

## Editorial

# Controversies in the Current Hematopathology Practice and Classification of Hematopoietic and Lymphoid Neoplasms

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## EDITORIAL

Historically, classification of lymphoid neoplasms has been a controversial topic from the very beginning. The early classification schemes suffered from poor insights into the nature and lineage of neoplastic cells and were based on subjective assumptions by the classification authors. Unsurprisingly, numerous competing classification systems were proposed over the years prior to the modern immunophenotyping, cytogenetics, and molecular genetics era and those were reviewed elsewhere [1]. On the other hand, some of the hematology terminology were coined early on in the discovery process, and despite their limitations and legacy problems, they persist in use to this day, making hematopathology a very confusing subject to teach. Fortunately, the modern approach to classifying lymphoid neoplasms based on immunophenotyping, cytogenetics, molecular genetics, and evidence-based medicine was very successful and culminated in the popular Revised European-American Lymphoma (REAL) classification and later World Health Organization (WHO) classifications, most recently published in 2008 [2-4].

Similarly, classification of hematopoietic neoplasms has been problematic as well and necessitated international standardization, designated French-American-British (FAB) classification, first published in 1976 [5]. FAB classification, while updated, long outlived its purpose and was in widespread use up to 2001 when it was replaced by the WHO classification. Ironically, while long obsolete, the FAB classification is still in use by some of our clinical colleagues, requiring teaching of both FAB and WHO classifications.

In view of the above historical notes, we are now very fortunate to practice hematopathology using the standardized and international WHO scheme. This is not to say that the current version cannot be improved, especially as it is due for a revision soon. Even the current WHO text contains provisional entities that are considered work in progress and are subject to future revisions. They are all too numerous to list, but include: refractory anemia (RA) with ringed sideroblasts associated with marked thrombocytosis, RA with excess blasts with fibrosis, acute myeloid leukemia (AML) with mutated NPM1,

chronic lymphoproliferative disorders of NK cells, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (TCL), primary cutaneous CD4-positive small/medium TCL, and anaplastic large cell lymphoma (ALCL), ALK-negative. The very wordy and descriptive designations reflect the uncertain and provisional nature of those mostly rare diseases. We are awaiting more studies on those entities, but at least we have a well-defined holding place. Of the above provisional entities, only one generated a considerable controversy, with some arguing that ALK-negative ALCL is not a distinct entity and it should be merged with peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS) [6]. On the other hand, recent molecular evidence shows that ALK-negative ALCL is distinct from PTCL, NOS [7].

An additional challenging aspect of hematopathology practice is that some cases do not neatly fit the defined disease entities. The 2008 edition of WHO classification made improvements in some areas by acknowledging the presence of "grayzone lymphomas." They include B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (HL). While these entities are very confusing to our clinical colleagues, they serve important roles for those cases with ambiguous features. Unfortunately, the definitions of the above "grayzone lymphomas" are not precise enough and allow for a variety of cases to meet the diagnostic criteria. For example, DLBCL/BL "grayzone lymphoma" can be diagnosed by having typical BL morphology and atypical immunophenotype/genotype or conversely, typical BL immunophenotype/genotype and atypical morphology. This allows for heterogeneity of cases diagnosed in this type of "grayzone lymphoma." This will probably be resolved in the future by higher utilization of cytogenetics and molecular genetics in DLBCL and better recognition of molecular subtypes of DLBCL, such as the so-called "double hit lymphoma" featuring c-myc and Bcl-2 rearrangements and associated with very poor prognosis [8]. I am looking forward to future WHO classification revisions that improve our ability to subdivide DLBCL in ways more beneficial to the patients.

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While many different subtypes of DLBCL currently recognized by WHO are clinically meaningful, a lion's share of DLBCL cases fall in the category of DLBCL, NOS, and the current molecular/immunohistochemical subgroups such as germinal centre B-cell-like and activated B-cell-like (non-germinal centre B-cell-like) mostly lost their prognostic significance in the current era of rituximab treatment [9].

There are rare and difficult cases that do not fit the WHO classification based on the fact that WHO is a lineage based classification and allows no lineage exceptions. For example, while HL is defined in the WHO as a B-cell neoplasm, sometimes with aberrant T-cell markers expression, rare lymphomas exist with typical HL morphology, and true T-cell lineage rather than aberrant T-cell marker expression [10]. When I encountered such a case recently and extensively documented T-cell rather than B-cell lineage, I decided to stay with the spirit of WHO classification and I chose not to classify it as HL, but rather a type of PTCL. When a second opinion was sought, another hematopathologist from a well-known cancer center decided to venture outside WHO classification and rendered the diagnosis of T-cell HL. Suffice to say the patient and oncologists were very confused and scrambled to find a suitable treatment. I hope the future revisions will provide better ways to deal with those rare lineage exceptions.

Regarding lineage, WHO is not fully consistent with the use of lineage and cell maturity to classify lymphoid neoplasms. One glaring exception is HL, historically separated from non-Hodgkin lymphomas (NHL), while being a type of peripheral B-cell lymphoma. While there is no doubt that classical HL deserves the separation from NHL, I have some doubts if that should apply to nodular lymphocyte predominant HL (NLPHL) as well. NLPHL immunophenotype and molecular genetics closely mimic that of DLBCL and occasional transformation of NLPHL to DLBCL suggest that NLPHL can be a DLBCL precursor lesion [11]. Furthermore, gene expression profiling showed that NLPHL was very closely related to T cell-rich B-cell lymphoma variant of DLBCL, while retaining some gene expression signature of HL [12]. Clearly, NLPHL spans the spectrum between HL and NHL.

The most recent edition of WHO classification recognized that some indolent B-cell neoplasms can be preceded by a precursor lesion of uncertain significance and those do not warrant a diagnosis of malignancy. The examples are monoclonal B-cell lymphocytosis versus chronic lymphocytic leukemia and intrafollicular neoplasia/"in situ" follicular lymphoma versus follicular lymphoma. This recognition is important and it emulates a better-defined relationship between monoclonal gammopathy of uncertain significance and plasma cell myeloma. But this also opens the door to precursors of other types of lymphoid neoplasia, as "in situ" marginal cell lymphoma has also been reported [13]. This illustrates a concept, well known from solid malignancies, where multistep tumorigenesis exists and one can encounter a spectrum of lesions before a fully malignant disease ensues. I count on future revisions of WHO classification to shine light on those transitional steps in a variety of B, T, and NK neoplasms. One should recognize that some indolent lymphoid neoplasms, conventionally designated "lymphoma" or "leukemia," behave in a benign fashion. A common example is

low stage, *Helicobacter pylori*-positive, MALT1 rearrangement-negative gastric extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALToma). Such cases are not malignant, respond to antibiotic therapy alone, and are perhaps merely precursors of less indolent types of MALToma associated with additional clonal cytogenetic or molecular abnormalities such as MALT1 gene rearrangements [14]. Similarly, evidence exists that cytopenias, autoimmune diseases, and neurologic conditions can be associated with clonal cytotoxic T-cell proliferations and not all of those need to be designated as T-cell neoplasms, even though some may satisfy the current diagnostic criteria for T-cell large granular lymphocytic leukemia [15]. In my opinion, many patients would greatly benefit if such very indolent lymphoproliferations were not designated as "lymphoma" or "leukemia," that are commonly referred to as "cancers" in the lay terminology, causing a considerable distress to the patients and their families.

The hematopoietic/myeloid neoplasia part of the WHO classification is not entirely without problems, as additional work is required to integrate the ever-increasing list of mutations into the classification of myeloid neoplasms, and especially AML. Ideally, the hematopathology practitioners should be also advised on rational ways of molecular testing, as I am not convinced more is better, at least in the current era of increased awareness of fiscal responsibility in the health care delivery.

One area that remains somewhat arbitrary is the blast count required for a diagnosis of AML. That count cutoff decreased from 50% in the early FAB classification to 30% in the updated FAB classification and 20% in the WHO classification. This arbitrary cutoff was validated in the diagnosis of a *de novo* AML, and it only rarely creates a diagnostic dilemma, especially if one detects translocations that are diagnostic of AML regardless of blast count. The 20% blast cutoff remains controversial in cases of transformation from myelodysplastic syndrome (MDS) to AML, currently designated AML with myelodysplasia-related changes (AML-MRC). Some of those cases with 20-30% blasts were previously designated as refractory anemia with excess blasts in transformation (RAEB-t) in the FAB classification. Evidence exists that some patients with AML-MRC, especially with 20-30% blasts, may benefit more from hypomethylating agents rather than AML induction chemotherapy and thus, behave more like MDS rather than AML [16]. That seems to validate the older concept of RAEB-t, but it is mostly a semantic issue. Another example of arbitrary blast count cutoff is the legacy concept of acute erythroid leukemia, erythroleukemia type. This is inherited from FAB AML: M6a mostly unchanged, except for decreased blast count from 30% to 20% of non-erythroid nucleated cells, combined with predominance of erythroid precursors in bone marrow. Many hematopathologists doubt if some of those cases should be really designated as a type of AML if they otherwise lack diagnostic criteria for AML-MRC [17].

In summary, the popularity and widespread use of WHO classification of hematopoietic and lymphoid neoplasms is well deserved. However, more work is needed to keep WHO classification current with the evolving concepts in hematopoietic and lymphoid neoplasia.

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