Protocol for the Examination of Specimens From Patients With Non-Hodgkin Lymphoma/Lymphoid Neoplasms

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs.

Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of these documents.

**PROTOCOL FOR THE EXAMINATION OF SPECIMENS FROM PATIENTS WITH NON-HODGKIN LYMPHOMA/ LYMPHOID NEOPLASMS**

This protocol applies to non-Hodgkin lymphoma/lymphoid neoplasms involving any site except the ocular adnexa or bone marrow or the primary cutaneous lymphomas mycosis fungoides and Sezary syndrome. The staging systems for non-Hodgkin lymphoma and plasma cell myeloma adopted by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), and the 2008 histologic classification for hematopoietic and lymphoid neoplasms of the World Health Organization (WHO) are recommended.

**SURGICAL PATHOLOGY CANCER CASE SUMMARY (CHECKLIST)**

Non-Hodgkin Lymphoma/Lymphoid Neoplasms: Biopsy, Resection

Select a Single Response Unless Otherwise Indicated

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Specimen (select all that apply) (note A)

___ Lymph node(s)
___ Other (specify): _______________________________
___ Not specified

Procedure

___ Biopsy
___ Resection
___ Other (specify): _______________________________
___ Not specified

Tumor Site (select all that apply) (note B)

___ Lymph node(s), site not specified
___ Lymph node(s)
___ Specify site(s): _______________________________
### Precursor Lymphoid Neoplasms

- **B lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)**
  - t(9;22)(q34;q11.2): BCR-ABL1
- **B lymphoblastic leukemia/lymphoma with t(11;14)(q13;q23): MLL rearranged**
- **B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22): TEL-AML1 (ETV6-RUNX1)**
- **B lymphoblastic leukemia/lymphoma with hyperdiploidy**
- **B lymphoblastic leukemia/lymphoma with hypodiploidy (hypodiploid acute lymphoblastic leukemia/lymphoma [ALL])**
- **B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32): IL3-IGH**
- **B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3): E2A-PBX1 (TCF3-PBX1)**
- **T lymphoblastic leukemia/lymphoma**

### Mature B-Cell Neoplasms

- **B-cell lymphoma, subtype cannot be determined**
  (Note: not a category within the WHO classification)
- **Chronic lymphocytic leukemia/small lymphocytic lymphoma**
- **B-cell prolymphocytic leukemia**
- **Splenic B-cell marginal zone lymphoma**
- **Hairy cell leukemia**
- **Splenic B-cell lymphoma/leukemia, unclassifiable**
- **Splenic diffuse red pulp small B-cell lymphoma**
- **Hairy cell leukemia variant**
- **Lymphoplasmacytic lymphoma**
- **γ Heavy-chain disease**
- **μ Heavy-chain disease**
- **α Heavy-chain disease**
- **Plasma cell myeloma**
- **Solitary plasmacytoma**
- **Extramedullary plasmacytoma**
- **Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)**
- **Nodal marginal zone lymphoma**
- **Pediatric nodal marginal zone lymphoma**
- **Follicular lymphoma**
- **Pediatric follicular lymphoma**
- **Primary intestinal follicular lymphoma**
- **Primary cutaneous follicle center lymphoma**
- **Mantle cell lymphoma**
- **Diffuse large B-cell lymphoma (DLBCL), NOS**
- **T cell/histiocyte-rich large B-cell lymphoma**
- **Primary DLBCL of the central nervous system (CNS)**
- **Primary cutaneous DLBCL, leg type**
- **Epstein-Barr virus (EBV)-positive DLBCL of the elderly**
- **DLBCL associated with chronic inflammation**
- **Lymphomatoid granulomatosis**
- **Primary mediastinal (thymic) large B-cell lymphoma**
- **Intravascular large B-cell lymphoma**
- **Anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma**
- **Plasmablastic lymphoma**
- **Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease**
- **Primary effusion lymphoma**
- **Burkitt lymphoma**
- **B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma**
- **B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma**
- **Other (specify):**

### Mature T- and NK-Cell Neoplasms

- **T-cell lymphoma, subtype cannot be determined**
  (Note: not a category within the WHO classification)
- **T-cell prolymphocytic leukemia**
- **T-cell large granular lymphocytic leukemia**
- **Chronic lymphoproliferative disorder of NK cells**
- **Aggressive NK-cell leukemia**
- **Systemic EBV-positive T-cell lymphoproliferative disease of childhood**
- **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**
- **Primary cutaneous anaplastic large cell lymphoma**
- **Lymphomatoid papulosis**
- **Primary cutaneous γδ T-cell lymphoma**
- **Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma**
- **Primary cutaneous CD4⁺ small/medium T-cell lymphoma**
- **Peripheral T-cell lymphoma, NOS**
- **Angioimmunoblastic T-cell lymphoma**
- **Anaplastic large cell lymphoma, ALK positive**
- **Anaplastic large cell lymphoma, ALK negative**
- **Other (specify):**

### Histiocytic and Dendritic Cell Neoplasms

- **Histiocytic sarcoma**
- **Langerhans cell histiocytosis**
- **Langerhans cell sarcoma**
- **Interdigitating dendritic cell sarcoma**
- **Follicular dendritic cell sarcoma**
- **Primary intestinal histiocytic lymphoma**
- **Lymphohistiocytoma**
- **Fibroblastic reticular cell tumor**
- **Disseminated juvenile xanthogranuloma**

### Posttransplant Lymphoproliferative Disorders (PTLDs)

- **Early lesions**
  - **Plasmacytic hyperplasia**
  - **Infectious mononucleosis-like PTLD**
  - **Polymorphic PTLD**
  - **Monomorphic PTLD (B- and T/NK-cell types)**
  
    **Specify subtype:**
    - **Classical Hodgkin lymphoma type PTLD**

Note: Italicized histologic types denote provisional entities in the 2008 WHO classification.
An initial diagnosis of “B lymphoblastic leukemia/lymphoma, NOS” may need to be given before the cytogenetic results are available.

These disorders are listed for completeness, but not all of them represent frank lymphomas.

Classic Hodgkin lymphoma type PTLD can be reported by using either this protocol or the separate College of American Pathologists protocol for Hodgkin lymphoma.

**Pathologic Extent of Tumor (select all that apply) (note D)**

* Involvement of a single lymph node region
  * Specify site: ____________________________

* Involvement of 2 or more lymph node regions on the same side of the diaphragm
  * Specify sites: ____________________________

* Involvement of lymph node regions on both sides of the diaphragm
  * Specify sites: ____________________________

* Spleen involvement

* Liver involvement

* Bone marrow involvement

* Other site involvement
  * Specify site(s): ____________________________

**Additional Pathologic Findings**

* Specify: ____________________________

**Immunophenotyping (Flow Cytometry and/or Immunohistochemistry) (note E)**

* Performed, see separate report: ____________________________

  * Performed

  * Specify method(s) and results: ____________________________

  * Not performed

* Cytogenetic Studies (note E)

* Performed, see separate report: ____________________________

  * Performed

  * Specify method(s) and results: ____________________________

  * Not performed

**Molecular Genetic Studies (note E)**

* Performed, see separate report: ____________________________

  * Performed

  * Specify method(s) and results: ____________________________

  * Not performed

**Clinical Prognostic Factors and Indices (select all that apply) (note F)**

* International Prognostic Index (IPI) (specify): ____________________________

* Follicular Lymphoma International Prognostic Index (FLIPI) (specify): ____________________________

* B symptoms present

* Other (specify): ____________________________

**Comment(s): ____________________________

**EXPLANATORY NOTES**

A: Specimen.—Any number of specimen types may be submitted in the evaluation of lymphoid neoplasms. Lymph nodes, skin, gastrointestinal (GI) tract, bone marrow, spleen, thymus, and tonsils are among the most common. Specimens submitted with a suspected diagnosis of lymphoma require special handling to optimize the histologic diagnosis and to prepare the tissue for molecular and other ancillary special studies. The guidelines detailed below are suggested for specimen handling in cases of suspected lymphoma.

- Tissue should be received fresh. Unsectioned lymph nodes should not be immersed in fixative, and care should be taken to make thin slices of the node to ensure optimal penetration of fixative.
- The fresh specimen size, color, and consistency should be recorded, as should the presence or absence of any visible nodularity, hemorrhage, or necrosis after serial sectioning at 2-mm intervals perpendicular to the long axis of the lymph node.
- Touch imprints may be made from the freshly cut surface, and the imprints fixed in alcohol or air-dried.
- For cytogenetic studies or culture of microorganisms: submit a fresh portion of the node (or other specimen type) steriley in appropriate medium.
- For immunophenotyping by flow cytometry: submit a fresh portion of the specimen in appropriate transport media such as RPMI-1640 (Roswell Park Memorial Institute–1640).
- Fixation (record fixative[s] used for individual slices of the specimen):
  - Estimated time from excision to fixation should be noted, if possible, as this may impact preservation or recovery of certain analytes such as RNA and phosphoproteins in fixed tissues.
  - Zinc formalin or B5 produces superior cytologic detail but is not suitable for DNA extraction and may impair some immunostains (eg, CD30). B5 also has the additional limitation of requiring proper hazardous-materials disposal.
  - Formalin fixation is preferable when the tissue sample is limited, as it is most suitable for many ancillary tests such as molecular/genetic studies, in situ hybridization, and immunophenotyping.
  - Overfixation (ie, more than 24 hours in formalin, more than 4 hours in zinc formalin or B5) should be avoided for optimal immunophenotypic reactivity.
- Snap-frozen tissue is optimal for DNA and RNA extraction.
  - Place in aluminum foil or cover in OCT (optimal cutting temperature) medium.
  - Immerse in dry ice/isopentane slush or liquid nitrogen.
  - Store at −80°C until needed.

B: Tumor Site.—The anatomic sites that constitute the major structures of the lymphatic system include groups and chains of lymph nodes, the spleen, the thymus, Waldeyer ring (a circular band of lymphoid tissue that surrounds the oropharynx, consisting of the palatine, lingual, and pharyngeal tonsils), the veriform appendix, and the Peyer patches of the ileum. Minor sites of lymphoid tissue include the bone marrow, mediastinum, liver, skin, lung, pleura, and gonads. Involvement of extranodal sites is more common in non-Hodgkin lymphomas (NHLs) than in Hodgkin lymphoma. In addition, some NHLs, such as mycosis fungoides and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), occur predominantly or entirely in extranodal sites.
C: Histologic Type.—This protocol recommends assigning histologic type on the basis of WHO classification of lymphoid neoplasms. It was originally published in 2001 and recently was revised and updated in 2008. This classification encompasses both nodal and extranodal lymphomas and provides distinction of individual lymphoid neoplasms based upon morphologic, immunophenotypic, cytogenetic, and clinical features. While histologic examination typically is the gold standard, most lymphoid neoplasms will require the utilization of 1 or more ancillary techniques, such as immunophenotyping, molecular studies, and/or cytogenetics to arrive at the correct diagnosis. If the specimen is inadequate or suboptimal for a definitive diagnosis and subtyping, this information should also be relayed to the clinician with an explanation of what makes the specimen inadequate or suboptimal.

D: Pathologic Extent of Tumor (Stage).—In general, the TNM classification has not been used for staging of lymphomas because the site of origin of the tumor is often unclear and there is no way to differentiate among T, N, and M. Thus, a special staging system (Ann Arbor system) is used for both Hodgkin lymphoma and NHL. It was originally published more than 30 years ago for staging Hodgkin lymphoma. The Ann Arbor classification for lymphomas has been applied to NHL by the AJCC and the UICC except for mycosis fungoides and Sezary syndrome.

For multiple myeloma, the Durie-Salmon staging system is recommended by the AJCC. The international staging system for multiple myeloma is useful for determining survival. The Ann Arbor classification and Durie-Salmon staging systems are shown below. It should also be realized that the St Jude staging system is commonly used for pediatric patients.

Pathologic staging depends on the biopsy of multiple lymph nodes on both sides of the diaphragm, splenectomy, wedge liver biopsy, and bone marrow biopsy to assess distribution of disease. Currently, staging of NHL is more commonly clinical than pathologic. Clinical staging generally involves a combination of clinical, radiologic, and surgical data. Physical examination, laboratory tests (eg, complete blood examination and blood chemistry studies including lactate dehydrogenase [LDH] and liver function tests), imaging studies (eg, computed tomography scans, magnetic resonance imaging studies, and positron emission tomography), biopsy (to determine diagnosis, histologic type, and extent of disease), and bone marrow examination are often required. In patients at high risk for occult CNS involvement, cerebrospinal fluid cytology should be performed.

There is almost universal agreement that the stage of the NHL is prognostically significant. Correct diagnosis and staging are the key factors in National Comprehensive Cancer Network treatment schema that most clinicians use.

AJCC/UICC Staging for Non-Hodgkin Lymphomas

Stage I: Involvement of a single lymph node region (I), or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE).‡

Stage II: Involvement of 2 or more lymph node regions on the same side of the diaphragm (II), or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement, with or without involvement of other lymph node regions on the same side of the diaphragm (IIIE).‡

Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (III S) or both (IIIE + S).‡

Stage IV: Diffuse or disseminated involvement of 1 or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver, bone marrow, or nodular involvement of the lung(s) or cerebral spinal fluid.

* Multifocal involvement of a single extralymphatic organ is classified as stage IE and not stage IV.
† For all stages, tumor bulk greater than 10 to 15 cm is an unfavorable prognostic factor.
‡ The number of lymph node regions involved may be indicated by a subscript: for example, IIE. For stages II to IV, involvement of more than 2 sites is an unfavorable prognostic factor.
§ For stages III to IV, a large mediastinal mass is an unfavorable prognostic factor.

Note: Direct spread of a lymphoma into adjacent tissues or organs does not influence classification of stage.

AJCC/UICC Staging for Plasma Cell Myeloma

Stage I: Hemoglobin level greater than 10.0 g/dL
Serum calcium level lower than or equal to 12 mg/dL
Normal bone x-rays or a solitary bone lesion
Immunoglobulin (Ig) G level lower than 5 g/dL
IgA level lower than 3 g/dL
Urine M protein amount less than 4 g/24 hours

Stage II: One or more of the following are included
Hemoglobin level lower than 8.5 g/dL
Serum calcium level greater than 12 mg/dL
Advanced lytic bone lesions
IgG level greater than 7 g/dL
IgA level greater than 5 g/dL
Urine M protein amount greater than 12 g/24 hours

Stage III: Disease fitting neither stage I nor stage III

Note: Patients are further classified as having (1) serum creatinine levels lower than 2.0 mg/dL or (2) serum creatinine levels 2.0 mg/dL or greater. The median survival for stage IA disease is about 5 years and that for stage IIIB disease is 15 months.

E: Immunophenotyping and Molecular Genetic Studies.—Immunophenotyping can be performed by flow cytometry or immunohistochemistry. Each has its advantages and disadvantages. Flow cytometry is rapid (hours), quantitative, and allows multiple antigens to be evaluated on the same cell simultaneously. Antigen positivity, however, cannot be correlated with architecture or cytopathic features. Immunohistochemistry requires hours/days to perform, quantitation is subjective, but importantly it allows correlation of antigen expression with architecture and cytology. Not all antibodies are available for immunohistochemistry, particularly in fixed tissues, but one of its advantages is that it can be performed on archival tissue.
Both techniques can provide diagnostic as well as clinically relevant information (eg, identification of therapeutic targets such as CD20). Molecular studies now play an increasingly important role in the diagnosis of hematopoietic neoplasms. They aid not only in helping establish clonality but also in determining lineage, establishing the diagnosis of specific disease entities, and monitoring minimal residual disease.

**Immunophenotypes and Genetics**

The following is to be used as a guideline for the more common immunophenotyping and cytogenetic findings for each entity. It is, however, not entirely comprehensive and individual cases may vary somewhat in their immunophenotypic and cytogenetic profile.

### Precursor Lymphoid Neoplasms

B Lymphoblastic Leukemia/Lymphoma, NOS: s Ig–, cytoplasmic μ chain (30%), CD19+, CD20+/−, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10−/+, CD34−, CD13−/+, CD33−/+, IGH gene rearrangement +/-, IGL gene rearrangement −/+, TCR gene rearrangement −/+, variable cytogenetic abnormalities.

B Lymphoblastic Leukemia/Lymphoma With t(9;22)(q34;q11.2); BCR-ABL1: s Ig–, cytoplasmic μ chain (30%), CD19+, CD20−/+, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10−/+, CD34−, CD13−/+, CD33−/+, IGH gene rearrangement +/-, IGL gene rearrangement −/+, TCR gene rearrangement −/+, variable cytogenetic abnormalities.

B Lymphoblastic Leukemia/Lymphoma With t(11;1q23); MLL Rearranged: s Ig–, cytoplasmic μ chain (30%), CD19+, CD20+/−, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10−/+, CD34−, CD13−/+, CD33−/+, CD15−, IGH gene rearrangement +/-, IGL gene rearrangement −/+, TCR gene rearrangement −/+, variable cytogenetic abnormalities.

B Lymphoblastic Leukemia/Lymphoma With t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1): s Ig–, cytoplasmic μ chain (30%), CD19+, CD20−/+, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10−/+, CD34−, CD13−/+, CD33−/+, CD15−, IGH gene rearrangement +/-, IGL gene rearrangement −/+, TCR gene rearrangement −/+, variable cytogenetic abnormalities.

B Lymphoblastic Leukemia/Lymphoma With Hyperdiploidy: s Ig–, cytoplasmic μ chain (30%), CD19+, CD20−/+, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10−/+, CD34−, CD13−/+, CD33−/+, IGH gene rearrangement +/-, IGL gene rearrangement −/+, TCR gene rearrangement −/+, variable cytogenetic abnormalities.

B Lymphoblastic Leukemia/Lymphoma With Hypodiploidy: s Ig–, cytoplasmic μ chain (30%), CD19+, CD20−/+, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10−/+, CD34−, CD13−/+, CD33−/+, IGH gene rearrangement +/-, IGL gene rearrangement −/+, TCR gene rearrangement −/+, variable cytogenetic abnormalities.

### B Lymphoblastic Leukemia/Lymphoma With t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1): s Ig–, cytoplasmic μ chain (30%), CD19+, CD20−/+, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10−, CD34−/+, CD13−/+, CD33−/+, CD15−, IGH gene rearrangement +/-, IGL gene rearrangement −/+, TCR gene rearrangement −/+, variable cytogenetic abnormalities.

### T Lymphoblastic Leukemia/Lymphoma: TdT+, CD7−, CD3−/− (usually surface CD3+), variable expression of other pan T antigens, CD1a−/−, often CD4 and CD8 double positive or double negative, Ig−, panB−; variable TCR gene rearrangements; IgH gene rearrangement −/+, chromosomal abnormalities are common and often involve 14q11–14, 7q35, or 7p14–15.

### Mature B-Cell Neoplasms

#### Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Faint s IgM+, s IgD−/+−, s Ig−, panB+ (CD19+, CD20+), CD5−, CD10−, CD23−, CD43−, CD11c−/−; IGH and IGL gene rearrangements; trisomy 12; del(13q), del(17p), or del(11q) can be seen.

B-Cell Prolymphocytic Leukemia: s IgM, s IgD−/−, pan B+ (CD19+, CD20+, CD22+, CD79a+), and FMC-7, CD5−, CD23−/−, del(17p), t(11;14)(q13;q32), breakpoints involving 13q14.

#### Splenic B-Cell Marginal Zone Lymphoma: s IgM+, s IgD−/−, CD20−, CD79a+, CD5+, CD10−, CD23+, CD43−, nuclear cyclin D1−/−, TCR gene rearrangement −/−, variable cytogenetic abnormalities.

#### Splenic Diffuse Red Pulp Small B-Cell Lymphoma: s IgG+, s IgD−/+−, s IgM−, CD20−, DBA.44+, CD5+, CD10−, CD23+, CD43−, CD11c+, CD25+, TCR gene rearrangement −/−, variable cytogenetic abnormalities.

#### Hairy Cell Leukemia: s IgM+ (IGH, IGD, IGG, or IGA), panB+, CD79a+, CD79b+, DBA.44+, CD123+, CD5−, CD10−, CD23−, CD11c−, CD25+, TCR gene rearrangement −/−, variable cytogenetic abnormalities.

#### Lymphoplasmacytic Lymphoma: s IgM+, s IgD−/−, CD10−, CD19−, CD20−, CD79a−, CD79b−, CD38−/−, CD5−, CD13−, CD20+ (in plasma cells), CD11c−, TCR−, TRAP−, variable cytogenetic abnormalities.

#### Heavy-Chain Disease (Immunoproliferative Small Intestinal Disease): cytoplasmic μ heavy chain +, CD20− (lymphocytes), CD31− (plasma cells), light chain −.

#### Heavy-Chain Disease: IgG heavy chain +, CD79a+, CD20− (on lymphocytes), CD31− (in plasma cells), CD5−, CD10−, light chain −, abnormal karyotype in 50% without recurring abnormalities.

#### Heavy-Chain Disease: monoclonal cytoplasmic μ heavy chain +, B-cell antigen +, CD5−, CD10−, surface light chain −.

#### Plasma Cell Myeloma: s IgG+, (IGH, IGA, rare IGD, IGM, or IGE or light chain only), panB− (CD19−, CD22−, CD79a−, CD45−, CD8−, HLA-DR−/−, CD38−, CD56−, CD138−, EMA−/−, CD43−, cyclin D1+; IGH and IGL gene rearrangements; numerical and structural chromosomal abnormalities are common, including trisomies (often involving odd-numbered chromosomes), deletions (most commonly involving 13q14), and translocations (often involving 14q32).
Solitary Plasmacytoma of Bone: clG+ (IGG, IGA, rare IGD, IGM, or IGE or light chain only), panB− (CD19−, CD20−, CD22−, CD79a−, CD45−/−, HLA-DR−/+; CD38+, CD56−/−, CD138−, EMA−/+; CD43−/−, cyclin D1+, IGH and IGL gene rearrangements; deletions, most commonly 13q, and occasional translocations, in particular t(11;14)(q13;q32).

Extramedullary Plasmacytoma: clG+ (IGG, IGA, rare IGD, IGM, or IGE or light chain only), panB− (CD19−, CD20−, CD22−, CD79a−, CD45−/−, HLA-DR−/+; CD38+, CD56−/−, CD138−, EMA−/+; CD43−/−, cyclin D1+, IGH and IGL gene rearrangements; deletions, most commonly 13q, and occasional translocations, in particular t(11;14)(q13;q32).

Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma): sIgG (IGM or IGA or IGG), sIgD−, clG−/+; panB+, CD5+, CD10−, CD23−, CD43−/+; IGH and IGL gene rearrangements, BCL1 and BCL2 germline, trisomy 3 or t(11;18)(q21;q21) may be seen.

Nodal Marginal Zone Lymphoma: sIgM+, sIgD−, clG−/+; panB+, CD5+, CD10+, CD23+, CD43−/+; IGH and IGL gene rearrangements, BCL1 and BCL2 germline.

Follicular Lymphoma: sIgG (usually IGM+/−/IGD, IGG, IGA), panB+, CD20+, CD10−, CD23−/−, CD43−, CD11c+, CD25−; overexpression of BCL2+/− (useful to distinguish from reactive follicles), BCL6+, IGH and IGL gene rearrangements, t(14;18)(q32;q21) with rearranged BCL2 gene (70%–95% in adults).

Pediatric Follicular Lymphoma: sIgG (usually IGM+/−IGD, IGG, IGA), panB+, CD20−/+, CD10−/+, CD43−, CD11c+, CD25−; overexpression of BCL2−; BCL6+, t(14;18) with rearranged BCL2 gene −/−.

Primary Cutaneous Follicle Center Lymphoma: CD20+, CD79a+, CD10−, CD23−, CD43+, CD11c+, CD25−; IGH and IGL gene rearrangements, t(11;14)(q13;q32); BCL1 gene rearrangements (CCND1/cyclinD1) common.

Diffuse Large B-Cell Lymphoma (DLBCL), NOS: panB+, surface or cytoplasmic IGM > IGG > IGA, CD45−/−, CD10−/+, CD56+, BCL6+/−, 3q27 region abnormalities involving BCL6 seen in 30% of cases, t(14;18) involving BCL2 seen in 20% to 30% of cases; MYC rearrangement seen in 10% of cases.

T-Cell/Histiocytic-Rich Large B-Cell Lymphoma: panB+, BCL6+, BCL2−/−, EMA−/+; background composed of CD3+ and CD5− T cells and CD68+ histiocytes.

Primary DLBCL of the CNS: CD20+, CD22+, CD79a+, CD10−, BCL6+/−, IRF4/MUM1−/+; BCL2−/+; BCL6 translocations −/−; del(6q) and gains of 12q, 22q, and 18q21 common.

Primary Cutaneous DLBCL, Leg Type: sIgG, CD20+, CD79a+, CD10+, BCL2+, BCL6+, IRF4/MUM1+, FOXP1+; translocations involving MYC, BCL6, and IGH genes are common.

EBV-Positive Diffuse Large B-Cell Lymphoma of the Elderly: CD20−/−, CD79a−, CD10+, IRF4/MUM1−/+; BCL6−, LMP+, EBER+.

DLBCL Associated With Chronic Inflammation: CD20−/−, CD79a−, CD138−, IRF4/MUM1−/+; CD30−, T-cell markers −/−, LMP+, EBER+.

Lymphomatoid Granulomatosis: CD20+, CD30−/−, CD79a−, CD15+, LMP−, EBER−.

Primary Mediastinal (Thymic) Large B-Cell Lymphoma: sIg−/−, panB+, (especially CD20, CD79a), CD45−/−, CD15−, CD30−/−(weak), IRF4/MUM1−/+; BCL2+/-, BCL6−, CD23+, MAL+, IGH and IGL gene rearrangements.

Intravascular Large B-Cell Lymphoma: panB+ (CD19, CD20, CD22, CD79a), CD5−, CD10−, IRF4/MUM1+.

ALK-Positive Large B-Cell Lymphoma: ALK+, CD138+, EMA+, VS38c+, CD45−, CD4−, CD20−, CD79a−, CD3−, CD30−, IRF4/MUM1−/+; ALK+, CD57−, PA5X−/+; EBER−/+, EMA−/-, CD30−/−.

Large B-Cell Lymphoma Arising in HHV8-Associated Multicentric Castleman Disease: CD20−/−, CD79a+, CD38−, CD138+, EBER−, light-chain restricted.

Primary Effusion Lymphoma: CD45−/−, CD30−/−, CD138−, EMA−/+, CD19+, CD20−, CD79a−, CD3−, BCL6−, HHV8/KSHV, EBV−/-, IGH and IGL gene rearrangements.

Burkitt Lymphoma: CD8+, panB+, CD5−, CD10+, BCL6+, CD38−, CD24−, CD79a−; Ki-67 95%–100%; BCL2−, TdT−, IGH and IGL gene rearrangements, t(8;14)(q24;q32) and variants t(2;8)(p12;q24) and t(8;22)(q24;q11); rearranged MYC gene; EBV common (95%) in endemic cases and infrequent (15%–20%) in sporadic cases, intermediate incidence (30%–40%) in HIV-positive cases.

B-Cell Lymphoma, Unclassified, With Features Intermediate Between Diffuse Large B-Cell Lymphoma and Burkitt Lymphoma: panB+, CD10+, BCL6−, BCL2−/−, IRF4/MUM1−, Ki-67 95%–100%, 8q24/MYC translocation (35%–50%), BCL2 translocation (15%), and occasionally both translocations (so-called double hit lymphoma).


Mature T-Cell and NK-Cell Neoplasms

T-Cell Prolymphocytic Leukemia, panT+ (CD2, CD3, CD5, CD7, CD25−, CD4+/CD8− > CD4+/CD8− > CD4−/CD8+, TCL1+, TdT−, CD1a−; TCR gene rearrangements, 75% show inv 14 with breakpoints at q11 and q32, 10% have a reciprocal tandem translocation t(14;14)(q11;q32).

T-Cell Large Granular Lymphocytic Leukemia: panT+ (CD2, CD3, CD5−/−, CD7+, TCR+, CD4+, CD8−, CD16+, CD56+, CD57−, TIA1+, granzyme B+, TdT−; most cases show clonal TCR gene rearrangements.

Chronic Lymphoproliferative Disorder of NK Cells: sCD3−, CD3−, CD16+, CD56 (weak), TIA1+, granzyme B−, CD8−, CD2−, CD7−, CD57−, EBV−, karyotype is typically normal.

Aggressive NK-Cell Leukemia: CD2−, sCD3−, cCD3+, CD56+, TIA−/−, CD16−, CD57+, Fas ligand +, EBV+, del(6)(q21q25) and del(11q) can be seen.

Systemic EBV-Positive T-Cell Lymphoproliferative Disease of Childhood: CD2−, CD3−, TIA+, CD8− (if associated with acute EBV infection), EBER+, CD56+, TCR gene rearrangements +.

Hydroa Vacciniforme-like Lymphoma: Cytotoxic T-cell or less often CD56+ NK-cell phenotype, EBER−/−, TCR gene rearrangement +.

Adult T-Cell Leukemia/Lymphoma (HTLV+): panT+ (CD2+, CD3+, CD5−, CD7+, CD4−, CD8+, CD10+, CD25−,
TdT−; TCR gene rearrangements, clonally integrated HTLV1.

Extranodal NK/T-Cell Lymphoma: CD2+, CD5−, CD7−/+, CD3−, CD56−, TdT−; usually no TCR or Ig gene rearrangements; usually EBV+

Enteropathy-Associated T-Cell Lymphoma: CD3+, CD7−, CD4+, CD8−, CD10−, TdT−.

Hepatosplenic T-Cell Lymphoma: CD2+, CD3−, TCR γ/δ+; TCR γ/δ rarely +, CD5−, CD7−, CD4+, CD8−, CD56+, TCR gene rearrangements +; isochromosome 7q and trisomy 8 common.

Subcutaneous Fatty-Like T-Cell Lymphoma: CD8+, granzyme B+, TIA1+, perforin+, TCR α/β+, CD4+, CD56−.

Lymphomatoid Papulosis: CD4+, CD2−/+, CD3+, CD5+, CD30+, TIA1+, granzyme B+−/−, CD30−/−; TCR gene rearrangements +−.


Primary Cutaneous γδ T-Cell Lymphoma: TCR γ/δ+, CD2+, CD3+, CD5+, CD7−/+, CD8−, βF1−.

Primary Cutaneous CD8-Positive Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma: CD3−, granzyme B+, perforin+, TIA1+, CD45RA−, CD2−/−, CD4+, CD5+, CD7−, EBV−, βF1+; TCR gene rearrangements (α/β) +.

Primary Cutaneous CD4-Positive Small/Medium T-Cell Lymphoma: CD3+, CD4+, CD8−, CD30−, TCR gene rearrangements +.

Peripheral T-Cell Lymphoma, NOS: panT variable (CD2−/−, CD3−/−, CD5−/−, CD7−/−), most cases CD4+, some cases CD8+, a few cases are CD4+/CD8−, or CD4+/CD8+; TCR gene rearrangements +.

Angioimmunoblastic T-Cell Lymphoma: panT+ (often with variable loss of some panT antigens), usually CD4+, PD1+, CXCL13++; TCR gene rearrangements in 75%; IGH gene rearrangements in up to 30%; EBV often positive in B cells.

Anaplastic Large Cell Lymphoma, ALK Positive: CD30+, ALK+, EMA+/−, CD3−/−, CD5−/−, CD7−/−, CD4+, CD8−/−, CD43−/−, CD25+, CD45R0−, TIA1−/−, granzyme+−/−, perforin+−/−, EBV−, TCR gene rearrangements +−, t(2;5)(p23;35) in 80% of cases, t(1;2)(q25;p23) in 10% to 15% of cases. Other various translocations can also be seen.


Hiostiocytic and Dendritic Cell Neoplasms

Histiocytic Sarcoma: CD45+, CD68+, CD68+, lysozyme+, CD45RO−/+, HLA-DR−, CD4−, CD3−, CD10−, TIA1−, CD21−, CD35−, CD33−, myeloperoxidase−, lack IGH and TCR gene rearrangements.

Langerhans Cell Histiocytosis: CD1a+, CD1a+, CD1a+, vimentin+, CD68+, HLA-DR+, CD4−, CD30−, most B- and T-cell markers are negative, there are no consistent cytogenetic abnormalities.

Langerhans Cell Sarcoma: CD1a+, CD1a+, vimentin+, CD68+, HLA-DR+, CD4−, CD30−, most B- and T-cell markers are negative, there are no consistent cytogenetic abnormalities.

Interdigitating Dendritic Cell Sarcoma: S100+, vimentin+, CD1a−, langerin−, CD45−, CD68−, lysozyme+, p53+−/−, CD21−, CD23−, CD35−, CD34−, CD30−, myeloperoxidase−, most B- and T-cell markers are negative, lack IGH and TCR gene rearrangements.


Disseminated Juvenile Xanthogranuloma: vimentin+, CD14+, CD68+, CD68+, factor XIIIa+−/−, TIA1−, CD1a+, langerin−, lack IGH and TCR gene rearrangements.

F: Clinical Prognostic Factors and Indices.—The specific histologic type of the lymphoid neoplasm, stage of disease, as well as the International Prognostic Index (IPI score) are the main factors used to determine treatment in adults. 13,21,28−35 The 5 pretreatment characteristics that have been shown to be independently statistically significant are: age in years (≤60 versus >60); tumor stage I or II (localized) versus III or IV (advanced); number of extranodal sites of involvement (0 or 1 versus >1); patient’s performance status (0 or 1 versus 2 to 4); and serum LDH (normal versus abnormal). On the basis of the number of risk factors, patients can be assigned to 1 of 4 risks groups: low (0 or 1), low intermediate (2), high intermediate (3), or high (4 or 5). Patients stratified by the number of risk factors were found to have very different outcomes with regard to complete response (CR), relapse-free survival (RFS), and overall survival (OS). 13 Studies show that low-risk patients had an 87% CR rate and an OS rate of 73% at 5 years as compared to high-risk patients who had a 44% CR rate and a 26% 5-year overall survival rate. 13 A revised IPI (R-IPI) has been proposed for patients with diffuse large B-cell lymphoma who are treated with rituximab plus CHOP (cyclophosphamide, Adriamycin, vincristine, prednisone) chemotherapy. 34 In pediatric cases, there is no equivalent of the IPI, and prognosis is based on stage and type of lymphoma. 36

A separate prognostic index has become accepted for follicular lymphoma. The Follicular Lymphoma International Prognostic Index (FLIPI) appears to provide greater discrimination and stratification among patients with follicular lymphoma. 35 It evaluates 5 adverse prognostic risk factors including age (>60 years versus ≤60 years), Ann Arbor stage (III to IV versus I to II), hemoglobin level (<120 g/L versus ≥120 g/L), number of nodal areas (>4 versus ≤4) and serum LDH level (above normal level versus normal or below). Patients are stratified into 3 risk groups: low risk (0−1 adverse factors), intermediate (2 adverse factors), and poor risk (≥3 adverse factors).

Prognostic indices are also under development in other lymphoid neoplasms such as mantle cell lymphoma and T-cell lymphomas.

Although not always provided to the pathologist by the physician submitting the specimen, certain specific clinical findings are known to be of prognostic value in all stages of NHL. In particular, systemic symptoms of fever (greater than 38°C), unexplained weight loss (more than 10% body weight) in the 6 months before diagnosis, and drenching night sweats are used to define 2 categories for
each stage of NHL: A (symptoms absent) and B (symptoms present). The presence of B symptoms is known to correlate with extent of disease (stage and tumor bulk), but symptoms also have been shown to have prognostic significance for cause-specific survival that is independent of stage.8,26–33,36

References
