Editorial

MDS or M6: The dilemma in classifying early leukemias

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Early leukemias are difficult to diagnose, even harder to classify, particularly in a time when classification ever evolves. Right after the revised WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues had published in 2008, I encountered the dilemma in classifying some early leukemias.

One example was a 68-year-old woman diagnosed with refractory anemia with excess blast (RAEB) who was admitted for possible allogeneic stem cell transplantation [1]. The patient was asymptomatic and her CBC was: WBC 14.5 x 10^9/L; Hgb 9.7 g/dL; and platelet 239 x 10^9/L. Peripheral blood (PB) smear showed approximately 15% circulating blasts. Bone marrow biopsy showed a differential count: 15% blasts, 3% promyelocytes, 4% myelocytes, 11% neutrophils, 4% eosinophils, 1% basophils, 0% monocytes, 11% lymphocytes, 3% plasma cells, and 48% nucleated RBCs. Flow cytometry revealed 15% blasts that were CD13+, CD33+, CD34+, CD38+, CD71+, CD117+, HLA-DR+, and subset MPO+. Florescence in situ hybridization (FISH) demonstrated the presence of 7q deletion. A diagnosis of high grade myelodysplastic syndrome (MDS: RAEB-2) was made. However, when reviewing a previous marrow biopsy obtained three months earlier, I found a markedly hypercellular marrow with prominent erythroid hyperplasia [Figure 1] and a differential count: 5% blasts, 1% promyelocytes , 1% myelocytes, 1% metamyelocytes, 1% band neutrophils, 4% segmented neutrophils, 1% eosinophils, 0% basophils, 1% monocytes, 2% lymphocytes, 0% plasma cells, and 83% nucleated RBCs. An accompanying PB smear showed frequent circulating blasts (13%) that were CD13+, CD33+, CD34+, CD117+, and HLA-DR+ by a reported flow cytometry. The earlier cytogenetic study also revealed an abnormal female karyotype: 46,XX,del(7)(q22)[13]/46,XX[7], and FISH studies demonstrated a deletion of 7q31 in 78% of the cells. Although this earlier marrow had fewer blasts (∼5%) in the marrow, it met the diagnostic criteria of acute erythroid leukemia [2] or acute myeloid leukemia, M6a. Because of the findings in the earlier marrow biopsy, I had to change my diagnosis from RAEB-2 to persistent acute erythroid leukemia (AEL), and communicated to the clinician that these two entities had overlapping features. The patient was treated with 7 days of Azacitadine for every 28 days and was followed up at home.

This unusual case has illustrated an example that erythroid hyperplasia alone could dictate the diagnosis and classification of myeloid leukemias, indicating that arbitrary diagnostic criteria (such as 50% nucleated RBCs) can create problems. To understand the cause of this problem, we need to revisit the history of leukemia classification.

In 1976, a group of hematopathologists from Britain, France, and the United States met in Washington, DC, and based on morphology and cytochemical studies classified acute leukemias into acute myeloid leukemia (AML) (M1-M6) and acute lymphoblastic leukemia (L1-L3), later known as the French-America-British (FAB) Classification [3]. AML-M6, also known as AEL, was classified based on the criteria of $\geq$30% myeloid precursors (including blasts and promyelocytes) and $\geq$50% erythroid cells of all the nucleated cells in the bone marrow. The blast requirement for the diagnosis of AML was changed to >30% of the marrow cells in a later FAB Classification on MDS [4]. Having realized that AML-M6 was quite rare, the authors of FAB Clas-

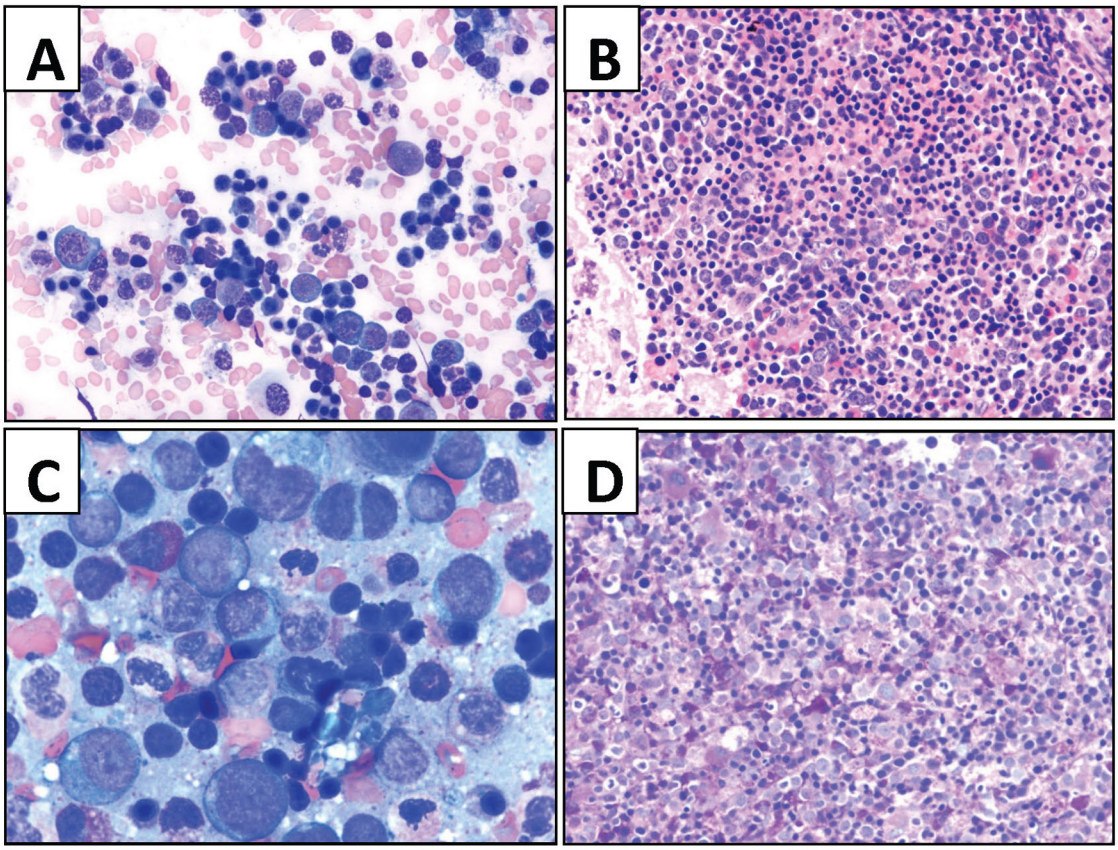

Figure 1: Early myeloid leukemia with erythroid hyperplasia.
First marrow aspirate (A, Wright-Giemsa, original magnification x400) and biopsy (B, H&E, original magnification x200) showed 5% myeloblasts and >50% erythroid precursors; Second marrow aspirate (C, Wright-Giemsa, original magnification x1000) and biopsy (D, Periodic acid-Schiff, original magnification x400) revealed increased myeloblasts (15%) and decreased erythroid precursors (<50%).

sification further modified the diagnostic criteria with ≥30% blasts of the non-erythroid cells when the erythroid precursors were ≥50% of the marrow cells [5]. When 2001 WHO Classification dropped the blast requirement from ≥30% to ≥20% of the marrow cells for the diagnosis of AML [6], the blast requirement of AML-M6 also dropped to ≥20% of the non-erythroid cells. While the previous RAEB in transformation (RAEB-T) became frank AML, some of the previous RAEB also became AML-M6 when there was erythroid hyperplasia (≥50% of the marrow cells). The 2008 revised WHO Classification summarized the criteria to differentiate AML with dysplasia-related changes (AML-MRC), RAEB and AEL [2], but diagnostic dilemma remains.

Hasserjian *et al*. compared the median overall survival (OS) of AEL patients with that of the patients with MDS or AML-MRC with erythroid hyperplasia and they found a similar OS [7]. Kasyan et al. retrospectively reviewed AEL, AML-MRC, therapy-related AML, and RAEB and they drew a similar conclusion [8]. Both groups found that there was little difference in OS between AEL and RAEB; complex cytogenetic abnormalities (>3) was the only statistically significant independent variable that adversely affected survival in the AEL. Having realized the problem with the diagnostic criteria for AEL, the newly revised WHO Classification (in 2016) has re-

defined AML-M6 by ≥20% myeloblasts and ≥50% erythroids of the marrow cells [9], whereas erythroid hyperplasia will create less ambiguity than before for the classification of myeloid leukemias. Forty years later, the saga of AEL and MDS classification comes to a temporary end.

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References

1. Zhao XF. MDS or M6: FAB Classification revisited. Presented at the Atlantic Regional Hematopathology Meeting. May 30, 2009. Philadelphia, PA.
2. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman J. (Eds.) WHO classification of tumours of haematopoietic and lymphoid tissues (4th ed.). IARC Press: Lyon 2008.
3. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. Br J Haematol. 1976; 33:451-458.
4. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982; 51:189-199.
5. Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia. Ann Intern Med. 1985; 103:620-625.
6. Jaffe ES, Harris NL, Stein H, Vardiman JW. (Eds.) World Health Organization classification of tumors. Pathology and genetics of tumors of haematopoietic and lymphoid tissues. IARC Press: Lyon 2001.
7. Hasserjian RP, Zuo Z, Garcia C, et al. Acute erythroid leukemia: a reassessment using criteria refined in the 2008 WHO classification. Blood. 2010; 115:1985-92.
8. Kasyan A, Medeiros LJ, Zuo Z, et al. Acute erythroid leukemia as defined in the World Health Organization classification is a rare and pathogenetically heterogeneous disease. Mod Pathol. 2010; 23:1113-26.
9. Arber DA. Proposed changes to the WHO Classification of acute leukemias and myeloid disorders. Presented at the Annual Symposium and CME Activity of San Diego Society of Hematopathology. November 14, 2015. San Diego, CA.