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Original Research Article

Unveiling Insights into Acute Megakaryoblastic Leukemia(FAB M7): A Comprehensive Analysis of a Case Series

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Abstract:

Acute Megakaryoblastic Leukaemia (AMKL) is a specific type of Acute Myelogenous Leukaemia (AML) classified as M7 according to the FAB system. This subtype is distinguishedby more than 20% immature blood cells, known as blasts, of which at least half belong to the megakaryocyte lineage. AMKL is a relatively uncommon form of AML that originates from undeveloped megakaryoblasts.

We have interesting Acute Myeloid Leukemia (AML) cases, subtype M7. Despite being recognized as a separate entity for a considerable period of time, the lack of clear clinical features and morphological criteria presents a significant challenge in accurately diagnosing this particular variant. Presented are the clinical, morphological, cytochemical, and immunocytochemical characteristics of six cases of Acute Megakaryoblastic Leukemia (AMKL).Various morphological features, such as the existence of abnormal platelet count, large-sized platelets, and cytoplasmic blebbing in blasts, have been identified as crucial factors in the diagnosis of the condition in question, owing to their significant diagnostic value... To achieve a reliable morphological diagnosis, the utilization of cytochemistry and immunocytochemistry becomes necessary due to the lack of consistency seen in the observed features.

Material and Methods: In the pathology department, Kasturba Medical College, Manipal Academy of Higher Education,Mangalore, Karnataka, India, a retrospective study spanning a decade-long period from January 2010 to December 2020 was conducted. The study involved retrieving a total of six cases, and detailed clinical histories and other relevant information were extracted from the corresponding case files.

Results: Among the 6 cases that were observed, the majority of them were males (M: F = 4:2). Out of the 6 cases, three of them belonged to the adult age group, while the other three were part of the paediatric age group, ranging from 1 year to 5 years old. Among the six cases analyzed, four cases(Case I, IV, V, VI) presented with symptoms of pancytopenia. Based on observations, the count of blasts in the peripheral blood typically falls within the range of 2% to 20%. Reticulin grade 2 was found in cases I and IV, grade 1 in cases II and V, and grade 3 in cases III and VI. PAS and NSE tests were positive, while fluoride resistance was negative in all six cases. Immunocytochemistry analysis revealed that all six cases were positive for myeloid markers (CD13, 33, 34, 45, 117) and CD 61 (Gp Illa), but negative for lymphoid markers (CD5, 7, 19, 20).

Conclusion: Accurately diagnosing this variant is crucial due to its impact on prognosis. While immunophenotyping is the preferred method, it may not be accessible in all medical facilities. However, identifying specific features such as cytoplasmic blebbing, platelet budding, bone marrow fibrosis, clustering of blasts and cytochemical positivity for nonspecific esterase that is fluoride resistant can aid in the correct diagnosis of a significant number of Acute Megakaryoblastic Leukemia cases.

Keywords: Acute myeloid leukaemia, Acute Megakaryoblastic Leukaemia, bone marrow biopsy,Cytochemistry, Immunophenotyping.

Introduction

AMKL, a rare hematopoietic malignancy primarily affecting children, is a specific type of AML. It is characterized by the proliferation of immature megakaryoblasts, which have an abnormal genetic makeup and impaired ability to differentiate into mature blood cells. Despite its low incidence rate of 3-5%, AMKL presents a grave prognosis and a significant risk of relapse, necessitating the development of more efficacious treatment approaches [1]. This is a rare subtype of acute myeloid leukemia (AML) known as acute megakaryoblastic leukemia (AMKL), which is

readily identified by the presence of atypical megakaryoblasts. [2] The medical condition known as acute megakaryoblastic leukaemia (AMegL) was initially documented by Von Boros et al. in 1931. It is a rare subtype of AML developing from primitive megakaryoblasts [3]. It is possible for other types of cells, like myeloblasts, to mix in with the leukemia cells, making diagnosis challenging, especially in adults. This is due to the small number of leukemia cells in the bloodstream and the difficulty in obtaining a bone marrow sample. Acute Myeloid leukemia (AML) can be categorized into subtypes, including Acute Megakaryoblastic Leukemia (AMKL). Unfortunately, AMKL is often associated with an unfavorable prognosis. Despite being describedin the literature for over 70 years, the low incidence of this condition has made it difficult to clearlydefine its clinical profile and morphological criteria for diagnosis [4]. Acute megakaryoblastic leukemia (AMKL) is a well-known type of cancer that affects two distinct age groups with great precision: adults and children aged 1-2 years interestingly; children with Down's syndrome are at a higher risk of developing AMKL [5]. However, this type of leukemia is quite rare in adults. Our institution encountered six cases of AMKL from a period of time, highlighting the importance of continued research and education on this challenging disease.

Materials and Methods

In the pathology department, Kasturba Medical College, Manipal Academy of Higher Education, Mangalore, Karnataka, India a retrospective study spanning a decade-long period from January 2010 to December 2020 was conducted. The study involved retrieving a total of six cases, and detailed clinical histories and other relevant information were extracted from the corresponding case files.

We thoroughly analysed the Wright's-stained peripheral smears and examined the bone marrow aspirate and biopsy smears to gain valuable insights. All cases had access to a comprehensive range of cytochemical tests, including myeloperoxidase (MPO), Sudan black B (SBB), periodic acid Schiff (PAS), and nonspecific esterase (NSE). In all the six cases, immunophenotyping was performed.

Results

Tables 1 and 2 contain in-depth clinical and haematological profiles for all six cases.

Among the 6 cases that were observed, the majority of them were males (M: F = 4:2). Out of the 6 cases, three of them belonged to the adult age group, while the other three were part of the paediatric age group, ranging from 1 year to 5 years old. This information provides a more detailed overview of the demographicdistribution of the studied cases.

Among the six cases, Case V exhibited distinct features indicative of Down's syndrome. Additionally, analysis revealed the presence of hepatosplenomegaly and lymphadenopathy in two and three patients,respectively, as outlined in Table 1.

Among the six cases analyzed, all patients exhibited anaemia. Leukocytosis was observed in one case (Case III), while thrombocytosis was present in another case (Case II). Four cases (Case I, II, III, IV) displayed the presence of giant platelets(Fig 3). Additionally, four cases (Case I, IV, V, VI) presented with symptoms of pancytopenia (Fig1).

Based on observations, the count of blasts in the peripheral blood typically falls within the range of 2% to20%. Further examination revealed that these blasts are larger than small mature lymphocytes, measuringapproximately 3-4 times their size. These blasts are characterized by moderate to abundant agranular basophilic cytoplasm, round to oval nuclei with fine to stippled chromatin, and 1-2 prominent nucleoli (Fig2,3). In some cases, a few blasts have been found to exhibit platelet budding and cytoplasmic blebbing (Fig4).

Four out of six cases of bone marrow aspirate smears were found to be highly cellular, with blasts accounting for 21% to 30% of all nucleated cells. The morphology of the blasts was similar to that seen in the peripheral blood (Fig 3), and micromegakaryocytes and promegakaryocytes were also observed. One of the cases (Case IV) showed metastases in the blasts. In two cases (Case I and VI), repeated attempts at bone marrow aspirate yielded diluted marrow.BM biopsy smears studied show hypercellular marrow made of predominantly uniform sheets of neoplastic cells with a high N:C ratio, scant cytoplasm,pleomorphic vesicular nuclei, and some with inconspicuous nucleoli. Dyspoietic megakaryocytes are seen. Other lineages are present but suppressed (Fig 5,6,7). Case VI, a 20- year-old patient, exhibits fibrosis (Fig 8: A, B). In the observed cases, Reticulin grade 2 was foundin cases I and IV, grade 1 in cases II and V, and grade 3 in cases III and VI. PAS and NSE tests were positive, while fluoride resistance was negative in all six cases. Immunocytochemistry analysis revealed that all six cases were positive for myeloid markers (CD13, 33, 34, 45, 117) andCD 61 (Gp Illa), but negative for lymphoid markers (CD5, 7, 19, 20).

Table 1: Clinical features and hematological parameters

Features	Case 1	Case 2	Case 3	Case4	Case 5	Case 6
Age	18 yrs	26yrs	2yrs	5yrs	1yr	20 yrs
sex	F	F	M	M	M	M
C/F	Fever, rashes, weakness, dizziness, pallor	Fever, rashes, petechiae, pallor.	Fever, minor rashes, pallor,	Fever, petechiea rashes, weakness.	Fever, petechia spots, fatigue.	Fever, minor rashes all over the body, Tiredness.
Down's syndrome	Absent	Absent	Absent	Absent	Present	Absent
Hepatomegaly	Absent	Absent	Present	Absent	Absent	Present
Splenomegaly	Present	Present	Absent	Absent	Absent	Present
Lymphadenopathy	Absent	Absent	Absent	Absent	Present	Absent
Hb (g/dL)	8.1	7	8	10	9	7.5
WBC (×109 /L)	3	2.5	39	4	4.4	3.8
Plt count (×109 /L)	40	500	50	35	55	45

Table 2: Morphology Cytochemistry and Immunocytochemistry

	Case 1	Case2	Case3	Case4	Case5	Case 6
Morphology						
*Red cells Normocytic Normochromic	Present	Present with few macrocytes	Present	Present	Present	Present
Peripheral smear						
*Blasts(%)	02%	01%	04%	03%	08%	19%
* Blast morphology						
a. agranular blue cytoplasm with cytoplasmic blebbing	Absent	Absent	Present	Present	Present	Present
b. Giant platelets	Present	Present	Present	Present	Absent	Absent
c. Platelet budding	Present	Present	Absent	Absent	Present	Present
Bone marrow aspiration/biopsy						
*Hypercellular marrow showing megakaryoblasts, micromegakaryocytes, promegakaryocytes (full range of differentiation)	BMA shows diluted blood with scattered blasts.	Present	Present	Present with mild metastasis	Present	Dilute BMA and biopsy shows blasts and fibrosis.
Blasts %	21%	21%	25%	23%	29%	30%
Reticulin grade	2	1	3	2	1	3
Cytochemistry						
PAS Positive	+	+	+	+	+	+
NSE positive ,fluoride resistant	+	+	+	+	+	+
MPO/SBB	–	–	–	–	–	–
Immunocytochemistry						
Lymphoid markers (CD5, 7,19, 20)	Negative	Negative	Negative	Negative	Negative	Negative
Myeloid markers (CD13,33,34,45,117)	Positive	Positive	Positive	Positive	Positive	Positive
CD61 (Gp IIIa)	Positive	Positive	Positive	Positive	Positive	Positive

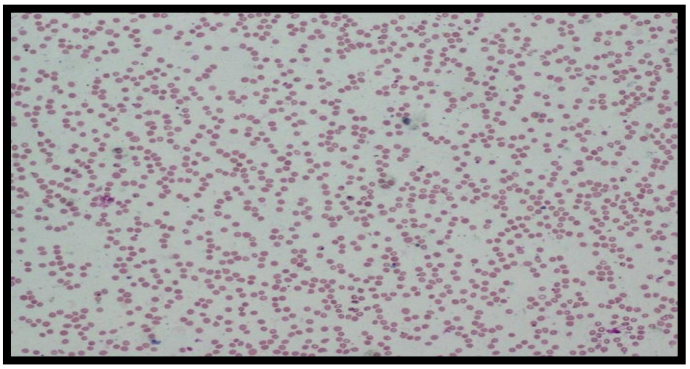

Figure 1: The peripheral smear indicates a condition calledpancytopenia

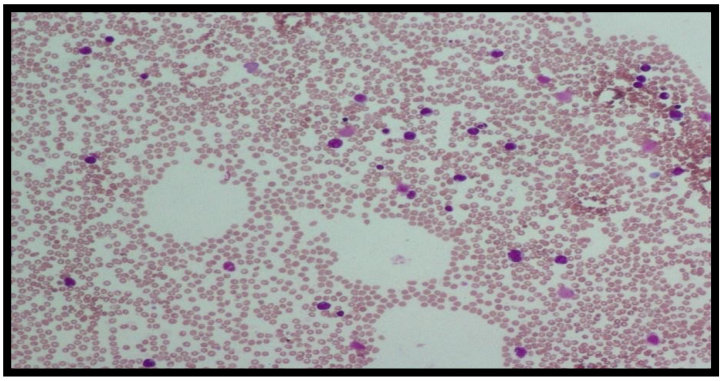

Figure 2: The peripheral smear showsmyeloid blasts

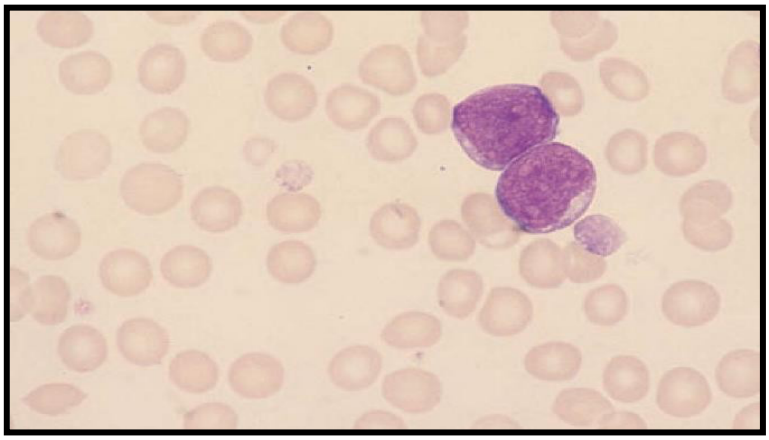

Figure 3: The BM aspirate analysis reveals the presence of two megakaryoblasts and two giant platelets

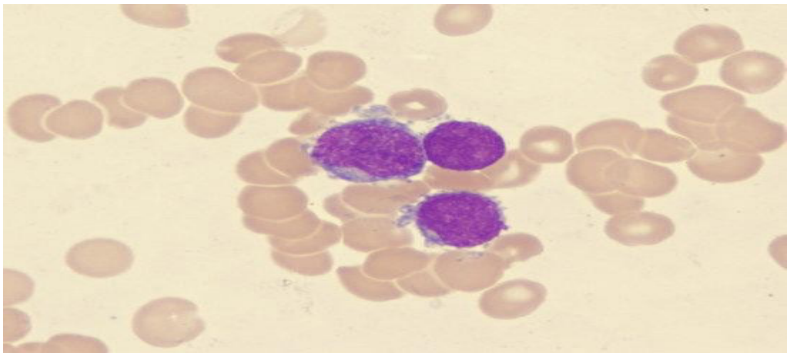

Figure 4: BM aspirate smear showsM7 blasts with pseudopod formation

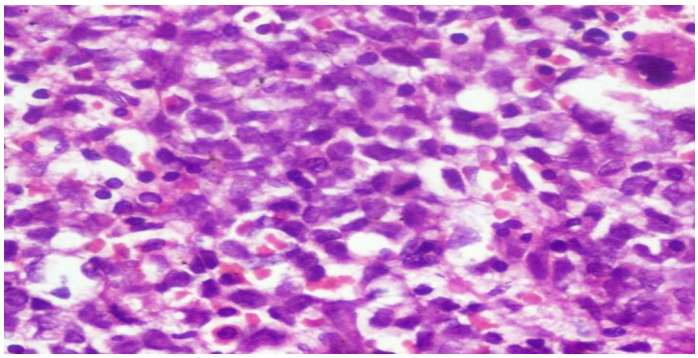

Figure 5: The bone marrow biopsy indicates an increase in cellcount and the presence of megakaryoblasts

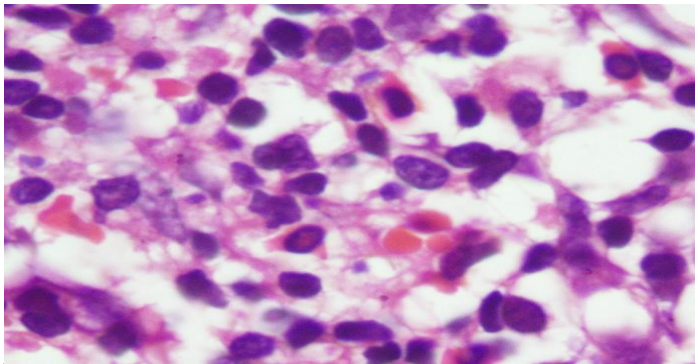

Figure 6: The bone marrow biopsy indicates the presence of cancerous cells arranged in uniform sheets. These cells have a high ratio of nucleus tocytoplasm, a small amount of cytoplasm, and irregularly shaped nuclei, with some having small or indistinct nucleoli.

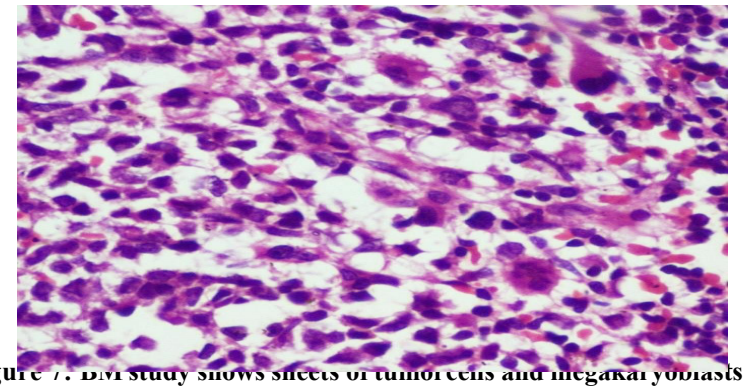

Figure 7: BM study shows sheets of tumor cells and megakaryoblasts

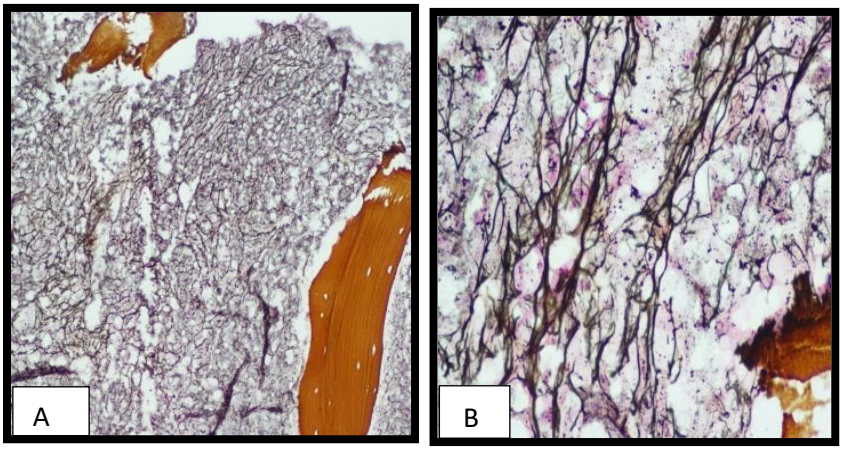

Figure 8: A, B – Bone marrow reticulin showing fibrosis and reticulin grade II

Discussion

AML M7, also known as AMKL, is a rare type of leukemia that is particularly challenging todiagnose due to its unique features. Unfortunately, 10% of childhood AML and 1- 2% of adult AML cases have a poor prognosis [6]. This paragraph discusses the development of Acute Megakaryoblastic Leukemia (AMKL) which can occur in three ways: as a de novo disease, as a secondary event following chemotherapy, or as a progression from Myeloproliferative Neoplasm (MPN) or Myelodysplastic Syndrome. Our study found one patient who possibly developed AMKL as a secondary event to MPN, specifically primary myelofibrosis.

Unlike other forms of leukemia, diagnosing AMKL based on morphology alone is difficult. However, certain features can be used to help identify it. These include the clustering of blasts, cytoplasmic blebbing, andplatelet budding [6].

To officially diagnose AML M7, more than 20% of the nucleated bone marrow cells must be blasts,and at least 50% must be of the megakaryocytic lineage. It's important to note that this type of leukemia can often be confused with ALL-L1/AML-M0 and can either arise in denovo or be secondary to chemotherapy or myelodysplastic syndromes [7,8,9].

A study carried out at M. D. Anderson Cancer Center discovered that out of 37 cases of AMKL, 62% had bone marrow fibrosis [10]. In our particular scenario, we were able to analyze a bone marrow biopsy that revealed the existence of fibrosis. Proving that AMKL is megakaryocytic requires either ultrastructural demonstration of platelet peroxidase or immunological demonstration of CD61, CD42, and CD41 on the surface of leukemia blasts. Cytoplasmic blebs and protrusions are often observed in patients with this type of leukemia, and as a result, immunologic phenotyping is necessary for diagnosis. Although cytochemistry has limited diagnostic value in this case, bone marrow fibrosis is often a critical feature in many cases. Patients with AMKL commonly exhibit multiple chromosomal aberrations, with chromosome 3 abnormalities being particularly characteristic. Unfortunately, evenafter complete remission, the outcomes for patients with AMKL are unfavourable. Allogenic transplantation during the first remission appears beneficial forthese patients.

Among the patients diagnosed with acute megakaryoblastic leukemia (AMKL), thrombocytosis was present in only one adult patient (a 26-year-old female), whereas the two other adult patientshad a low platelet count. In contrast, all three pediatric patients were thrombocytopenic [11]. This finding is consistent with previous studies and highlights the fact that AMKL can be classifiedas either undifferentiated or differentiated, with the latter being more prevalent in adults. [12,13]

Conclusion

Despite being a rare type of leukemia, acute megakaryoblastic leukemia (AMKL) has a poor prognosis and needs a precise diagnosis. However, our highly skilled team uses advanced diagnostic methods, allowing us to accurately identify this Subtype and provide the best possible treatment for our patients. Diagnosis involves a careful examination of both physical characteristics and immunophenotyping techniques. With proper identification, many AMKL cases canbe diagnosed correctly.

Although immunophenotyping is the gold Standard, it is not available in all the centers. A careful search for features like cytoplasmic blebbing, platelet budding, bone marrow fibrosis, clustering of blasts and cytochemical positivity for nonspecific esterase, which is fluoride resistant, can help in correctly diagnosing a significant number of AMKL cases.

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