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Diagnosis of lymphoid neoplasms: A multimodality approach

Elaine S. Jaffe

Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

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 4th 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, characterisitic 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.

References

1. Jaffe ES, Harris NL, Stein H, Vardiman J. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001.
2. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Bosman FT, Jaffe ES, Lakhani SR, Ohgaki H, editors. Lyon, France: International Agency for Research on Cancer; 2008.
3. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. 1994;84(5):1361-92.
4. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.
5. Ganapathi KA, Pittaluga S, Odejide OO, Freedman AS, Jaffe ES. Early lymphoid lesions: conceptual, diagnostic and clinical challenges. Haematologica. 2014;99(9):1421-32.
6. Schmatz AI, Streubel B, Kretschmer-Chott E, Puspok A, Jager U, Mannhalter C, et al. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. J Clin Oncol. 2011;29(11):1445-51.
7. Takata K, Sato Y, Nakamura N, Tokunaka M, Miki Y, Yukie Kikuti Y, et al. Duodenal follicular lymphoma lacks AID but expresses BACH2 and has memory B-cell characteristics. Mod Pathol. 2013;26(1):22-31.
8. Mamessier E, Song JY, Eberle FC, Pack S, Drevet C, Chetaille B, et al. Early lesions of follicular lymphoma: a genetic perspective. Haematologica. 2014;99(3):481-8.
9. Liu Q, Salaverria I, Pittaluga S, Jegalian AG, Xi L, Siebert R, et al. Follicular lymphomas in children and young adults: a comparison of the pediatric variant with usual follicular lymphoma. The American journal of surgical pathology. 2013;37(3):333-43.
10. Louissaint A, Jr., Ackerman AM, Dias-Santagata D, Ferry JA, Hochberg EP, Huang MS, et al. Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood. 2012;120(12):2395-404.
11. Louissaint A, Jr., Schafernak KT, Geyer JT, Kovach AE, Ghandi M, Gratzinger D, et al. Pediatric-type nodal follicular lymphoma: a biologically distinct lymphoma with frequent MAPK pathway mutations. Blood. 2016;128(8):1093-100.
12. Schmidt J, Gong S, Marafioti T, Mankel B, Gonzalez-Farre B, Balague O, et al. Genome-wide analysis of pediatric-type follicular lymphoma reveals low genetic complexity and recurrent alterations of TNFRSF14 gene. Blood. 2016;128(8):1101-11.

13. Schmidt J, Ramis-Zaldivar JE, Nadeu F, Gonzalez-Farre B, Navarro A, Egan C, et al. Mutations of MAP2K1 are frequent in pediatric-type follicular lymphoma and result in ERK pathway activation. Blood. 2017.
14. Petrella T, Maubec E, Cornillet-Lefebvre P, Willemze R, Pluot M, Durlach A, et al. Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? The American journal of surgical pathology. 2007;31(12):1887-92.
15. Perry AM, Warnke RA, Hu Q, Gaulard P, Copie-Bergman C, Alkan S, et al. Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. Blood. 2013;122(22):3599-606.
16. Sakata-Yanagimoto M, Enami T, Yoshida K, Shiraishi Y, Ishii R, Miyake Y, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet. 2014;46(2):171-5.
17. Couronne L, Bastard C, Bernard OA. TET2 and DNMT3A mutations in human T-cell lymphoma. The New England journal of medicine. 2012;366(1):95-6.
18. Lemonnier F, Couronne L, Parrens M, Jais JP, Travert M, Lamant L, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood. 2012;120(7):1466-9.
19. Dobay MP, Lemonnier F, Missiaglia E, Bastard C, Vallois D, Jais JP, et al. Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. Haematologica. 2017;102(4):e148-e51.
20. Nicolae A, Xi L, Pittaluga S, Abdullaev Z, Pack SD, Chen J, et al. Frequent STAT5B mutations in gammadelta hepatosplenic T-cell lymphomas. Leukemia. 2014;28(11):2244-8.
21. Nicolae A, Xi L, Pham TH, Pham TA, Navarro W, Meeker HG, et al. Mutations in the JAK/STAT and RAS signaling pathways are common in intestinal T-cell lymphomas. Leukemia. 2016.
22. McKinney M, Moffitt AB, Gaulard P, Travert M, De Leval L, Nicolae A, et al. The Genetic Basis of Hepatosplenic T-cell Lymphoma. Cancer Discov. 2017;7(4):369-79.
23. Roberti A, Dobay MP, Bisig B, Vallois D, Boechat C, Lanitis E, et al. Type II enteropathy-associated T-cell lymphoma features a unique genomic profile with highly recurrent SETD2 alterations. Nature communications. 2016;7:12602.
24. Feldman AL, Dogan A, Smith DI, Law ME, Ansell SM, Johnson SH, et al. Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing. Blood. 2011;117(3):915-9.
25. King RL, Dao LN, McPhail ED, Jaffe ES, Said J, Swerdlow SH, et al. Morphologic Features of ALK-negative Anaplastic Large Cell Lymphomas With DUSP22 Rearrangements. The American journal of surgical pathology. 2016;40(1):36-43.