The New WHO Nomenclature: Lymphoid Neoplasms

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ABBREVIATIONS: ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; FAB = French-American-British; FLC = follicular large cell lymphoma; FMC = follicular mixed cell lymphomas; FSC = follicular small cleaved lymphomas; LBL = lymphoblastic lymphoma; REAL = Revised European American Classification of Lymphoid Neoplasms; WHO = World Health Organization.

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Focus Continuing Education Credit: *see pages 60 to 63 for learning objectives, test questions, and application form.*

LEARNING OBJECTIVES

1. Compare and contrast the FAB and WHO classifications for lymphoid neoplasms.
2. Explain the four parameters on which the REAL and WHO classifications of lymphoid neoplasms are based.
3. State the three major categories of lymphoid neoplasms in the WHO system.
4. Differentiate between leukemia and lymphoma.
5. Correlate favorable and unfavorable cytogenetic abnormalities with cases of ALL.
6. Compare pre-B and pre-T leukemia with Burkitt leukemia/lymphoma as regards characteristic cells, incidence, immunophenotype, cytogenetic aberrations, and prognosis.

The World Health Organization (WHO) project of classifying tumors of the hematopoietic and lymphoid tissues began in 1995 as a collaborative effort of the European Association for Haematopathology and the Society for Haematopathology. The WHO classification is based on the premise that a classification should define distinct diseases by using all available information instead of relying on one or two major criteria.[1] To that end they used as a starting point the principles defined in the Revised European American Classification of Lymphoid Neoplasms (REAL), published in 1994 by the International Lymphoma Study Group.[2] The REAL classification uses morphology, immunophenotype, genetic features, and clinical features to define an entity. The relative importance of each of these features varies among diseases, i.e., there is no one 'gold standard'. Morphology is always important, but other adjuncts are more characteristic than others in specific subtypes, e.g., immunology might be an important criterion in one disorder, while cytogenetics may be the defining characteristic in another. Although considerable controversy was provoked by the publication of the REAL classification, experience over the next six years proved that the system was reproducible when used by expert hematopathologists.[3]

The WHO classification proposes stratifying lymphoid neoplasms into B cell, T/NK cell neoplasms, and Hodgkin's lymphoma (Hodgkin's disease). The next level of classification separates T and B cell neoplasms into precursor (lymphoblastic) versus mature cell conditions. These are then further subdivided into clinical presentations: leukemic, primary extranodal, and nodal diseases. As to be expected with the lymphoid neoplasms, there is still controversy concerning the subclassification of B cell lymphoma, mature T cell lymphomas, follicular lymphoma, and the use of clinical groupings of the non-Hodgkin lymphomas. The focus of this article will be on the leukemias/lymphomas more commonly seen by the clinical laboratory professional. The tables will include the complete classification. Those readers who desire more information on the histology of the lymphomas not discussed in this article are referred to the WHO publication.[3]

PRECURSOR NEOPLASMS

The French-American-British (FAB) classification divides lymphoblastic leukemias into three categories based on morphology and without any reference to immunophenotypes, genetic features, or prognosis. These three elements are now commonly available and have been shown to be important considerations. Consequently, the FAB nomenclature was determined to be irrelevant. It was also determined that lymphoblastic lymphoma and lymphoblastic leukemia are the same disease with different clinical presentations. There was consensus that marrow and blood involvement are issues for prognosis, not classification. Because precursor lymphoid neoplasms typically present as leukemias, the term acute lymphoblastic leukemia (ALL), should refer to acute leukemia presentations of T/NK and B cells. These are synonymous with FAB L1 and L2.

As with the discussions concerning acute myelogenous leukemia (AML), was it appropriate to include genetic anomalies that, while frequently seen in lymphoid neoplasms, are not on the same level of significance as the Philadelphia chromosome? It was determined these anomalies *do* have prognostic significance and should be part of the classification scheme (Tables 1 and 2).

Precursor B lymphoblastic leukemia/lymphoblastic lymphoma (B-ALL/B-LBL)[3]
When the process of precursor B-cell neoplasm is confined to a mass without evidence of blood or marrow involvement the disorder is referred to as lymphoma. When the process involves extensive blood and marrow involvement, lymphoblastic leukemia is the appropriate term. B-ALL is primarily a disease of children, accounting for 80% to 85% of childhood ALL. B-LBL is an uncommon type of lymphoma with a median age presentation of 20 years.

Precursor B-ALL always involves blood and bone marrow and frequently there is extramedullary involvement, especially in the central nervous system, lymph nodes, spleen, liver and gonads. The WBC count at presentation may be decreased, normal or increased. Bone marrow failure is evidenced by thrombocytopenia and/or anemia and/or neutropenia. Patients often complain of bone pain and arthralgia.

The blasts in both B-ALL and B-LBL vary from small blasts with scant cytoplasm, condensed nuclear chromatin, and indistinct nucleoli (similar to FAB L1) to larger cells with moderate amounts of light blue-to-blue-grey cytoplasm. There may be vacuoles and variable prominent nucleoli (similar to FAB L2). In about 10% of cases there are azurophilic granules. Occasionally cells with cytoplasmic pseudopods are seen (hand mirror cells). Cytochemical stains are not helpful in ALL, but immunophenotype is quite beneficial (Table 2).

Table 1. FAB classification of ALL compared to WHO classification of lymphoproliferative syndromes

FAB classification	WHO classification
ALL L1	Precursor B lymphoblastic leukemia/lymphoblastic lymphoma (Precursor B-cell acute lymphoblastic leukemia)
ALL L2	Precursor T lymphoblastic leukemia/lymphoblastic lymphoma (Precursor T-cell acute lymphoblastic leukemia)
ALL L3	Burkitt leukemia/lymphoma

Table 2. Immunological differentiation of acute lymphoblastic leukemia

MARKER	B-lineage cells				T-lineage cells	
	null	cALL	pre-B	B-ALL	pre-T	T-ALL
Precursor cell antigens						
HLA-Dr	+	+	+	+	0 to 0/+	0
Tdt	+	+	+	0 to 0/+	+	+
CD34	+	+	+	0	0	0
B cell antigens						
CD19	+	+	+	+	+	0
CD22	+	+	+	+	+	0
CD10	0	+	+	+	0 to 0/+	0
CD20	0	0 to +	+	+	0	0
Cytμ	0	0	+	+	0	0
SmIg	0	0	0	+	0	0
T Cell antigens						
CD7	0	0	0	0	+	+
CD3	0	0	0	0	+	+
CD5	0	0	0	0	0 to +	+
CD2	0	0	0	0	0	+
CD1	0	0	0	0	0	0 to +

Several groups of cytogenetic abnormalities are found in B-ALL/B-LBL and are considered in groups: hypodiploid, hyperdiploid <50, hyperdiploid >50, translocations, and pseudodiploid. Cytogenetics is important in prognosis. Precursor B-ALL generally carries a good prognosis with an overall complete remission rate in children of 95% and in adults of 60% to 85%. Those abnormalities that are associated with a favorable prognosis include hyperdiploidy >50 and t(12;21)(p13;q22);TEL/AML1; the latter can only be detected by molecular studies. Unfavorable prognoses are associated with t(9;22)(q34;q11.1); BCR/ABL, hypodiploidy, and t(4:11)(q21;q23);AF4/MLL . Over 50% of children with B-ALL have the good hyperdiploid karyotype or the t(12;21) which predicts an 85% to 90% long-term survival. Because of frequent CNS involvement, treatment must include intrathecal medications.[4] Precursor B-LBL has a high remission rate and a median survival of approximately 60 months.

Precursor T lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/T-LBL)[3]

Precursor T-ALL/T-LBL is a neoplasm committed to T-cell lineage. The designation as leukemia or lymphoma depends on involvement of mass or of blood and bone marrow. T-ALL constitutes 15% of childhood ALL and 25% of adult ALL. Precursor T-LBL comprises about 85% to 90% of lymphoblastic lymphoma. T-ALL presents with a high leukocyte count and often a large mediastinal mass, as contrasted to B-ALL, which has a variable WBC count and only a rare mass. The blasts in T-ALL resemble those seen in B-ALL; however, the number of mitotic figures in T-ALL has been reported to be higher than in B-ALL. Lymph nodes in T-LBL characteristically show complete effacement of normal architecture and a 'starry-sky' effect may be present. Cytochemistry is somewhat helpful in that the T-lymphoblasts show focal acid phosphatase positivity. Immunophenotyping is very helpful.

About one-third of T-ALL/T-LBL cases have abnormalities involving the T-cell receptor loci at 14q11.2, beta locus at 7q35, and the gamma locus at 7p14-15. T-ALL in children is treated as a high risk disease, as is T-LBL. Prognosis for children with T-ALL had been bleak, but with current treatment regimens, survival is comparable to B-ALL.

MATURE B AND T/NK NEOPLASMS

Burkitt leukemia/lymphoma[3]

What the FAB classification called acute lymphoblastic leukemia, L3, is the peripheral blood manifestation of Burkitt lymphoma. The acute leukemia is composed of medium-sized B cells with deeply basophilic cytoplasm, which usually contain lipid vacuoles. Multiple centrally placed nucleoli are usually seen. Very few cases of Burkitt lymphoma present purely as acute leukemia (1% to 2% of ALL cases); extranodal sites are most often involved. In contrast to the blasts of precursor B-ALL, blasts in Burkitt leukemia have a mature cell phenotype. Central nervous system is usually involved and bone marrow involvement is a poor prognostic sign. This is a highly aggressive disease with high tumor burden due to the short doubling time of the tumor. High uric acid levels and elevated lactate dehydrogenase are seen due to rapid cell turnover. A constant genetic feature is translocation involving *MYC*. This is commonly t(8:14) or less commonly t(2:8) or t(8:22). Other genetic aberrations include inactivation of TP53.

Although Burkitt lymphoma is highly aggressive, recent advances in therapy make it potentially curable. Treatment differs from that of other acute lymphoblastic anemias in that it consists of very intensive chemotherapy for a relatively short time. Most patients have a very good prognosis, with 80% to 90% survival. Results are better in children than in adults.[5]

Other B cell neoplasms

A major assumption for this category is that a lymphoma and a leukemia of the same cell type are the same disease, albeit with different presentations. For example, B cell chronic lymphocytic leukemia and mature B cell lymphoma should fundamentally be considered the same disease (Table 3). Although data from several studies suggests that plasmacytoid differentiation of CLL may be a sign of adverse prognosis, the committee felt that there was not enough support for a separate entity. This decision was strongly supported by the data from immunophenotyping (Table 4).

Two points of concern with the inclusion of the lymphomas into this category were discussed. Should lymphoma, specifically the follicular lymphomas, be graded or reported by the presence of large cells? First, the follicular small cleaved lymphomas (FSC) and the follicular mixed cell lymphomas (FMC) seem to be related to each other by sequential biopsies, transitions from one presentation to the other and similar prognoses. Follicular large cell lymphoma (FLC) appears to be more aggressive with earlier relapse and is not seen to transition into either small or mixed cell lymphoma. Additionally, there seemed to be some difficulty in discriminating between small cell and mixed cell follicular lymphoma.

In opposition to the concept that only two categories of follicular lymphoma be used was the pathologists' belief that changing the nomenclature would be confusing. They would prefer a reporting system that defines a grade I lymphoma as having an average of 0 to 5 centroblasts/high power field; grade 2: 6-10 centroblasts/high power field; and grade 3: >15 centroblasts/high power field over ten high power fields. Centroblasts are defined as those activated, rapidly proliferating B cells which occupy the area of the lymphoid follicle close to the T zone of follicle architecture. Centroblasts undergo a high rate of somatic mutation, which alters the affinity of the surface Ig expressed on centrocytes. On binding to an antigen, centrocytes undergo a selection process in which those with high affinity receptors survive to become memory cells or further differentiate into plasma cells. The rest die by apoptosis.[6]

Additionally, they determined that the distinction of 'diffuse' vs. 'follicular' involvement was of value to the prognosis of the patient. The

Table 3. The FAB classification of CLL and lymphomas compared to the WHO classification of lymphoproliferative syndromes

FAB classification	WHO classification
Chronic lymphocytic leukemia	Mature (peripheral) B-cell neoplasms
Non-Hodgkin lymphoma	B-cell CLL/SLL
	Mu HCD
	B-cell prolymphocytic leukemia
	Burkitt lymphoma/Burkitt cell leukemia
	Lymphoplasmacytic leukemia
	Waldenström's macroglobulinemia
	Heavy chain (gamma HCD) disease
Hairy cell leukemia	Hairy cell leukemia
	Plasma cell myeloma/plasmacytoma
	Systemic light chain disease
	Primary amyloidosis
	Splenic marginal zone B-cell lymphoma
	Extranodal marginal B-cell lymphoma
	Heavy chain (alpha HCD) disease
	Follicular lymphoma
	Mantle cell lymphoma
	Diffuse large B-cell lymphoma
	Mature (peripheral T-cell neoplasms)
	Chronic T-cell leukemia/lymphoma
	Smoldering T-cell leukemia/lymphoma
	T-cell prolymphocytic leukemia/ lymphoma
	Small cell
	Cerebriform cell
	Sezary syndrome (mycosis fungoides)
Hodgkin lymphoma	Hodgkin lymphoma

recommended criteria for reporting would be that the term 'follicular' would describe a biopsy in which at least 75% of the material was follicular in architecture; the term 'follicular and diffuse' would describe a biopsy in which between 25% to 75% of the architecture is follicular; and 'diffuse' would describe an architecture that contained less than 25% follicular organization.[7]

Would the unusual mucosa-associated lymphoid tissue be a separate disease or would it be described simply as an extranodal marginal zone B cell lymphoma? The decision was to use the term 'extranodal marginal zone B cell lymphoma' only when the lymphoma was composed of small cells. Should these entities be further graded or stratified was left for future study.

Diffuse large B cell lymphoma (DLBCL) or Burkitt-like lymphoma will not at present be subclassified into centroblastic and immunoblastic. While this may happen at a later date, there was insufficient data to support this at this time. This term 'Burkitt-like' lymphoma will be reserved for high grade tumors with more pleomorphism or larger cells than classical Burkitt, a nearly 100% proliferation fraction, and the presence of c-MYC rearrangement (Table 5). While many B-cell lymphoid disorders are also seen in connection with immunodeficient patients, others are not. Myelomas with their unique bone associated damage have been listed separately (Table 6).

T/NK NEOPLASMS

It was determined that the clinical presentation, location, and course are integral to the classification of the peripheral T/NK cell neoplasms. However, cytologic subclassification is not necessary (Table 3).

Anaplastic large cell lymphoma appears to have two presentations, based on whether the disease is localized to the skin or systemic. Primary cutaneous large cell lymphoma is typically lacking the t(2;5)(p23;q35) mutation, ALK protein negative, and has a slowed course. Future study may find additional and more significant testing for this disorder.

Hodgkin Lymphoma

As it has been determined that Hodgkin disease is a lymphoma, the correct nomenclature should be Hodgkin lymphoma. The committee felt that this change would probably be slow and that both terms, Hodgkin disease and Hodgkin lymphoma, will be used for some time. There was no clear consensus on the use of grading of this disease, only that immunophenotyping is the preferred method when classifying morphologically borderline presentations.

SUMMARY

The development of the WHO classification of lymphoid neoplasms is a remarkable example of cooperation and communication between pathologists and oncologists from around the world. Joint classification committees of the major hematopathology societies will periodically review and update this classification, facilitating further progress in the understanding and treatment of hematologic malignancies.[3]

Table 4. Immunologic classification of chronic lymphocytic leukemia/lymphoma

B-cell disorders	**CD19/20**	**CD24**	**CD5**	**Surface Ig**	**CD10 (CALLA)**	**CD11c**
'Typical' CLL	+	+	+	weak	0	0 (rarely +)
CLL variants	+	+	0	variable	0	0 or +
Prolymphocytic leukemia	+	+ or 0	+	usually moderate	0	?
Hairy cell leukemias	+	+	0	variable	0	+
'Lymphosarcoma' cell leukemia	+	+ or 0	0	strong	+/0	0
T-cell disorders	**CD3/CD2 (pan T)**	**CD4**	**CD8**	**CD7**	**CD25**	**NK Ag**
Sezary leukemia	+	+ (rare 0)	0	0	0 (rare +)	0
Adult T leukemia	+	+	0	0	+	0
T-CLL ('helper')	+	+	0	+	0 to +	0
T-cell ('suppressor')	+	0	+	+	0 or +	0
Large granular lymphocyte syndrome	+	0	+	+ or 0	0	+

Table 5. Burkitt lymphoma described by morphologic variants and clinical types

Morphologic variants Burkitt lymphoma
- Burkitt-like
- with plasmacytoid differentiation (AIDS-associated)

Clinical types of Burkitt lymphoma
- endemic
- sporadic
- immunodeficiency-associated

Table 6. Plasma cell disorders described by morphologic variants and clinical types

Monoclonal gammopathy of undetermined significance (MGUS)

Plasma cell myeloma variants
- indolent myeloma
- smoldering myeloma
- osteosclerotic myeloma (POEMS syndrome)
- plasma cell leukemia
- non-secretory myeloma

Plasmacytoma variants
- solitary plasmacytoma of bone
- extramedullar plasmacytoma

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