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Acute leukemia with erythroid hyperplasia. Our experience on a series of cases with acute myeloid leukemia

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Abstract

Diagnosis of myeloid malignancies with erythroid hyperplasia may sometimes confront hematologists with a mathematical dilemma, if cut-off criteria of blast percentage as proposed by the *World Health Organization* (*WHO*) 2008 Classification are applied. Several questions have been raised regarding differentiation of acute erythroid leukemia (AEL) from myelodysplastic syndrome with erythroid hyperplasia and some aspects still remain unclear. This paper discusses the differential diagnosis and presents our own experience in a series of patients with acute myeloid leukemia. Although the diagnostic criteria of AEL have been repeatedly refined, it remains a diagnosis primarily based on morphology and on exclusion criteria. Many of the cases designated before 2001 as AEL, actually fit into other disease categories, most often into myelodysplasia related changes – acute myeloid leukemia.

Keywords: acute myeloid leukemia, myelodysplastic syndrome, erythroid hyperplasia.

Introduction

Diagnosis of myeloid malignancies with erythroid hyperplasia by the cut-off criteria of blast percentage for acute erythroid leukemia (AEL) and myelodysplastic syndrome (MDS) according to the *World Health Organization* (*WHO*) 2008 Classification may sometimes confront hematologists with a mathematical dilemma. In many cases only a careful patient history, a close follow-up and even medical common sense will solve this problem. The attitude in such cases is "watch and don't wait" because prognosis might be poor if it turns out that we are dealing with a case of acute erythroid leukemia.

Diagnostic criteria for AEL were first defined by the *French–American–British Cooperative Group* (*FAB*) in 1976 [1]. In 1985 [2], these criteria were stated as follows: erythroblasts represent 50% or more of all nucleated bone marrow cells, prominent dyserythropoiesis is present and myeloblasts represent 30% or more of the non-erythroid cells in the bone marrow.

The 2001 *WHO* Classification [3] lowered the blast percentage threshold for acute myeloid leukemia (AML) at 20%, consequently eliminating the refractory anemia with excess of blasts in transformation (RAEB-T) category. As to AEL, it was defined as a myeloid proliferation with at least 20% myeloblasts from all non-erythroid cells, on a background of erythroid hyperplasia (at least 50% erythroblasts irrespective of their maturation stage). A more rarely encountered type is pure erythroid leukemia (PEL), where at least 80% of bone marrow cells are erythroblasts, irrespective of the myeloblast percentage. AEL is a diagnosis of exclusion, because first line criteria to categorize AML are recurrent cytogenetic alterations, history of MDS, prominent dysplasia or MDS related cytogenetic changes, history of cytotoxic therapy, radiotherapy or immunosuppressive therapy. Also, prior erythropoietin therapy must be ruled out.

Several questions have been raised regarding differentiating AEL from MDS with erythroid hyperplasia and some aspects remain unclear even after the 2008 *WHO* Classification was devised [4]. If MDS is diagnosed according to blast percentage from total nucleated cell count (lymphocytes and plasma cells excluded) and AEL is diagnosed according to blast percentage from non-erythroid cell count, there remains a grey zone where cases can belong to either of these categories.

This paper discusses the differential diagnosis and presents our personal experience in a series of patients with acute myeloid leukemia with erythroid hyperplasia.

Materials and Methods

Materials

In order to document our own experience in the diagnosis of acute myeloid leukemia with erythroid hyperplasia, we retrospectively studied a series of 88 patients with acute leukemia admitted to the Department of Hematology, "Prof. Dr. Ion Chiricuţă" Oncology Institute, Cluj-Napoca, Romania, between 2006 and 2009. All patients had at admission a complete blood count (CBC), blood film, biochemistry, coagulation testing and bone marrow aspirate. Other investigations performed at diagnosis were immunophenotyping by flow cytometry, karyotyping and molecular biology.

Methods

Morphological description

Morphological description of the blasts was made according to *FAB* [2] and *WHO* [4] criteria, reviewed and refined by the *International Working Group on Morphology of MDS* (*IWGM–MDS*), taking into account: cell size, chromatin appearance, cytoplasm appearance, granularity, the presence of Auer rods, positivity and appearance of myeloperoxidase in cytochemistry. We used the May-Grünwald Giemsa (MGG) staining and myeloperoxidase stain (the benzidine and hydrogen peroxide method, internal protocol of the Laboratory of Medical Analysis, Department of Hematology).

Immunophenotyping

Immunophenotyping was performed on bone marrow aspirate samples. The surface marker antibody panel consisted of: CD45, CD33, CD34, CD117, HLA-DR, CD3, CD7, CD19, CD13, CD14, CD15, CD56, CD11b, CD11c, CD61, CD235, CD38, CD133, CD41, CD42b, CD71, CD184, CD47, CD243. The intracytoplasmatic antibody panel comprised: CD45, TdT, MPO, CD79a, CD3, CD22. The analysis was performed on an Epics-XL-MCL flow cytometer (Beckman Coulter) using a four-color protocol. Gating strategy was SSC/FSC and/or CD45/SSC and the results were expressed as the percentage of positive cells in the gate. A population was defined as positive for a marker if it was present in 20% of the cells for surface antigens and 10% for cytoplasmic antigens.

Karyotype analysis

Karyotype analysis was done on bone marrow samples using the G-banding technique. Numerical and structural aberrations were described according to the *International System for Human Cytogenetic Nomenclature*.

Mutational analysis

Mutational analysis was done by RT-PCR for: RUNX1/RUNX1T1, MLL-PTD, CBFB/MYH11, FLT3-TKD, PML/RARA, FLT3-ITD, AF9/MLL, NPM1.

Results

From the group of 88 cases of acute myeloid leukemia we identified seven patients, which displayed erythroid hyperplasia at the initial bone marrow aspirate. General characteristics of these patients are depicted in Table 1.

Table 1 – ***General description of our cases***

Case No.	Gender	Age [years]	WBC [$\times 10^9$/L]	Hb [g/dL]	Plt [$\times 10^9$/L]
1.	M	55	2	6	20
2.	F	70	2	6	70
3.	M	49	3	6	56
4.	F	55	1.7	9	220
5.	M	66	4	9	20
6.	M	36	15	7	25
7.	M	70	7.4	8.6	73

M – Male; F – Female; WBC – White blood cells; Hb – Hemoglobin; Plt – Platelets.

Only one patient (No. 6) presented a mild leukocytosis and one patient (No. 4) had platelets into the normal range. Anemia was present in all patients.

Bone marrow cytology

The most striking bone marrow finding was erythroid hyperplasia, frequently with a shift to more immature forms. Dysplasia was present in all maturational stages, with megaloblastosis, multinuclearity, nuclear budding and strange looking nuclei. The erythroblast cytoplasm presented vacuolation and cytoplasmic buds.

All patients had erythroid hyperplasia at diagnosis (erythroblasts at least 50% of all nucleated bone marrow cells – lymphocytes, plasma cells were excluded).

Cell counts on bone marrow samples are presented in Table 2.

Table 2 – ***Cell count on bone marrow samples***

Case No.	Erythroid lineage [%]	Blasts per total nucleated cells [%]	Blasts per non-erythroid cells [%]
1.	55	18	40
2.	65	11	32
3.	50	12	25
4.	*	40	–
5.	**	20	–
6.	50	50	100
7.	70	9	30

*Not specified, because of the specimen quality, erythroid hyperplasia was confirmed by flow cytometry. **Not specified, but hyperplastic.

The erythroid lineage was described, except for case No. 4, as megaloblastic and highly dysplastic. Nuclear budding was described in all the remaining six cases. Bi- and multi-nuclearity was described in all cases except for case No. 6, but this was the only case in which Pappenheimer bodies and hemoglobinization defects were described. Case No. 7 was the only case with cytoplasmic vacuolization. Cases No. 1 and 3 had nuclear bridges and case No. 5 had frequent Howell–Jolly bodies.

In the whole group (n=88), erythroid dysplasia was described in 33 cases, but only the M6 cases had such impressive morphologic abnormalities, as illustrated in Figures 1–4.

Granulocytic series dysplasia was present in four cases (No. 2, 3, 5 and 6). Case No. 6 was the only one with Auer rods. A high degree of granulocytic dysplasia was present in Cases No. 2 and 3, with frequent pseudo Pelger–Huët cells, hypogranularity and nuclear-cytoplasmic maturation asynchronism.

Megakaryocytic morphology could be assessed in four cases (No. 1, 2, 3 and 5) and all were described as being dysplastic with hypolobulated megakaryocytes or both hypolobulated and hyperlobulated nuclei.

Out of the 88 cases, 49 cases had granulocytic dysplasia and 13 cases had megakaryocytic dysplasia.

Immunophenotying

Immunophenotying was available in five cases.

Case No. 2 was diagnosed by flow cytometry as acute erythroid leukemia with virtually all cells expressing CD235 (glycophorin). CD34 and MPO were positive in 30% of the cells.

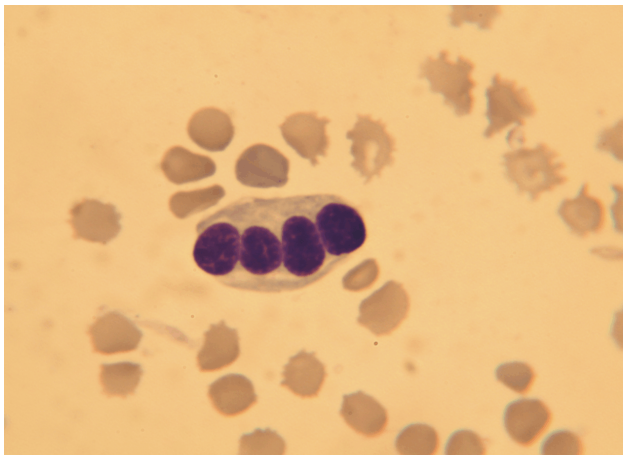

Figure 1 – ***Multinucleated oxyphilic erythroblast in bone marrow aspirate, MGG staining, 1000×.***

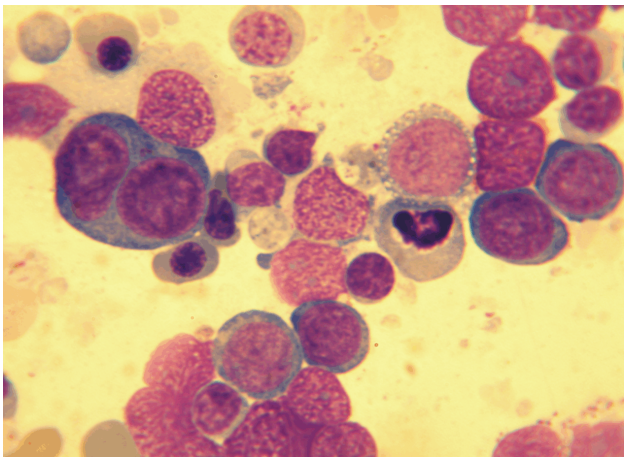

Figure 2 – ***Erythroid hyperplasia, binucleated basophilic erythroblast, cytoplasmic vacuolation, myeloid blasts in bone marrow aspirate, MGG staining, 1000×.***

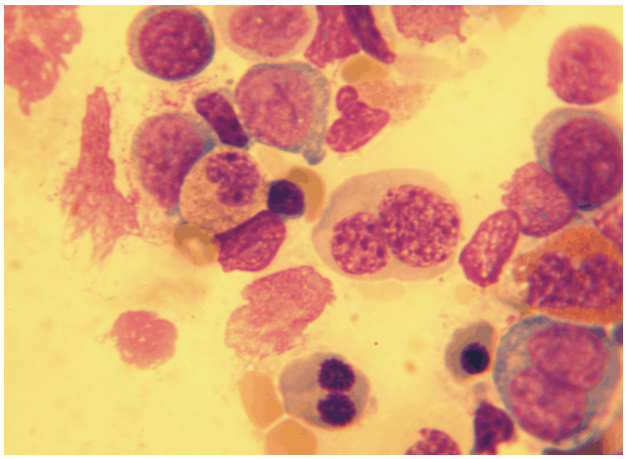

Figure 3 – ***Binucleate erythroblasts, nuclear bridge, granulocytic dysplasia: pseudo Pelger–Huët in bone marrow aspirate, MGG staining, 1000×.***

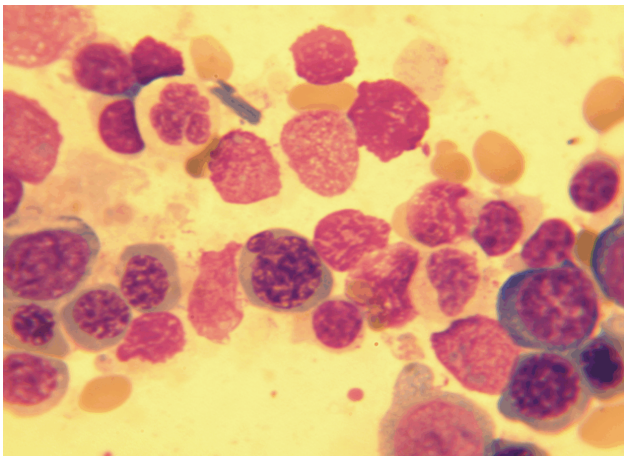

Figure 4 – ***Erythroblast with nuclear budding in bone marrow aspirate, MGG staining, 1000×.***

Case No. 3 was diagnosed by flow cytometry as RAEB because blast percentage was reported as being 17%. Blasts were positive for CD117, CD33, MPO, CD38 and weak CD133.

For case No. 4, flow cytometry data suggested MDS/AML6, because 50% of the total cells were CD45 negative and therefore suspected to be erythroblasts. The myeloblast population was small (6%) and positive for CD33, CD34, CD117, CD13, but negative for MPO and HLA-DR.

In case No. 5, flow cytometry showed a small myeloid blast population not sufficient for the diagnosis of AML. The cells expressed CD13, CD33, HLA-DR, CD34 and CD117, and were negative for MPO. Glycophorin was not included in the panel and the final diagnosis of AML had to be reassessed by morphology. Case No. 7 had 5% blast cells, all positive for CD13, CD33, CD34, CD117.

Karyotyping

Karyotyping was available in six cases. Three cases showed a normal karyotype and the other three cases showed the following abnormalities: case No. 6 showed trisomy 8, cases No. 4 and 5 had complex karyotypes (-5, -7, +8, -12, -17 for case No. 4 and a highly complex karyotype, including several unidentified marker chromosomes for case No. 5).

Molecular biology

Six of the cases were investigated by PCR for certain molecular aberrations (RUNX1/RUNX1T1, MLL-PTD, CBFB/MYH11, FLT3-TKD, PML/RARA, FLT3-ITD, AF9/MLL, NPM1), but none of them were positive.

Discussion

A critical approach to diagnostic criteria has already been proposed since 2002, when Selby *et al.* [5] have shown that a blast count of 20% of non-erythroid cells, in a bone marrow with overt erythroid hyperplasia (70–90%), could mean a total blast count of 5–10%, which is far below the diagnostic cut-off for acute leukemia and that these cases would better fit into the MDS group, avoiding aggressive therapy.

In 2004, Zini and d'Onofrio wrote an "epitaph for erythroleukemia" [6], showing that for 13 cases diagnosed between 1996–2002 in their institution as AEL, full diagnostic agreement to reclassify these cases as MRC-AML was achieved after reviewing the data. So, they concluded that if the 1985 FAB classification has determined an increase of the AML-M6 diagnosis, the *WHO* Classification will cause a disappearance of this subgroup.

According to the hierarchy of diagnostic criteria imposed by the *WHO* 2008 Classification of myeloid neoplasms [4], we have to consider first cytogenetics and patient history.

If the patient has a MDS history, either refractory anemia with excess of blasts (RAEB) or refractory cytopenias with multilineage dysplasia (RCMD), then AML is declared when a blast percentage of 20% of the total nucleated cell count is observed. Similarly, if there is a history of chronic myeloproliferative disease (CMPD), more often chronic myeloid leukemia (CML), but also polycythemia vera (PV), the evolution to a high blast percentage is regarded as an acute blastic transformation of the prior disease. Prior history of chemotherapy, radiotherapy for malignant hematological or non-hematological processes, immunosuppressive therapy for organ transplantation or for benign conditions, exposure to chemotoxic agents (benzene) are criteria for secondary AML diagnosis. Another important issue is erythropoietin therapy, which is known to cause erythroid hyperplasia and dyserythropoiesis. None of our patients fitted into any of these categories.

Karyotyping and molecular testing

Karyotyping and molecular testing are mandatory in AML because of their high prognostic value. AEL cases show a high degree of heterogeneity regarding genetic alterations. Among the frequently encountered abnormalities are monosomy 5, del(5q), monosomy 7, del(7q), trisomy 8, but also inv(3q), anomalies of 11q, 17p, del(20q) and +13. Because of the relatively small number of cases, but probably also because of the heterogeneity of the disease, there are no definite conclusions in the literature regarding the frequency of molecular abnormalities. NPM1, FLT3, core binding factor and RUNX1 mutations have been reported. The presence of a recurrent cytogenetic aberration requires the assignment of the case to that *WHO* 2008 AML category, irrespective of morphology and blast count. In our series, cases No. 4 and 5 showed MDS related cytogenetic abnormalities: -5, -7, -12 for case No. 4; case No. 5 included in his highly complex karyotype also MDS specific changes: -7 and -12 [7, 8].

Immunophenotying

Immunophenotying is not of great help in AEL. It is rather important in diagnosing PEL, where expression of at least one erythroid-associated antigen is required to differentiate of AML-M0, AML-M7 and other hematological neoplasms: acute lymphoblastic leukemia, lymphomas [9], and even multiple myeloma [10]. Erythroblasts show positivity for the transferrin receptor (CD71), and variably express hemoglobin A (HbA), glycophorin A, spectrin, blood group antigens, HLA-DR. More immature erythroblasts are positive for carbonic anhydrase 1 (Gerlich blood group antigen) and CD36 [9]. In our experience, immunophenotyping in acute erythroid leukemia is of value only in conjunction with morphology. Myeloblasts express, as expected, myeloid antigens: CD13, CD33, CD117 (KIT) and MPO; CD34 and HLA-DR are variable present.

Cytology and cytochemistry

Acute erythroid leukemia presents usually with pancytopenia, but this is also the case of MDS and megaloblastic anemia. Peripheral blood picture might show some erythroblasts and in most cases prominent anisocytosis, poikilocytosis and anisochromasia. Basophilic stippling, hemoglobinization defects and schistocytes are also often encountered. Granulocytic dysplasia consisting mostly of pseudo Pelger–Huët abnormality and hypogranularity may also be present. If these other lineages are also dysplastic, a careful quantification of dysplasia is required, because such cases may be categorized as AML with myelodysplastic syndrome related changes (MRC-AML) if at least 50% of the nucleated elements in at least two lineages are affected. Myeloblasts belonging to the malignant clone show positivity for myeloperoxidase (MPO). In our experience, cases were primarily diagnosed as AEL if erythroid dysplasia was extreme, except for case No. 4. Cases No. 1, 2, 3, 5, and 6 showed a degree of dysplasia which according to the *WHO* 2008 criteria would primarily define such cases as MRC-ML, but meanwhile the prognostic value of this subclass based only on morphological criteria is also questionable [11]. Therefore, all our cases had cytogenetic or morphologic MDS related changes.

Differential diagnosis

As stated before the most difficult challenge in myeloid malignancies with erythroid hyperplasia, especially in the presence of a low blast count, is whether to include the case in the MDS or in the AEL group. This task is more complicated if there is no sufficient data to fulfill criteria for AML with recurrent cytogenetic alterations, for MRC-AML or for secondary AML. Morphological aspects suggestive for megaloblastic anemia or severe dyserythropoietic anemia can also be confusing [12].

Pointing on these diagnostic problems did not brought significant changes for AEL in the *WHO* 2008 Classification and this represented hereinafter a study aim for several groups, as illustrated in Table 3.

Table 3 – ***Review of recent literature data concerning AEL***

	Zuo *et al.* (2012) [13]	**Bacher *et al.* (2011) [14]**	**Hasserjian *et al.* (2010) [15]**	**Kasyan *et al.* (2010) [16]**	**Santos *et al.* (2009) [17]**
Overall survival [months]	–	14.5	8	19	9
Unfavorable karyotypes (according to MRC criteria) [%]	50	39	64	–	61
De novo AEL [%]	–	70	35	–	50
FLT3 [%]	7.2	3.4	6	16	–
NPM1 [%]	1.2	26.3	–	–	–
MLL-PTD [%]	–	11.9	–	–	–
RAS [%]	4.8	–	2	0	–
KIT [%]	0	–	–	0	–

MRC – Medical Research Council; AEL – Acute erythroid leukemia; FLT3 – Fms-like tyrosine kinase 3; NPM1 – Nucleophosmin1; MLL-PTD – Mixed lineage leukemia gene-partial tandem duplications.

Analysis performed by Bacher *et al.* [14] on 108 patients with AML with erythroid hyperplasia (described as AEL, PEL and AML-MRC) *versus* MDS with erythroid hyperplasia, showed no significant differences within the AML group; however, separating AML from MDS had clinical relevance. The authors proposed to create a combined group of "AML with increased erythropoiesis",

which might facilitate inclusion in studies and development of specific therapy.

Cytogenetics remains the most important prognostic marker in Bacher *et al.* [14] and also in Hasserjian *et al.* study [15]. In addition, Hassejian *et al.* suggests that MDS and AML with erythroid hyperplasia (AEL and PEL) are a continuum in the evolution of the same pathological process, where blast percentage is a rather arbitrary cut-off.

Santos *et al.* [17] concluded in his study on 91 patients with AEL that it was associated with previous MDS, poor-risk karyotype and that treatment decisions should be made as for any other AML.

Although morphologic criteria seem obvious, AEL overlaps with other types of erythroid-rich AML and MDS. Concerning blast percentage assessment, Wang *et al.* suggested in 2008 [18] that for MDS, blast counting should be reported to non-erythroid cells; however, in a review written in 2012 [19] the same author states that MDS, MRC-AML and AEL are a continuum for which cytogenetic changes are more important than blast count in assessing prognosis.

In our series, overall blast percentage would have favored towards MDS in cases No. 1, 2, 3 and 7; nevertheless, clinical reasoning and close follow-up prompted us to treat these cases as AML.

Conclusions

Although the diagnostic criteria of AEL have been repeatedly refined, it remains a diagnosis primarily based on morphology and on exclusion criteria. Many of the cases designated before 2001 as AEL, actually fit into other disease categories. Adding the fact that these cases are rare, retrospective analysis of previously reported series is difficult and might not yield definite conclusions. AEL diagnosis should be established with caution, after excluding all other possibilities mentioned above. In situations with low overall blast count, impressive erythroid dysplasia, a severe clinical status and rapidly progressive disease can shift the diagnosis in favor of AEL instead of MDS. More specific diagnostic criteria, ideally based on complex genomic characterization, are needed in order to get a better understanding of the disease.

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