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CORRESPONDENCE

ICC-2022 versus WHO-2022 classification systems for acute leukemias and myeloid neoplasms: The perspective from two classical morphologists

To the Editor:

The recent evolutions of classification approaches in the critical field of the classification of neoplasms of the hematopoietic system[1–4] lead us to bring to your attention some considerations, in the hope that they may be helpful to the scientific community that refers to them.

What we learned from the past: The microscope's development and blood cell staining methods have been powerful instruments in understanding acute and chronic leukemias, a story that took up the whole of the 19th century. The first modern classification which recognized a common hematopoietic progenitor and defined acute leukemias as "diseases of the hematopoietic tissues due to tumor proliferation … characterized by the constant infiltration of immature and atypical cells in the various organs and tissues and by habitual but the not obligatory presence of said cells in the circulating blood" appears in the middle of 20th century.[5,6] Based on a panoptic stain and two cytochemical stains, Sudan Black B and Periodic Acid Schiff of peripheral blood cells observed under the microscope, acute leukemias were differentiated into hemocytoblastic, myeloid, lymphoid, and monocytic.

We had to wait until 1976 when the first French, American, and British(FAB) classification of acute leukemias was published,[7] based on morphology, cytochemistry, and the "newly developed cell-surface markers." It was the first worldwide adopted classification that taught us not only to identify blasts with qualitative criteria but also to count them, having introduced the threshold of ≥30% to diagnose acute leukemia.

Since then, this painstaking and tiring work of identifying, classifying, and counting cells from the microscope has accompanied us in the diagnostic journey of our patients. The subsequent FAB classifications on myelodysplastic syndromes (MDS) with four subtypes and as a revision of the classification of acute leukemias, introduced new quantitative criteria, including the concept of calculating blasts out of the nonerythroid cell (NEC) quote in the presence of a myeloid/erythroid (M/E) ratio <1. The FAB group proposed quantitative criteria in the differential diagnosis of chronic myeloid leukemia (CML), atypical CML, and chronic myelomonocytic leukemia (CMML): in addition to counting the percentage of blasts, immature granulocytes, and monocytes, the concept of quantification of dysplastic cells was introduced.

The continuing development of multicolor flow cytometry has enhanced our ability and skills as morphologists to fine tune our diagnoses. In 1999 the first World Health Organization (WHO) classification stated its goals: "Guidelines for an integrated diagnosis based on morphology, cytochemistry, immunophenotype, genetics, and clinical features to define clinically significant disease entities, for a classification that can be used in daily clinical practice and that can serve as a common language for clinical trials and laboratory investigation."[8] Surely the emphasis on flow and immunophenotyping of histologic paraffin-embedded material has been critical in the diagnoses of lymphoid neoplasms. We continue to utilize flow cytometry as complementary to morphology in MDS and AML, particularly in quantifying the blast profile, and aberrations in monocyte and granulocyte CD antigens. It is of less relevance in myeloproliferative neoplasms.

New morphologic rules were introduced: the blast threshold for acute leukemias was lowered ≥20% of absolute nucleated cell count (ANC), and/or NEC, except for a few entities of acute myeloid leukemia (AML) with recurrent cytogenetic abnormalities.

Eight subtypes of MDS were defined with rules for dysplasia identification at different cutoffs in the context of MDS and AML, and new primary hemato-oncologic group disease, the myelodysplastic/myeloproliferative syndromes (MDS/MPS) with its morphologic rules, was introduced. The 2008 WHO classification increased the list of specific genetic abnormalities and introduced the new main category of myeloid/lymphoid neoplasms with eosinophilia and *PDGFRA*, *PDGFRB*, or *FGFR1* abnormalities.[9] It was a revolution for morphologists. Introducing the blast-equivalent category was a real challenge, mainly in monocytic lineage, providing a clear definition of monoblasts and promonocytes, both considered as blasts. For the first time, the basic rules of the international committees for the standardization of hematology diagnostics, such as the International Council for Standardization in Hematology (ICSH),[10] the Clinical and Laboratory Standard Institute (CLSI),[11] the College of American Pathologists (CAP)[12] reached all the involved operators on very detailed rules: among these, the evaluation of suitability of the films, which and how many and which cells to count, and include in the myelogram, which cells with dysplasia to count on how many cells evaluated, and when different cells should be included into the blast percentage. Methodological aspects considered only in the contexts of standardization and quality committees were provided to a global clinical context as diagnostic prerequisites for classifying myeloid tumors. The 2016 WHO revised classification is the last unanimously recognized document adopted worldwide in all hematological scientific fields.[13] Changes were introduced in nomenclature (as in MDS, *BCL::ABL1* positive CML, and

AML), in disease subgroups (such as for mastocytosis, now reported as a separate category), in immunophenotyping's role in the diagnosis and follow up in the appropriate context, in the increased value of genetics and molecular genetics not only for prognostication but also for diagnosis in the proper contexts, and morphology, as for the ring sideroblast count related to the presence/absence of the molecular abnormality (*SF3B1* mutation) and the abolition of the NEC count diagnostic value.

These 65 years, summed up so briefly, were also a time of real revolutions mainly linked to the introduction of molecular and genomic techniques, new drugs, the direct identification of prognostic factors, and the progress in marrow/stem cell transplantation.

The "war on cancer" in the field of onco-hematology has achieved impossible goals relatively quickly, and this war is certainly not over. In these years, worldwide groups of morphologists, aware of the limits of diagnostics under the microscope concerning the request for accuracy of quantitative and qualitative counts, have worked on harmonization, standardization, verification, and comparison criteria to provide the most accurate report possible. They would allow patients' diagnosis and harmonic stratification within studies and clinical trials. In a collective effort, we have learned to take observation under the microscope, from a subjective observation to a report generated based on current rules for a harmonized diagnostic tool for our patients worldwide.

What do we continue to do today: In July 2022, the proposed 5th Edition of the WHO Classification was published as beta version online[1] as a review article,[2] in combination with an internet preview of the 5th WHO edition Blue BOOK. It was followed by comments in which the WHO classification approach for hematolymphoid tumors was defended[14] and criticized.[15] In September 2022, the International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemia also appeared in Blood.[3] In a recent December issue of Virchow Archives, several articles expand on the initial ICC publication with extensive comments by authors from their committee.[6–19] Many authors were present in the clinical advisory committee (CAC), contributing to the 2016 revision of the 4th WHO classification. In both the new papers, the introduction declared that they aimed to propose a revision of the 2016 WHO classification based on scientific evidence. By comparing the two works, we understand and appreciate the importance of molecular diagnostics and the scientific motivations assumed by the two groups in proposing their own rules and nomenclature.[20,21] This objective, however, is far from being achieved. Morphologists who operate in hematology laboratories were reassured by the agreement of both publications in much of the definition of myeloid and lymphoid subtypes. However, substantial differences in several areas need to be addressed. Some have recommended that formal pathology reports mention both articles where this is apparent. To date, this has not occurred.

As far as only myeloproliferative syndromes are concerned, just as examples, diagnostic criteria for the accelerated phase (AP) in CML are still highlighted in the ICC classification (blasts 10%–19%), presence of additional clonal cytogenetic abnormalities and even peripheral blood basophilia >20% (only mentioned in a table, but not in the explanatory text). On the other hand, the 5th WHO paper considers the designation of AP "less relevant" and only provides criteria for progression to the blastic phase (BP). Moreover, different WBC levels are specified for diagnosing chronic neutrophilic leukemia in the presence of *CSF3R* mutations (in the ICC paper from =/> 25 000 to =/- > 13 000 $\times$ 10^9). The WHO-22 has not changed to that lower level. Time will determine whether this is appropriate.

The concept of "clonal monocytosis of undetermined significance" is specified only in the ICC paper, while the 5th WHO insists on the formal definition of "clonal hematopoiesis of indeterminate potential" (CHIP).

On the other hand, many, if not the majority, of other innovative criteria appear to overlap in the two documents, being rightly based on new diagnostic, clinical and molecular knowledge. This is the case of the presence of an increased proportion of lymphoblasts (>5%) as a criterium for the BP of CML.

A recent editorial by Niemeyer et al.[22] has challenged the elimination of Refractory Cytopenia of Childhood and introduced Childhood MDS with low blasts. This would ignore cases that could evolve into MDS subsequently. With the increasing use of molecular markers, these cases may resemble CCUS in adults where progression to overt MDS is very likely. Careful application of seeking out morphologic dysplasia and blast% is encouraged. The authors also challenge the statement in the WHO-22 that JMML lacks "bona fide stigmata of myelodysplastic neoplasia." This has certainly not been our experience, where morphology often demonstrates the same features seen in adults with CMML.

Moreover, there continues to be a debate between both groups of the ICC and WHO-22 as to the minimal percentage of blasts that define AML with defining genetic abnormalities (a minimum of 10% for ICC and no specific % for the WHO). This emphasizes the importance of performing a 500-cell bone marrow count to reduce the error rate and to use caution when labeling cases with <20% blasts as AML, particularly in older patients with co-morbidities. This is particularly relevant since the ICC has created a new category of MDS/AML with 10%–19% blasts and eliminated MDS with excess blasts −2.

The diagnostic criteria for the diagnosis of chronic eosinophilic leukemia, such as the presence of clonality and morphological dysplasia in other cell lineages, have been updated. However, the ICC only continues to adopt the qualifier "not otherwise specified" (NOS), and the 5th WHO shortens the required time interval for "sustained hypereosinophilia" from 6 months to 4 weeks. Similar inconsistencies and overlaps between the two approaches have been highlighted for MDS and AML,[23] and B-cell lymphomas.[24]

After almost two decades, the presence of two separate classifications goes against the need for a common shared language in the interest of patients, clinicians, morphologists, experimental trials, and novel pharmacological interventions. In the absence of a harmonized recomposition of the diagnostic criteria of myeloid neoplasms, our patients' peripheral blood and bone marrow aspiration tests must, in any case, be harmoniously reported. By applying the rules required by the international guidelines,[25–28] morphology remains solidly placed as an initial diagnostic screening and follow-up tool, therefore capable of quickly intercepting patients with peripheral blood and/or

bone marrow alterations. We strongly suggest that fellow morphologists remaining anchored to the 2016 4th WHO revised guidelines,[13] which were the starting point of both the new approaches and to implement the report following the new proposals, clearly specifying the chosen reference classification or the final diagnostic category for both of them, according to each one's affinities and preferences.

The advice is to maintain and share morphological competence, always to study and compare continuously, to apply the classification rules under the microscope: creativity requires confirmation by experts[25–28] to put the patient as a person at the center of the pathway and to manage and treat the patient even when experts disagree.

DATA AVAILABILITY STATEMENT

All data (references) available at request.

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