Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Hematology Am Soc Hematol Educ Program. Author manuscript; available in PMC 2019 January 08.

Published in final edited form as:

Hematology Am Soc Hematol Educ Program. 2009 ; : 523–531. doi:10.1182/asheducation-2009.1.523.

The 2008 WHO classification of lymphomas: implications for clinical practice and translational research

Elaine S. Jaffe[1]

[1]Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, NCI, Bethesda, MD

Abstract

The 4th edition of the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* published in 2008 builds upon the success of the 2001 3rd edition; new entities are defined, and solutions for problematic categories are sought. Recent studies have drawn attention to the biological overlap between classical Hodgkin lymphoma (CHL) and diffuse large B-cell lymphomas (DLBCL). Similarly, there is a greater appreciation of the borderlands between Burkitt lymphoma and DLBCL. Strategies for the management of these borderline lesions are proposed. Additionally, age-specific and site-specific factors play an important role in the definition of several new entities, which also have biological underpinnings. Among the peripheral T-cell lymphomas (PTCL), more precise definitions were introduced for several entities, including anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma. Several new variants of primary cutaneous T-cell lymphomas are proposed. Finally, the subclassification and categorization of the most common lymphoma subtypes, follicular lymphoma (FL) and DLBCL, were altered to enhance diagnostic accuracy and aid in clinical management. The 2008 WHO classification also draws attention to early events in lymphomagenesis. These lesions help delineate the earliest steps in neoplastic transformation and generally mandate a conservative therapeutic approach. The 2001 classification was rapidly adopted for clinical trials and successfully served as a common language for scientists comparing genetic and functional data. The modifications made in the 2008 classification are the result of this successful partnership among pathologists, clinicians, and biologists, but are only a stepping stone to the future.

In 2008 the International Agency for Research on Cancer (IARC) published the 4th Edition of the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*,[1] an effort that involved 138 authors and two clinical advisory committees comprising 62 clinical specialists with expertise in lymphoid and myeloid disorders. As in the 3rd edition, the effort was coordinated by the European Association for Haematopatholgy and the Society for Hematopatholgy, led by the eight editors, who served as a steering committee.

Correspondence Elaine S. Jaffe, MD, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; Phone: 301-496-0184; elainejaffe@nih.gov.

Disclosures

Conflict-of-interest disclosure: The author declares no competing financial interests.

Off-label drug use: None disclosed.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

This review will focus on changes in the classification of lymphomas, which resulted from new insights derived from clinical and laboratory research to better define heterogeneous or ambiguous categories of disease. The areas of modification relate to several discrete topics: (1) a greater appreciation of early or in situ lesions that challenge us to define the earliest steps in neoplastic transformation; (2) the recognition of age as a defining feature of some diseases, both in young and the elderly; (3) further appreciation and recognition of site-specific impact on disease definitions; and (4) a recognition of borderline categories, in which current morphological, immunophenotypic, and genetic criteria do not permit sharp delineations into existing disease categories. Finally, the 4th edition incorporates some provisional entities for which sufficient data are lacking, either clinically or biologically, leading to uncertainty in definitional criteria.

Continued challenges remain in the stratification and subclassification of major disease groups including follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). Genomic and genetic studies have led to significant new insights with the identification of biological and clinical subgroups. Nevertheless, the authors concluded that application of this research to clinical practice on a daily basis was premature, as many of the relevant techniques are not yet available in the clinical laboratory. The thematic approach to peripheral T-cell lymphomas (PTCL) is unchanged. Some diseases are defined based on clinical, pathological, immunophenotypic, or genetic parameters, while the others are provision-ally lumped in PTCL, not otherwise specified (NOS).

The 2008 classification has incorporated minor changes in terminology, reflecting our better understanding of disease entities and their relationship to the immune system. For example, the authors concluded that the modifier “B-cell” was no longer required for nodal, extranodal or splenic marginal zone lymphomas (MZL), as there are no T-cell marginal zone neoplasms (Table 1). The modifier “B-cell” previously had been eliminated from chronic lymphocytic leukemia (CLL). The names for the precursor lymphoid neoplasms also were simplified to eliminate redundancy; thus, the modifier “precursor” is no longer required for either B- or T-lymphoblastic leukemia/lymphoma, as the term lymphoblastic itself carries this meaning.

Early Events in Lymphoid Neoplasia— Borderlands of Malignancy

The multi-step pathway of tumorigenesis has parallels in most organ systems, best documented in the evolution of colonic adenocarcinoma.[2] Histological progression is a well-recognized feature of many lymphoid neoplasms, but the earliest events in lymphoid neoplasia are difficult to recognize. In fact, the lymphoid system historically has had no recognized “benign neoplasms,” a fact that may be related to the propensity of lymphoid cells to circulate or home, and not remain confined to a single anatomic site.[3] The 2008 WHO classification addresses the problem of clonal expansions of B cells, or less often T cells, that appear to have limited potential for histological or clinical progression.

The use of flow cytometry on a routine basis led to the recognition that populations of monoclonal CD5^{+} B-cells could be identified in the healthy, unaffected first-degree relatives of patients with CLL, and in 3% of healthy adults over the age of 40.[4,5] Many of these

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

clones have genetic abnormalities associated with CLL including 13q14 deletion and trisomy 12, similar to sporadic CLL.[6] Nevertheless, only a small percentage of these patients progress to clinically significant CLL, at a rate of less than 2% per year. This condition has been termed monoclonal B-cell lymphocytosis (MBL) and should be distinguished from CLL. The minimal diagnostic criteria for a diagnosis of CLL have been modified to require $\geq 5 \times 10^9$/L of monoclonal B cells in the peripheral blood or evidence of extramedullary tissue involvement. A level below this threshold is considered MBL. The data suggest that most patients ultimately diagnosed as CLL go through a prolonged prodromal phase, with evidence of the circulating clone found many years prior to diagnosis.[7] Thus, the distinction of MBL from CLL is largely one of practice guidelines, as we lack any proven biological parameters that can distinguish MBL from CLL or identify which patients will progress to clinically significant disease more rapidly. A recent report suggested that the cutpoint between MBL and CLL should be modified and increased to a B-cell count of 11×10^9 L.[8]

Another area that challenges us to define “lymphoma” is early events in follicular lymphoma. Up to 70% of normal healthy adults have circulating clonal memory B cells with the t(14;18)(q32;q21); however, these cells presumably lack other genetic alterations necessary for development of malignant behavior.[9,10] The tissue equivalent of this process is thought to be *in situ* FL, also termed “intrafollicular neoplasia” in the WHO classification.[11] These lesions are often discovered incidentally, and comprise isolated scattered follicles colonized by monoclonal t(14;18) B-cells over-expressing both BCL2 and CD10 within an otherwise uninvolved lymph node. Rarely the *in situ* FL lesion may be discovered in lymph nodes involved by a clonally unrelated process.[12] Further evaluation reveals evidence of FL at another site in about half of the patients, but in approximately 50% progression to FL does not occur, at least with current follow-up. The challenge is to distinguish the true *in situ* FL case from lymph nodes with partial involvement by FL due to the naturally occurring dissemination of the disease. In instances of partial involvement by FL many or most of the follicles are involved, but definitive criteria for this distinction are lacking.

A related condition is localized FL presenting as small polyps in the duodenum; these duodenal FLs rarely, if ever, progress to nodal or systemic disease.[13,14] Duodenal FL cells express intestinal homing receptors that may retain the clonal B cells within the intestinal mucosa.[15] A similar *in situ* form of mantle cell lymphoma has been described in a few isolated cases, although little is known about the clinical outcome of this lesion.[16,17] There are other instances in which one encounters clonal proliferations with limited potential for clinical aggressiveness. This phenomenon is exemplified by Epstein-Barr virus (EBV)–driven B-cell proliferations arising in the setting of altered immunity, but also pertains to early gastric extranodal marginal zone (MALT) lymphomas lacking secondary genetic alterations. These lymphomas appear dependent upon continued antigen activation from *Helicobacter pylori* and may regress with antibiotic therapy alone.[18] In the T-cell system lymphomatoid papulosis (LYP), part of the spectrum of primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders, is a clonal T-cell proliferation that also has limited malignant potential.[19–21]

The 3rd edition of the WHO classification included a category of B-cell or T-cell proliferations of uncertain malignant potential. This category encompassed conditions such

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

as LYP or lymphomatoid granulomatosis, in which spontaneous regression may be seen. However, the decision was made to eliminate this designation, as a broader view of lymphoid malignancies indicates that within many wellrecognized disease entities one encounters “proliferations of uncertain malignant potential.” This is especially true among some pediatric lymphomas, as will be discussed below. It is incumbent upon the pathologist and clinician to be aware of the spectrum of disease and to manage each case appropriately, taking into consideration biological and clinical factors. These early events of lymphomagenesis also can provide instructive models of lymphocyte homing and migration.

Age as a Key Feature in Disease Definition

The 2008 WHO classification utilizes patient age as a defining feature in a number of newly incorporated disease entities. For example, within the categories of FL and nodal MZLs there are distinctive variants that present almost exclusively in the pediatric age group, and differ from their adult counterparts clinically and biologically. The pediatric variant of FL usually presents with localized disease and is of high histological grade. These lymphomas lack *BCL2/ IGH@* translocations and do not express BCL2 protein. They may present at nodal or extranodal sites (testis; gastrointestinal tract; Waldeyer’s ring).[22] Pediatric FL have a good prognosis, with the optimal management not yet determined.[22–24] A challenging area of diagnosis is rare cases of florid reactive follicular hyperplasia in children that have been reported to contain clonal populations of $CD10^+$ germinal center B cells and yet do not progress to overt lymphoma.[25]

Nodal MZL in children, while monoclonal at the immunophenotypic and genetic level, also appear to have a low risk of progression.[26] Most patients present with stage I disease and have a low risk of recurrence following conservative therapy. Pediatric nodal MZL are often associated with marked follicular hyperplasia and changes resembling progressive transformation of germinal centers, with the distinction from pediatric FL sometimes being problematic. As there is no molecular hallmark for adult nodal MZL, knowledge of the biological underpinnings of this diagnosis are lacking. Interestingly, pediatric MZL are relatively more common in males, in contrast to female predominance in adult MZL.

The 2008 classification also recognizes two rare EBV associated T-cell diseases that occur almost entirely in children, primarily affecting children of Asian origin but also seen in ethnic populations from Mexico and Central/ South America. (Table 2) These are systemic EBV^+ T-cell lymphoproliferative disease of childhood and hydroa vacciniforme–like lymphoma. Both types lesions have been included under the broad heading of chronic active EBV infection in the Japanese literature,[27] and are derived from EBV^+ clonal T cells.[28] Hydroa vacciniforme-like lymphoma has a chronic and protracted clinical course, with remissions often during winter months. It may resolve spontaneously in adult life or progress to more systemic and aggressive disease. Systemic EBV^+ T-cell lymphoproliferative disease is highly aggressive, with survival measured in weeks to months, and is usually associated with a hemophagocytic syndrome.[29]

By contrast, some diseases appear to occur most often at advanced age, such as EBV^+ DLBCL of the elderly, which likely arises because of decreased immune surveillance.[30]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

These lymphomas are clinically aggressive and occur more often in extranodal rather than nodal sites. The neoplastic cells may mimic Hodgkin/Reed-Sternberg cells and exhibit marked pleomorphism, with a broader range in morphology than typically seen in CHL. Necrosis and an inflammatory background are common. EBV^+ DLBCL of the elderly should be distinguished from reactive hyperplasia associated with EBV, also encountered in the elderly, which usually has a benign outcome with spontaneous regression in most patients.[31,32]

Aggressive B-cell Lymphomas and Borderline Malignancies

In the past 20 years there has been a greater appreciation of morphologic and immunophenotypic overlap between CHL and some large B-cell lymphomas, usually primary medias-tinal large B-cell lymphoma (PMBL) and mediastinal nodular sclerosis classical Hodgkin lymphoma (NSCHL).[33,34] The use of gene expression profiling further confirmed a biological relationship.[35,36] Prior case reports had identified cases of PMBL followed by CHL or vice versa, or other cases in which both lymphomas were composite in the same tumor mass.[37] Notably, both neoplasms occur in young adults and involve the mediastinum. In most biopsies one or the other diagnosis can be made, but in some cases the lymphoma exhibits transitional features that defy traditional diagnostic boxes; these tumors have been termed “grey zone” lymphomas. The 2008 WHO classification recognizes a provisional category of B-cell neoplasms with features intermediate between DLBCL and classical Hodgkin lymphoma.[37,38] These tumors occur predominantly in young men and appear to be more aggressive than either PMBL or NSCHL.[39] There are other diagnostic settings in which the diagnosis between DLBCL and CHL is challenging. For example, some EBV-associated B-cell lymphomas may exhibit features that closely resemble or mimic CHL.[40] The borderline category should be used sparingly, but is appropriate in those cases in which a distinction between CHL and DLBCL is not possible.

The WHO classification of 2008 recognizes a group of high-grade B-cell lymphomas that are not readily classified as either Burkitt lymphoma (BL) or DLBCL. This provisional category is termed: *B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL*. These rare lymphomas, which occur predominantly in adults, have a germinal center phenotype that resembles BL but exhibit atypical cytological features for BL.[41] Also included are cases with translocations of both *MYC* and *BCL2* (“double hit”). While gene expression profiling may show similarities with classical BL,[42,43] other data, including a very aggressive clinical course, support segregation from BL.[44]

The 2008 WHO classification eliminated the variant category of “atypical BL,” which had been included in the 2001 classification.[45] Thus, a case with the typical BL phenotype ($CD20^+$, $BCL6^+$, $CD10^+$, $BCL2^-$) and genotype (so-called *MYC*-simple or *MYC/IG* in the absence of other major cytogenetic anomalies) may be classified as BL, even if there is some cytological variability in the morphology of the neoplastic cells. Likewise, cases of otherwise typical DLBCL with a very high growth fraction should not be included in this “intermediate” group.[46] It should be noted that a *MYC* translocation does not mandate a diagnosis of either BL or the borderline category, and that a *MYC* translocation may be

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

found in cases of otherwise typical DLBCL.[43,42] Thus, the final diagnosis rests on integration of morphologic, immunophenotypic and molecular data.

Other changes in the classification of aggressive B-cell lymphomas recognize the importance of site or clinical factors in defining variants of DLBCL. I have already noted the subtype, EBV$^+$ DLBCL of the elderly.[47] DLBCL associated with chronic inflammation is another EBV$^+$ DLBCL arising in a specialized clinical setting, most often in association with long-standing pyothorax,[48] but also in other instances of prolonged chronic inflammation, such as chronic osteomyelitis, or reaction to metallic implants in a joint or bone.[49] Other site-specific categories are primary DLBCL of the central nervous system (CNS),[50] and primary cutaneous DLBCL, leg-type.[51] Interestingly, the "leg-type" of primary cutaneous DLBCL exhibits an activated B-cell (ABC) gene expression profile in most cases.[52] One might expect that in the future biological and genetic parameters might drive the subclassification of DLBCL, rather than clinical features. However, clinical features remain important in clinical management.[50] In addition, primary CNS DLBCL has a distinctive gene expression signature that may continue to justify it as a separate entity.[53,54]

After separation of the specific new subtypes of DLBCL, we are still left with a large group of DLBCL for which pathological features are lacking to further stratify them for predicting prognosis or response to therapy. These are designated as DLBCL, not otherwise specified (NOS) in the WHO classification. Stratification according to gene expression profiling as germinal center B-cell (GCB) versus activated B-cell (ABC) types has proven prognostic value.[55] However, the GBC and ABC subtypes were not formally incorporated into the classification based on (1) the lack of availability of gene expression profiling as a routine diagnostic test and (2) the imperfect correlation of immunohistochemical surrogate markers with genomic studies. Moreover, these designations do not as yet direct therapy, although recent studies suggest that ABC versus GCB lymphomas will exhibit differential sensitivity to certain drugs.[56] Further development of targeted therapies and recognition of additional markers of clinical behavior will likely result in additional modifications to this category in the future.[57,58]

Several aggressive B-cell lymphomas have an immunoprofile resembling the plasma cell stage of differentiation. These include plasmablastic lymphoma, ALK$^+$ large B-cell lymphoma, and the HHV-8–associated malignancies, primary effusion lymphoma, and large B-cell lymphoma associated with multicentric Castleman's disease. Most cases of plasmablastic lymphoma are associated with EBV and arise in setting of immunodeficiency, usually secondary to HIV infection, but also advanced age.[59]

Follicular Lymphoma—How Many Grades? How Many Entities?

The grading of FL was the subject of spirited discussion, both among the authors and the participants in the Clinical Advisory Committee. FL has traditionally been graded according to the proportion of centroblasts and stratified into three Grades, 1–3. However, most studies have shown poor interobserver and intraobserver reproducibility. Moreover, the clinical significance of the separation of Grades 1 and 2 has been questioned, with minimal

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

differences seen in long term outcome. Thus, the 2008 WHO classification lumps cases with few centroblasts as “FL Grade 1–2 (low grade)” and does not require or recommend further separation.

FL Grade 3 is divided into Grades 3A and 3B, based on the absence of centrocytes in the latter category. Several studies have identified biological differences between these two subtypes, with most cases of FL Grade 3B being more closely related to DLBCL at the molecular level.[60–63] However, in clinical practice the separation of Grades 3A and 3B can be challenging and thus far imperfectly segregates the two variants. Diffuse areas in any Grade 3 FL should be designated as DLBCL (with FL) and are more commonly observed in Grade 3B.[62] Further studies are likely to lead to more precise delineation of the Grade 3 cases truly belonging within FL and those representing an intrafollicular variant of the GCB type of DLBCL.

Pediatric and intestinal FL have already been mentioned as distinctive variants, with pediatric FL lacking an association with the t(14;18). Primary cutaneous follicle center lymphoma (PCFCL) is now segregated as a distinct disease entity, whereas it was considered a variant of FL in the 2001 edition. Notably, PCFCL may contain a high proportion of large B-cells including large centrocytes and centroblasts.[51] Evidence of the t(14;18) is uncommon and most cases are BCL2 negative. Dissemination beyond the skin is rare, and the prognosis is usually excellent.

Peripheral T-cell Lymphomas—Challenges Remain

PTCL, NOS, remains a “wastebasket” category, analogous to DLBCL, NOS. Most cases lack distinct genetic or biological alterations, and prognostic models have largely relied on clinical features or generic factors, such as proliferation.[64,65] Nevertheless, progress has been made in the understanding of a number of PTCL entities. Angioimmunoblastic T-cell lymphoma has been shown to bear to close relationship to the T_{FH} cell of the germinal center, and the follicular variant of PTCL, NOS shares a similar phenotype, although interestingly differs genetically and clinically.[66–68] The majority of nodal PTCL appear related to effector T-cells.

The WHO classification of 2008 has applied more stringent criteria to the diagnosis of enteropathy-*associated* T-cell lymphoma (EATL), and the change in the diagnostic term from enteropathy-*type* T-cell lymphoma reflects these changes in criteria. It is appreciated that a variety of PTCL can present with intestinal disease, and not all of these are associated with celiac disease. For example, intestinal involvement can be seen at presentation, or with progression, in extranodal NK/T-cell lymphoma and some gamma delta T-cell lymphomas. To make the diagnosis of EATL, one should have evidence of celiac disease, either at the genetic level, with the appropriate HLA-phenotype, or histologically, in the adjacent uninvolved small bowel mucosa. A variant of EATL was introduced into the classification, termed the monomorphic variant of EATL or Type II. These cases have some distinctive immunophenotypic and genotypic features. The tumor cells are $CD8^+$, $CD56^+$, and *MYC* amplifications have been shown in a subset of cases.[69,70] The monomorphic variant occurs in the setting of celiac disease, but also occurs sporadically.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Anaplastic large cell lymphoma (ALCL), ALK-positive is considered a distinct disease, which must be distinguished from the provisional entity of ALCL, ALK-negative. More serious debate revolved around the decision to segregate the ALK^- ALCL cases from PTCL, NOS. Recent clinical studies appear to support this resolution, as the former has a better prognosis and evidence of a plateau, at least in a proportion of patients.[71] Stringent morphologic and immunophenotypic criteria are required for the diagnosis of ALK^- ALCL as CD30 may be expressed in a variety of PTCL subtypes, and CD15 may be negative in CHL.

Three new variants of primary cutaneous PTCL were introduced: primary cutaneous gamma delta T-cell lymphoma, and the provisional entities of primary cutaneous $CD4^+$ small/medium T-cell lymphoma and primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma. Cutaneous gamma delta T-cell lymphomas have a diverse histological and clinical spectrum and may display a panniculitis-like pattern.[72] However, this disease has a much poorer prognosis than subcutaneous panniculitis-like T-cell lymphoma,[73] which is defined as a lymphoma exclusively of alpha-beta phenotype in the 2008 WHO.[74]

Conclusion

The 2008 WHO classification is the continuation of a successful international collaboration among pathologists, biologists and clinicians interested in the hematological malignancies. The 2001 classification was rapidly adopted for clinical trials and successfully served as a common language for scientists comparing genetic and functional data. The modifications made in the 2008 classification are the result of this successful partnership, but are only a stepping stone to the future. It is evident that many areas will still be the subject of intense investigation, including the admittedly heterogeneous groups of DLBCL, NOS and PTCL, NOS. The inclusion of borderline categories is an intermediate step, and further modifications in these areas are expected.

References

1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon, France: IARC Press; 2008.
2. Smith D, Ballal M, Hodder R, Selvachandran SN, Cade D. The adenoma carcinoma sequence: an indoctrinated model for tumorigenesis, but is it always a clinical reality? Colorectal Dis 2006;8:296–301. [PubMed: 16630233]
3. Jaffe ES. Follicular lymphomas: possibility that they are benign tumors of the lymphoid system. J Natl Cancer Inst 1983;70:401–403. [PubMed: 6339775]
4. Marti G, Abbasi F, Raveche E, et al. Overview of monoclonal B-cell lymphocytosis. Br J Haematol 2007;139:701–708. [PubMed: 18021084]
5. Rawstron AC, Green MJ, Kuzmicki A, et al. Monoclonal B lymphocytes with the characteristics of “indolent” chronic lymphocytic leukemia are present in 3.5% of adults with normal blood counts. Blood 2002;100:635–639. [PubMed: 12091358]
6. Rawstron AC, Bennett FL, O’Connor SJ, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Engl J Med 2008;359:575–583. [PubMed: 18687638]
7. Landgren O, Albitar M, Ma W, et al. B-cell clones as early markers for chronic lymphocytic leukemia. N Engl J Med 2009;360:659–667. [PubMed: 19213679]
8. Shanafelt T, Hanson CA. Monoclonal B-cell lymphocytosis: definitions and natural history. Leuk Lymphoma 2009;50:493–497. [PubMed: 19347733]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

9. Limpens J, de Jong D, van Krieken J, et al. Bcl-2 in benign lymphoid tissue with follicular hyperplasia. Oncogene 1991;6:2271–2276. [PubMed: 1766674]
10. Roulland S, Navarro JM, Grenot P, et al. Follicular lymphoma-like B cells in healthy individuals: a novel intermediate step in early lymphomagenesis. J Exp Med 2006;203:2425–2431. [PubMed: 17043145]
11. Cong P, Raffeld M, Teruya-Feldstein J, Sorbara L, Pittaluga S, Jaffe ES. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Blood 2002;99:3376–3382. [PubMed: 11964306]
12. Fend F, Quintanilla-Martinez L, Kumar S, et al. Composite low grade B-cell lymphomas with two immunophenotypically distinct cell populations are true biclonal lymphomas. A molecular analysis using laser capture microdissection. Am J Pathol 1999;154:1857–1866. [PubMed: 10362812]
13. Yoshino T, Miyake K, Ichimura K, et al. Increased incidence of follicular lymphoma in the duodenum. Am J Surg Pathol 2000;24:688–693. [PubMed: 10800987]
14. Poggi MM, Cong PJ, Coleman CN, Jaffe ES. Low-grade follicular lymphoma of the small intestine. J Clin Gastroenterol 2002;34:155–159. [PubMed: 11782611]
15. Bende RJ, Smit LA, Bossenbroek JG, et al. Primary follicular lymphoma of the small intestine: alpha4beta7 expression and immunoglobulin configuration suggest an origin from local antigen-experienced B cells. Am J Pathol 2003;162:105–113. [PubMed: 12507894]
16. Richard P, Vassallo J, Valmary S, Missoury R, Delsol G, Brousset P. “In situ-like” mantle cell lymphoma: a report of two cases. J Clin Pathol 2006;59:995–996. [PubMed: 16935977]
17. Aqel N, Barker F, Patel K, Naresh KN. In-situ mantle cell lymphoma—a report of two cases. Histopathology 2008;52:256–260. [PubMed: 18184277]
18. Liu H, Ruskon-Fourmestraux A, Lavergne-Slove A, et al. Resistance of t(11;18) positive gastric mucosaassociated lymphoid tissue lymphoma to Helicobacter pylori eradication therapy. Lancet 2001;357:39–40. [PubMed: 11197361]
19. Weiss LM, Wood GS, Trela M, Warnke RA, Sklar J. Clonal T-cell populations in lymphomatoid papulosis. Evidence of a lymphoproliferative origin for a clinically benign disease. N Engl J Med 1986;315:475–479. [PubMed: 3488502]
20. Willemze R, Beljaards RC. Spectrum of primary cutaneous CD30 (Ki-1)-positive lymphoproliferative disorders. A proposal for classification and guidelines for management and treatment. J Am Acad Dermatol 1993;28:973–980. [PubMed: 8388410]
21. Paulli M, Berti E, Rosso R, et al. CD30/Ki-1-positive lymphoproliferative disorders of the skin—clinico-pathologic correlation and statistical analysis of 86 cases: a multicentric study from the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Project Group. J Clin Oncol 1995;13:1343–1354. [PubMed: 7751878]
22. Lorsbach RB, Shay-Seymore D, Moore J, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. Blood 2002;99:1959–1964. [PubMed: 11877266]
23. Finn LS, Viswanatha DS, Belasco JB, et al. Primary follicular lymphoma of the testis in childhood. Cancer 1999;85:1626–1635. [PubMed: 10193956]
24. Heller KN, Teruya-Feldstein J, La Quaglia MP, Wexler LH. Primary follicular lymphoma of the testis: excellent outcome following surgical resection without adjuvant chemotherapy. J Pediatr Hematol Oncol 2004;26:104–107. [PubMed: 14767197]
25. Kussick SJ, Kalnoski M, Braziel RM, Wood BL. Prominent clonal B-cell populations identified by flow cytometry in histologically reactive lymphoid proliferations. Am J Clin Pathol 2004;121:464–472. [PubMed: 15080297]
26. Taddesse-Heath L, Pittaluga S, Sorbara L, Bussey M, Raffeld M, Jaffe ES. Marginal zone B-cell lymphoma in children and young adults. Am J Surg Pathol 2003;27:522–531. [PubMed: 12657939]
27. Kimura H Pathogenesis of chronic active Epstein-Barr virus infection: is this an infectious disease, lymphoproliferative disorder, or immunodeficiency? Rev Med Virol 2006;16:251–261. [PubMed: 16791843]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

28. Cohen JI, Kimura H, Nakamura S, Ko YH, Jaffe ES. Epstein-Barr virus associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8–9 September 2008. Ann Oncol 2009;20:1472–1482. [PubMed: 19515747]
29. Quintanilla-Martinez L, Kumar S, Fend F, et al. Fulminant EBV(+) T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. Blood 2000;96:443–451. [PubMed: 10887104]
30. Oyama T, Ichimura K, Suzuki R, et al. Senile EBV+ B-Cell Lymphoproliferative Disorders: A Clinicopathologic Study of 22 Patients. Am J Surg Pathol 2003;27:16–26. [PubMed: 12502924]
31. Schrager J, Pittaluga S, Raffeld M, Jaffe ES. EBV reactivation syndromes in adults without known immunodeficiency [abstract]. Mod Pathol 2009;22:285A.
32. Kojima M, Kashimura M, Itoh H, et al. Epstein-Barr virus-related reactive lymphoproliferative disorders in middle-aged or elderly patients presenting with atypical features. A clinicopathological study of six cases. Pathol Res Pract 2007;203:587–591. [PubMed: 17662540]
33. Jaffe ES, Wilson WH. Gray zone, synchronous, and metachronous lymphomas: diseases at the interface of non-Hodgkin's lymphomas and Hodgkin's lymphoma. In: Mauch PM, Armitage JO, Coiffier B, Dalla-Favera R, Harris NL, eds. Non-Hodgkin's Lymphoma Philadelphia, PA: Lippincott, Williams, and Wilkins; 2004:69–80.
34. Jaffe ES, Zarate OA, Medeiros LJ. The interrelationship of Hodgkin's disease and non-Hodgkin's lymphomas— lessons learned from composite and sequential malignancies. Semin Diagn Pathol 1992;9:297–303. [PubMed: 1480852]
35. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood 2003;102:3871–3879. [PubMed: 12933571]
36. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med 2003;198:851–862. [PubMed: 12975453]
37. Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. Am J Surg Pathol 2005;29:1411–1421. [PubMed: 16224207]
38. Rudiger T, Jaffe ES, Delsol G, et al. Workshop report on Hodgkin's disease and related diseases ('grey zone' lymphoma). Ann Oncol 1998;9 Suppl 5:S31–38.
39. Dunleavy D, Pittaluga S, Grant N, et al. Gray zone lymphomas: clinical and histological characteristics and treatment with dose-adjusted EPOCH-R [abstract]. Blood 2008;112:3590.
40. Kamel OW, Weiss LM, van de Rijn M, Colby TV, Kingma DW, Jaffe ES. Hodgkin's disease and lymphoproliferations resembling Hodgkin's disease in patients receiving long-term low-dose methotrexate therapy. Am J Surg Pathol 1996;20:1279–1287. [PubMed: 8827036]
41. Haralambieva E, Boerma EJ, van Imhoff GW, et al. Clinical, immunophenotypic, and genetic analysis of adult lymphomas with morphologic features of Burkitt lymphoma. Am J Surg Pathol 2005;29:1086–1094. [PubMed: 16006805]
42. Hummel M, Bentink S, Berger H, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J Med 2006;354:2419–2430. [PubMed: 16760442]
43. Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med 2006;354:2431–2442. [PubMed: 16760443]
44. Karsan A, Gascoyne RD, Coupland RW, Shepherd JD, Phillips GL, Horsman DE. Combination of t(14;18) and a Burkitt's type translocation in B-cell malignancies. Leuk Lymphoma 1993;10:433–441. [PubMed: 8401180]
45. Jaffe ES, Harris NL, Stein H, Vardiman J. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues Lyon, France: IARC Press; 2001.
46. Chuang SS, Ye H, Du MQ, et al. Histopathology and immunohistochemistry in distinguishing Burkitt lymphoma from diffuse large B-cell lymphoma with very high proliferation index and with or without a starry-sky pattern: a comparative study with EBER and FISH. Am J Clin Pathol 2007;128:558–564. [PubMed: 17875505]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

47. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. Clin Cancer Res 2007;13:5124–5132. [PubMed: 17785567]
48. Aozasa K, Takakuwa T, Nakatsuka S. Pyothoraxassociated lymphoma: a lymphoma developing in chronic inflammation. Adv Anat Pathol 2005;12:324–331. [PubMed: 16330929]
49. Cheuk W, Chan AC, Chan JK, Lau GT, Chan VN, Yiu HH Metallic implant-associated lymphoma: a distinct subgroup of large B-cell lymphoma related to pyothorcix-associated lymphoma? Am J Surg Pathol 2005;29:832–836. [PubMed: 15897752]
50. Deangelis LM, Hormigo A. Treatment of primary central nervous system lymphoma. Semin Oncol 2004;31:684–692. [PubMed: 15497122]
51. Willemze R, Jaffe ES, Burg G, et al. WHOEORTC classification for cutaneous lymphomas. Blood 2005;105:3768–3785. [PubMed: 15692063]
52. Hoefnagel JJ, Dijkman R, Basso K, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005;105:3671–3678. [PubMed: 15308563]
53. Tun HW, Personett D, Baskerville KA, et al. Pathway analysis of primary central nervous system lymphoma. Blood 2008;111:3200–3210. [PubMed: 18184868]
54. Courts C, Montesinos-Rongen M, Martin-Subero JI, et al. Transcriptional profiling of the nuclear factor-kappa B pathway identifies a subgroup of primary lymphoma of the central nervous system with low BCL10 expres-sion. J Neuropathol Exp Neurol 2007;66:230–237. [PubMed: 17356384]
55. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002;346:1937–1947. [PubMed: 12075054]
56. Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B cell lymphoma. Blood 2009;113:6069–6076. [PubMed: 19380866]
57. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med 2008;359:2313–2323. [PubMed: 19038878]
58. Polo JM, Juszczynski P, Monti S, et al. Transcriptional signature with differential expression of BCL6 target genes accurately identifies BCL6-dependent diffuse large B cell lymphomas. Proc Natl Acad Sci U S A 2007;104:3207–3212. [PubMed: 17360630]
59. Colomo L, Loong F, Rives S, et al. Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. Am J Surg Pathol 2004;28:736–747. [PubMed: 15166665]
60. Ott G, Katzenberger T, Lohr A, et al. Cytomorphologic, immunohistochemical, and cytogenetic profiles of follicular lymphoma: 2 types of follicular lymphoma grade 3. Blood 2002;99:3806–3812. [PubMed: 11986240]
61. Bosga-Bouwer AG, van Imhoff GW, Boonstra R, et al. Follicular lymphoma grade 3B includes 3 cytogenetically defined subgroups with primary t(14;18), 3q27, or other translocations: t(14;18) and 3q27 are mutually exclusive. Blood 2003;101:1149–1154. [PubMed: 12529293]
62. Katzenberger T, Ott G, Klein T, Kalla J, Muller-Hermelink HK, Ott MM. Cytogenetic alterations affecting BCL6 are predominantly found in follicular lymphomas grade 3B with a diffuse large B-cell component. Am J Pathol 2004;165:481–490. [PubMed: 15277222]
63. Karube K, Guo Y, Suzumiya J, et al. CD10-MUM1+ follicular lymphoma lacks BCL2 gene translocation and shows characteristic biologic and clinical features. Blood 2007;109:3076–3079. [PubMed: 17138820]
64. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474–2479. [PubMed: 14645001]
65. Cuadros M, Dave SS, Jaffe ES, et al. Identification of a proliferation signature related to survival in nodal peripheral T-cell lymphomas. J Clin Oncol 2007;25:3321–3329. [PubMed: 17577022]
66. de Leval L, Rickman DS, Thielen C, et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T cells (TFH). Blood 2007;109:4952–4963. [PubMed: 17284527]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

67. Streubel B, Vinatzer U, Willheim M, Raderer M, Chott A Novel t(5;9)(q33;q22) fuses ITK to SYK in unspeci-fied peripheral T-cell lymphoma. Leukemia 2006;20:313–318. [PubMed: 16341044]

68. Rodriguez-Pinilla SM, Atienza L, Murillo C, et al. Peripheral T-cell lymphoma with follicular t-cell markers. Am J Surg Pathol 2008;32:1787–1799. [PubMed: 18779728]

69. Deleeuw RJ, Zettl A, Klinker E, et al. Whole-genome analysis and HLA genotyping of enteropathytype T-cell lymphoma reveals 2 distinct lymphoma subtypes. Gastroenterology 2007;132:1902–1911. [PubMed: 17484883]

70. Zettl A, deLeeuw R, Haralambieva E, Mueller-Hermelink HK. Enteropathy-type T-cell lymphoma. Am J Clin Pathol 2007;127:701–706. [PubMed: 17511112]

71. Savage KJ, Harris NL, Vose JM, et al. ALK-anaplastic largecell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496–5504. [PubMed: 18385450]

72. Toro JR, Beaty M, Sorbara L, et al. Gamma delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. Arch Dermatol 2000;136:1024–1032. [PubMed: 10926739]

73. Kumar S, Krenacs L, Elenitoba-Johnson K, et al. Subcutaneous panniculitic T-cell lymphoma is a tumor of cytotoxic T-lymphocytes. Hum Pathol 1998;29:397–403. [PubMed: 9563791]

74. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitislike T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111:838–845. [PubMed: 17934071]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

WHO 2008: the mature B-cell neoplasms.

Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma[*]
Hairy cell leukemia-variant[*]
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Heavy chain diseases
Alpha heavy chain disease
Gamma heavy chain disease
Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma (MZL)
Pediatric type nodal MZL
Follicular lymphoma
Pediatric type follicular lymphoma
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
T cell/histiocyte rich large B-cell lymphoma
DLBCL associated with chronic inflammation
Epstein-Barr virus (EBV)+ DLBCL of the elderly
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK^+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma
Hodgkin Lymphoma
Nodular lymphocyte-predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma

*These represent provisional entities or provisional subtypes of other neoplasms.

Diseases shown in italics are newly included in the 2008 WHO classification.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

WHO 2008: the mature T-cell and NK-cell neoplasms.

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK-cells *
Aggressive NK cell leukemia
Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorder
Lymphomatoid papulosis
Primary cutaneous anaplastic large-cell lymphoma
*Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma**
Primary cutaneous gamma-delta T-cell lymphoma
*Primary cutaneous small/medium CD4+ T-cell lymphoma**
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma (ALCL), ALK+
*Anaplastic large cell lymphoma (ALCL), ALK-**

* These represent provisional entities or provisional subtypes of other neoplasms.

Diseases shown in italics are newly included in the 2008 WHO classification.