

The Pure Erythroleukemia: A Case Report and Literature Review

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Introduction

Pure acute erythroleukemia is a rare form of acute myeloid leukemia (AML) with predominant erythroid lineage proliferation. It is a heterogeneous entity amongst AML that can occur at any age, including childhood, and comprises less than 5% of AML. Di Guglielmo reported the original case of acute erythroleukemia in 1917; he described it as a syndrome composed of immature erythroid and myeloid elements characterized by a pure normoblastic proliferation.^{1,2}

Classification

In 1985, the French-American-British (FAB) Cooperative group revised its criteria by requiring at least 30% of the non-erythroid elements to be type I or II blasts, and defined AML-M6 as “a proliferation of more than 50% erythroblast and more than 30% myeloblasts within non-erythroid cells.”³

According to new World Health Organization (WHO) classification, 2 subtypes are recognized based on the presence or absence of a significant myeloid (granulocytic) component. The first subtype, pure erythroid leukemia (FAB subtype B), represents a neoplastic proliferation of immature cells (undifferentiated or proerythroblastic in appearance) committed exclusively to the erythroid lineage (>80% of bone marrow cells) with no evidence of a significant myeloblastic component. The second subtype, erythroleukemia (erythroid/myeloid FAB subtype A), is defined by the presence in the bone marrow of more than 50% erythroid precursors in the entire nucleated cell

population and more than 20% myeloblasts in the non-erythroid cell population (the myeloblasts are calculated as a percent of the non-erythroid cells).⁴

Case Report

A 57-year-old African American woman presented to the emergency room with shortness of breath and chest pain. The patient complained of fatigue, generalized body aches, and pain during the previous weeks. She denied fever, chills, weight loss, or night sweats. The patient had no significant medical history and was not taking any medications. She had no family history of malignancy; she smoked 1 pack daily for many years and had a history of heavy alcohol use in the distant past, but denied any drug abuse. The review of systems was negative for fever, chills, weight loss, night sweats, ecchymosis, or bleeding. Physical examination revealed a pale-looking woman without any obvious distress. She was afebrile with normal vitals. There were no petechiae or gum bleeding. There was no palpable lymphadenopathy or hepatosplenomegaly, and the rest of the physical examination was normal.

Pathologic Findings and Hospital Course

The patient's initial complete blood count profile showed pancytopenia, with a white blood cell count of $3.3 \times 10^3/\mu\text{L}$, a hemoglobin level of 4.4 g/dL, and a platelet count of $29.0 \times 10^3/\mu\text{L}$. Numerous nucleated red blood cells, occasional erythroblasts, and a rare circulating megakaryoblast (Figure 1A) were identified on peripheral smear examination.

Examination of the initial bone marrow aspirate and biopsy revealed a markedly hypercellular bone marrow essentially replaced by erythroid precursors, representing approximately 80–90% of the marrow cells (Figure 1B). The erythroid precursors displayed dysplastic morphology, including megaloblastic features, multinucleation,

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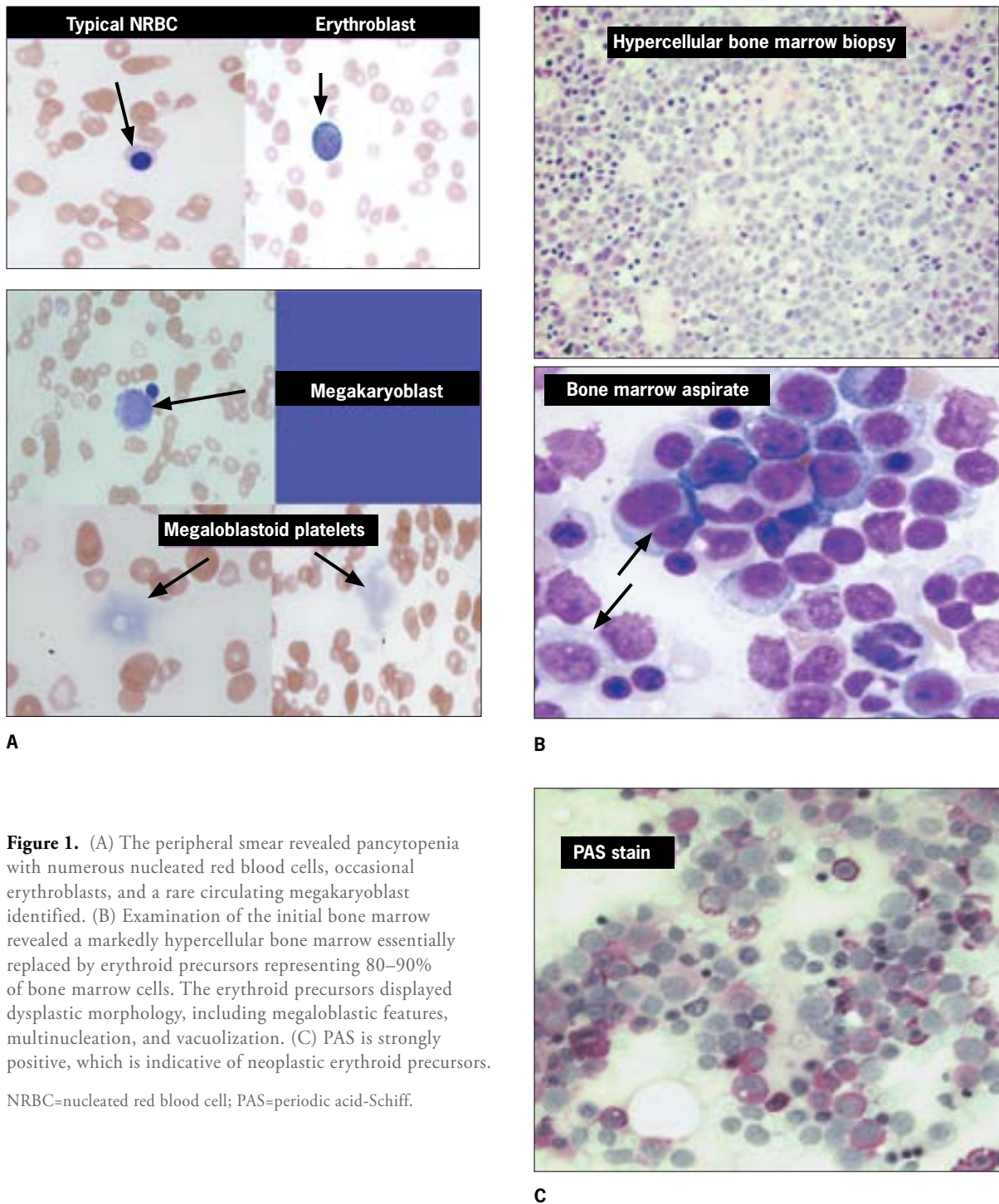


Figure 1. (A) The peripheral smear revealed pancytopenia with numerous nucleated red blood cells, occasional erythroblasts, and a rare circulating megakaryoblast identified. (B) Examination of the initial bone marrow revealed a markedly hypercellular bone marrow essentially replaced by erythroid precursors representing 80–90% of bone marrow cells. The erythroid precursors displayed dysplastic morphology, including megaloblastic features, multinucleation, and vacuolization. (C) PAS is strongly positive, which is indicative of neoplastic erythroid precursors. NRBC=nucleated red blood cell; PAS=periodic acid-Schiff.

and vacuolization, and they were strongly periodic acid-Schiff (PAS)-positive (Figure 1C). Occasional myeloid and megakaryocytic elements were encountered with myeloblasts representing less than 5% of marrow cells. These findings are consistent with pure erythroid leukemia.

Flow cytometric analysis of the bone marrow aspirate also revealed numerous immature cells, which were positive for CD36 and glycophorin A, consistent with erythroblasts/erythroid precursors. Only 3% of the total cells analyzed were CD34/CD13-positive myeloblasts. These flow cytometric and immunophenotypic findings

also supported the diagnosis of pure erythroid leukemia (acute erythroid leukemia) FAB subtype M6b. Significant cytogenetic abnormalities were found on chromosomal analysis, including a complex karyotype (45xx, der(5)t(5;17)(q13;q11.2),r(7)(p14q36),-16,-17,add(19)(q13.4)+mar(14)/46xx(6) without the typical deletions of chromosomes 5 and 7 that are often seen in myelodysplastic syndrome and associated with poor prognosis.

The patient was treated with a standard induction (7+3) chemotherapy regimen consisting of daunorubicin 45 mg/m² daily for 3 days and cytarabine 100 mg/m² daily continuous infusion for 7 days. She tolerated treatment well and required blood and platelet transfusions. On post-induction day 14, the bone marrow biopsy showed residual disease with 10% erythroblasts, treatment effects, and abnormal myeloid precursors. Cytogenetics showed persistent multiple abnormalities including 42-44,XX,-3,der(5;17)(q13;q11.2),r(7)(p14q36),-15,-17,+mar(cp3)/46,XX.¹⁷

The patient received 3 more cycles of consolidative high-dose cytarabine chemotherapy without complete cytogenetic or molecular remission. The treatment regimen was switched to mitoxantrone and etoposide, but the patient's disease transformed into AML. Four months after the initial bone marrow examination and treatment, the patient converted to a true AML. Flow cytometric analysis of the bone marrow aspirate revealed abnormal vacuolated erythroblasts, which were positive for CD36 and glycophorin A, consistent with residual erythroleukemia. In addition, there was now a significant myeloblast population (30%) of total cells analyzed, which were positive for CD13 and CD34, which had increased from the first presentation of 3%.

Histologically, the bone marrow was hypercellular and virtually replaced by erythroid and myeloid precursors representing approximately 70–80% of marrow cells. The erythroid precursors continued to display dysplastic morphology. Numerous smaller vacuolated blasts consistent with myeloblasts with therapy effect and occasional megakaryocytic elements were also seen. Further supporting the transformation of pure erythroleukemia to AML was a new cytogenetic finding: the acquisition of trisomy of chromosome 8 (+8), the most frequent trisomy in malignant myeloid disorders. Trisomy 8 is also associated with the development of myeloid blast phase of chronic myelogenous leukemia (CML).

The patient could not achieve complete remission and opted for supportive care for her refractory disease; she expired 5 months after diagnosis.

Clinical Presentation

The incidence of acute erythroid leukemia is rare and ranges from 3–8% with an approximate 50% chance

of patients developing either de novo or secondary erythroleukemia.⁵⁻⁸ There is a male preponderance, and age distribution appears to be bimodal, with a smaller peak below 20 years and a more definitive and broader peak in the seventh decade of life.⁹ In almost 50% of cases, AML-M6 occurs secondary to chemotherapy with alkylating agents or occupational exposure to mutagenic agents (eg, benzene exposure). Our patient had a remote history of heavy alcohol abuse, consistent with some reports of alcoholism and erythroid leukemia. AML-M6 may also develop as a blast crisis of myeloproliferative disease or a final evolution of myelodysplastic syndrome. The most common presentation in patients with erythroid leukemia is anemia, which is often severe (mean hemoglobin, 7.5 g/dL). In a series, one-third of the patients were reported to have hemorrhage.¹⁰ The presence of hepatosplenomegaly varies between 20–40%.¹⁰ Fifty percent of the patients have no blasts on the peripheral blood smear. Neutrophil and platelet counts are mildly to markedly diminished. Peripheral blood findings may also include a high level of schistocytes, nucleated red cells, and pseudo Pelger-Huet neutrophils. However, these abnormalities are not specific for erythroleukemia and can present in other dyserythropoiesis etiologies such as myelodysplastic syndrome.

The bone marrow is usually hypercellular and shows major dysplasia in the red cells. Erythroid lineage is dysplastic, with megaloblastoid cells (asynchronous nucleocytoplasmic maturation), Howell-Jolly bodies, and lack of hemoglobinization and multinucleation. Multilineage dysplasia is present in most reports.¹⁰ Megakaryocytes are often dysplastic, with abnormalities of segmentation of the nucleus or abnormalities of size (micromegakaryoblasts); rarely, megakaryoblasts may circulate in the peripheral blood. Dysgranulopoiesis is described in 50% of patients.¹¹ This heterogeneity of trilineage dysplasia can be explained by the fact that erythroleukemia includes both primary and secondary diseases.

Morphology and Cytochemistry

Pure Erythroid Leukemia (FAB Subtype B)

The undifferentiated form of pure erythroid leukemia is usually characterized by the presence of medium to large erythroblasts usually with round nucleoli (proerythroblast); the cytoplasm is deeply basophilic, often agranular, and frequently contains poorly demarcated vacuoles that are often PAS-positive. Occasionally, the blasts are smaller and resemble the lymphoblasts of ALL. The cells are negative for myeloperoxidase; they show reactivity with alpha-naphthyl acetate esterase, acidic phosphatase, and PAS; the latter usually in a block-like staining pattern. In the bone marrow biopsies of pure acute erythroid leukemia, the cells appear undifferentiated.⁴

A large variety of cytochemical stains are available for characterization of erythroid lineage. The PAS reaction is always negative in normal erythroid differentiation. Aberrant PAS positivity is often observed in the pronormoblasts and basophilic normoblasts in AML-M6. The Prussian blue stain demonstrates increased iron stores in AML-M6, sometimes with ringed sideroblasts. Some authors reported occasional positivity of myeloperoxidase in erythroid cells of erythroleukemia.¹²

Flow Cytometry and Immunophenotyping

The erythroblasts in erythroleukemia generally lack myeloid-associated markers and are negative with anti-myeloperoxidase stains. The best known markers for erythroleukemia have included glycophorin A and CD36. However, glycophorin A has been reported to be completely negative in some cases of AML-M6b, probably because it is a late erythroid marker. CD36, a nonspecific marker, detects erythroid precursors at earlier stages of differentiation and is also expressed by monocytes and megakaryocytes. An aberrantly low expression of CD71 may be present in erythroleukemia; a nonspecific activation marker can be present in other AML cases. The immunophenotype of the myeloid population usually corresponds to that of AML without differentiation or AML with minimal differentiation and is now called *pure erythroid leukemia* in the new WHO classification.^{4,13-15}

The more differentiated form of pure erythroid leukemia can be detected by the expression of glycophorin A, the absence of myeloperoxidase, and other myeloid markers. The blasts are often negative for HLA-DR and CD34, but may be positive for CD117.

Cytogenetics

A large array of chromosomal abnormalities has been described in AML-M6b, but no consistent pattern has been specified. Clonal chromosomal abnormalities are found in 70–100% of patients. This heterogeneity is probably due to inclusions of secondary or therapy-related AML-M6 in some series. Loss of all or part of the long arm, -5/del(5q), -7/del(7q), and trisomy 8 were observed in approximately 65% of de novo and secondary AML-M6. In only 1 series, the overall frequency of the abnormalities of chromosomes 5 and/or 7 observed in de novo AML-M6 patients is similar to that observed in patients with therapy-related AML and substantially higher than that noted in patients with other types of de novo AML.¹⁶ In every series, the incidence of patients with an unfavorable karyotype is higher than in other types of AML with inv 3, 11q23, and 17p abnormali-

ties.¹⁷ However, the cases with -5/Del (5q), -7/Del (7q), and/or complex chromosomal abnormalities should be classified as AML with myelodysplastic-related changes if the other requirements for that category are satisfied.

The karyotypes are often complex, with multiple abnormalities and subclones. Using fluorescence in situ hybridization, some cases of AML-M6 clearly demonstrated similar karyotypic abnormalities within both myeloid and erythroid cells. Atkinson and colleagues proposed that a characteristic of this disease may be the presence of an altered primitive cell with features of both erythroid and myeloid lineages.¹⁶ This theory may provide a possible explanation for why many cases of acute erythroid leukemia progress to AML, as was observed in our patient.

Differential Diagnosis

Erythroleukemia (erythroid/myeloid) should be distinguished from refractory anemia with excess blasts, AML with myelodysplasia-related changes, AML with increased erythroid precursors, and reactive erythroid hyperplasia following therapy or administration of erythropoietin.

A bone marrow biopsy with differential count of all nucleated cells should be performed. If the overall percentage of blast cells is more than 20% and multilineage dysplasia is present in more than 50% of the cells in 2 or more lineages, a diagnosis of AML with myelodysplasia-related changes should be made. When there are less than 20% total blasts and the erythroid precursors are more than 50% of all cells, the differential count of non-erythroid cells should be calculated. If the blasts are more than 20% of non-erythroid cells, the diagnosis is erythroleukemia (erythroid/myeloid); if they are less than 20%, the diagnosis is usually myelodysplastic syndrome.

The differential diagnosis of pure erythroleukemia includes megaloblastic anemia due to vitamin B₁₂ deficiency. Pure erythroid leukemia without morphologic evidence of erythroid maturation may be difficult to distinguish from other types of AML, particularly megakaryoblastic leukemia, and also from acute lymphoblastic leukemia and lymphoma. Lack of expression of lymphoid markers will exclude the latter diagnosis.⁴

Treatment and Prognosis

The outcome is usually very poor for erythroleukemia. In de novo AML-M6b, treatment with intensive chemotherapy (anthracycline and cytarabine) gives a complete remission (CR) rate of approximately 50–60%.¹⁰ In other series, the CR rate was only 10–40%, especially in secondary AML-M6¹⁷; if CR was obtained, it was brief.

The median survival in AML-M6B is approximately 4–5 months, and survival is related to karyotypic abnormalities.¹⁰ Allogeneic bone marrow transplantation remains the best treatment option for patients with abnormalities of 5q or 7q because they carry a worse prognosis.¹⁸ Even for therapy-related erythroleukemia, transplantation seems to be favorable for long-term disease-free survival.¹⁹ The response to chemotherapy and the length of survival is dependent on many factors, the most important of which is cytogenetics and karyotype abnormality.^{16,20–22} The CR rate in patients with 5q or 7q abnormalities is approximately 20%, and median survival reaches 16 weeks, compared to 77 weeks for patients without these abnormalities.¹⁰ The difference in prognosis between de novo and secondary leukemia is related to karyotype abnormalities. According to Kowal-Vern and associates, the percentage of pronormoblasts appears to be an important factor for survival, with a mean survival of 34 months in AML-M6a, 3.5 months in AML-M6b, and 10.5 months for AML-M6c.¹² Age is another important prognostic factor; older patients have a low CR and a short survival time. Expression of P-glycoprotein is clearly a poor prognostic factor for survival.¹¹ Other prognostic factors include good performance status, normal organ function, de novo presentation, and lack of multidrug resistance (MDR) expression.²³ The management of AML-M6b subtype for younger patients (eg, 55–65 years) with good performance status is an induction chemotherapy (7+3) regimen (7 days of continuous infusion of cytarabine [ara C] and 3 days of anthracycline); 2–6 cycles of consolidation with high-dose cytarabine are given if CR occurs. Cytarabine remains the most active agent in the management of AML, and various regimens are designed to be combined with this agent. The dose of induction chemotherapy with cytarabine, anthracycline (idarubicin or daunorubicin) or anthracenedione (mitoxantrone) varies, and the new dosing recommendations for anthracycline as induction chemotherapy for younger patients are up to 90 mg/m².²⁴ There are 2 options for consolidation therapy: the high-dose ara-C regimen consists of intravenous ara-C at 3 g/m² every 12 hours on days 1, 3, and 5, and the 5 + 2 regimen includes ara-C at 100 mg/m²/day continuous infusion on days 1–5 plus intravenous anthracycline at 45–90 mg/m² on days 1 and 2.

A bone marrow biopsy should be performed on day 14 to 21 after induction chemotherapy to assess remission status. If bone marrow shows persistent blasts, re-induction with the 5+2 regimen is recommended. If the bone marrow is hypoplastic, the second course should be delayed until the bone marrow is recovered enough to clearly distinguish the type of recovery (leu-

kemic vs normal marrow). The recovering bone marrow usually have immature cells, which can be distinguish from myeloblast by immunophenotyping, flow-cytometry, and cytogenetics.

Conclusion

AML-M6 is a heterogeneous disease with poor response to standard chemotherapy that carries a poor prognosis. The new WHO classification subdivides acute erythroid leukemia into erythroleukemia (erythroid/myeloid) and pure erythroid leukemia. AML-M6 appears to be bilineage leukemia; our case initially presented as pure erythroleukemia with 80–90% erythroblasts and less than 5% myeloblasts, but after treatment with chemotherapy, it transformed into AML with an increase in myeloblasts up to 30%. Our patient transformed from pure erythroleukemia to AML after treatment, probably due to the erythroid component of leukemia achieving remission and the myeloid component remaining refractory to therapy and becoming predominant. Erythroleukemia usually presents with pancytopenia and mostly carries complex cytogenetics, including abnormalities of chromosomes 5, 7, and 8. There are other poor-risk molecular abnormalities like the presence of P-glycoprotein, Flt3 mutation,²⁵ Kit mutation,²⁶ and high MRD. Flt3 and Kit mutations can be useful for therapeutic implication; Flt3 inhibitors are in phase I/II trials with some promising results. The new higher dose of anthracycline (90 mg/m²) should be used for induction chemotherapy if cardiac function is normal. Allogeneic bone marrow transplant should be considered upfront for appropriate candidates once remission is achieved in AML-M6, as the risk of relapse and mortality is very high with this disease.

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Review

Erythroleukemia: Clinical Course and Management

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Latif and colleagues¹ reported a case of erythroleukemia presenting as acute myeloid leukemia (AML) in a patient who was treated with a standard induction regimen. The patient experienced disease evolution and required treatment with salvage treatment, but expired due to disease progression. Erythroleukemia is a rare subtype of AML, which is categorized in the poor-risk group (French-American-British [FAB] M6, or Di-Guglielmo's disease <5%). Since the initial recognition, the diagnosis and classification of erythroleukemia has been significantly modified. The FAB classification in 1976 recognized erythroleukemia as M6; in 1985, the FAB classification defined erythroleukemia as leukemia with a major erythroid component of at least 50% and a myeloid component of approximately 30% of the non-erythroid cells.^{2,3} The World Health Organization (WHO) classifies erythroleukemia into 2 distinct variants, one with a combined erythroid and myeloid component and the other, which is pure erythroleukemia.

Historically, the identification of erythroleukemia dates back to 1912, when it was initially recognized by Copelli as a hematologic disorder and named as *erythematosis*; in 1917 Di Guglielmo described *eritroleucemia* as proliferation of abnormal erythroid cells, myeloblasts, and megakaryocytes with the presence of immature forms of all 3 lineages in the peripheral blood. Di Guglielmo used the term *eritroleucopiastrinaemia* to demonstrate trilineage involvement and presented the idea that the abnormality was arising in the myeloid tissue with involvement of all 3 cytopoietic components.⁴ Moeschlin described the term *erythroleukemia* in 1940 and was followed by Dameshek and Baldini, who described the Di Guglielmo syndrome as propagation of 3 phases in the bone marrow: an erythremic phase, an erythromyeloblastic phase, and a myeloblastic phase analogous to AML.⁵

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Erythroleukemia represents 3–5% of adult AML cases; the incidence is also rare in children. The median age at diagnosis is in the fifth to sixth decade of life.^{6,7} Another distinguishing feature of erythroleukemia is the predominant association of antecedent diagnosis of myelodysplastic syndrome along with multiple poor-risk chromosomal abnormalities identified on cytogenetic analysis.^{6,8} Erythroleukemia presents with a significant number of genomic aberrations, the common being abnormalities of chromosome 5 and/or 7 and complex karyotype abnormalities, which have been reported in most series.^{8,9} Aberration of chromosome 19 has also been reported in 1 study.¹⁰ The median survival varies from 4 to 14 months.⁷

The characteristic hematologic features of erythroleukemia include anemia, which is usually normochromic and normocytic, with severe anisocytosis.¹¹ Nucleated red blood cells are preponderant, with the most immature and basophilic forms found in the largest numbers. Atypical nucleated red blood cells are also commonly seen, and reticulocytes are few, with a gradual decrease seen with disease progression.¹¹ Leukocytes exhibit leukopenia along with thrombocytopenia as the common abnormalities. Reticulo-endothelial cells have also been observed in peripheral blood. The bone marrow examination exhibits an increase in red cell series and a decrease in the number of white cells.¹¹ The nucleated red to white cell ratio is reversed, with a predominance of basophilic erythroblasts as well as proerythroblasts resulting in the appearance of arrested red cell maturation. The cells that stain positive for PAS, and the absence of staining of other lineage-specific markers, such as myeloperoxidase (MPO) and terminal transferase detection (TDT), are suggestive of erythroleukemia.⁸ The infiltration of these primitive red cells and reticulo-endothelial cells is observed in hematopoietic and extra-hematopoietic organs like the kidneys, adrenals, myocardium, lungs, pancreas, testes, uterus, larynx, trachea, and spleen.¹¹

The standard induction therapy for AML continues to be based on anthracycline and cytarabine, which results in complete remission (CR) rates of approximately 70%, with a long-term survival of 30–40%; however, the prognosis for the high-risk group continues to be worse, with a long-term survival rate of less than 10%.^{12,13} Erythroleukemia is considered in the high-risk group and is associated with poor prognosis due to the common association with high-risk chromosomal abnormalities; it evolves in the background of dysplasia, with a median survival of 4–14 months. Additionally, the rarity of this leukemia makes it difficult for evaluation of treatment in randomized studies.

Although the data are scarce for allogeneic transplantation in erythroleukemia due to the rarity of disease,

allogeneic stem cell transplantation offers durable responses as compared to conventional chemotherapy alone. Anecdotal reports along with a study from the Royal Marsden Group presented outcomes of 27 patients undergoing allogeneic transplantation; 19 patients who underwent allogeneic transplantation achieved an overall survival rate of 66% at 2 years.^{14,15} The European Group for Blood and Marrow Transplantation (EBMT) reported the largest series of patients with erythroleukemia treated with autologous or allogeneic stem cell transplantation in first CR. For autologous transplantation, the 5-year leukemia-free survival was 26% \pm 5%, the relapse incidence was 70% \pm 6%, and the transplant-related mortality was 13% \pm 4%; for allogeneic transplantation, the 5-year leukemia-free survival was 57% \pm 5%, the relapse incidence was 21% \pm 5%, and transplant-related mortality was 27% \pm 5%.⁶

The outcome of patients with AML is heterogeneous and dependent on a number of risk factors. The important prognostic indicators in AML include karyotype, presence of antecedent hematologic disorders, age, and performance status. Among the new prognostic markers, the *fms*-tyrosine kinase (FLT3) accounts for the most frequent molecular mutations in AML.¹⁶ FLT3 is a transmembrane tyrosine kinase receptor that stimulates cell proliferation upon activation. FLT3 length mutation (FLT3-LM or FLT3-ITD for internal tandem duplication) is among the frequent genetic alterations in AML associated with prognostic implications. The frequency of FLT3-LM is 20–27% in adult AML and 10–16% in childhood AML.¹⁶ Studies with patients harboring this mutation have reported an estimated 2-year progression-free survival of 20% and 4-year overall survival of 20%.^{17,18} Additionally, FLT3 also harbors mutations in the tyrosine kinase domains (FLT3-TKD mutations). Although the FLT3-TKD is less frequent than FLT3-ITD mutations, an incidence of 5.8–7.7% has been described in reports. The prognosis of patients with the FLT3-TKD mutations is not associated with dismal outcomes.¹⁸ Ongoing research is delineating the impact of various types of FLT3 mutations on the outcomes of patients with AML.¹⁹ It has been observed that the incidence of FLT3-TKD is less frequent in erythroleukemia, which is attributed to an association with a complex aberrant karyotype.¹⁶

Erythroleukemia is a rare subtype of AML with a frequent association with aberrant karyotype and resultant aggressive disease course. Thus, it is a challenge to investigate and identify new treatments. Newer prognostic markers are being applied in AML along with erythroleukemia. Better understanding and identification of molecular markers offers new avenues for therapy. FLT3 inhibitors are already being applied in clinical trials with promising results, and clinical applications are eagerly

awaited.^{20,21} Identification of new molecular markers and development of targeted therapies hold promise for patients with this disease. The current treatment is standard induction along with consolidation with allogeneic transplant, if available, which appears to provide better disease control than consolidation chemotherapy alone.

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