



## ACUTE ERYTHROID LEUKEMIA – CLINICO-PATHOLOGICAL REVIEW OF A DISTINCTIVE ENTITY: A TERTIARY CENTRE EXPERIENCE

### Haematology

<b>Pratibha Singh</b>	Senior Resident, Department of Hematology, Nil ratan Sircar Medical College and Hospital, Kolkata.
<b>Abhishek Sharma</b>	Assistant Professor, Department of Hematology, Nil ratan Sircar Medical College and Hospital, Kolkata.
<b>Shuvra Neel Baul</b>	Associate Professor, Department of Hematology, Nil ratan Sircar Medical College and Hospital, Kolkata.
<b>Kaustav Ghosh</b>	Senior Resident, Department of Hematology, Nil ratan Sircar Medical College and Hospital, Kolkata.
<b>Tuphan Kanti Dolai</b>	Professor and Head, Department of Hematology, Nil ratan Sircar Medical College and Hospital, Kolkata.

### ABSTRACT

Acute Erythroid Leukemia (AEL), also known as Acute Myeloid Leukemia-M6 (AML-M6), is an exceptionally rare subtype of acute myeloid leukemia, accounting for less than 1% of all AML cases. It is characterized by the predominance of erythroid precursors in the bone marrow, with more than 80% erythroid elements and over 30% being erythroblasts. The diagnosis may also be supported by the presence of TP53 mutation, however, this is considered a desirable, not essential, criterion. We conducted a retrospective analysis of six cases diagnosed with AEL over a six-month period from October 2024 to March 2025 in the Department of Hematology at a tertiary care hospital in East India. Diagnosis was established through bone marrow examination and supported by multiparametric flow cytometry (3-laser, 10-colour). Clinical and pathological features were analysed in conjunction with relevant literature. The median patient age was 52 years (range: 32–56), with a male-to-female ratio of 1:1. All patients presented with pallor as a primary symptom, with a mean duration of symptoms being approximately eight weeks. Bleeding, organomegaly, and lymphadenopathy were infrequent. All cases exhibited anemia and thrombocytopenia without pancytopenia. Laboratory investigations showed hemoglobin levels ranging from 6–8.4 g/dL, total leukocyte counts between 4.6–16.8  $\times 10^9/L$ , and platelet counts from 20–70  $\times 10^9/L$ . Dysplastic features were evident in all cases, but cytogenetic analysis was inconclusive. Although TP53 mutation is desirable, but mutation was detected in only one patient, highlighting its variable occurrence. Treatment with standard Cytarabine and Anthracycline-based regimens resulted in poor outcomes in two of the six patients. AEL remains a diagnostically challenging and under-recognized entity due to its overlap with other hematological disorders and lack of standardized diagnostic approaches. Our findings reinforce the need for early and accurate diagnosis to guide therapy, especially in settings with limited resources and access to advanced molecular tools.

### KEYWORDS

Acute Erythroid Leukemia, Acute Myeloid Leukemia-M6, TP53 mutation, Multiparametric flow cytometry

### INTRODUCTION:

Acute Erythroid Leukemia (AEL/AML-M6) is a rare form of acute myeloid leukemia, accounting for less than 1% of all cases. It involves an abnormal increase in immature erythroid cells due to a halt in their maturation. In some instances, it is linked to a high frequency of biallelic TP53 mutations. The condition primarily affects older adults, typically in their late 60s, with a higher prevalence in men. The diagnostic criteria for AEL erythroid leukemia was updated in the recent WHO 2022 classification of AML, the essential criteria involves a predominance of erythroid cells, making up more than 80% of bone marrow elements, with over 30% being erythroblasts and the desirable criteria include evidence of TP53 mutation status.<sup>[1]</sup> The earlier classification identified two subtypes: AML M6a (Acute Erythroid Leukemia), characterized by 50% or more erythroid precursors and at least 30% blasts among the non-erythroid cells; and Pure Erythroid Leukemia (M6b), defined by 80% or more immature erythroid precursors with minimal maturation and no significant increase in myeloblasts.<sup>[2]</sup> Since its first discovery nearly a century ago by Di Guglielmo in 1917, this condition has remained difficult to diagnose, with its classification and criteria constantly evolving.<sup>[3]</sup> Erythroleukemia exhibits clinical and pathological characteristics similar to those seen in myelodysplastic syndromes. It often involves dysplasia across multiple cell lines, frequently presents with cytogenetic abnormalities typical of myelodysplastic syndromes, and has a mutation profile more closely aligned with these syndromes than with de novo acute myeloid leukemia.<sup>[4][5]</sup> Its similarity to some other non-malignant disorders (viral infection, drugs-erythropoietin, granulocyte colony stimulating factor therapy, hypersplenism, blood loss, hemolysis, hemoglobinopathies, nutritional deficiency- iron, folate and pernicious anemia) continues to complicate accurate diagnosis.<sup>[6]</sup> Hence, in the current case series, the clinico-pathological features along with hematological parameters of AEL cases were studied.

### MATERIALS AND METHODS

This was a retrospective analysis of six cases diagnosed as AEL as per

the WHO criteria<sup>[1]</sup>, over a study period of six months from October 2024 to March 2025 in the Department of Haematology at a Tertiary Care Centre in East India. In all the cases complete blood count with peripheral blood smear and bone marrow aspiration, imprint smear, trephine biopsy were reviewed. Cytochemistry, cytogenetics and immunophenotyping were also done as per availability. Clinical details and hematological data were retrieved from archived records. Written informed consent was taken from all the patients.

### RESULTS

A total of 198 cases of Acute Leukemia were diagnosed at our center over the study period, out of which 92(46.46%) cases were that of Acute Lymphoblastic Leukemia (ALL) of which 80(86.9%) were B-ALL, 12(13.05%) were T-ALL. 2 cases were diagnosed as Mixed Phenotypic Acute Leukemia (MPAL). 104 (52.5%) cases were that of Acute Myeloid Leukemia (AML), of which 5 (4.8%) cases were AML-M3 and, 6 cases were diagnosed to be AEL (5.7%) [Figure 1]

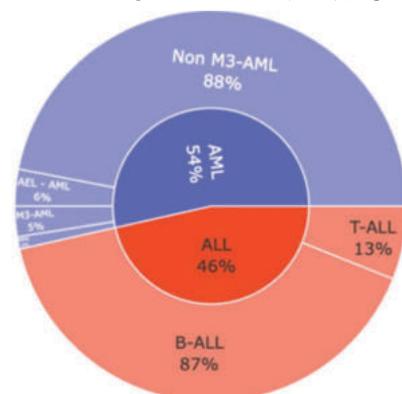


Figure 1

A thorough evaluation and analysis of the cases diagnosed as AEL that they exhibited unique clinical and morphological characteristics. The comparative

evaluation of presenting clinical features and hematological laboratory parameters are summarized in **Tables I** and **Table II**, respectively.

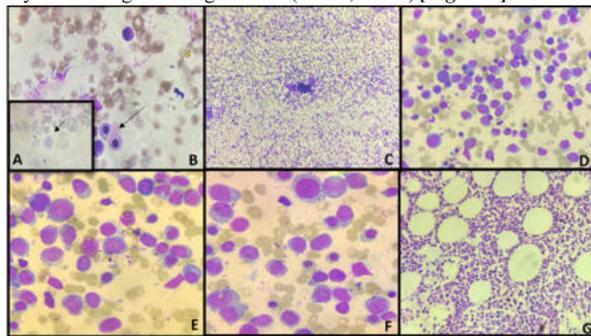
**Table I: Clinical Characteristics**

Case no.	Age	Sex	Duration of symptoms (months)	Fever	Asthenia	Pallor	Bleeding	Lymph-adenopathy	Organo-megaly	Jaundice
1.	32	Female	1	-	+	+	-	-	-	-
2.	54	Male	4	+	+	+	+	-	-	-
3.	54	Female	3	+	+	+	-	-	-	-
4.	39	Male	1	-	+	+	-	+	+	-
5.	50	Male	1	+	+	+	-	-	+	-
6.	56	Female	2	-	+	+	+	+	+	-

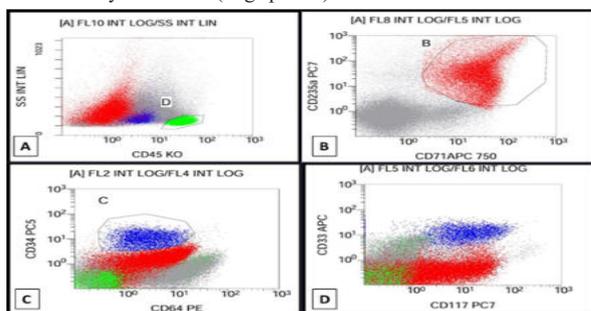
**Table II: Laboratory Characteristics**

Case No.	Hemoglobin (g/dl)	Total leukocyte count (x10 <sup>9</sup> /L)	Platelets (x10 <sup>9</sup> /L)	Dysplastic lineage	Bone Marrow Megakaryocytes	Erythroid Precursors (%)	Erythroblasts (%)	Cytogenetics
1.	6.4	4680	70	Erythroid	Reduced	53%	38%	46XX
2.	7.2	11610	20	Erythroid	Reduced	40%	42%	46XY
3.	7.0	16800	90	Erythroid	Reduced	45%	36%	46XX
4.	6.0	1100	45	Erythroid	Reduced	12%	74%	46XY
5.	6.2	9800	20	Erythroid	Reduced	55%	37%	46XY
6.	8.4	4500	28	Erythroid	Reduced	58%	32%	46XX

On complete blood count all the patients had anemia and thrombocytopenia. Peripheral blood smear had some clues like polychromatophils, occasional macrocytes, nucleated red blood cells in the background of immature cells [Figure 2]. On bone marrow aspiration, it was noted that majority of cells were proerythroblasts with round nuclei, high nuclear-cytoplasmic ratio and basophilic, agranular cytoplasm. Chromatin was denser than myeloblast chromatin and dysplasia was noted in all the cases in the form of nuclear budding, cytoplasmic blebbing and binucleated forms. In one of the six patients, Block Periodic Acid-Schiff (PAS) positivity was seen. Biopsy section revealed markedly hypercellular marrow with sheets of blasts and immature erythroid cells in all the cases [Figure 2]. Flowcytometry was used for confirmation of diagnosis. It was seen, that three out of four patients had CD71, CD36 and CD235a along with myeloid lineage defining markers (CD13, CD33) [Figure 3].



**Figure 2:**  
 A and B: Peripheral blood smear showing polychromatophils and nucleated red blood cells (MGG stain, 1000x)  
 C: Bone marrow aspiration smears showing hypercellular marrow with marked erythroid hyperplasia (May-Grunwald Giemsa [MGG], 40X)  
 D: Bone marrow aspiration showing dysplastic erythroid precursors. (May-Grunwald Giemsa [MGG], 400X)  
 E and F: Bone marrow aspiration showing immature erythroid precursors, including many proerythroblasts. (MGG stain, 1000X)  
 G: Bone marrow biopsy section (Hematoxylin and Eosin stain) showing markedly hypercellular marrow with sheets of blasts and immature erythroid cells (High power)



**Figure 3:** Flow cytometric analysis reveals an immunophenotypic

profile consistent with Acute Erythroid Leukemia.

**Plot A (CD45 vs SSC):** Demonstrates distinct populations with erythroid precursors (red, CD45 dim/negative, low SSC), myeloblasts (blue, CD45 dim, low SSC), and lymphocytes (green, CD45 bright, low SSC).

**Plot B (CD71 vs CD235a):** Shows a significant erythroid precursor population strongly expressing CD71 (transferrin receptor) and CD235a (glycophorin A), supporting erythroid lineage proliferation.

**Plot C (CD64 vs CD34):** Myeloblasts (blue) express CD34 (stem cell marker) and are negative for CD64, distinguishing them from monocytic lineage.

**Plot D (CD117 vs CD33):** Myeloblasts co-express CD117 (c-Kit) and CD33, further supporting immature myeloid lineage involvement.

Four patients had poor outcomes with the standard Cytarabine and Anthracycline-based regimen. One patient experienced prolonged cytopenia following induction therapy and unfortunately died due to complications related to febrile neutropenia. Two patients showed no response to the 3+7 regimen and was re-induced with a Mitoxantrone-based therapy. The fourth patient was lost to follow-up after induction therapy, and later presented with a morphological relapse. Considering age-related comorbidities and baseline performance status, the fifth and sixth patient, along with the one with morphological relapse were initiated on an Azacitidine-based regimen in the day care setting, are under regular follow-up, and have been responding well and have a significantly reduced transfusion need.

**DISCUSSION**

AEL is a unique bone marrow disorder marked by abnormal growth of immature erythroid cells (undifferentiated or proerythroblastic in appearance) committed exclusively to the erythroid lineage (> 80% of the bone marrow cells are erythroid, with ≥ 30% proerythroblasts), with no evidence of a significant myeloblastic component.

This entity has been infrequently documented in the Indian population. At our centre, over a span of 6 months, around 104 patients were diagnosed to be a case of AML, out of which six patients were categorized as AEL as per WHO 2022. This translates to approximately 5.55% of all AML patients, which is roughly the present incidence as per the literature. Median age in the current series was 52 years with male:female ratio 1:1. Median age was comparable to the study done by Attili et al<sup>[7]</sup> in which the median age was 37.5 years, however it was on the higher side (66 years) in the study done by Olopade et al.<sup>[8]</sup> Male predominance was seen in the studies done by Attili et al<sup>[7]</sup> and Kasyan et al<sup>[9]</sup>. All the patients presented with pallor, for a median duration of 2 months, whereas bleeding symptoms, organomegaly and lymphadenopathy was less commonly seen. Similar findings were observed by Attili et al<sup>[7]</sup> and Olopade et al<sup>[8]</sup>. However, in the series presented by Nayak et al<sup>[10]</sup>, four out of 5 patients had organomegaly.

In the complete blood count and peripheral blood smear, it was observed that all the patients had anemia and thrombocytopenia, with none having pancytopenia. Range of hemoglobin (g/dl), total leukocyte count (x10<sup>9</sup>/L) and platelet count (x10<sup>9</sup>/L) were 6-8.4, 4.6-16.8 and 20-70 respectively, which was comparable to the study done

by Nayak et al<sup>[10]</sup>. Normal cytogenetics was found in all the patients in the present study which was comparable to the study done by Attili et al<sup>[7]</sup>. But, in the studies done by Olopade et al<sup>[8]</sup> and Nayak et al<sup>[10]</sup>, only 23% and 40% of the patients, respectively had normal cytogenetics. Dysplasia was evident in all the cases, which can be frequently misdiagnosed as non-neoplastic conditions such as vitamin B12 deficiency, folate deficiency, or hemolytic anemia. Concordant results were found in the studies done by Attili et al<sup>[7]</sup>, Kasyan et al<sup>[9]</sup>, Nayak et al<sup>[10]</sup> and Calvo et al<sup>[11]</sup>, in which all the patients had evidence of dysplasia. Although TP53 mutation is desirable, but mutation was detected in only one patient, highlighting its variable occurrence.

AEL shares significant morphological, molecular, cytogenetic, and prognostic similarities with therapy-related myeloid neoplasms. There is extensive literature on myelodysplastic syndromes (MDS), and it is frequently regarded as a key differential diagnosis for AEL, given the shared features of erythroid hyperplasia and dysplasia. It has also been noted that patients with blasts of non-erythroid origin tend to have a

more favourable prognosis<sup>[12]</sup>. As a result, comprehensive diagnostic workup—including ancillary laboratory tests, mutation profiling, and cytogenetic analysis—is crucial for distinguishing reactive erythroid precursors from malignant immature cells and excluding other differential diagnoses.

One of the major challenges in managing AML, particularly AEL—a rare and aggressive subtype—is determining the optimal treatment approach, as well as assessing outcomes and overall survival. While our dataset was not robust enough to draw long-term conclusions, previous studies have explored treatment outcomes in AEL patients receiving hypomethylating agents (HMAs) compared to those on conventional chemotherapy or HMA-based regimens such as Decitabine.<sup>[13][14]</sup> Both treatment groups showed similar overall survival (25.4 months), but the Decitabine group demonstrated a notably higher complete remission rate of 80%. Limitation of the current study was low number of patients. Comparison of the results of current series with other studies in literature are summarised in **Table III**.

**Table III: Comparison Of The Results Of The Present Study With Existing Studies In Literature.**

Study	Number of patients	Male (%)	Median age (years)	Hepato-splenomegaly, lymphadenopathy (%)	Pallor (%)	Range Hemoglobin count (g/dl)	Range Total leukocyte count (x10 <sup>9</sup> /L)	Range Platelet count (x10 <sup>9</sup> /L)	Normal cytogenetics (%)	Dysplasia (%)
Olopade et al <sup>[8]</sup>	26	61.5	66	38,0	100	4.5-10.1	1.2-10.6	12-819	23	96
Attili et al <sup>[7]</sup>	14	78.5	37.5	43,14	100	4-10.5	2.3-18.2	10-318	71	100
Kasyan et al <sup>[9]</sup>	20	80	53	-	95	-	-	-	55	100
Calvo et al <sup>[11]</sup>	59	64	71.09	-	-	4.8-14.7	-	12-394	59.3	100
Nayak et al <sup>[10]</sup>	5	60	43	80,20	100	2.3-9.3	2.3-7.3	26-71	40	100
<b>Present study</b>	<b>6</b>	<b>50</b>	<b>52</b>	<b>50,33.3</b>	<b>100</b>	<b>6-8.4</b>	<b>4.6-16.8</b>	<b>20-70</b>	<b>100</b>	<b>100</b>

## CONCLUSION

AEL is a complex and diverse disease that can resemble several other neoplastic and non-neoplastic conditions, such as megaloblastic anemia, acute lymphoblastic leukemia, and myelodysplastic syndrome. Its diagnosis and management present significant challenges for both hematologists and hematopathologists, largely due to its rarity and the continually evolving diagnostic criteria. Given the limited literature available on optimal treatment approaches and outcomes, it is crucial to ensure timely identification, accurate diagnosis, and appropriate management of affected patients. Early and precise evaluation plays a key role in determining both prognosis and therapeutic success.

## REFERENCES

1. Khoury JD, Solary E, Abal O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022 Jul; 36(7): 1703-19.
2. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood, The Journal of the American Society of Hematology*. 2009 Jul 30; 114(5): 937-51.
3. Guglielmo D. Ricerche di ematologia. I. Un caso di eritroleucemia. *Megacariociti in circolo e loro funzione plastrinopoitica*. *Folia Medica (Pavia)*. 1917; 13: 386.
4. Lessard M, Struski S, Leymarie V, Flandrin G, Lafage-Pochitaloff M, Mozziconacci MJ, et al. Cytogenetic study of 75 erythroleukemias. *Cancer genetics and cytogenetics*. 2005 Dec 1; 163(2): 113-22.
5. Bacher U, Haferlach C, Alpermann T, Kern W, Schnittger S, Haferlach T. Comparison of genetic and clinical aspects in patients with acute myeloid leukemia and myelodysplastic syndromes all with more than 50% of bone marrow erythropoietic cells. *Haematologica*. 2011 May 23; 96(9): 1284.
6. Zuo Z, Polski JM, Kasyan A, Medeiros LJ. Acute erythroid leukemia. *Archives of pathology & laboratory medicine*. 2010 Sep 1; 134(9): 1261-70.
7. Attili SV, Dadhich HK, Jacob LA, Anupama G, Bapsy PP, Devi L, et al. A retrospective study of clinico-hematological and cytogenetic profile of erythroleukemia from South India. *Turk J Haematol: official journal of Turkish Society of Haematology*. 2006 Sep 1; 23(3): 158-63.
8. Olopade OI, Thangavelu M, Larson RA, Mick R, Kowal-Vern A, Schumacher HR, et al. Clinical, morphologic, and cytogenetic characteristics of 26 patients with acute erythroblastic leukemia. (1992): 2873-2882.
9. Kasyan A, Medeiros LJ, Zuo Z, Santos FP, Ravandi-Kashani F, Miranda R, et al. Acute erythroid leukemia as defined in the World Health Organization classification is a rare and pathogenetically heterogeneous disease. *Modern Pathology*. 2010 Aug 1; 23(8): 1113-26.
10. Nayak D, Manohar C, Belurkar SV, Rai N, Suvarna N, Khanna R. Acute Erythroid Leukemia—A Hematological review of 5 cases in a tertiary care centre. *Int J Sci Res Pub*. 2014; 4: 1-5.
11. Calvo X, Arenillas L, Luño E, Senent L, Arnan M, Ramos F, et al. Erythroleukemia shares biological features and outcome with myelodysplastic syndromes with excess blasts: a rationale for its inclusion into future classifications of myelodysplastic syndromes. *Modern Pathology*. 2016 Dec 1; 29(12): 1541-51.
12. Arenillas L, Calvo X, Luño E, Senent L, Alonso E, Ramos F, et al. Considering bone marrow blasts from nonerythroid cellularity improves the prognostic evaluation of myelodysplastic syndromes. *Journal of Clinical Oncology*. 2016 Sep 20; 34(27): 3284-92.
13. Pierdomenico F, Almeida A. Treatment of acute erythroleukemia with Azacitidine: A case series. *Leukemia Research Reports*. 2013 Jan 1; 2(2): 41-3.
14. King R, Crouch A, Radojic V, Marini BL, Perissinotti AJ, Bixby DL. Therapeutic outcomes of patients with acute erythroid leukemia treated with hypomethylating agents. *Blood*. 2016 Dec 2; 128(22): 5203.