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Short Communication

The World Health Organization revisits the classification of the myelodysplastic syndromes: Improvement and insufficiencies

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The World Health Organization monograph "Classification of Tumours of Haematopoietic and Lymphoid Tissues" published in 2008 [1] has been modified to introduce changes in the classification of the myelodysplastic syndromes and the acute leukemias; these modifications were published in the journal *Blood* in May 2016 [2]. This Commentary describes the principal changes in the classification of the myelodysplastic syndromes with comments on their merits.

1. The Committee wisely eliminated the term "refractory" in describing clonal cytopenias, as in "refractory anemia" or in describing oligoblastic myelogenous leukemia, as in "refractory anemia with excess blasts". The term "refractory anemia" had been used for over 80 years to describe anemias that did not respond to iron or liver therapy and, later, vitamin B_{12} or folic acid treatment. The term was misapplied to describe overt neoplasms (leukemias) for nearly 50 years [3,4]. In addition, some patients with "refractory" anemia respond to drug therapy (e.g. azacytidine or lenalidomide). This correction in terminology as applied to neoplasms of the hematopoietic stem cell is overdue [5,6] and is applauded.

2. The new classification uses the term myelodysplasia, abbreviated as "MDS", to initiate the designation of each subtype, thereby choosing to retain a misapplied term, "dysplasia" to describe neoplasia [5,7]. Hypoplasia (aplasia), hyperplasia, metaplasia, dysplasia, and neoplasia are distinct pathological entities. Neoplasia is distinguished from dysplasia and the aforementioned other pathological tissue abnormalities by being the only tissue abnormality that is monoclonal, that is results from the expansion of a single mutated (stem) cell. Today, this feature, monoclonality, can be uncovered with greater facility since the marrow and blood cell findings may include a clonal cytogenetic pattern or a relevant somatically mutated gene (oncogene) or genes, identified now by standard molecular analysis [8]. When the designation "myelodysplasia" was embraced in September 1975 at a meeting at the Institut de Pathologie Cellulaire in Kremlin-Bicêtre, France entitled "Hematopoietic Dysplasias (Preleukemic States)", the understanding of these neoplasms and the ability to determine clonality was limited [7]. This misapplication of pathological terminology could have been corrected in the updated WHO guidelines by using the designation "clonal cytopenia(s)" for the neoplasms in which an increase in leukemic blast cells (>2% blasts) is not evident in marrow by microscopy or by a qualitative abnormality detected by flow cytometric characterization [9].

3. MDS is now followed by modifiers including: (a) single lineage dysplasia; (b) multilineage dysplasia; (c) ring sideroblasts; (d) isolated del(5q); (e) excess blasts.
3(a & b). The terms single lineage or multilineage could be replaced by designating the specific clonal lineage abnormalities (e.g. clonal anemia or clonal anemia, neutropenia and thrombocytopenia or clonal anemia, neutropenia, and thrombocytosis) thereby providing more specificity.
3(c). In the recent modification of the classification of myelodysplastic syndromes, it has been recognized that the percentage of ring sideroblasts in the marrow is of no prognostic significance [10]. The boundary of 15% or more ring sideroblasts used to diagnose refractory anemia with ring sideroblasts never had a sound pathobiological basis that I could uncover [5,7]. If the marrow contains ≥5% ring sideroblasts and the *SF3B1* mutation is present, the diagnosis of MDS-RS (ring sideroblasts) is proposed. In the absence of the *SF3B1* mutation, the diagnosis of MDS-RS (ring sideroblasts) is retained and requires ≥15% ring sideroblasts in the marrow. This decision seems contradictory. If the percentage of ring sideroblasts has no prognostic significance, in the absence of the *SF3B1* mutation, it is unclear why one would designate this morphological feature as distinguished from any other (e.g. acquired Pelger-Huët nuclear anomaly). Is there a justifiable reason to draw a distinction between

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Table 1
Blood cell findings in a patient who developed myelodysplastic syndrome: evolution over eight years of observation.

Date	Hemoglobin ($N \geq 13.5$)	Mean cell volume ($N \leq 95$)	RDW ($N \leq 14$)	WBC count ($N \geq 4.5$)	Neut/mono ($N \geq 2.0/\geq 0.20$)	Platelets ($N \geq 150$)	Comments
Nov. 2001	14.2	94	14	6.2		168	
Oct. 2002	14.0	94	14	6.6	4.6/0.46	130[a]	
Jan. 2003	13.7	97[b]	14	5.7		156	
Dec. 2003	15.7	98	15[a]	5.3		163	
Dec. 2004	15.1	100	14	4.9		141[a]	
Dec. 2004	14.7	99	15[a]	4.8		126[a]	
Jan. 2005	14.3	98	14	5.5	4.2/0.4	153	Serum folate, Vitamin B12, and iron normal
Nov. 2005	13.9	102	14	4.5		137[b]	
Jan. 2006	13.6	103	15[b]	4.2[b]		120	
Nov. 2006	12.8[b]	107	16	3.1		95	
Nov. 2006	12.6	107	16	3.7	2.7/0.37		CT abdomen mild splenomegaly but not palpable.
Mar. 2007	12.6	109	16	4.0	2.9/0.52	138	
Mar. 2007	11.7	107	15	4.2	3.2/0.55	150	
Jan. 2008	13.2	105	16	5.6		126	
Jul. 2008	11.7	107	17	6.2	5.0/0.62	116	FISH July 2008: chromosome 20q deletion among four chromosomes examined, [5q31, 7q31, 8, & 20].
Jul. 2008	Marrow: hypercellular (90%); normal maturation of erythroid and granulocytic cells but marked erythroid dysplasia; 3% blasts; normal number megakaryocytes with atypia; no reticulin fibrosis; no ring sideroblasts; marrow iron present						Dx: myelodysplastic syndrome. Refractory anemia.
Feb. 2009	11.8	105	16	3.4	2.4/0.48	92	
Oct. 2009	10.1	115	18	3.9		88	
Oct. 2009	8.9	116	18	2.9		67	
Dec.2009	10.8	112	22	5.0	3.8/0.50	115	
Dec.2009	Marrow: hypercellular (70%); trilineage dysplasia; erythropoiesis increased with megaloblastic and dysplastic changes; myeloid cells decreased; myeloblasts 5%; megakaryocytes increased with atypia; no ringed sideroblasts; no reticulin fibrosis						G-banding: 46XY, idic(20) (p11.1) del(20) (q11.2, q13.3) [20] myelodysplasia (RAEB-1)

Normal (N) values indicate relevant normal limit (upper or lower) only. [a]Indicates abnormal value. [b]Indicates more consistent abnormality, thereafter. Hemoglobin expressed as g/dL; cell counts expressed as 10^9/L; mean cell volume expressed as fL/cell. CT, computerized tomography; idic, isodicentric; Neut, neutrophils; Mono, monocytes; RAEB, refractory anemia with excess blasts; RDW, red cell distribution width; WBC, white blood cell. Note that on July 2008 when a clonal cytogenetic abnormality and a marrow consistent with findings compatible with a clonal myeloid neoplasm were present, the blood counts are above the values proposed by the WHO in order to make a diagnosis of MDS. (Reference [2], page 2396, first column, second paragraph.)

14% ring sideroblasts and 15% ring sideroblasts? Why complicate the disease designations with epiphenomena? One could (and should) identify a category as MDS with *SF3B1* mutation, if the latter is present, since it is a mutation with prognostic import. There is some ambiguity about its prognostic significance in cases with multilineage dysplasia, but if the lineages were delineated as suggested in paragraph 3(a & b) above, the physician can make a judgement about its utility or it could, for the time being, be shown with "clonal cytopenia-anemia- *SF3B1* mutation" until clarified. There is no apparent need for the category MDS with ring sideroblasts (MDS-RS). The findings of ring sideroblasts in the absence of the *SF3B1* mutation would fall under MDS with single or multilineage dysplasia, simplifying the classification without any loss of information useful to the physician. This suggestion does not minimize the importance of recognizing ring sideroblasts as concrete evidence of erythropoietic dysmorphia in the marrow; but, this feature is no different from megakaryocyte dysmorphia, as in micromegakaryocytes, megakaryocytes with odd numbers of nuclear lobes, and other overt abnormalities of that lineage, or of agranular neutrophils or bilobed (pince nez-shaped) neutrophil nuclear anomaly and other changes used to identify dysmorphia in neutrophilopoiesis.

3(e). The term "excess blasts" has a misleading connotation. Neoplastic (leukemic) blast cells are qualitatively different from normal myeloblasts and indicate overt leukemic hematopoiesis. They carry oncogenic mutations. The term "excess" is a quantitative distinction, implying hyperplasia, not neoplasia, and, thus, is pathobiologically erroneous [5,7]. The use of the designation "oligoblastic myelogenous leukemia" instead of "MDS with excess blasts" would correct this anomaly and speak more specifically to the neoplasm represented by those findings. Moreover, why divide this category into type 1, 5–9% blasts, and type 2, 10–19% blasts in marrow? What is the distinction between 9% and 10% blast cells in marrow, for example, especially given the variability of the blast count in marrow samples? Why not, if one decides that a blast count between 5 and 19% is important or useful to designate, provide the actual count after the diagnosis, as in "oligoblastic myelogenous leukemia-6% blasts" or "oligoblastic myelogenous leukemia-15% blasts". Thus, no arbitrary boundary is invoked and the physician can integrate that finding into the cytogenetics, patient age, and other relevant variables. Of course, >2% blasts in the marrow, especially if associated with concurrent cytopenias and dysmorphia, indicates a quantitatively abnormal marrow blast population [7]. Even if blasts in a case of MDS are 0.1 to 2.0%, they are neoplastic, since in virtually all cases of a hematopoietic neoplasm all marrow cells evident microscopically are part of the neoplastic clone. It would seem more informative and less arbitrary to provide the blast count as part of the designation "oligoblastic myelogenous leukemia" beginning with 3% blasts, if such an appendage is useful in a classification.

4. The use of at least 10% dysplastic cells in a lineage to assign it as dysplastic is reaffirmed with important caveats. The abnormality in morphology of neoplastic cells is dysmorphia, not dysplasia, as the latter changes are polyclonal, by definition. Thus, the term "dysmorphia" should be used to describe these morphological epiphenomena, which are critical in arriving at a diagnosis, when a quantitative increase in leukemic blast cells is not evident.

5. Thresholds are given to define (significant) cytopenias: hemoglobin <10 g/dL, neutropenia $<1.0 \times 10^9$/L, thrombocytopenia $<100 \times 10^9$/L. The physician should recognize that these thresholds are arbitrary