Acute myeloid leukemia with expanded erythropoiesis

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Depending on previous clinical history, number of blasts in the bone marrow, and results of cytogenetic analysis, hematologic malignancies with expanded erythropoiesis (more than 50% of bone marrow erythropoietic cells) may fall under various categories of the 2008 edition of the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues (Table 1).[1] The general threshold of blast percentage for the diagnosis of acute myeloid leukemia (AML) is 20% of total peripheral blood or bone marrow cells. However, cases with fewer than 20% blasts and more than 50% of erythroid precursors in the bone marrow are classified as acute erythroid leukemia (AEL, erythroid/myeloid) if blasts account for 20% or more of the non-erythroid cells. If blasts constitute less than 20% of non-erythroid cells, the cases are classified into various categories of myelodysplastic syndromes (MDS). Patients with 80% or more of bone marrow cells representing immature cells committed exclusively to the erythropoietic lineage are classified as having pure erythroid leukemia.

The WHO 2008 classification has also defined the category of AML with myelodysplasia-related changes (AML-MRC) as acute leukemia with 20% or more peripheral blood or bone marrow blasts with morphological features of myelodysplasia or a prior history of MDS or MDS/myeloproliferative neoplasm or MDS-related genetic abnormalities (Table 2), and absence of prior cytotoxic therapy and the specific genetic abnormalities that would classify the case as AML with recurrent genetic abnormalities. Several studies confirmed the negative prognostic significance of the MDS-related genetic abnormalities.[2,3] Concerning cases with more than 50% erythroid precursors, the authors of the WHO 2008 classification stated that cases with 20% or more blasts should be classified as AML-MRC if MDS-related cytogenetic abnormalities or multilineage dysplasia in more than 50% of cells in two or more lineages are found. It has also been pointed out that patients with AEL often have complex karyotypes but the possibility of including AEL cases with complex karyotypes and less than 20% bone marrow blasts in the AML-MRC category has not been addressed.[1]

Several groups have recently discussed the diagnosis, definition and prognosis of AEL and MDS with expanded erythropoiesis (>50% erythropoietic precursors in bone marrow smears).[4-6] The common findings were high incidence of unfavorable karyotypes, low frequency of *NPM1*, *FLT3* and *RAS* mutations, and poor prognosis.[4,6-10]

In this issue of Haematologica, Bacher *et al.*[4] have compared some genetic and clinical aspects of AML and MDS with expanded erythropoiesis. On the basis of the observed better 2-year overall survival rate of MDS patients (n=104) in comparison to those classified as having AML (combined cohort of 77 AEL and 24 AML-MRC), the authors propose continuing separating MDS with expanded erythropoiesis from AML. It should be noted that the patients in this study classified as having MDS and carrying an unfavorable karyotype had a 2-year overall survival similar to that of patients with AML. The authors also propose combining all AEL and AML-MRC with more than 50% erythropoiesis, introducing a new category of "acute myeloid leukemia with increased erythropoiesis". When all AML patients in this study (combined AEL, AML-MRC, and therapy-related AML WHO categories, all with >50% erythropoiesis) were analyzed, cytogenetic changes were found to be the most significant prognostic factor in the multivariate analysis. However, no comparison was made within the AEL group between patients carrying unfavorable cytogenetics and the remainder.

In an early study using the French-American-British (FAB) classification, Olopade *et al.* proposed that AEL patients could be divided in two distinct groups: one of mainly elderly patients, carrying cytogenetic abnormalities similar to those in therapy-related leukemias and characterized by poor prognosis, and a second group of younger patients with mainly

Table 1. Classification of hematologic malignancies with expanded erythropoiesis (>50% of bone marrow cells) according to WHO2008.

WHO 2008 category[1]	% blasts of total BM cells	% myeloid blasts of non-erythropoietic BM cells	Cytogenetics
Pure erythroid leukemia	>80% erythroid blasts	<20%	Majority MR*
Acute erythroid leukemia	>20%	>20%	not MR
Acute myeloid leukemia with myelodysplasia-related changes	>20%	>20%	MR
Acute erythroid leukemia	<20%	>20%	Many MR
Myelodysplastic syndrome refractory anemia with excess of blasts-2 (RAEB 2)	10-19%	<20%	Many MR
Myelodysplastic syndrome refractory anemia with excess of blasts-2 (RAEB 1)	5-9%	<20%	Many MR
Myelodysplastic syndrome refractory anemia with ring sideroblasts	<5%	<20%	Not MR
Myelodysplastic syndrome refractory cytopenia with multilineage dysplasia with ring sideroblasts	<5%	<20%	Many MR
Therapy-related myeloid neoplasms	<1-49%	<1-99%	Most MR

**MR: myelodysplasia related (see Table 2), BM: bone marrow.*

normal karyotypes and more favorable prognosis when treated with intensive chemotherapy.[11]

More recently, Hasserjian *et al.*[6] analyzed various prognostic factors in a cohort of 124 AEL patients and confirmed that overall survival was related to the cytogenetic risk group. Patients with therapy-related AEL had a dismal prognosis confirming the clinical significance of classifying this type of AEL within the "therapy-related myeloid neoplasms" category which has a worse prognosis independently of clinical characteristics and morphological classification.[12,13] The median overall survival of the AEL patients with unfavorable cytogenetics was 6 months, similar to the 8-month median overall survival observed in a separate group of 41 patients with AML-MRC and 50% or more erythropoiesis.[6] The AEL patients with intermediate cytogenetics (most of whom would not classify as having MRC disease) had a much longer median overall survival (30 months). In a different study, the same authors analyzed a cohort of patients with MDS and expanded erythropoiesis and found that cytogenetic risk-category and blast numbers counted as a percentage of non-erythroid bone marrow cells (<5% *versus* ≥5%) had a strong prognostic significance.[5] The same authors also separately described a group of 18 patients with primary erythroid leukemia in which complex karyotypes were noted in all 16 patients with available cytogenetic data.[14]

Kasyan *et al.*[8] reviewed a cohort of 90 patients with hematologic malignancies with expanded erythropoiesis, dividing them according to the WHO 2008 classification. Although the separate groups of patients were rather small, this study confirmed the negative prognostic significance of complex karyotypes within the AEL group and the negative prognostic significance of therapy-related AEL, independently of cytogenetics. A small group of AEL patients with normal or non-complex karyotypes had a much better overall survival.

The pathogenesis of hematologic malignancies with expanded erythropoiesis is still poorly understood. In the

Table 2. Cytogenetic abnormalities supporting a diagnosis of AML with myelodysplasia-related changes. Complex karyotype (more than 3 unrelated abnormalities, no 'recurrent genetic abnormality' type)

Unbalanced abnormalities
-7 or del(7q)
-5 or del(5q)
i(17q) or t(17p)
-13 or del(13q)
del(11q)
del(12p) or t(12p)
del(9q)
idic(X)(q13)
Balanced abnormalities
t(11;16)(q23;p13.3)
t(3;21)(q26.2;q22.1)
t(2;11)(p21;q23)
t(1;3)(p36.3;q21.1)
t(5;12)(q33;p12)
t(5;7)(q33;q11.2)
t(5;17)(q33;p13)
t(5;10)(q33;q21)
t(3;5)(q25;q34)

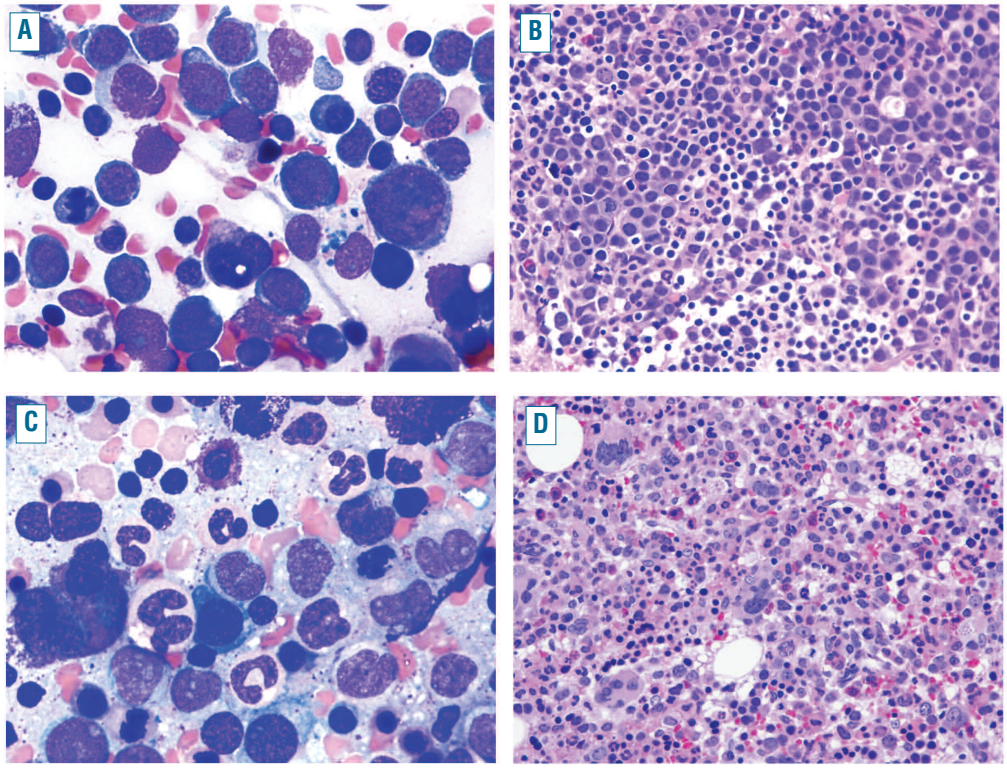

Figure 1. A 63-year-old woman presented with pancytopenia, including severe anemia (Hb=5g/dL). A bone marrow aspirate (A) and biopsy (B) were obtained. There were 82% erythroid precursors and 8% blasts (57% of the non-erythroid cells). A diagnosis of AEL was made. The patient received multiple units of packed red cells but no definitive therapy, and 6 days later was transferred to a tertiary care center for further treatment. At that time, Hb=9.8g/dL. A repeat aspirate (C) and biopsy (D) were performed and showed that erythroid precursors accounted for 42% of the marrow cells and blasts for 16%. The patient had a complex karyotype (56, XY) with gains of numerous chromosomes, including +8 and +9, loss of chromosome 22, and structural abnormalities of chromosomes 3 and 7. A diagnosis of refractory anemia with excess of blasts-2 was made.

Mitelman database of chromosome aberrations and gene fusions in cancer,[15] there are more than 600 cases of AEL, most of which display genetic abnormalities that would qualify as MRC. A translocation t(1;16)(p31;q24) rearranging the *CBFA2T5* gene encoding for z protein in the myeloid translocation gene family of transcriptional co-repressors has recently been described as associated with AEL.[16]

Erythropoiesis is mediated by a relatively small number of lineage-restricted transcription factors, including GATA-1, SCL/TAL1, LMO2, LDB1, and KLF1.[17] GATA-1 is a Zn-finger DNA binding transcription factor that activates expression of numerous genes in concert with *SCL/TAL-1*. During hematopoiesis, GATA-1 interacts with the transcription factor PU.1 encoded by the *Sfpi1* gene, one of the key regulators of hematopoiesis. The GATA-1 and PU.1 proteins are co-expressed in erythroleukemic cells (MEL cells) of mice that harbor the Friend virus integration within the upstream regulatory element of the *Sfpi1* gene.[18] This viral integration causes an aberrant and constitutive expression of the PU.1 protein resulting in development of erythroleukemia. Both transgenic mice over-expressing PU.1 and mice carrying hypomorphic *Sfpi1* alleles that reduce PU.1 levels develop erythroleukemias with a high rate of aberrant karyotypes.[19,20] The role of GATA-1 and PU.1 in the development of human erythroleukemia is still unclear, but GATA-1 mutations were not found in the cases of AEL studied.[21]

It may also be important to differentiate whether the erythroid proliferation in a patient with AML is secondary to increased erythropoietin production due to the severe anemia, or caused by autonomous proliferation of the erythroid lineage. High levels of erythropoietin have been detected in patients with AML.[22] In some AML patients, however, a marked decrease of primarily expanded erythropoiesis could be observed after blood transfusion (illustrated in Figure 1).

In summary, from the literature we reviewed, we could not find support for the proposal of introducing a new category of "acute myeloid leukemia with increased erythropoiesis" by combining all AEL and AML-MRC with greater than 50% erythropoiesis. Current data suggest that therapy-related malignancies have a very poor prognosis, independently of the presence or absence of expanded erythropoiesis. Growing evidence indicates that high-risk cytogenetics is more important for prognosis than morphology, thus, patients fulfilling the morphological criteria for AEL and carrying myelodysplastic-related cytogenetic abnormalities may have to be considered as having AML-MRC.

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