Review

Acute Erythroid Leukemia: A Review

Daniela Mihova, MD, FCAP;[1]* Lanjing Zhang, MD, MS, FCAP[2,3]

[1] Pathology Department and Clinical Laboratories, Flushing Hospital Medical Center, Flushing, NY
[2] Department of Pathology, University Medical Center at Princeton, Princeton, NJ
[3] Department of Pathology and Laboratory Medicine, Robert Wood Johnson Medical School-UMDNJ, New Brunswick, NJ

Acute erythroid leukemia is a rare form of acute myeloid leukemia. It accounts for <5% of all acute myeloid leukemia cases. According to the World Health Organization 2008 classification, it falls under the category of acute myeloid leukemia, not otherwise specified and is further divided into two subtypes: erythroid leukemia (erythroid/myeloid) and pure erythroid leukemia. Currently, erythroleukemia (erythroid/myeloid) is defined as 50% or more erythroid precursors and ≥20% blasts of the non-erythroid cells. By definition, pure erythroid leukemia is composed of ≥80% erythroid precursors. Acute erythroid leukemia is a diagnosis of exclusion and difficulty. This review discusses its differential diagnoses, which present with erythroid proliferation, such as myelodysplastic syndrome with erythroid proliferation, acute myeloid leukemia with myelodysplasia related changes, therapy related acute myeloid leukemia, myeloproliferative neoplasms with erythroblast transformation, acute myeloid leukemia with recurrent genetic abnormalities and other types of hematologic neoplasms. Additionally, reactive conditions such as erythropoietin treatment, vitamin B12 and folate deficiency, toxin exposure and congenital dyserythropoiesis should be excluded. As a result, the frequency of acute erythroid leukemia diagnosis has been reduced. Important adverse prognostic factors will be summarized, including presence of complex cytogenetic karyotype as the most important one. Additional larger studies are needed to better understand acute erythroid leukemia, with a focus on diagnostic tools, its heterogeneity and cytogenetic and molecular characteristics for potential therapeutic targets.

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BACKGROUND

Acute erythroid leukemia (AEL) is a rare form of acute myeloid leukemia (AML). It accounts for less than 5% of all AML cases.[1] In 1912, Coppelli, described condition he named eritromatosis in a patient who presented with anemia, splenomegaly, foci of erythroblast in liver, spleen, lymph nodes and bone marrow but no circulating blasts.[2] This is considered the first case of documented AEL. In 1917, Giovanni Di Guglielmo published his first significant original observation on erythroleukemia, when he described a patient with proliferation of abnormal erythroids, myeloblasts and megakaryocytes. Then, the idea of erythroblastic proliferation analogous to leukemia developed, although his observation was in fact of panmyelosis. Later, in 1923 Di Guglielmo presented the first case of pure erythroid leukemia (pEL) (eritremia acuta). Series of articles followed elaborating his observations. He defined erythroid leukemia as a pure process, which was designated as Di Guglielmo disease (GD). In 1958, Dameshek described the equivalent to erythroid/myeloid leukemia as an evolution from erythremic proliferation through erythroleukemia to myeloblastic leukemia, and he named it - Di Guglielmo syndrome (GS).[3]

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***Corresponding Author:** Department of Pathology and Clinical Laboratories, Flushing Hospital Medical Center, Flushing, NY 11355. Tel: 718-670-5723. (Email: dmihova.flushing@jhmc.org)

In 1976, French-American-British (FAB) cooperative group designated AEL as AML-M6 defined as erythroid precursors ≥ 30% and dyserythropoiesis ≥10%.[4,5] In 1985, the FAB classification made the following changes for AML-M6: ≥ 50% erythroblast of all nucleated cells, prominent dyserythropoiesis and ≥ 30% of blast of all non-erythroid precursors.[6] Pure erythroid leukemia did not meet the criteria for the FAB classification and was included in the category of refractory anemia with excess blasts in transformation (RAEB-t). In 1992, Kowal-Vern proposed that Di Guglielmo disease defined as erythroleukemia with ≥ 30% proerythroblasts should be a separate category in the FAB classification because of its worse prognosis compared to Di Guglielmo syndrome.[7] Goldberg (1998) confirmed that GD besides the worse prognosis has distinct clinical, laboratory and cytogentics characteristic.[8] Kowal-Vern et al and Mazzela et al proposed three subsets of AML-M6: M6a (myeloblast-rich erythroleukemia) equivalent to erythroid/myeloid leukemia; M6b (proerythroblast-rich erythroleukemia) equivalent to pure erythroid leukemia and M6c (myeloblast and proerythroblast-rich mixed variant).[9,10] Additionally, Mazzela described worse prognosis with unfavorable cytogenetics, high proliferation index, high pronormoblasts to myeloblasts ratio and glycoprotein-P expression.[11]

Table 1. AEL Classifications Comparison and Changes.

			Bone Marrow Findings		Dyserythropoiesis	Comment
Classification	Year	Subtype	Erythroid Precursors	Blast % of Non-Erythroid Precursors		
FAB Classification	1976	AML-M6	≥30%	N/A	≥10%	
	1985	AML-M6	≥50%	≥30%	Prominent	
WHO Classification	2001	Erythroid/myeloid	≥50%	≥20%	Prominent	Dysplasia in <50% of Myeloid cells and megakaryocytes
		Pure erythroid	≥80%		Prominent	
WHO Classification	2008	Erythroid/myeloid	≥50%	≥20%	Prominent	Dysplasia in <50% of cells in < 2 cell lines Exclude AML-MRC, t-AML, erythropoietin treatment
		Pure erythroid	≥80%		Prominent	

World Health Organization (WHO) 2001 classification included morphology, immunophenotype, genetic, molecular and clinical features in the classification of the myeloid neoplasms, and divided AEL into two subtypes: erythroid/myeloid leukemia ≥50% erythroid precursors and ≥20% of myeloid blasts of the non-erythroid cells population and pEL with ≥80% erythroblasts (see **Table 1**).[12] The current WHO 2008 classification kept the subcategories of erythroid/myeloid leukemia and pEL, but made erythroleukemia a diagnosis of exclusion. One therefore must exclude a series of differential diagnoses, such as AML with myelodysplasia-related changes (AML-MRC), therapy-related AML (t-AML), AML with erythroblast proliferation and recurrent genetic abnormalities, erythroblast phase of myeloproliferative neoplasms (MPN) and reactive erythroid hyperplasia after erythropoietin treatment (EPO), before the diagnosis of erythroleukemia is rendered. As a result the frequency of AEL diagnosis has been reduced and included in different categories.

EPIDEMIOLOGY AND CLINICAL FEATURES

Acute erythroid leukemia accounts for <5% of all acute myeloid leukemias, mainly affecting adult population, mostly people above 50 years old. The age range is broad (from children to elderly people > 90 years old) with male predominance. The male to female ratio varies from 2.4:1 to 4:1.[13,14,15,16] Clinical presentation is non-specific including weakness, pallor, fever and hemorrhages, rarely intracranial hemorrhages. Patients may also present with hepatosplenomegaly, hepatomegaly or splenomegaly.[17,18] Anemia (mean hemoglobin Hgb 7.5 g/dL reported in 1 study)[17] and thrombocytopenia are present in all the cases, while the neutrophil count varies from normal to low.

Extramedullary involvement is uncommon. There are only few reported cases of extramedullary involvement: 1) erythroid leukemia involving lymph node[19] 2) congenital erythroid leukemia presenting as a hemangioma[20] and 3) bilateral ovarian involvement by pEL in a 3.5 year old female.[21] Hemophagocytic lymphohistiocytosis (HLH) also known as hemophagocytic syndrome is rarely reported in association with AEL. In one case, the patient presented with pEL with increased erythroblasts in the peripheral blood smear, severe anemia (Hgb 3.8 g/dL), increased lactate dehydrogenase (LDH), triglycerides, ferritin, and splenomegaly. Subsequent cytogenetic analysis showed a complex karyotype.[22] Two more cases of AEL with HLH are described in the literature, one arising from RAEB-1/RAEB-2 and progressing to erythroid/myeloid leukemia with complex karyotype, and another one presenting as de novo erythroid/myeloid leukemia.[23] Rare familial cases of AEL show autosomal dominant association and distinct genetic abnormalities. In one of the families six members were affected by erythroleukemia as five of them were 54-75 years old and one 31, they were living in a rural area without known hazard.[24,25]

Pure erythroid leukemia is extremely rare disease. It can involve any age group including infants. It has dismal prognosis and shorter survival (3 ± 3.6 months) compared with M6a (25 ± 28 months).[9] Pure erythroid leukemia is associated with unfavorable genetic abnormalities.[14]

Acute erythroid leukemia is defined as leukemia with erythroid hyperplasia with erythroid precursors presenting ≥50% of all nucleated bone marrow cells. Acute erythroid leukemia can occur de novo in 1% of all de novo AML. Secondary AEL are described associated with previous diseases such as myelodysplastic syndrome (MDS), AML with recurrent genetic abnormalities, chronic myelogenous leukemia (CML) blast phase, and previous cytotoxic treatment. According to the current WHO 2008 classification, these AEL cases previously described in the literature should be reclassified in the appropriate category.

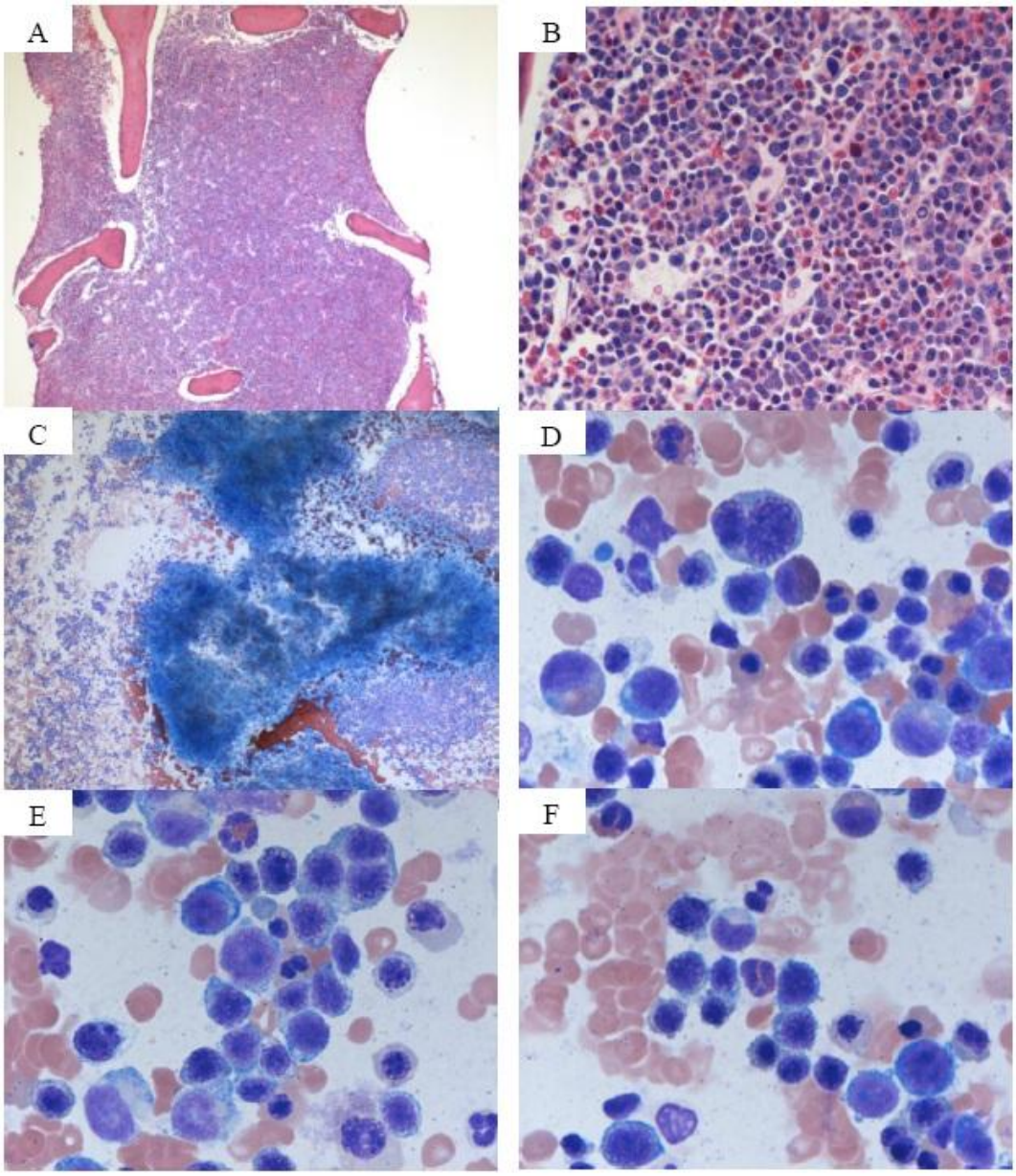

Figure 1. Hypercellular bone marrow with effaced architecture H&E 4x (1A); Left shifted maturation H&E 40x (1B); Hypercellular spicules Wright-Giemsa 4x (1C); Marked dyserythropoiesis, left shifted erythroid precursors and rare blasts Wright-Giemsa 100x (1D-F).

MORPHOLOGY

Bone marrow aspirate and bone marrow biopsy show increased number of immature erythroid progenitor. The blasts in the peripheral blood vary and sometimes may be absent. Anemia with non-specific red blood cell abnormalities such as anisopoikilocytosis, anisochromia, basophilic stippling and schistocytes is seen. Thrombocytopenia is present. Neutrophil counts vary and occasionally show pseudo-Pelger-Hu¨et abnormalities.

Bone marrow aspirates and touch preparations are best for cytologic evaluation. Most of the cases show hypercellular spicules (**Figure 1C**). To fulfill the most recent definition for erythroid/myeloid leukemia, it is required that the erythroid precursors should be ≥50% of the nucleated cells and the myeloid blasts should be ≥ 20% blast of the non-erythroid precursors. Erythroid elements are left shifted with prominent dysplasia including numerous megaloblastoid forms, nuclear budding, nuclear irregularities, bi and multinucleated forms, cytoplasmic vacuolization, karyorrhexis, nuclear bridging (**Figure 1D-1F**). Rare Auer rods can be observed in myeloblasts. Dysplastic changes involving myeloid elements or megakaryocytes are common, but should count for < 50% of the cells.

Pure erythroid leukemia is defined by more than 80% erythroblasts of all nucleated cells. The pronormoblasts are increased and present as medium to large blasts with round

nuclei, fine chromatin, occasional prominent nucleoli, deep blue agranular cytoplasm with variable cytoplasmic vacuolization and no Auer rods. Dyserythropoiesis is prominent, while myeloid and megakaryocytic dysplasia is not an obvious feature. In some cases the erythroblasts could be small with scant cytoplasm and resemble lymphoblasts.

Bone marrow biopsy and clot section usually show hypercellular marrow (> 95%) involved predominantly by immature cells effacing the normal bone marrow architecture. (**Figure 1A, 1B**). Pure erythroid leukemia most often resembles undifferentiated leukemia. A complex approach is required to the correct diagnosis involving morphologic evaluation, special and immunohistochemical stains, flow cytometric analysis, genetic and molecular studies and most importantly clinical history of previous chemotherapy and radiation therapy, MDS, MPN, EPO treatment, vitamin B12 or folate deficiency.

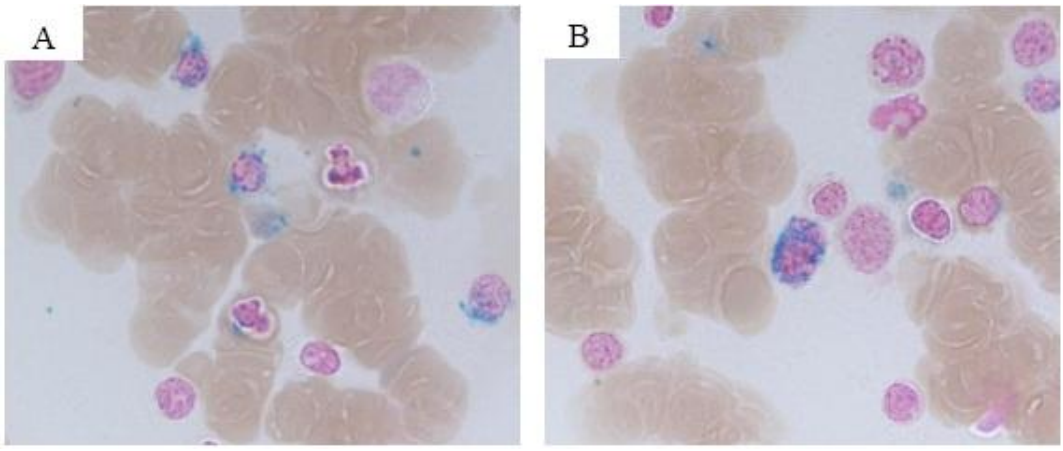

Figure 2. Iron stain shows numerous ring sideroblasts 100x (2A, B).

CYTOCHEMISTRY

Proerythroblasts show deep basophilic cytoplasm and vacuoles, which show Periodic Acid-Shiff (PAS) globular and diffuse pattern. Diffuse PAS positivity is seen in more mature differentiated cases. PAS positivity is considered a result of maturation defect. Erythroblasts are negative for myeloperoxidase (MPO) and sudan black B (SBB), while myeloblasts are positive for MPO, SBB and chloroacetate esterase (CAE). Erythroblasts occasionally show alfa-naphtyl acetate esterase and alfa-naphthyl butyrate esterase reactivity. In erythroid/myeloid leukemia the iron stain is highly positive and shows an increased number of ring sideroblasts (**Figure 2A, 2B**). In pEL ring sideroblasts are not a common finding. The cytochemistry of pEL shows PAS block positivity.

IMMUNOHISTOCHEMISTRY AND FLOWCYTO-METRY

Erythroblasts are not reactive for MPO, CD34, HLA-DR but are often CD117 dim positive (**Figure 3A, 3B, 3E, 3F, 3G, 3H**). The immature erythroid elements, normal and dyspoietic, express strongly CD71 (transferin receptor-1) (**Figure 3C, 3D**). It is expressed in the earliest erythroid precursors, and has been useful for flow cytometry. CD71 is absent in the mature red blood cells in general and is negative in the normal non-erythroid elements as well as in myeloproliferative disorders and nearly all acute myeloid leukemia. Weak CD71 expression is described in acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), and one case of acute megakaryoblastic leukemia but it could be due to a high background stain.[26,27] Erythroblasts are also positive for Glycophorin A (GlyA) and hemoglobin A, although there are cases when the blasts are negative for these markers, since they are expressed in more mature cells. Additional markers are used to identify immature erythroblasts such as carbonic anhydrase 1, Gero antibody against the Gerbich blood group or CD36 antibody. CD36 is non-specific and may be expressed in myeloids, monocytes and megakaryoblasts. Spectrin can be also used for evaluation of immature erythroblasts in core biopsies but shows a high background stain.

E-cadherin, an epithelial adhesion molecule, is used to study malignant vs normal erythroblasts in bone marrow. Acs et al showed that cells in AML-M6 lack membrane E-cadherin expression in contrast to their counterpart normal erythroblasts, which have strong membrane positivity. Additionally, normal erythroblasts showed stronger expression in more immature erythroid precursors.[28] Liu et al showed that E-cadherin was specific for erythroid lineage in bone marrow with reactivity confined to the very immature erythroblasts. Erythroid/myeloid leukemia showed only a small subset of positive erythroblasts, while in pEL majority of erythroblast were positive.[14]

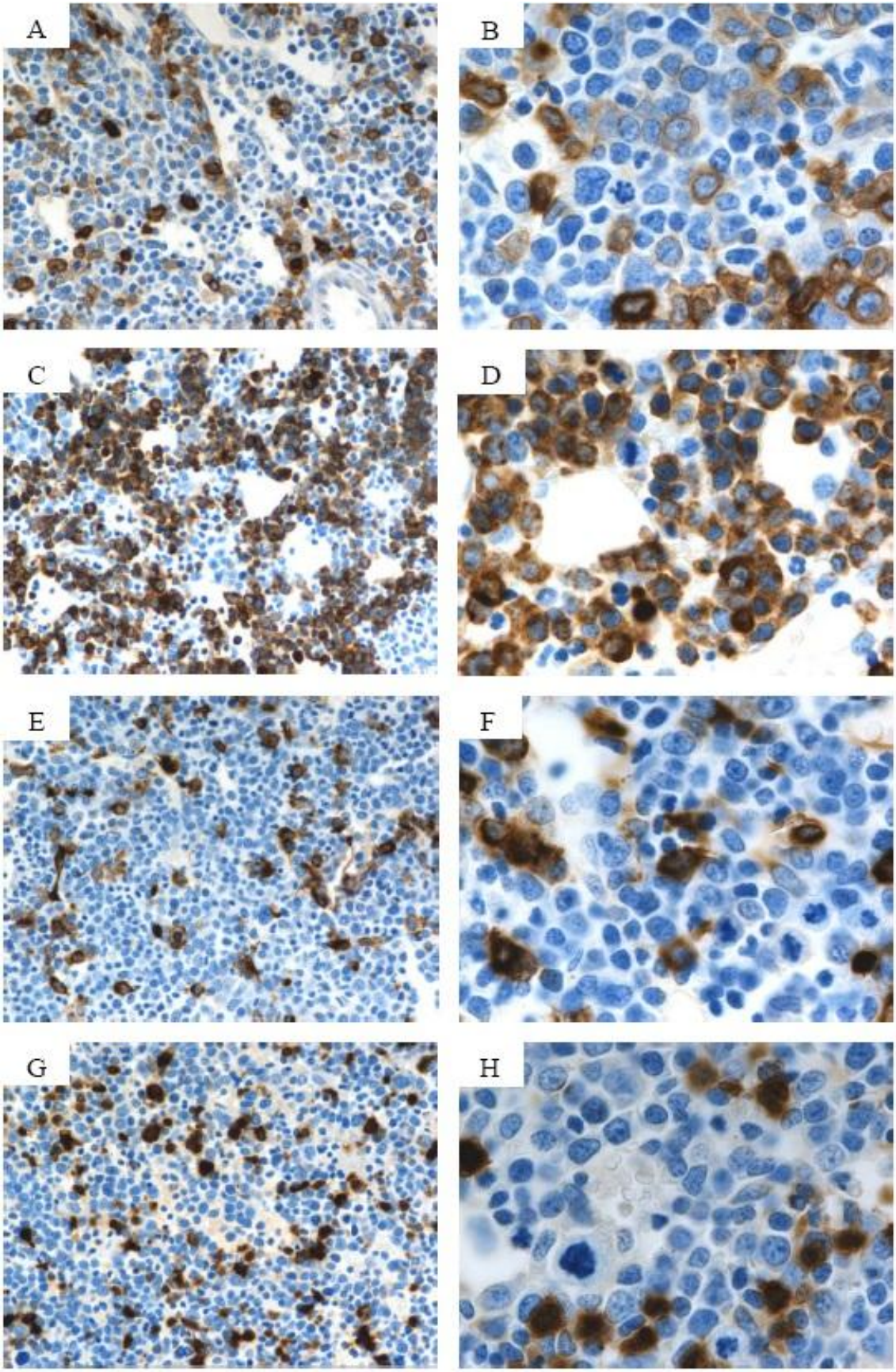

Figure 3. CD117 stain shows dim positive erythroblasts and strongly positive immature myeloid precursors and mast cells 40x and 100x, (3A, B); CD71 stain highlights numerous immature erythroid precursors 40x and 100x (3C, D); Erythroblasts are CD34 negative, only rare CD34 myeloblasts are highlighted 40x and 100x (3E, F); Erythroblasts are MPO negative 40x and 100x (3G, H).

The myeloblasts are CD13, CD33, CD117 strong, MPO positive with variable expression of CD34 and HLA-DR. Megakaryoblasts express one or more of the platelet glycoproteins CD41 (glycoprotein IIb/IIIa) and CD61 (glycoprotein IIIa) and less commonly CD42 (glycoprotein Ib).

Flow cytometry (FC) is valuable in diagnosis of AEL. The relative proportion of erythroid cells by FC is often less than in the aspirate smear and bone marrow biopsy, since many of the late erythroid precursors are likely to be eliminated at red cell lysis stage during the specimen preparation. Currently CD71 and GlyA antibodies are available to evaluate the erythroid cells by showing positive expression. CD45 versus side scatter (SS) demonstrates blast population that is CD45 negative. The erythroblasts are CD117 dim positive, CD71 bright positive and GlyA positive and are negative for myeloid markers (MPO, CD13, CD33), B- or T-ALL markers (CD10, CD19, CD22, HLA-DR, CD1a, CD5, CD7, cytoplasmic CD3, terminal deoxynucleotidyl transferase (TdT)) and monocytic markers (CD14, CD11c). Megakaryocytic markers CD41 and CD61 are usually negative in AEL. There are cases described as partially or dim expressed megakaryocytic markers by flow cytometry, though it could be a case of biphenotypic leukemia with maturation arrest at burst-forming unit erythrocyte or a result of platelets adherence to the blasts.[1,29]

CYTOGENETICS AND MOLECULAR FINDINGS

The data regarding the genetic abnormalities in AEL are collected predominantly from conventional karyotyping. Numerous chromosomal abnormalities have been described in AML-M6. At this moment, there is no specific genetic abnormality associated with erythroleukemia. The cytogenetic abnormalities, however, may carry different prognostic risk. Good and intermediate risks are associated with normal karyotype, +8, del(20q) and other non-complex abnormalities. High risk ones present with complex abnormalities, -7/add(7q) and del(5q)/-5/add(5q).[15] Complex karyotype is often reported in AEL. However, Hasserjian et al recently report that there is no significant difference in overall survival in patients with good and intermediate cytogenetic abnormalities.[30] Bacher et al use only intermediate risk group, which includes normal karyotype. They showed that of the 77 AEL patients studied 35 (45.5%) had normal karyotype and 42 (54.5%) had aberrant karyotype; intermediate risk karyotypes were 47 (61%) and unfavorable risk karyotypes 30 (39%). From the 7 pEL patients studied, 2 (28.6%) showed normal karyotypes and 5 (71.4%) aberrant karyotypes; or 3 (42.9%) intermediate risk karyotype and 4 (57.1%) unfavorable risk karyotype.[15] Kasyan et al studied twenty patients with AEL, of them 10 (50%) had diploid karyotype, 5 (25%) had non-complex (<3) and 5 (25%) complex karyotype (≥3). The group of AEL with diploid or non-complex cytogenetics had better overall survival compared to the group of AEL with complex cytogenetics. [31]

The current WHO classification includes AEL with MDS-related cytogenetic abnormalities (balanced and unbalanced) in the category of AML-MRC. Cases presenting as erythroleukemia with reported (9;22)/*BCR-ABL1* belong to CML in blast phase. Reported AEL cases with genetic abnormalities such as t(15;17)/*PML-RARA* belong to the group of AML with recurrent genetic abnormalities.[32] If the patient has a history of previous chemotherapy or radiation therapy then these cases will be included in the group of t-AML.

Molecular findings are very limited at this time and need more study. Bacher et al reported in their cohort of 77 patients with AEL (erythroid/myeloid) frequency of 26.3% *nucleophosmin* gene (*NPM1*) mutation, 3.4% *fms-like tyrosine kinase 3* gene internal tandem duplication (*FLT3*-ITD), 2.9% *FLT3* tyrosine kinase domain (*FLT3*-TKD), 3.3% *N-RAS*, 11.9% *MLL*-PTD positive mutations and 1(16.7%) out of 6 patients with pEL with *NPM1* mutation.[15] Another study found that 1 out of 5 patients (20%) has *NPM1* mutation.[33] Thiede et al reported 4% *FLT3*-ITD mutated cases.[34] Kasyan et al found 3 out of 15 patients (16%) with *FLT3* (ITD or TKD) mutation.[35] *RAS* mutations and *Janus kinase 2* (*JAK2*) mutations are infrequent. *TP53* was in the wild type form in all 5 cases in one study.[36]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for AEL is broad. It includes reactive and neoplastic processes, and requires clinical history as well as genetic and molecular data (**Table 2**). Acute erythroid leukemia should be distinguished from RAEB. Although both entities can present with anemia, dyserythropiesis and ring sideroblasts, the blast number is the key diagnostic factor. If the blasts are <20% of all non-erythroid elements, then the diagnosis of RAEB should be made.

With the current WHO 2008 classification, AML-MRC encompasses a large group of the AML diagnosis. By definition, it requires ≥ 20% blasts in the peripheral blood or bone marrow and one of the following: > 50% dyspoiesis in at least two bone marrow cell lineages, previous history of MDS or MDS/MPN, or MDS-related cytogenetic abnormalities, and absence of both recurrent AML cytogenetic abnormalities and previous history of cytotoxic or radiation therapy for an unrelated disease.

Therapy related AML should be separated from AEL even though it can present with increased erythroid elements of >50% of all nucleated cells, dyserythropoiesis and increased ring sideroblasts. It was shown that t-AML carry significantly worse overall survival compared to AEL.

The differential diagnosis also includes other myeloid leukemias e.g. AML with recurrent cytogenetic abnormalities such as t(15;17) that present with increased erythroids. AML-M0 is negative for MPO by cytochemistry and may resemble pEL. The differentiation between pEL and megakaryoblastic leukemia is challenging since both leukemias are MPO negative and PAS positive. Useful immunohistochemical markers are expression of CD71, Glycophorin A and spectrin in erythroleukemia, and the positivity of CD41 and CD61 in

megakaryoblasts. Reportedly, erythroid leukemia can partially and weakly express these markers as well, even though the latter is considered most probably a biphenotypic leukemia presenting with megakaryoblastic and erythroblastic population or a result of platelet adherence.[29,37] Other hematologic malignancies that can resemble pEL, include ALL, plasma cell myeloma, Burkitt lymphoma and other lymphomas. B and T cell markers as well as TdT can distinguish pEL from ALL. Neoplastic plasma cells are CD138+ CD38+ and cytoplasmic immunoglobulin+, additionally CD20, CD117 and CD56 can be expressed in some plasma cell myeloma cases. Burkitt lymphoma is CD10+ CD20+ BCL6+ BCL2-, shows proliferation index (Ki67) ~100% and *MYC* gene translocation.

Table 2. Diagnosis and Differential Diagnosis of Acute Erythroid Leukemia.

Entity	**Diagnostic Features and Studies**
Acute Erythroid Leukemia	
Erythroid/myeloid leukemia	≥ 50% erythroid cells; ≥ 20% myeloblasts of non-erythroid cells, dysplasia < 50% of cells in <2 cell lines
Pure erythroid leukemia	≥ 80% erythroblasts
MDS (RAEB)	< 20% blasts; dyspoiesis, MDS genetic abnormalities
AML-MRC	≥ 20% blasts; ≥ 50% dysplastic cells of 2 or 3 lineages; MDS-related cytogenetics, prior history of MDS or MDS/MPN
t-AML	history of cytotoxic or radiation therapy
AML, NOS	≤ 50% erythroid cells; immunophenotypic studies
AML with recurrent genetic abnormalities	genetic/molecular studies
CML in blast phase	t(9;22); *BCR-ABL1*
MPN with blast transformation	previous diagnosis of MPN with or without *JAK2* V617F mutation
Non-neoplastic erythroid proliferations	
Megaloblastic anemia (vit B12/folate deficiency)	methylmalonic acid, homocystein erythroid hyperplasia with left shift, hypersegmented neutrophils, giant metamyelocytes, giant platelets
Erythropoietin treatment	clinical history
Congenital dyserythropiesis	clinical history, genetic studies; ineffective erythropiesis, dyserythropoiesis, multinucleation
Medication and toxins	previous history of metotrexate, benzene
Parvovirus infection	ELISA, PCR
Other malignancies	immunophenotypic and genetic studies
Plasma cell myeloma ALL (B or T) Ambiguous lineage leukemias Burkitt lymphoma Other lymphomas Metastatic tumors	*MYC* translocation

Myeloproliferative neoplasms in blast transformation with previous MPN diagnosis with or without *JAK2* mutation as well as blast phase of CML with erythroblasts should be separated from AEL and treated appropriately.

A curious case of mastocytosis associated with a clonal hematological non-mast cell lineage disease (SM-AHNMD) is reported, where the associated disease is acute erythroid leukemia (erythroid/myeloid type) and the molecular studies showed *KIT*(D816V+) mutation in both mast cells and erythroblast population.[38]

The current WHO classification excludes cases of patients treated with EPO from the AEL group. EPO stimulates erythropoiesis by increasing the number of earlier and late erythroid precursors. Bone marrow findings show striking erythroid hyperplasia and dyserythropoiesis. The clinical findings with EPO treatment are improvement of hemoglobin levels and transfusion independence.

The most common reactive process that can mimic pEL is megaloblastic anemia caused by vitamin B12 and folate deficiency. There are reports of patients with pernicious

anemia erroneously treated with chemotherapy. Features associated with pernicious anemia are hemolysis with increased mean corpuscular volume (MCV), hypersegmented neutrophils, leukopenia and thrombocytopenia increased LDH and urobilinogen. Bone marrow findings show hypercellular blastic changes.[39] Other non-neoplastic diseases mimicking pEL are post-chemotherapy recovery, parvovirus infection, drug effect, heavy metal intoxication and congenital dyserythropoiesis.[5,40] A detailed clinical history, laboratory work up, peripheral blood and bone marrow examination, cytochemical, immunoshistochemical, flow cytometry, cytogenetic and molecular studies are required for the diagnosis of AEL.

PROGNOSIS AND TREATMENT

Acute erythroid leukemia is an aggressive disease with heterogeneous presentation (after MDS, t-AML or de novo). The outcome is generally poor. In 1992 Olopade et al, concluded that M6 patients with advanced age and abnormalities of chromosomes 5 and/or 7 had a shorter median survival (16 vs 77 weeks [P = .005]) than M6 patients without these abnormalities. They did not find correlation between cytogenetic abnormalities or clinical outcome and morphologic features.[17] Hasserjian et al showed 8 months overall survival for all patients presenting as AEL including MDS and therapy related AEL (MDS-AEL and t-AEL). In the same study, the median survival of patients with de novo AEL (11 months) and MDS-AEL (17 months) was superior to t-AEL (4.5 months). The overall survival was not dependant on the number of peripheral blood and/or bone marrow blast count, peripheral blood nucleated red blood cells, extend of dysplasia or presence of ring sideroblasts, but it was related to unfavorable cytogenetic abnormalities, number of cytopenias, hemoglobin level and treatment type (bone marrow transplant vs not). There was no significant difference in overall survival (OS) in patients with AEL and MDS with erythroid hyperplasia and AML-MRC. Bone marrow transplantation with high-intensity chemotherapy improved significantly OS (23 months) compared with patients who received high-intensity induction chemotherapy alone (9 months), and with patients who received only supportive care or low-intensity therapy (4 months). There is no significant difference between the patients without bone marrow transplantation who received and who did not receive high intensity chemotherapy.[30] Kasyan et al showed that AEL has better OS than AML-MRC, t-AML and similar OS to that of RAEB with preceding/concurrent history of erythropoietin therapy (RAEB-EPO). The OS of AEL with non-complex karyotype (22 months) is significantly better than AEL with complex karyotype (12 months), AML-MRC (9 months), t-AML (3 months), and RAEB-EPO (8 months).[31]

Patients with AEL may be treated similarly to patients with other types of AML, NOS. Stem cell transplantation seems to be the best treatment approach for now, although the procedure is associated with high morbidity and mortality rate, especially in allogenic bone marrow transplantation.[41] Using HLA identical sibling SCT increase the leukemia free survival with 60%.[42] Erythropoietin and granulocyte colony stimulating factor have been used to induce clinical remission in elderly patients.[43] Mazzela et al showed that P-glycoprotein expression correlates with unfavorable cytogenetic abnormalities, poor response to chemotherapy with multidrug resistance development, and short survival[44] Cyclosporin A and cyclosporin D analogue PSC 833 (valspodar) are used for clinical drug modulation to overcome multidrug resistance. These agents can be administered at sufficient doses to achieve effective serum levels, and can be combined with cytotoxic agents without increase of toxicity.[45] Recently, a successful morphologic and cytogenetic remission after sorafenib initiation treatment in a *FLT3*-ITD-positive patient with a refractory acute erythroid leukemia and abnormal cytogenetics was reported.[46]

CONCLUSION AND PERSPECTIVES

Acute erythroid leukemia is a heterogenous disease, which may arise de novo, secondary to MDS or after cytotoxic therapy. According to the current WHO classification, there are two subgroups depending on the number of erythroid precursors and the presence of myeloid blasts: erythroid/myeloid leukemia and pEL. The two subgroups differ clinically with pEL having worse prognosis. Recent studies showed that the group of erythroid/myeloid leukemia is also heterogeneous and has different prognosis depending on the cytogenetics results. The most important adverse prognostic factor is the type of cytogenetic abnormalities. The prognosis is poorer with unfavorable and complex karyotypes. Based on the WHO 2008 criteria, AEL becomes diagnosis of exclusion and its frequency is decreased. The differential diagnosis is broad and includes reactive processes or other hematological malignancies. A thorough clinical history, laboratory data, cytochemical and immunophenotypic analysis, genetic and molecular studies are necessary for the correct diagnosis. Additional cytogenetic and molecular studies are required to elaborate our understanding of this disease.

CONFLICT OF INTEREST
None.

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