review

The Current Lymphoma Classification: New Concepts and Practical Applications—Triumphs and Woes

Nasir Bakshi,[a] Irfan Maghfoor[b]

From the [a]Department of Pathology and Laboratory Medicine and the [b]Department of Clinical Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Correspondence: Nasir Bakshi · Department of Pathology and Laboratory Medicine, MBC 10, King Faisal Specialist Hospital and Research Center, P.O. Box 3354, Riyadh, Saudi Arabia · nbakshi@kfshrc.edu.sa

The World Health Organization (WHO) classification of lymphomas updated in 2008 represents an international consensus for diagnosis of lymphoid neoplasms based on the recognition of distinct disease entities by applying a constellation of clinical and laboratory features. The 2008 classification has refined and clarified the definitions of well-recognized diseases, identified new entities and variants, and incorporated emerging concepts in the understanding of lymphoid neoplasms. Rather than being a theoretical scheme this classification has used data from published literature. Recent knowledge of molecular pathways has led to identification and development of new diagnostic tools, like gene expression profiling, which could complement existing technologies. However, some questions remain unresolved, such as the extent to which specific genetic or molecular alterations define certain tumors. In general, practical considerations and economics preclude a heavily molecular and genetic approach. The significance of early or precursor lesions and the identification of certain lymphoid neoplasms is less clear at present, but understanding is evolving. The borderline categories having overlapping features with large B-cell lymphomas, as well as some of the provisional entities, are subject to debate and lack consensus in management. Lastly, the sheer number of entities may be overwhelming, especially, for the diagnosing pathologist, who do not see enough of these on a regular basis.

Classification schemes of diseases, as reference frameworks for both clinical practice and research, continue to evolve while keeping pace with new discoveries and understanding of diseases. The World Health Organization (WHO) classification of lymphoid neoplasms was published in 2001 and updated in 2008.[1,2] It represents a worldwide consensus on the diagnosis of these tumors, adopted for use by pathologists, clinicians, and basic scientists. The basic principle of this classification is the recognition of "distinct" diseases utilizing a multiple parametric approach that is based on morphology, immunophenotype, genetic, molecular, and clinical features. For the record, the 2008 classification does not contain major changes from the 2001 edition, but it does redefine or refine some well-recognized categories and also identifies some new entities and variants, while incorporating emerging concepts in our understanding of lymphomas. With success and triumphs come woes, newer and unfathomed issues such as the practical usefulness of this classification by pathologists as well as treating oncologists, considering the vast number of entities (approaching 60), which they have to deal with and a somewhat complicated work-up for many entities with emphasis on molecular and genetic studies. While not providing extensive details about the classification scheme itself, this review emphasizes those diseases for which changes have had an effect on clinical practice. Moreover, since the release of this classification in 2008, new findings and ideas have been generated and this re-

view expands on these emerging concepts. The key elements of the classification are presented in **Table 1**.

B-cell lymphomas (Table 2)

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma reported worldwide as well as in Saudi Arabia (Saudi Cancer Registry, 2006).[1,3] DLBCLs that do not have specific clinical or pathologic features have traditionally been included in the group diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). Newer studies have shed further light in helping understand this heterogeneous group of lymphomas. Recent data has, therefore, led to modification of the classification scheme further dissecting this broad group into subtypes based on the following:

By providing newer insights, gene expression profiling (GEP) has helped identify two principal molecular subtypes of DLBCL: the germinal center B cells (GCB) and activated B cell (ABC, also called non-GCB) forms of DLBCL.[4,5] These subsets are associated with specific genetic alterations, different molecular signaling pathways, and different clinical outcomes. A variety of immunohistochemical algorithms have been proposed to delineate these subsets in the routine clinical laboratory, eg, CD10, BCL-6 and MUM-1 (**Figure 1**).[6] Treated similarly, outcomes are remarkably different for either entity underscoring the importance of newer therapeutic strategies.[7] Currently new therapeutic strategies are being designed to differentially treat GCB and ABC DLBCL. The results of these trials are being critically evaluated and it is likely that soon we will have different treatment modalities for each genetic group in routine clinical practice.[8]

The new classification recognizes several DLBCL entities characterized by EBV infection of the tumor cells. In addition to lymphomatoid granulomatosis (introduced 2001) two new entities have now been added to the WHO 2008 as separate subtypes of DLBCL: (a) EBV+ DLBCL of the elderly, initially described in Asia, occurs in patients >50 years without known immunodeficiency or prior lymphoma[9-11] and (b) DLBCL associated with chronic or long standing inflammation, most often chronic pyothorax (pyothorax associated lymphoma, PAL).[12-14] Both of these lymphomas have an aggressive clinical course with short median survival. Again the GEP of PAL is distinct from nodal DLBCL.

Following cues from the well-recognized primary mediastinal large B-cell lymphoma (PMBL, introduced 2001) the current classification delineates two other DLBCL that originate in specific topographic locations:

Table 1. Key Elements of WHO Classification of Lymphomas, 2008.

- Disease entities defined by a combination of morphology, immunophenotype, genetics and clinical features.

  No single "gold standard" for diagnosis though molecular and genetic features increasingly important.

  Inclusion of provisional entities as current data not enough to be regarded as full entities, like ALK-Negative, ALCL

  Recognition of grey zone lymphomas with overlapping features between DLBCL and Classical Hodgkin lymphoma (CHL).

  Early ('in-situ') lesions identified in low grade B-cell lymphomas: follicular, mantle and small lymphocytic lymphomas.

- CHL now recognized as a B-cell lineage lymphoma

- More organ/site specific lymphomas delineated like primary cutaneous DLBCL, leg type

- Redefinition of enteropathy-associated T-cell lymphoma (EATL)

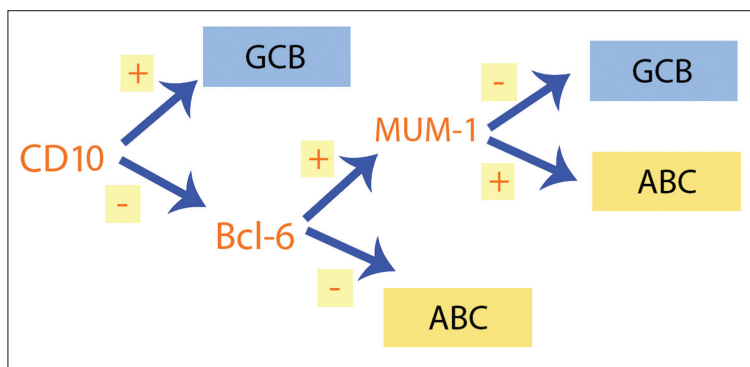- Data from gene expression profiling studies included but still not ready required for routine use

Figure 1. Germinal center B cells (GCB) vs activated B cell (ABC) diffuse large B-cell lymphoma (Non-GCB) by immunohistochemistry based on Hans et al.[6]

(a) primary DLBCL of the CNS and (b) primary cutaneous DLBCL, leg type. Primary CNS DLBCL has been reported to have a particular gene expression and genomic profile that differs from nodal DLBCL, and the patients are managed with different protocols.[15,16] Optimal management of primary CNS lymphomas remains to be defined; however, current evidence suggests a combination of high-dose methotrexate and cytosine arabinoside followed by whole brain radiation may produce the best long-term disease-free survival. Long-term central nervous system toxicity from this approach remains a concern.[17] The distinction of primary cutaneous DLBCL, leg type, as a specific entity is based on its aggressive clinical behavior and phenotype that differ from the more indolent primary cutaneous fol-

Table 2. The WHO lymphoma classification, 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

Table 2 (cont). The WHO lymphoma classification, 2008: the mature B-cell neoplasms.

- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, features intermediate between DLBCL & 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

licle center lymphomas and is managed differently too. Notably, DLBCL, leg type resembles systemic DLBCL of the ABC subtype by GEP.[18,19]

Changes in grading and reporting of follicular lymphoma

The 2001 edition of the WHO classification recommended use of a three-tier grading scale for FL (Berard and Mann), according to the number of centroblasts (grade 1: 0-5, grade 2: 6-15, and grade 3: > 15 per high-power field). Grade 3 was further subdivided for the purposes of clinical research into 3A (centrocytes still present) and 3B (sheets of centroblasts with no centrocytes present).[20] Many problems have beset this grading system and it is now clearly acknowledged that not only is it poorly reproducible among pathologists, but more importantly there appear to be no major biologic or clinical differences between grades 1 and 2 as both are treated similarly. Finally, several publications have suggested that grade 3B FL is actually biologically distinct from grades 1-3A, with features suggesting a close relationship to the ABC-type of DLBCL (more frequent lack of CD10 and BCL2, expression of IRF4/MUM1, and rearrangement of BCL6 but not BCL2).[21] Although no alternative grading scheme has been suggested, it is recommended to separately report grade 3B in FL that is otherwise grade 1 or 2. Furthermore, reporting any area of DLBCL in a FL as a primary diagnosis is a sound recommendation due to distinct differences in the treatment protocols between DLBCL and FL. The fourth edition of the WHO classification recognizes some distinctive clinical and genetic subtypes of FL, such as

primary duodenal FL and the pediatric type of FL (see below). Primary duodenal FL carries the t(14;18) but usually remains localized to the intestinal mucosa.[22-23]

Management of follicular lymphomas has evolved over the course of last decade from single agent alkylating therapy to combination chemotherapy, which includes anti-CD20 antibody (rituximab). Although appropriate induction regimen remains controversial, it is now recognized that any regimen should include rituximab. Induction regimens may range from rituximab alone to ritixumab combined with cyclophosphamide, vincrisitne and prednisone or more aggressive combination chemotherapy. After optimum cytoreduction (complete and/or partial remission) has been achieved, rituximab maintenance therapy has now been firmly established as the standard of care for both initially diagnosed and relapsed follicular lymphomas as demostrated by the PRIMA study.[24]

Chronic lymphocytic leukemia/small lymphocytic lymphoma, Lymphoplasmacytic lymphoma (LPL) and Waldenström macroglobulinemia

Newer defining criteria for chronic lymphocytic leukemia, lymphoplasmacytic lymphoma and Waldenström macroglobulinemia (WM) have been established. Since the recognition of monoclonal B-cell lymphocytosis (MBL) (see below) the International Workshop on CLL has proposed new diagnostic criteria for CLL. The requirement for a diagnosis of CLL was modified from a chronic absolute lymphocytosis >5.0×10⁹/L to an absolute count of >5.0×10⁹/L monoclonal B cells with a CLL immunophenotype in the peripheral blood in the absence of disease-related symptoms or cytopenias, or tissue involvement other than bone marrow. A diagnosis of small lymphocytic lymphoma (SLL) is made when there is lymphadenopathy or splenomegaly because of infiltrating CLL cells with < 5×10⁹ CLL-type cells in the blood. Because many patients with Rai stage 0 CLL, even as currently defined, are not treated, the change in terminology relates more to how patients are "labeled," rather than indicating a change in patient management.[25] Patients with early stage CLL/SLL may be observed. However, when therapy is indicated, younger and physically fit patients may be optimally treated with a combination of rituximab, fludarabine and cyclophosphamide (FCR), which results in significantly superior progression-free survival compared to non-rituximab based therapies.[26]

LPL continues to be a diagnosis of exclusion due to lack of defining biomarkers. It is now acknowledged that sometimes it may not be possible to differentiate LPL from closely related marginal zone lymphoma with plasmacytic differentiation and in such cases a diagnosis of small B-cell lymphoma with plasmacytic differentiation

can be rendered. Newer data has shown that translocation t(9;14)(PAX5/IGH@), previously thought to help diagnose LPL, is now recognized to be rarely, if ever, found in LPL. The problematic relationship of WM with LPL seems to have been solved by adopting the approach of the Second International Workshop on Waldenström Macroglobulinemia, which defined it as the presence of an IgM monoclonal gammopathy of any concentration associated with BM involvement by LPL. Therefore, LPL and WM are not synonymous, with WM now defined as a subset of LPL. The presence of even a large IgM paraprotein in the absence of a LPL is no longer considered WM, and LPL in the absence an IgM paraprotein is not WM.[27]

Pediatric lymphomas: variations from adults and new entities

The concept that lymphomas in children often differ from lymphomas in adults is a recurrent theme in the WHO classification. Changes related to the pediatric lymphomas can be briefly grouped as those related to mature B-cell lymphomas and those related to EBV-associated T-cell lymphoproliferative disorders in children.

FL in children tends to present with localized disease in nodal and extranodal sites and is frequently composed of large cells. Despite high-grade (grade 3) cytology, they have a good prognosis with fewer relapses. The t(14;18) translocation or BCL6 rearrangements are uncommon, although BCL2 protein expression may be found in a subset of the tumors (~30%). Recurrent breaks in the *IGH@* gene are seen in several cases, but the corresponding partners have not been identified. Some children have had long survival with only local treatment, and the most appropriate management of these patients is yet to be defined.[28-30]

Nodal marginal zone lymphoma (NMZL) in children differ from NMZL in adults. Similarly to pediatric FL, NMZLs in children show a striking male predominance, present as localized disease, and are relatively well controlled with only local therapies. The biologic characteristics are not well known, but recent genetic studies have shown similar chromosomal aberrations as in the adult counterparts (trisomies 3 and 18 and occasional *IGH@* and *MALT1* rearrangement) but at a lower frequency. Florid follicular and marginal zone hyperplasias that occur in children further complicate the diagnosis of both pediatric MZL and FL; these cases occasionally have monotypic expression of immunoglobulin light chains, and in some cases evidence of clonality of IG genes at the molecular level. Pediatric patients with FL/MZL should be managed with caution and, as with other in situ type lesions, may represent very early events in neoplasia, with a low risk of clinical consequences.[31-33]

EBV associated T-cell lymphoproliferative disorders in children

The 2008 WHO classification now recognizes 2 uncommon EBV-associated T-cell lymphoproliferative disorders in children. These disorders have a particular geographic distribution, more frequently affecting Asians and indigenous populations of Latin and Central America: (a) Hydroa vacciniforme-like lymphoma is a proliferation of clonal T-cells or less often NK cells infected by EBV. The disease has an indolent clinical course with long periods of recurrent skin lesions in sun-exposed areas that tend to regress spontaneously. After several years the process may resolve or progress to systemic disease.[34-35] (b) systemic EBV+ lymphoproliferative disease of the childhood is an aggressive condition with a fulminant course evolving rapidly to multiple-organ failure and death. The disease has overlapping features with aggressive NK-cell leukemia, but the cells have a T-cell phenotype and clonal TCR rearrangement. It may emerge in a background of chronic active EBV infection and progress from a polyclonal, to oligoclonal, to monoclonal EBV-driven proliferation. These lesions may occur less often in young adults.[36]

Early lesions in lymphoid neoplasms: Is this in situ lymphoma?

Though universal in solid organ cancer pathobiology, the idea of an in situ or precursor neoplastic lesion/s is relatively new in lymphoma biology. Currently, there is now an increasing recognition of clonal expansions of lymphoid cells that appear to correspond to early steps in lymphomagenesis. In some cases it is not clear whether these lesions will ever progress to clinically significant disease. The identification of these lesions raises new issues such as how to manage these patients.[37] Entities wherein early stage or in situ lesions are now well recognized and acceptable include the following:

In situ follicular lymphoma: Early and possibly neoplastic or preneoplastic proliferations, corresponding to the immunophenotypic and molecular phenotypes of FL have been observed in tissues. These have been designated as in situ FL or intrafollicular neoplasia, referring to the fact that the clonal population is restricted in its distribution to its normal anatomic location, the germinal center. These lesions should be distinguished from partial involvement of the lymph node by overt lymphomas. Cases of in situ FL represent expansions of CD10 and BCL2-positive lymphoid cells carrying the t(14;18) translocation found in germinal centers of an otherwise reactive lymph node. The finding is usually incidental. The involved follicles are often scattered and generally not completely replaced by BCL2-positive cells. More than 50% of the patients do not have evidence of FL beyond the initial node and with existing follow-up. This situation may represent tissue infiltration of circulating antigen-experienced, clonal expansions of B cells carrying the t(14;18) translocation commonly detected in healthy persons, termed FL-like B cells. These circulating t(14;18)-positive clones, which are more prevalent among persons with pesticide exposure, appear to lack additional oncogenic events to develop into an overt lymphoma. Interestingly some patients with hepatitis C virus have clones carrying the t(14;18) that may disappear after antiviral therapy.[38-42]

In situ mantle cell lymphoma: Similar to in situ FL, clonal expansion is restricted in distribution to the mantle zone. Early involvement of lymph nodes by cells carrying the t(11;14) translocation and over expression of cyclin D1 has been previously reported. The cyclin D1-expressing cells are predominantly found in the inner area of the mantle zone of the follicles, but usually the rest of the mantle and the follicle have a reactive appearance. The finding is usually incidental in an otherwise reactive lymph node. Some of these patients have circulating t(11;14)-positive cells, but they have not developed a clinically significant neoplasm after several years of follow-up, even without treatment. However, some cases may progress to overt MCL. Similar to the t(14;18) translocation, persisting circulating clones carrying the t(11;14) translocation may be detected in healthy persons, again without evidence of progression. However, some patients with clinically detected MCL, usually presenting with leukemic but non-nodal disease, also can have stable disease for many years even without chemotherapy. These cases lack chromosomal aberrations other than the t(11;14) (MCL notably carries a high number of non-random secondary chromosomal aberrations) and show differential expression of SOX11 (also expressed in cyclin D1 negative MCL) and other genes of the high-mobility group of transcription factors, in comparison with conventional MCL. These observations could alter our current view of the pathogenesis and evolution of MCL and may warrant different therapeutic strategies on the basis of particular biologic characteristics.[43-50]

Monoclonal B-cell lymphocytosis (MBL)/ in situ SLL: Akin to monoclonal gammopathy of undetermined significance, monoclonal B-cell lymphocytosis (MBL) ($<5\times10^9$/L monoclonal B-cells) is regarded as a potential precursor of CLL and, less frequently, other leukemic lymphoid neoplasms. MBL is frequently found in first-degree family members of patients with CLL and in 5% of tested subjects older than 60 years, but the incidence increases to 14% in subjects with lymphocytosis ($>4.0\times10^9$/L). Population-based studies with the use of highly sensitive

detection methods have identified clonal B-cells in 12% of the population and >20% of persons older than 65 years. Epidemiologic studies have found evidence of the CLL clone in the blood many years before diagnosis, supporting the idea of a long silent phase. The rate of progression of MBL to overt CLL is about 1% to 2% per year. A small number of clonal B-cell populations with an atypical CLL phenotype (bright CD20/surface immunoglobulin, lack of CD23) or even a non-CLL phenotype (CD5-) have been detected in some healthy persons.[51-57]

Recognition of overlap of lymphoid neoplasms: gray zones between Hodgkin lymphoma and diffuse large B-cell lymphoma

Previously GEP studies have shown that PMBL and CHL share a common gene expression signature, supporting a close biologic relationship between these two diseases. Tumors with transitional or intermediate morphologic and phenotypic features have lately been described suggesting that a true biologic gray zone between these two entities could exist, further supported by profiling at the genetic level. The 2008 WHO classification incorporates these new ideas and recognizes a provisional category of B-cell neoplasms with features intermediate between DLBCL and CHL (**Figure 2**). The category does not include the composite or sequential cases of both neoplasms. Other intermediate forms between CHL and DLBCL, as may be seen with EBV transformation, represent a different biologic phenomenon. Based on this concept it appears that these tumors have more aggressive behavior than either DLBCL or CHL. The optimal therapeutic management of these lymphomas has not been determined although in one series therapy for an aggressive large B-cell lymphoma has been proposed as effective.[58-64]

Gray zones between Burkitt and diffuse large B-cell lymphoma

The diagnostic criteria for Burkitt lymphoma (BL) and DLBCL have been relatively well defined for many years. However, over the years, cases have been encountered with intermediate features between these categories that have been difficult to classify, resulting in different names used over the years such as atypical BL, Burkitt-like lymphoma, small noncleaved cell lymphoma, non-Burkitt type, and high-grade B-cell lymphoma. Not surprisingly, these borderline cases have been among the least reproducible diagnoses, even among expert pathologists. Two recent GEP studies of BL have provided evidence that the difficulties in recognizing the border between BL and DLBCL reflect a true biologic gray zone. One study found the molecular sig-
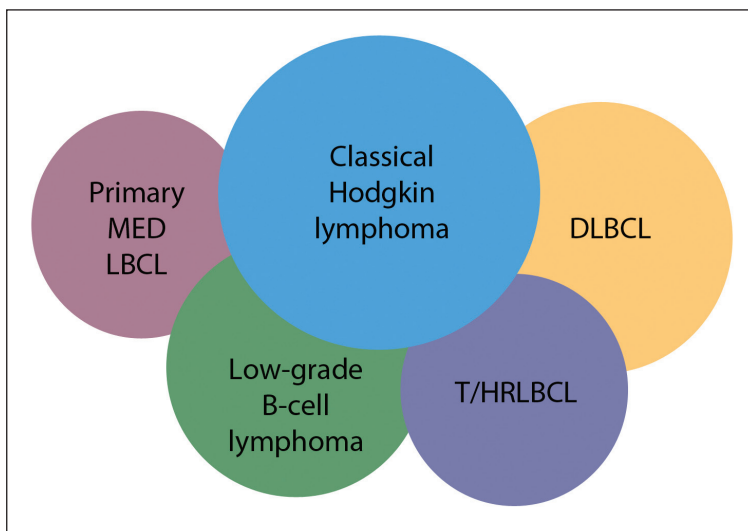

Figure 2. Biologic interfaces or gray zones classical Hodgkin lymphoma and other B-cell lymphomas. MED LBCL: Mediastinal large B-cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; T/HRLBCL: T-cell/histiocyte rich large B-cell lymphoma

nature of BL in a group of cases diagnosed as DLBCL. Despite the molecular signature of BL, these cases differed clinically and genetically from classic BL. They were identified in older patients, had an equal male/female ratio, and had complex karyotypes, including simultaneous t(8;14) and t(14;18) translocations referred to as double-hit lymphomas (DHL). The clinical behavior was aggressive. Similarly, a second GEP study of BL found a subset of tumors with an intermediate expression profile between BL and DLBCL. These cases also had complex karyotypes and MYC translocations with a non-IG gene partner, both uncommon features in typical BL. The WHO classification of 2008 assigned these high-grade B-cell lymphomas that are not readily classified as either BL or DLBCL to an intermediate group. B-cell lymphomas with otherwise typical DLBCL morphology and MYC rearrangement or a high proliferative index or a combination should not be included in this intermediate group. These lymphomas, however, have aggressive clinical behavior and optimal therapy is not well defined. There is emerging opinion that B-cell lymphomas with DLBCL morphology and MYC rearrangement may be best managed with aggressive combination chemotherapy programs like those used for BL.[65-69]

The Importance of the microenvironment in B-cell lymphomas

The recognition of T-cell/histiocyte-rich large B-cell lymphoma (T/HRLBCL) as a distinct category of DLBCL highlights the importance of the microenvi-

ronment in the biology of some diseases. GEP studies identified a subgroup of DLBCL with a high host immune response signature associated with bad prognosis that includes most of the cases diagnosed as T/HRLBCL.[5] Other lymphomas beside DLBCL, where tumor microenvironment has been extensively studied for prognostic outcome include FL. GEP studies have shown that a FL with macrophage profile in the microenvironment do worse than those with T-cell profile in the microenviroment.[70-71]

T-cell lymphomas (Table 3): What's new?

Newer categories have been recognized in the cutaneous T-cell lymphoma or CTCL (not discussed here for the sake of brevity) and pediatric lymphomas (already considered above). The reader is advised to refer to detailed monographs for review of CTCL and other skin lymphomas.[72-73]

The ALK-positive and ALK-negative anaplastic large cell lymphoma were recognized in the category of ALCL in the 2001 WHO classification and excluded primary cutaneous ALCL. The 2008 classification concluded that current evidence warranted delineation of ALK-positive ALCL as a distinct entity (provisional category). ALK-positive ALCL occurs mainly in pediatric and young age groups, has a better prognosis than ALK-negative ALCL, and exhibits differences in genetics and GEP. The categorization of ALK-negative ALCL was more controversial but also felt to be distinguishable from other peripheral T-cell lymphoma (PTCL). Recent studies by the International Peripheral T-Cell Lymphoma Project have supported this view, showing that ALK-negative ALCL has an intermediate survival between the better outcome of ALK-positive ALCL and the more aggressive PTCL, NOS and that the gene signature of ALK-negative ALCL is indeed distinct from that of PTCL, NOS.[74-77]

The WHO classification of 2008 has applied more stringent criteria to the diagnosis of enteropathy-associated T-cell lymphoma (EATL), with a concomitant change in terminology from enteropathy-type T-cell lymphoma to EATL. It is recognized that a variety of T-cell lymphomas such as extranodal natural killer NK/T-cell lymphoma and some gamma-delta T-cell lymphomas can present with intestinal involvement, but not all are associated with celiac disease. To make the diagnosis of EATL, one should have evidence of celiac disease, either clinically, 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, the monomorphic variant of EATL (Type II EATL). The monomorphic

Table 3. The WHO Lymphoma Classification, 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.

variant may occur sporadically without clear risk factors or clinical manifestations of celiac disease, and it appears to represent a distinct disease entity.[78] More recently Mansoor et al, described atypical but non-malignant NK-cell lymphoproliferative lesions of the intestine referred to as "NK-cell enteropathy" mimicking NK- or T-cell lymphomaNK/T cell proliferations.[79]

Problems and Issues

The current lymphoma classification, as anticipated, has helped clarify many issues besetting lymphoma pathobiology. It has successfully incorporated the new body of research and clinical data as well as molecular findings since the last update in 2001. Despite this one of the main criticisms of this classification has been the

difficulty on the part of both the practicing patholo-gist and the treating physician to comprehensively ap-ply this classification in routine practice. From the very outset the classification itself appears very specialized in approach and the sheer number of entities is daunting. For some pathologists, who see 10 or 20 lymphomas a year—if each one is different it is a potential cause for concern, not to mention the extensive work-up with immunostaining and molecular studies that may be needed to correctly classify the lymphoma. This also has the unfortunate tendency of making pathologists somewhat discouraged about lymphoma, as a disease. Especially frustrating is the perception that hematopa-thology is becoming so specialized as to preclude the general pathologist from practicing hematopathology. Some tend to overcome this by sending cases for con-sultation, which although good for standardization of diagnoses, may not always be practical. The treating on-cologist on the other hand may not be as resistant to the complexity of lymphoma, mainly because separate regimens for all individual entities have not yet evolved.

Several recent observations challenge the idea of a precise separation between "definite" entities. The iden-tification of the gray zones between CHL and DLBCL highlights how tumor cells may cross boundaries be-tween current categories, suggesting that some enti-ties may just be ends of a spectrum in the pathogenetic pathway of the tumor cells and their relationship with the microenvironment. The increasing recognition of a clonal relationship between the different components of composite lymphomas such as FL and MALT lympho-ma or HL and FL or MCL also underscore the complex ontogeny of these tumors, which may share a common cell of origin and initial transformation events. This phenomenon recapitulates in a clinical setting the plas-ticity of hematopoietic cells observed in experimental models, in which modulation of specific transcription factors can reprogram cells to enter disparate differen-tiation pathways.[80] This raises the question: why have such huge number of separate entities if there is a rea-sonable potential for cross-over and overlap?

In sharp contrast to B-cell lymphomas, most of the T-cell lymphomas lack defining chromosomal translo-cations or biomarkers to recognize them. Even differen-tiating PTCL, NOS from other T-cell lymphomas such as AILT or ALCL may not always be possible. Despite the recognition of some specific subtypes, most PTCL still remain under a broad category of NOS. Only re-cently the identification of follicular T-helper cells has led to the association of angioimmunoblastic lympho-ma to this type of germinal center T-cell. Furthermore, the classification scheme for the T-cell lymphomas in general has little to offer in terms of prognostic value and does not relate to the functional aspects of T-cells nor, with few exceptions like ALK+ALCL does it pro-vide much insight into the molecular pathways that may be potential for future targeted therapy. In contrast to what occurred among DLBCL, GEP has not dra-matically changed the PTCL, NOS scenario by allow-ing specific subtype identification.[81-82] The relative lack of success in T-cell lymphomas is probably secondary to the rarity of this group of tumors, the heterogeneity of the cellular infiltrates that comprise neoplastic and reactive cells, and our limited knowledge of the normal cellular counterparts.

Gene expression profiling: Not ready for prime time in lymphoma work-up

The design of this classification scheme is very much based on morphology, phenotype and clinical features with molecular and genetic studies required in a hand-ful of entities. The scheme does nonetheless incorporate data from GEP studies on various entities. In general GEP and RNA extraction is laborious and expensive and are therefore currently not ready for real time di-agnosis in clinical practice. This, however, may change if advances in informatics and chip technology make it a reality for routine diagnostics as well as prognosis. Intriguingly, GEP have helped to discover only a limited number of new possible entities such as the GCB and ABC molecular subtypes of DLBCL or some catego-ries of T-cell lymphoblastic leukemia, indicating that the classic pathologic and immunophenotypic approach to the study of lymphomas has been a robust and suc-cessful tool of disease discovery.[83] Deriving useful algo-rithms from GEP studies for routine practice has not been reliable and recently there is data to indicate that immunohistochemistry misclassified cases that were defined by GEP as GCB versus non-GCB. In addi-tion none of the immunostaining algorithms was able to retain the prognostic impact of the groups (GCB vs non-GC).[84] Therefore, stratification based on immu-nostaining algorithms should be used with caution in guiding therapy, even in clinical trials. In summary, elu-cidating the whole genome sequence of a large number of tumors at an affordable cost still remains an elusive goal. New technologies like GEP, CGH array, SNP ar-ray and whole genome sequencing promise new insights into basic biology, allowing us to refine our clinical and pathologic perspectives about lymphomas.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.

2. Jaffe ES, Harris NL, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001.

3. Cancer Incidence Report Saudi Arabia. Kingdom of Saudi Arabia, Ministry of Health. National Cancer Registry. 2006.

4. 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(25):1937-1947.

5. Monti S, Savage KJ, Kutok JL, et al. Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. Blood. 2005; 105(5):1851-1861.

6. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004; 103:275-282.

7. Lossos IS, Czerwinski DK, Alizadeh AA, et al. Prediction of survival in diffuse large-B-cell lymphoma based on the expression of six genes. N Engl J Med. 2004 Apr 29;350(18):1828-37.

8. 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(24):6069- 6076.

9. 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(17):5124-5132.

10. Park S, Lee J, Ko YH, et al. The impact of Epstein-Barr virus status on clinical outcome in diffuse large B-cell lymphoma. Blood. 2007;110(3): 972-978.

11. Asano N, Yamamoto K, Tamaru J, et al. Age-related Epstein-Barr virus (EBV)-associated B-cell lymphoproliferative disorders: comparison with EBV-positive classic Hodgkin lymphoma in elderly patients. Blood. 2009;113(12):2629-2636.

12. Aozasa K, Takakuwa T, Nakatsuka S. Pyothorax associated lymphoma: a lymphoma developing in chronic inflammation. Adv Anat Pathol. 2005; 12(6):324-331.

13. Loong F, Chan AC, Ho BC, et al. Diffuse large B-cell lymphoma associated with chronic inflammation as an incidental finding and new clinical scenarios. Mod Pathol. 2010;23(4):493-501.

14. Miller DV, Firchau DJ, McClure RF, et al. Epstein-Barr virus-associated diffuse large B-cell lymphoma arising on cardiac prostheses. Am J Surg Pathol. 2010;34(3):377-384.

15. Tun HW, Personett D, Baskerville KA, et al. Pathway analysis of primary central nervous system lymphoma. Blood. 2008;111(6):3200-3210.

16. Rubenstein JL, Fridlyand J, Shen A, et al. Gene expression and angiotropism in primary CNS lymphoma. Blood. 2006;107(9):3515-3723.

17. Ferreri AJ, Reni M, Foppoli M, Martelli M, Pangalis GA, Frezzato M, et al. International extramural Lymphoma Study Group (IELSG). High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomized phase 2 trial. Lancet. 2009 Oct 31;374(9700):1512-20.

18. 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(9):3671-3678.

19. Dijkman R, Tensen CP, Jordanova ES, et al. Array-based comparative genomic hybridization analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphoma. J Clin Oncol. 2006; 24(2):296-305.

20. 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(10):3806 - 3812.

21. 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(3):1149-1154.

22. Hans CP, Weisenburger DD, Vose JM, et al. A significant diffuse component predicts for inferior survival in grade 3 follicular lymphoma, but cytologic subtypes do not predict survival. Blood. 2003;101(6):2363-2367.

23. Piccaluga PP, Califano A, Klein U, et al. Gene expression analysis provides a potential rationale for revising the histological grading of follicular lymphomas. Haematologica. 2008;93(7):1033-1038.

24. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3 randomised controlled trial. Lancet. 2011;377(9759):42-51.

25. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group, 1996 guidelines. Blood. 2008;111(12):5446-5456.

26. Chanan-Khan A, Porter CW. Immunomodulating drugs for chronic lymphocytic leukaemia. Lancet Oncol. 2006 Jun;7(6):480-8.

27. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003;30(2):110-115.

28. Lorsbach RB, Shay-Seymore D, Moore J, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. Blood. 2002;99(6):1959-1964.

29. Swerdlow SH. Pediatric follicular lymphomas, marginal zone lymphomas, and marginal zone hyperplasia. Am J Clin Pathol. 2004;122(Suppl): S98-S109.

30. Oschlies I, Salaverria I, Mahn F, et al. Pediatric follicular lymphoma–a clinico-pathological study of a population-based series of patients treated within the Non-Hodgkin's Lymphoma–Berlin-Frankfurt-Munster (NHL-BFM) multicenter trials. Haematologica. 2010;95(2):253-259.

31. Taddesse-Heath L, Pittaluga S, Sorbara L, et al. Marginal zone B-cell lymphoma in children and young adults. Am J Surg Pathol. 2003;27(4):522-531.

32. Rizzo KA, Streubel B, Pittaluga S, et al. Marginal zone lymphomas in children and the young adult population; characterization of genetic aberrations by FISH and RT-PCR. Mod Pathol. 2010; 23(6):866-873.

33. Attygalle AD, Liu H, Shirali S, et al. Atypical marginal zone hyperplasia of mucosa-associated lymphoid tissue: a reactive condition of childhood showing immunoglobulin lambda light-chain restriction. Blood. 2004;104(10):3343-3348.

34. 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(2):443-451.

35. Rodríguez-Pinilla SM, Barrionuevo C, Garcia J, et al. EBV-associated cutaneous NK/T-cell lymphoma: review of a series of 14 cases from Peru in children and young adults. Am J Surg Pathol. 2010;34(12):1773-1782.

36. Ohshima K, Kimura H, Yoshino T, et al. Proposed categorization of pathological states of EBV-associated T/natural killer-cell lymphoproliferative disorder (LPD) in children and young adults: overlap with chronic active EBV infection and infantile fulminant EBV T-LPD. Pathol Int. 2008;58(4):209-217.

37. Jaffe ES. Follicular lymphomas: possibility that they are benign tumors of the lymphoid system. J Natl Cancer Inst. 1983;70(3):401-403.

38. Cong P, Raffeld M, Teruya-Feldstein J, et al. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Blood. 2002;99(9):3376-3382.

39. 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(11):2425-2431.

40. Agopian J, Navarro JM, Gac AC, et al. Agricultural pesticide exposure and the molecular connection to lymphomagenesis. J Exp Med. 2009; 206(7):1473-1483.

41. Zignego AL, Ferri C, Giannelli F, et al. Prevalence of bcl-2 rearrangement in patients with hepatitis C virus-related mixed cryoglobulinemia with or without B-cell lymphomas. Ann Intern Med. 2002; 137(7):571-580.

42. Montes-Moreno S, Castro Y, Rodriguez-Pinilla SM, et al. Intrafollicular neoplasia/in situ follicular lymphoma: review of a series of 13 cases. Histopathology. 2010;56(5):658-662.

43. Roullet MR, Martinez D, Ma L, et al. Coexisting follicular and mantle cell lymphoma with each having an in situ component: a novel, curious, and complex consultation case of coincidental, composite, colonizing lymphoma. Am J Clin Pathol. 2010;133(4):584-591.

44. Aqel N, Barker F, Patel K, Naresh KN. In-situ mantle cell lymphoma–a report of two cases. Histopathology. 2008;52(2):256-260.

45. Espinet B, Sole F, Pedro C, et al. Clonal proliferation of cyclin D1-positive mantle lymphocytes in an asymptomatic patient: an early-stage event in the development or an indolent form of a mantle cell lymphoma? Hum Pathol. 2005;36(11):1232-1237.

46. Nodit L, Bahler DW, Jacobs SA, Locker J, et al. Indolent mantle cell lymphoma with nodal involvement and mutated immunoglobulin heavy chain genes. Hum Pathol. 2003; 34(10):1030-1034.

47. Richard P, Vassallo J, Valmary S, et al. "In situlike" mantle cell lymphoma: a report of two cases. J Clin Pathol. 2006;59(9):995-996.

48. Lecluse Y, Lebailly P, Roulland S, et al. t(11;14)-positive clones can persist over a long period of time in the peripheral blood of healthy individuals. Leukemia. 2009; 23(6):1190-1193.

49. Fernandez V, Salamero O, Espinet B, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res. 2010;70(4):1408-1418.

50. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica. 2009;94(11):1555-1562.

51. 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(2):635-369.

52. Molica S, Mauro F, Giannarelli D, et al. Differentiating chronic lymphocytic leukemia from monoclonal B-lymphocytosis according to the clinical outcome: on behalf of the GIMEMA Chronic Lymphoproliferative Diseases Working Group. Haematologica. 2011;96(2):277-283.

53. Shanafelt TD, Kay NE, Jenkins G, et al. B-cell count and survival: differentiating chronic lymphocytic leukemia from monoclonal B-cell lymphocytosis based on clinical outcome. Blood. 2009;113(18):4188-4196.

54. Rawstron AC, Bennett FL, O'Connor SJ, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Engl J Med. 2008; 359(6):575-583.

55. Shanafelt TD, Ghia P, Lanasa MC, et al. Monoclonal B-cell lymphocytosis (MBL): biology, natural history and clinical management. Leukemia. 2010;24(3):512-520.

56. Nieto WG, Almeida J, Romero A, et al. Increased frequency (12%) of circulating chronic lymphocytic leukemia-like B-cell clones in healthy subjects using a highly sensitive multicolor flow cytometry approach. Blood. 2009;114(1):33-37.

57. Landgren O, Albitar M, Ma W, et al. B-cell clones as early markers for chronic lymphocytic leukemia. N Engl J Med. 2009;360(7):659-667. 67. Dagklis A, Fazi C, Sala C, et al. The immunoglobulin gene repertoire of low-count chronic lymphocytic leukemia (CLL)-like monoclonal B lymphocytosis is different from CLL: diagnostic implications for clinical monitoring. Blood. 2009; 114(1):26-32.

58. 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(11):1411-1421.

59. 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(6):851-862.

60. 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(12):3871-3879.

61. Jaffe ES, Zarate-Osorno A, 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(4):297-303.

62. Garcia JF, Mollejo M, Fraga M, et al. Large B-cell lymphoma with Hodgkin's features. Histopathology. 2005;47(1):101-110.

63. Eberle FC, Rodriguez-Canales J, Wei L, et al. Methylation profiling of mediastinal gray zone lymphoma reveals a distinctive signature with elements shared by classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma. Haematologica. 2011;96(4):558-566.

64. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood. 2010;116(17):3268-3277.

65. Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med. 2006; 354(23):2431-2442.

66. Salaverria I, Zettl A, Bea S, et al. Chromosomal alterations detected by comparative genomic hybridization in subgroups of gene expression-defined Burkitt's lymphoma. Haematologica. 2008;93(9):1327-1334

67. 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(23):2419-2430.

68. Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. Am J Surg Pathol. 2010;34(3):327-340.

69. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. Blood. 2011;117(8): 2319-2331.

70. Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med 2004;351:2159-69.66.

71. Koster A, Tromp HA, Raemaekers JM, et al. The prognostic significance of the intra-follicular tumor cell proliferative rate in follicular lymphoma. Haematologica. 2007;92(2):184-190.

72. LeBoit PE, Burg G, Weedon D, Sarasin A, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Skin Tumours. 3rd ed. Lyon, France: IARC Press; 2007.

73. Willemze R, Jaffe ES, Burg G, et al. WHOEORTC classification for cutaneous lymphomas. Blood. 2005;105(10):3768-3785. 10. Marti GE, Rawstron AC, Ghia P, et al. Diagnostic criteria for monoclonal B-cell lymphocytosis. Br JHaematol. 2005;130(3):325-332.

74. Iqbal J, Weisenburger DD, Greiner TC, et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood. 2010; 115(5):1026-1036.

75. Piva R, Agnelli L, Pellegrino E, et al. Gene expression profiling uncovers molecular classifiers for the recognition of anaplastic large-cell lymphoma within peripheral T-cell neoplasms. J Clin Oncol. 2010;28(9):1583-1590.

76. Salaverria I, Bea S, Lopez-Guillermo A, et al. Genomic profiling reveals different genetic aberrations in systemic ALK-positive and ALK-negative anaplastic large cell lymphomas. Br J Haematol. 2008;140(5):516-526.

77. Savage KJ, Harris NL, Vose JM, et al. ALK-anaplastic large-cell 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(12):5496-5504.

78. deLeeuw RJ, Zettl A, Klinker E, et al. Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. Gastroenterology. 2007;132(5):1902-1911.

79. Mansoor A, Pittaluga S, Beck PL, et al.. NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinico-pathologic features and follow-up in a unique case series. Blood. 2011;117(5):1447-52.

80. Cobaleda C, Busslinger M. Developmental plasticity of lymphocytes. Curr Opin Immunol. 2008; 20(2):139-148.

81. 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 (TFH) cells. Blood. 2007;109(11):4952-4963.

82. Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of Angioimmunoblastic lymphoma indicates derivation from T follicular helper cells and vascular endothelial growth factor deregulation. Cancer Res. 2007;67(22): 10703-10710.

83. Hudson TJ, Anderson W, Artez A, et al. International network of cancer genome projects. Nature. 2010;464(7291):993-998.

84. Gutiérrez-García G, Cardesa-Salzmann T, Climent F, et al. Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Blood. 2011;117(18):4836-43.