

Laboratory Medicine in the Era of Disruptive Technology

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### Diagnosis of lymphoid neoplasms: A multimodality approach

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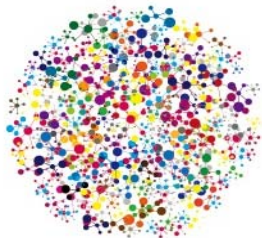
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The WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues embraces the principles of the REAL and WHO classifications of lymphoma, recognizing that accurate diagnosis requires an integrated approach, utilizing clinical data, morphological features, immunophenotypic features, and genetic profile.(1-3) A revision of the 2008 4<sup>th</sup> Edition classification has been accomplished through the efforts of pathologists and clinicians, recognizing significant changes that have occurred in the field since 2008.(4) Disease definitions are not static, and new data have helped to clarify areas of uncertainty. A clinical advisory committee meeting, held in 2014, discussed potential changes in the classification and impact on clinical practice.

Advances have occurred in our understanding of the earliest events in lymphoid neoplasia, leading to refinements in the definition of monoclonal B-lymphocytosis, in situ follicular neoplasia (formerly follicular lymphoma in situ) and in situ mantle cell neoplasia (formerly mantle cell lymphoma in situ).(5) Duodenal-type follicular lymphoma is another condition with limited potential for progression.(6, 7) All of the above entities show a low level of genetic aberrations, aside from the BCL2 and CCND1 translocations, characteristic of the category.(8) A second group of “indolent” and indeterminate clonal lymphoid proliferations do not have a counterpart among the currently recognized subtypes of lymphoma, but appear to have a limited potential for progression. These include pediatric-type follicular lymphoma and indolent T-cell proliferations involving the skin and GI tract.(9-15)

The 2008 WHO classification had introduced the category of “B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL” (BCLU) to recognize a subset of aggressive lymphomas that were difficult to categorize as DLBCL or BL. Further data have shown that many tumors in the BCLU group were “double-hit” or “triple-hit” lymphomas with MYC and BCL2 or BCL6 translocations. A consensus emerged that it was useful to segregate these tumors in a single category, rather than classifying them primarily based on cytological features.(4) However, a category of High Grade B-cell lymphoma, unclassified, was retained for cases lacking double hit/triple hit, and displaying high grade cytological, including blastoid features.

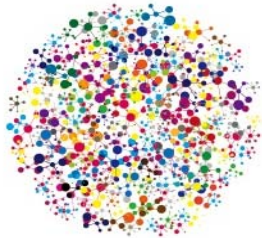
There also have been significant advances in the understanding of T-cell lymphomas, in part brought about by advances in the genomic analysis of these tumors. Genetic studies have shown recurrent mutations that affect a significant proportion of cases of angioimmunoblastic T-cell lymphoma (AITL).(16-19) Importantly, many of same genetic changes (mutations in TET2, RHOA, DNMT3A, ITK-SYK) are found in cases of PTCL, NOS that manifest a T follicular helper (TFH) phenotype. Additionally, recent data also have identified recurrent genomic aberrations in



intestinal T-cell lymphomas and other cytotoxic T-cell malignancies.(20-23) Genomic approaches also have provided insights into the spectrum of CD30-expressing T-cell lymphomas, and have facilitated the distinction of ALK-negative anaplastic large cell lymphoma (ALCL) from PTCL with evident CD30 expression.(24, 25)The revisions to the WHO classification show how a multimodality approach leads to the improved definition of disease entities, and improved management of patients with lymphoma.

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