Am J Blood Res 2025;15(4):96-101
www.AJBlood.us /ISSN:2160-1992/AJBR0160672

Case Report

Acute erythroid leukemia in a child: insights from a rare case

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Received September 22, 2024; Accepted July 29, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Acute erythroid leukemia (AEL) is an extremely rare subtype of acute myeloid leukemia (AML), accounting for less than 1% of AML cases. It predominantly affects older adults and is characterized by a proliferation of erythroid precursors, typically constituting >80% of bone marrow components, with ≥30% being proerythroblasts and often associated with poor prognosis. We present the case of a 15-year-old female who developed de novo AEL, an unusual presentation in a pediatric patient. The patient presented with fever, increased vaginal bleeding, leukocytosis, severe anemia, and 87% erythroid cells in peripheral blood smear. Bone marrow analysis revealed 90% erythroid precursors, 60% of which were proerythroblasts. Immunophenotyping confirmed AEL, showing positive expression of CD71, CD235a, CD36, and negative myeloid markers. Next-generation sequencing identified mutations in ARID1A and ATM genes, without *TP53* mutation. The patient was treated with AML induction therapy (7+3 regimen). This report highlights a rare case of de novo AEL in a pediatric patient, emphasizing its clinical presentation, the diagnostic challenges posed by its rare occurrence and overlapping features with other hematological disorders, and the critical role of a comprehensive diagnostic evaluation, including morphology, flow cytometry, and genetic studies, in achieving timely diagnosis and appropriate management. Further research is needed to understand the molecular landscape better and identify optimal therapeutic strategies for pediatric AEL.

Keywords: Acute erythroid leukemia, pediatric leukemia, immunophenotyping, erythroid-lineage blasts

Introduction

Acute erythroid leukemia (AEL), previously known as Pure Erythroid Leukemia, is a rare subtype of leukemia representing less than 1% of Acute myeloid leukemia (AML) cases [1]. It is recognized as a distinct morphological entity in both 2016 and 2022 World Health Organization (WHO) classifications [1, 2]. However, the 2022 International Consensus Classification (ICC) places AEL within a broader category termed "AML with TP53 mutations" [3]. The primary diagnostic criteria for AEL involve a predominance of erythroid cells, typically constituting >80% of bone marrow components, with ≥30% being proerythroblasts and no evidence of significant myeloblastic component [1]. There is variable expression of the erythroid-specific antigens with presence of biallelic *TP53* alterations and complex/monosomal karyotype [4]. While AEL may develop spontaneously (de novo), it more often occurs as progression of a prior Myelodysplastic Syndrome (MDS) or myeloproliferative neoplasm or as therapy-related disease [1]. AEL primarily affects adults, with a median age of diagnosis in late 60s, progresses rapidly and aggressively, lacks established treatment protocols. The treatment of AEL generally follows principles established in other AML, but outcomes are often poor, due to high-risk cytogenetic abnormalities and frequent *TP53* mutations, with a median survival of less than 2 months [4, 5].

Case presentation

A 15-year-old female with no prior medical history presented with fever and increased per vaginal bleeding for 8 days. On physical examination, she was found to have pallor. Contrast-Enhanced Computed Tomography of chest and abdomen revealed mild bilateral pleural effu-

https://doi.org/10.62347/GCUG1405

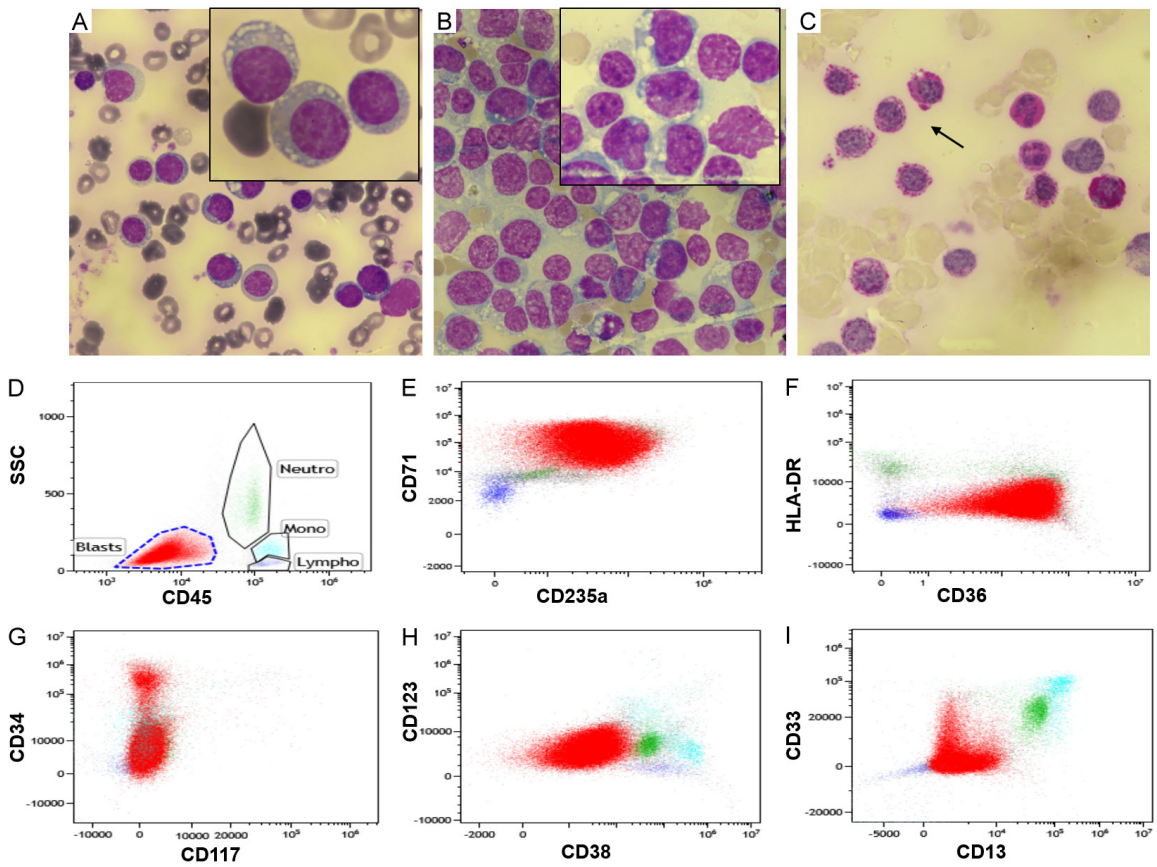

Figure 1. (A) Peripheral blood smear showing erythroblasts with bi-nucleate forms (Jenner-Giemsa stain, X1000). (B) Bone marrow aspirate smear showing marked erythroid hyperplasia with prominence of immature erythroid precursors (erythroblasts), with prominent nucleoli and deep basophilic vacuolated cytoplasm. (Jenner- Giemsa stain, X1000). (C) Periodic acid-Schiff stain show globular and coarsely granular cytoplasmic positivity (PAS, X1000). (D-I) Flow cytometric analysis of bone marrow aspirate detected blasts (red) that were (D) CD45 (dim to negative); positive for (E) CD71, CD235a; (F) CD36; (G) CD34 (subset 10%); and negative for (F) HLA-DR; (G) CD117; (H) CD38, CD123; (I) CD13, CD33.

sion, hepatomegaly, and multiple intra-thoracic and intra-abdominal lymphadenopathies. A complete blood count (CBC) revealed leucocytosis (162×10^9/L) with low normal platelet count (112×10^9/L), and anemia (6 g/dL). The peripheral blood smear (PBS) showed 87% erythroid cells including proerythroblasts with severe neutropenia (**Figure 1A**). Bone marrow (BM) aspirate was hypercellular with 90% erythroid cells of which 60% were proeythroblasts. These blasts were large with large central nucleus, fine chromatin, prominent nucleoli and moderate amount of vacuolated, agranular, basophilic cytoplasm. Few bi and multinucleated forms were also noted (**Figure 1B**). The blasts showed cytoplasmic block positivity for Periodic acid-Schiff (PAS) stain (**Figure 1C**) and were negative for Myeloperoxidase cytochemistry. The PBS and BM morphology suggested a diagnosis of AML, likely AEL.

On multiparametric flow-cytometry (**Figure 1D-I**), these cells (88%) were positive for CD71, CD235a (glycophorin A), CD36, CD34 (10% subset), CD45 (dim to negative) and negative for CD117, CD13, CD33, CD7, CD38, CD123, HLA-DR, cyto myeloperoxidase (MPO), CD64, CD14, cyto CD61, cyto CD41 and other B and T cell markers. This confirmed the diagnosis of AEL. The karyotyping showed 46XX, add (4) (p16) [5]. Next Generation Sequencing (NGS) identified a frame-shift insertion ARID1A variant, specifically ARID1A-p.Gly370Argfster30, along with a missense variant in the ATM gene noted as p.Leu1606Val. The patient was started with AML induction therapy (7+3) as per the institutional protocol with duanorubicin (45

mg/m^2) daily for 3 days along with Cytarabine (100 mg/m^2) daily for 7 days.

Discussion

AEL is uncommon in younger age group (median age 66-68 years). To the best of our knowledge, only a few cases have been reported in pediatric population [5-9] (**Table 1**). To confirm a diagnosis of acute erythroid leukemia, a systematic approach combining clinical, morphological, immunophenotypic, and genetic findings is essential. Peripheral blood findings often include severe anemia, variable white blood cell and platelet counts (most commonly pancytopenia), circulating nucleated red blood cells (NRBCs), dysplastic erythroid precursors, and a few blasts [10]. However, our case deviates from this typical presentation as it exhibited increased count, with 87% of the cells being erythroid, including many proerythroblasts. In AEL, bone marrow aspirates and biopsy typically reveal hypercellularity with dysplastic erythroid precursors displaying megaloblastoid changes, nuclear budding, or multinucleation [11]. Erythroid precursors in AEL are negative for myeloperoxidase (also Sudan Black B and esterase) and often show strong PAS positivity, characterized by a coarse granular or block-like pattern. This helps differentiate malignant erythroid precursors from normal or reactive erythroid precursors, which are typically PAS-negative or weakly positive [1]. Immunophenotyping by flow cytometry identifies erythroid precursors expressing CD71 and glycophorin A, while excluding myeloid lineage markers (CD13, CD33) [11]. These erythroblasts usually negative for CD34 and HLA-DR; and express CD36 and CD117 (partial to homogenous) with dim CD45 and decreased or negative CD38 expression, contrasting to reactive early erythroid precursors that are bright CD38 [4]. Although there are no recurring cytogenetic or molecular abnormalities specific to AEL, cytogenetic and molecular analyses frequently reveal complex karyotypes, including deletions or monosomies involving chromosomes 5 and 7, as well as *TP53* mutations, which are associated with poor prognosis [12]. TP53 mutation is more frequent in adult AEL cases compared to pediatric ones [13]. AEL poses a diagnostic challenge, particularly in cases with subtle or absent morphological evidence of erythroid differentiation and due to morphologic similarity of pronormoblasts with other cell types and also due to CD34 negativity of these blasts [14]. Thus, comprehensive clinical, laboratory, morphological, immunophenotypic, and cytogenetic evaluations are necessary for an accurate and timely diagnosis. Various mimickers of AEL include acute megakaryoblastic leukemia, AML with myelodysplasia related changes with erythroid hyperplasia or MDS with excess blasts with erythroid hyperplasia, rarely lymphoblastic leukemia or lymphoma. Megaloblastic anemia, typically associated with vitamin B12 or folate deficiency, may present with elevated proerythroblasts, resembling AEL. However, this possibility was ruled out in our case as serum vitamin B12 and folate levels were notably high at 2000 pg/mL (reference range: 200 to 600 pg/mL) and 20 ng/mL (reference range: 4.6 to 18.7 ng/mL), respectively. Parvovirus B19 infection can mimic some features of AEL by causing erythroid hyperplasia or aplasia, was ruled out in our case by serological and molecular testing [15]. Additionally, non-hematopoietic malignancies such as carcinomas and sarcomas must be excluded, as occasionally, the erythroblasts display an unusual morphology with clustering that may be confused with metastatic tumor cells [16]. Fortunately in our case the morphology showed erythroid differentiation and also the immunophenotyping confirmed the same.

The treatment of AEL is similar to other AML. Induction therapy typically involves a standard AML-like regimen such as cytarabine (7 days continuous infusion) combined with an anthracycline (3 days), though responses are often suboptimal in AEL [17]. Hypomethylating agents, such as azacitidine or decitabine, with or without venetoclax, are alternative options for elderly or unfit patients and may also benefit those with *TP53* mutations [18]. Consolidation therapy includes high-dose cytarabine or allogeneic hematopoietic stem cell transplantation (HSCT), the latter being particularly important for patients with high-risk cytogenetics or TP53 mutations, as it offers the best chance for long-term remission. In relapsed or refractory disease, salvage regimens such as FLAG-IDA or CLAG-M, targeted therapies (e.g., FLT3 or IDH inhibitors), or clinical trials should be considered. Supportive care, including transfusions, infection prophylaxis, and tumor lysis syndrome management, is critical throughout treatment. Given the poor prognosis of AEL, novel therapeutic strategies, including targeted

Table 1. Acute Erythroid Leukemia cases reported in pediatric population

Cases	Age/Sex	Presentation	HB/ANC/Platelet	PBS findings	BMA findings	FCMI	Karyotype	Follow up
Case 1 Ouahidi et al [5].	16 yrs/F	Fever, severe fatigue and mucocutaneous bleeding	7.8 g/dL/0.468×10^9/L/67×10^9/L	5% myeloblasts, 12% erythroblasts	93% erythroblasts with >30% proerythroblasts	Positive for CD4 (33%), CD13 (46.2%), CD33 (63.3%), CD71 (42%), glycophorin A (27%), HLA-DR (56.4%), and negative for other myeloid and lymphoid markers	N/A	Died 3 days of starting the induction chemotherapy (Daunorubicin andcytarabine)
Case 2 Abrantes et al [6].	5 yrs/M	Pain in leg, fever, gingival hypertrophy	6 g/dL/leukocytes and platelets normal in number	Anaemia	85% erythroblasts	Positive for CD71, CD235a, HLA DR, CD45, CD38, CD13 and negative for CD41, CD4, CD34, CD14	46 XY (Normal)	N/A
Case 3 Prabawa et al [7].	1 yrs/M	Fever, pallor, bleeding gums, bruising, splenomegaly	8.2 g/dL/3.62×10^9/L/8×10^9/L	Anemia, erythroblast predominance, leukocytosis severe thrombocytopenia	74% Erythroblasts with 50% proethroblasts and 10% myeloblasts	N/A	N/A	Died at 16th day of starting induction chemotherapy
Case 4 Day et al [8].	4 mos/F	Pallor, wheezing, irritability, Flu like symptoms, hepatosplenomegaly	5.4 g/dL/leukocytes normal in number/86×10^9/L	N/A	75% Erythroblasts	Positive for CD71, CD235a	Complex 48, XX, +8, +22 [12] 48, idem, del (10) (q23) [7]/46,XX [7]	Died 8 months after diagnosis (Daunorubicin and cytarabine) relapsed at 4 months
Case 5 Day et al [8].	4 yrs/F	Pain abdomen, fever, pallor, hepatosplenomegaly	8.4 g/dL/N.A/70×10^9/L	N/A	77% Erythroblasts	Positive for CD71, CD11b	Complex 48-51, XX, der(1) t(1;6)(q10;q12), +i(1) (q10;q12), +7, del(13) (q32). Add (16)(q24), +18, +21 [25]/46.XX [2]	Died 1 month after initiation of induction chemotherapy
Case 6 Bhattacharya et al [9].	2 yrs/M	Proptosis and bleeding from left eye, fever	N/A	30% blasts and thrombocytopenia	90% Blasts	N/A	Complex	Relapsed at 6 months (cytarabine, doxorubicin and etoposide)
Present case	15 yrs/F	Fever, increased bleeding per vaginal	6 g/dL/0.0×10^9/L/112×10^9/L	87% erythroids including proerythroblasts	90% erythroid cells with 60% proeythroblasts	Positive for CD71, CD235a (glycophorin A), CD36, CD34 (10% subset), and negative for other myeloid and lymphoid markers	46XX, add (4) (p16)	Alive, 3 months Post induction (Duanorubicin and Cytarabine)

HB: Haemoglobin; ANC: Absolute Neutrophil Count; PBS: Peripheral Blood Smear; BMA: Bone Marrow Aspirate; FCMI: Flow Cytometric Immunophenotyping; yrs: years; mos: months; F: female; M: male; N/A: Not Available.

agents and immunotherapies, are being actively investigated. Regular post-treatment monitoring for relapse and late complications is essential for long-term disease management.

Treatment of AEL is associated with several complications due to the aggressive nature of the disease, high-risk cytogenetics, and intensive therapies required [19]. Common complications include prolonged cytopenias following chemotherapy, leading to severe anemia, thrombocytopenia, and neutropenia, which increase the risk of infections and bleeding. Febrile neutropenia is a frequent and potentially life-threatening complication, requiring prompt antimicrobial therapy. Patients are also at risk of tumor lysis syndrome during induction therapy.

Cardiotoxicity from anthracycline-based regimens is a concern, particularly in older patients or those with pre-existing cardiac conditions [20]. Hepatotoxicity and renal dysfunction may occur due to chemotherapy toxicity or infections, exacerbated by the frequent use of supportive medications. Gastrointestinal toxicity, including mucositis, nausea, vomiting, and diarrhea, is common and can impair nutrition and quality of life. For patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), additional complications include graft-versus-host disease (GVHD), infections, and organ toxicities related to conditioning regimens.

Long-term complications include secondary malignancies, such as therapy-related myelodysplastic syndrome (t-MDS) or secondary AML, particularly in patients receiving DNA-damaging agents [21]. Proactive management of these complications, including rigorous supportive care and regular monitoring, which is critical to improve treatment tolerability and outcomes in AEL.

In conclusion, we encountered an extremely rare de novo AEL case in a paediatric patient with an unusual peripheral blood picture, without *TP53* mutation and complex karyotype. Given its rarity and morphological similarities to other benign, hematopoietic, and non-hematopoietic malignancies, timely and accurate diagnosis is crucial in AEL, which can be attained with a multidisciplinary approach encompassing detailed clinical history, morphology, immunophenotyping, cytogenetic and molecular studies.

Disclosure of conflict of interest

None.

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