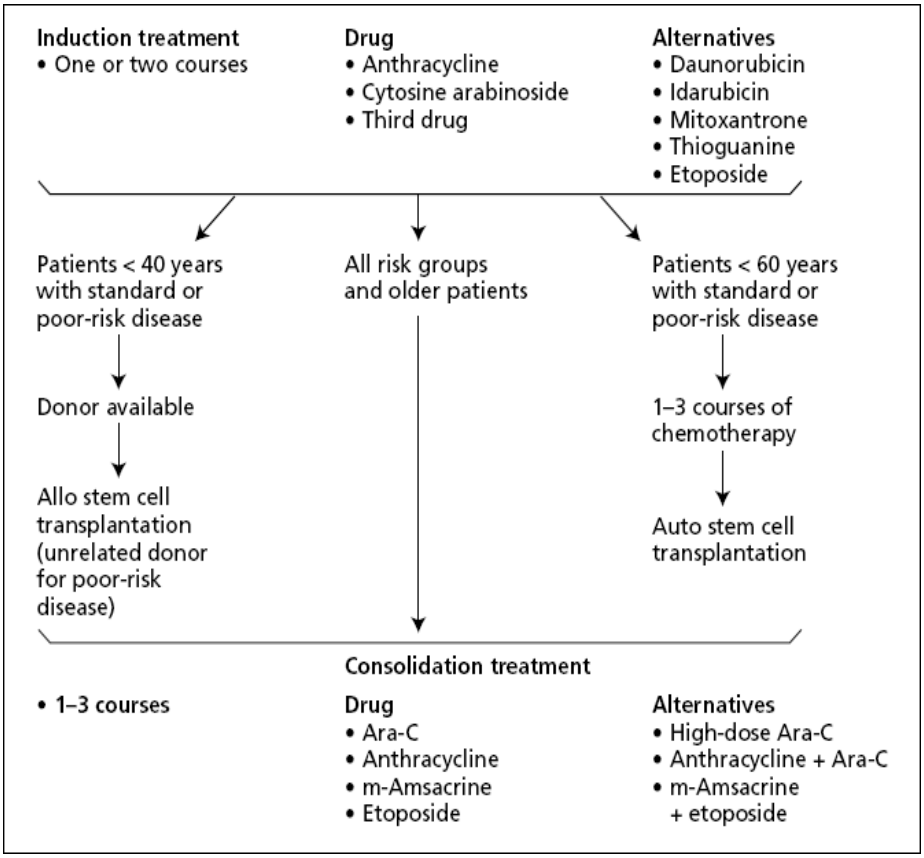
This patient needed special treatment strategy. The initial main concern was giving the child induction therapy to improve bone marrow function and to reduce tumor cells to an amount which are no longer detectable in the bone marrow and peripheral blood. As a result of this, bone marrow was able to generate normal number of circulating cells. The meaning of complete remission was based on these premises, blasts in the bone marrow <5% durable for at least 4 weeks, platelet count >100 × 10^9/L, neutrophil count 1.5 × 10^9/L, and lack of extramedullary disease. During this course of therapy, the patient was regularly taken a combination of cytosine arebinoside (Ara-C) and daunorubicin. Daunorubicin was given in a dose of 45 g/m^2 per day for the first 3 days. Arebinoside (Ara-C) was given in a dose of 100 mg/m^2 per day for the first 7 days. Roughly 30% of patients with AML require daunorubcin for 2 days and arebinoside (called 2 + 5 reinduction) for 5 days because the induction period of daunorubcin and arebinoside is not adequate to induce remission [21]. Most of the patients receive essential supportive medicines to minimize the chemotherapy side effects such as, prophylactic antibiotics and antifungals which play an important role to reduce the risk of infection during the period of neutropenia. This step of induction therapy takes about 4 weeks.

Following remission, the second step was consolidation therapy which is used to stop relapse and prevent the patient from nonhematological toxicities induced via intensive chemotherapy (Figure 2). However, during postremission, there are three other options which are further chemotherapy at induction level or chemotherapy with autologous stem cell transplantation or in some cases, allogeneic stem cell transplantation is preferable (Figure 2). It has been reported that allogenic stem cell transplantation (alloBMT) is appropriate for some patients with AML [22] and applied following the failure of reinduction therapy; thus, this treatment may be helpful in this case.

Evaluation of the child's bone marrow and peripheral blood after the first cycle and the second round of chemotherapy confirmed that this patient tended to have a poorer prognosis. In addition, according to luquet *et al*. (2008), patients with hyperdiploid (49 or more chromosomes) have the worst prognosis.

Subsequent to chemotherapy treatment and laboratory investigations, the final diagnosis for this patient is AMKL and non-Down syndrome.

Figure 2: Treatment options in AML (Adapted from ref. [21]).



The process of pathogenesis of this disease (AML) involves a molecular alteration in the activity of tyrosine kinase signaling pathways and transcriptional factors leading to disrupt cell differentiation, regulation of cell proliferation, survival, and apoptosis [23].

Molecular alterations impact receptor tyrosine kinase (RTK) signaling pathway. FLT3 tyrosine kinase, a member of RTK-RAS signaling, is the most common somatic mutation in AML which also play an essential role in cell proliferation, survival, and differentiation. This gene is expressed on hematopoietic stem cells and approximately 30% of AML patients have a mutation within the FLT3 gene [24].

FLT3 is activated by internal tandem duplication within juxtamembrane or activated by mutation at position D835 within the activation loop resulting in stimulation of tyrosine kinase activity and activation of the signaling pathways [25].

In contrast, RTK c-KIT is another transmembrane receptor which is activated by stem cell factor and it has been shown that over-activation of this receptor contributes to abnormal differentiation and excessive proliferation of myeloid leukemic cells [26]. However, there are several transcriptional factors associated with mutations in AML such as GATA1, RUNX1, and CEBPA [27].

The GATA binding protein 1 (GATA1) is one of the most important transcriptional factors that is essential for erythroid and megakaryocytic cell development [28, 29] and is generally absent in other cell types. Previous studies demonstrated that DNA-binding of GATA1 and its interaction with its cofactor FOG-1 are required for platelet production. However, acquired mutations have been detected in megakaryocytic leukemia in human Down syndrome (AMKL-DS) patients and result in thrombocytopenia and familial dyserthropoietic anemia [29, 30]. Mutations in RUNX1 have been associated with platelet deficiency and progressive pancytopenia, and CEBPA transcriptional factors increase the risks of developing AML [31].

4. CONCLUSION

AML M7 is a rare condition and type of AML. It is diagnosed and confirmed by several tests including bone marrow examination, blood cell morphology, and immunophenotyping test. Frequencies and differences between adult and infant acute megakaryoblastic leukemia can be assessed by immunophenotyping and cytogenetic data. We reviewed a pediatric case study report of acute megakaryoblastic leukemia which should be included in differential diagnosis of undifferentiated acute leukemia accompanied by thrombocytopenia.

CONFLICT OF INTEREST

None.

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