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

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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 our 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. 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). 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. 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). Treated similarly, outcomes are remarkably different for either entity underscoring the importance of newer therapeutic strategies. 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.

- 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 and (b) DLBCL associated with chronic or long standing inflammation, most often chronic pyothorax (pyothorax associated lymphoma, PAL). 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: (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. 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. 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-

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**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

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**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.
lymphoid center lymphomas and is managed differently too. Notably, DLBCL, leg type resembles systemic DLBCL of the ABC subtype by GEP. 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). 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). 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 rituximab combined with cyclophosphamide, vincristine 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 demonstrated 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 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/NMZL 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) (<5×10⁹/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 (>4.0×10⁹/L). Population-based studies with the use of highly sensitive
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 signature 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-
environment 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 microenvironment.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 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 lymphoma

Problems and Issues

The current lymphoma classification, as anticipated, has helped clarify many issues besetting lymphoma pathology. 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

Table 3. The WHO Lymphoma Classification, 2008: The Mature T-cell and NK-cell Neoplasms.

| Neoplasm                                                                 |
|--------------------------------------------------------------------------|
| 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.
difficulty on the part of both the practicing pathologist and the treating physician to comprehensively apply 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 hematopathology is becoming so specialized as to preclude the general pathologist from practicing hematopathology. Some tend to overcome this by sending cases for consultation, which although good for standardization of diagnoses, may not always be practical. The treating oncologist 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 identification of the gray zones between CHL and DLBCL highlights how tumor cells may cross boundaries between current categories, suggesting that some entities 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 lymphoma or HL and FL or MCL also underscore the complex ontology of these tumors, which may share a common cell of origin and initial transformation events. This phenomenon recapitulates in a clinical setting the plasticity of hematopoietic cells observed in experimental models, in which modulation of specific transcription factors can reprogram cells to enter disparate differentiation pathways. This raises the question: why have such huge number of separate entities if there is a reasonable potential for cross-over and overlap?

In sharp contrast to B-cell lymphomas, most of the T-cell lymphomas lack defining chromosomal translocations or biomarkers to recognize them. Even differentiating 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 recently the identification of follicular T-helper cells has led to the association of angioimmunoblastic lymphoma 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 provide much insight into the molecular pathways that may be potential for future targeted therapy. In contrast to what occurred among DLBCL, GEP has not dramatically changed the PTCL, NOS scenario by allowing specific subtype identification. 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 handful 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 diagnosis 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 categories of T-cell lymphoblastic leukemia, indicating that the classic pathologic and immunophenotypic approach to the study of lymphomas has been a robust and successful tool of disease discovery. Deriving useful algorithms 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. Therefore, stratification based on immunostaining algorithms should be used with caution in guiding therapy, even in clinical trials. In summary, elucidating 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 array and whole genome sequencing promise new insights into basic biology, allowing us to refine our clinical and pathologic perspectives about lymphomas.
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