

RECOMMENDATIONS FOR THE REPORTING OF LYMPHOID NEOPLASMS

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THE ASSOCIATION OF DIRECTORS OF ANATOMIC AND SURGICAL PATHOLOGY

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Introduction for ADASP reporting Guidelines

It has been evident for decades that pathology reports are very variable even within a single institution. Standardization of reporting is the optimal way to insure that information necessary for patient management, prognostic and predictive factor assessment, grading, staging, analysis of outcomes and tumor registries are included in pathology reports. In recent years, two societies (first ADASP and then the CAP), have undertaken to publish guidelines for the reporting of common cancers. The CAP assigned multidisciplinary groups of pathologists, surgeons, radiation and medical oncologists to develop the protocols. Other pathologists and clinicians then reviewed them. After those reviews the protocols were reviewed by multiple CAP committees and finally approved by the Board of Governors.

The ADASP, in contrast, chose a pathologist expert in each field to assemble a group from within the pathology community (with clinician input if desired) to write specific cancer protocols. These were then approved by the ADASP council and subsequently by the membership. Even though both societies began the process at approximately the same time the streamlined approach adopted by the ADASP enabled them to publish years earlier in pathology journals frequented by anatomic pathologists. While the formats are somewhat different, the contents are essentially the same.

The American College of Surgery (ACS) Commission on Cancer (COC) accredits cancer centers in the USA. Recently, the COC decided to require elements, deemed as essential by the CAP, to be described in all pathology reports in their accredited cancer centers as of January 2004. Importantly they do not require that the specific CAP protocols or synoptic reports be utilized. ADASP has updated all of its protocols to comply with the COC requirements in the form of 37 uniform checklists. The checklists use the staging criteria cited in the American Joint Committee on Cancer (AJCC) 2002 staging manual (sixth edition) but include a variety of other references listed in each of the checklists. Moreover, the checklists are formatted for ease of use. They may be used as templates for uniform reporting and are designed to be compatible with voice-activated transcription.

The different elements in these revised ADASP Diagnostic Checklists have been divided into *Required* and *Optional*. The term *Required* in this context only signifies compliance with the COC guidelines. ADASP realizes that specimens and practices vary and it will not be possible to report these elements in every case. However, ADASP hopes that pathologists will find these checklists to be useful in daily clinical practice, while facilitating compliance with the new COC requirements.

The checklists are in standard PDF file format, and may be easily downloaded from the ADASP website. They are not to be reproduced, altered or used for commercial purposes without consent from ADASP.

INTRODUCTION

In this report, the Association of Directors of Anatomic and Surgical Pathology (ADASP) provides guidelines for the reporting of lymphoid neoplasms. The World Health Organization Classification of Tumours of the Haematopoietic and Lymphoid Tissues is the preferred international standard for diagnostic criteria (disease definition) and nomenclature. Ancillary studies are often required, and the association recommends that immunophenotypic and genotypic information be integrated into the final report, to the extent possible.

I. Features the Association recommends to be included in the final report.

A. Background clinical information

The Association recommends the inclusion of pertinent clinical history, when this information is available. The pathologist is encouraged to obtain clinical history, if possible. For some diseases, an accurate history may be essential to diagnosis; e.g., post-transplant-associated lymphoproliferative disease.

1. Previous diagnosis of a lymphoid neoplasm, if known. Specify dates and site(s), and treatment status, if available.
2. Presence of generalized or localized lymphadenopathy.
3. Evidence of organomegaly (e.g., hepatosplenomegaly)
4. Pertinent hematological findings (e.g., lymphocytosis, pancytopenia)
5. Constitutional symptoms
6. HIV status
7. Prior immune abnormality, including congenital immune disorders.
8. Autoimmune disease
9. Other pertinent serology (e.g., HTLV-I, Epstein-Barr virus)
10. Other known co-factors, e.g., *Helicobacter pylori* infection

B. Gross Description

The proper handling of the lymph node biopsy specimen is critical to ensure proper fixation, which is essential for the preparation of high quality histological sections.(1) The Association recommends that the pathologist receive lymph node biopsies fresh, intact, and that an unsectioned lymph node biopsy never be immersed in fixative. It is recommended that each laboratory establish a protocol for the handling of lymph node biopsies that ensures both optimal histological sections and preservation of material for ancillary studies. *These principles, and the procedures outlined below, apply as well to extranodal sites that may be biopsied or resected for a potential diagnosis of lymphoma.*

1. Identification: State how the specimen was identified; labeled with the patient name, medical record number, organ or site.
2. State how the specimen was received (fresh, in fixative, intact vs. sectioned)
3. State the surgical procedure used to procure the specimen (excisional biopsy vs. incisional, vs. core biopsy)
4. State the dimensions of the specimen.
5. State if there is a capsule, and if it is intact or altered grossly.
6. Describe the color and consistency, (firm vs. fleshy); presence of nodularity, necrosis, hemorrhage.
7. The Association recommends that lymph nodes be sectioned at 2 mm. intervals, to ensure appropriate fixation.(1)

8. If the size of the lymph node permits it, it is preferable to cut sections perpendicular to the long axis of the lymph node. This orientation provides the greatest assessment of the architecture.
9. If the specimen is spleen, provide the weight. Describe the appearance of any focal lesions (e.g., infarcts, nodules, hemorrhage), and gross abnormalities of red or white pulp.
10. If the specimen is a spleen obtained for staging, the Association recommends that the spleen be sectioned at 3-5mm intervals, to look for grossly identifiable lesions. First fixing thicker slices (1 cm) briefly in formalin may facilitate sectioning at the desired thickness. For staging laparotomy specimens for Hodgkin's lymphoma, the number of grossly identifiable lesions, if less than 10, should be stated. The presence of more than 4 nodules has been shown to be of prognostic significance.(2)
11. Unique identifiers should be used for each cassette, and the gross description should also specify the type of fixation used for each paraffin block.
12. It is often desirable to fix tissue in more than one fixative. Some fixatives provide excellent cytological detail (B5, B+), but compromise the ability to extract DNA for molecular studies. Formalin is most suitable if PCR studies from the paraffin-embedded sections are anticipated.

13. Snap freezing is useful for preserving tissue for frozen section immunohistochemistry, or future molecular studies. The following is a suitable procedure.
- a. One or more blocks of fresh tissue approximately 1.0 x 1.0 x 0.3cm are cut from the specimen.
 - b. The tissue blocks are placed in a mold, cork, or other suitable form and immersed in OCT (Sakura Tissue Tek; Torrance, CA) embedding compound.
 - c. A sludge is made of dry ice and isopentane (2-methyl-butane) and the tissue and mold are immersed into the solution and snap frozen.
 - d. The blocks are labeled and stored at -80°C or over liquid nitrogen.
 - e. Blocks in OCT are suitable for frozen section immunohistochemistry and also can be used for molecular analyses. If there is sufficient tissue blocks can be snap frozen without OCT for molecular studies and held at -80° or over liquid nitrogen until needed.

C. Diagnostic Information

1. Specify exact anatomic site, if known; and tissue (lymph node or other).
2. Specify procedure (excisional biopsy, incisional biopsy, needle core)
3. Histological tumor type. The Association recommends the use of the WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissues (Tables 1-4).(3) The designation of morphologic or clinical variants is considered optional for most clinical purposes. If an alternative classification scheme is used, it should be so specified in the diagnosis.
4. Specify if the specimen is only focally or incompletely involved.
5. Specify if more than one histologic type is identified, i.e. composite lymphoma, or progression to lymphoma of higher histologic grade.
6. Specimen adequacy. A precise diagnosis may not be possible in some instances due to limitations of specimen adequacy (e.g., needle biopsy, necrotic or fibrotic specimen). If specimen adequacy is of concern, this fact should be stated explicitly.
7. If ancillary studies (e.g., immunocytochemistry, molecular diagnostics) were performed, the diagnosis or comment should contain a statement regarding these studies and their diagnostic implications (Table 5).

II. Features that may be optional in the final report

A. Immunophenotypic information

For many subtypes of lymphoid neoplasms (e.g., peripheral T-cell lymphomas, diffuse large B-cell lymphoma, precursor B-cell lymphoblastic lymphoma/leukemia) immunophenotypic studies are essential to accurate diagnosis.(4, 5) In some instances, immunophenotypic studies may not be required (e.g., many instances of follicular lymphoma). If immunophenotypic studies are performed, we recommend that the results be included in an integrated single report (Table 6).(6) If ancillary studies are performed in a reference laboratory, the results should be discussed in an integrated report, and the reference laboratory report appended.

1. State how immunophenotypic studies were performed (flow cytometry vs. immunohistochemistry).
2. State if immunohistochemistry was performed on paraffin sections or frozen sections.
3. Specify all markers that were investigated, both positive and negative.
4. It is recommended that antigens usually be identified by the CD nomenclature. Use of the common or commercial name is optional, but may be important in some cases as different antibodies to the same CD antigen may show varying sensitivities and specificities (e.g., CD20: L26 vs. Leu 16).
5. Avoid use of generic identifiers (e.g., B-cell marker, T-cell marker).
6. Specify which population is expressing the antigen.

7. Specify if the antigen is only focally expressed. It may be helpful in some instances to provide an approximation of the % positive cells.
8. Specify where the studies were performed, if not done in the local laboratory.
9. A discussion of the significance of the immunophenotypic studies is recommended.

B. Molecular genetic studies

Molecular genetic studies may provide useful diagnostic information about the clonality of the lymphoid infiltrate, the lineage of the lymphoid cells, or a precise molecular abnormality associated with a specific disease. As with immunophenotypic studies, if molecular analysis is performed, the Association recommends that this information be discussed in the context of the histological findings, if possible. Important information to include is:

1. Type of specimen used for the study (frozen tissue vs. paraffin-embedded specimen).
2. Specify the method used: polymerase chain reaction (PCR) vs. Southern blot vs. RT-PCR, vs. other.
3. Specify the exact type of test performed; e.g., VJ-PCR for IgH gene rearrangement.
4. Specify if the studies were done in a reference laboratory or in the local laboratory.
5. Specify the result (monoclonal, polyclonal, oligoclonal) and its possible diagnostic significance.

C. Viral studies

Viruses are important cofactors for many lymphoma types, and corroboration of a viral association may be essential for the diagnosis of some diseases, such as adult T-cell leukemia/ lymphoma (HTLV-I) or primary effusion lymphoma (HHV-8/ KSHV). The pathologist should state method of identification, results (positive or negative), and which cell population is affected for Methods #1 and #2.

1. Immunohistochemical stain
2. In situ hybridization
3. PCR
4. Serology (see clinical history)

D. Cytogenetic studies

Cytogenetic studies may provide ancillary diagnostic information useful in the diagnosis or subclassification of lymphoma. The identification of a clonal cytogenetic abnormality supports a diagnosis of malignancy. Some cytogenetic abnormalities are highly associated with specific lymphoid malignancies; e.g., t(14;18) with follicular lymphoma. The Association recommends that the cytogenetic data be discussed in the context of the histological findings and the complete report appended to the Surgical Pathology report.

1. Conventional cytogenetics
2. Fluorescence in-situ hybridization

Table 1. WHO Classification of B-Cell Lymphoid Neoplasms

Precursor B-cell neoplasm

- Precursor B-lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
Variant: with plasmacytoid differentiation or monoclonal gammopathy
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes)
- Hairy cell leukemia
Variant: Hairy cell variant
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of MALT type
- Nodal marginal zone B-cell lymphoma (+/- monocytoid B cells)
- Follicular lymphoma

Grading:

Grade 1: 0-5 centroblasts/hpf

Grade 2: 6-15 centroblasts/hpf

Grade 3: >15 centroblasts/hpf

Grade 3a: >15 centroblasts, but centrocytes are still present

Grade 3b. >Centroblasts form solid sheets with no residual centrocytes

Variants:

Cutaneous follicle center lymphoma

Diffuse follicle center lymphoma

Grade 1: 0-5 centroblasts/hpf

Grade 2: 6-15 centroblasts/hpf

Table 1, cont.

- Mantle cell lymphoma

Variant: Blastoid

- Diffuse large B-cell lymphoma

Subtypes:

Mediastinal large B-cell lymphoma

Intravascular large B-cell lymphoma

Primary effusion lymphoma

Morphologic Variants:

Centroblastic

Immunoblastic

Anaplastic large B-cell

T-cell/ histiocyte-rich

Plasmablastic

Lymphomatoid granulomatosis-type

- Burkitt lymphoma/ Burkitt cell leukemia

Morphologic variants:

Classical

Atypical (Burkitt-like)

With plasmacytoid differentiation (AIDS-associated)

Subtypes (clinical and genetic)

Endemic

Sporadic

Immunodeficiency-associated

B-cell proliferations of uncertain malignant potential

- Lymphomatoid granulomatosis (Grades 1, 2 and 3)
- Post-transplant lymphoproliferative disease

Table 2. WHO Classification of T-Cell & NK-Cell Lymphoid Neoplasms

Precursor T-cell neoplasm

- Precursor T-lymphoblastic lymphoma/leukemia

Mature (peripheral) T-cell and NK-cell neoplasms

- T-cell prolymphocytic leukemia

Morphologic Variants: small cell, cerebriform cell

- T-cell granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Blastic “NK-cell” lymphoma**
- Adult T-cell leukemia/lymphoma (HTLV-1+)

Clinical Variants

Acute

Lymphomatous

Chronic

Smoldering

Hodgkin-like

- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides/Sezary syndrome

Variants:

Pagetoid reticulosis

MF-associated follicular mucinosis

Granulomatous slack skin disease

Table 2, cont.

- Primary cutaneous CD30 + T-cell lymphoproliferative disorder

Variants:

Lymphomatoid papulosis (type A and B)*

Primary cutaneous anaplastic large cell lymphoma

Borderline lesions

- Peripheral T-cell lymphoma, not otherwise characterized

Morphologic variants: Lymphoepithelioid (Lennert's), T-zone

- Angioimmunoblastic T-cell lymphoma

- Anaplastic large cell lymphoma, (ALK+/ ALK-)

Morphologic variants: Lymphohistiocytic, small cell

Abbreviations: *, For clinical purposes not considered a neoplasm, of uncertain malignant potential.

** Neoplasm of uncertain lineage and stage of differentiation.

Table 3. WHO Classification of Hodgkin's Lymphoma (Hodgkin's disease)

- **Nodular lymphocyte predominant Hodgkin lymphoma**
- **Classical Hodgkin lymphoma**
 - Nodular sclerosis Hodgkin lymphoma (Grades 1 and 2)
 - Lymphocyte-rich classical Hodgkin lymphoma
 - Mixed cellularity Hodgkin lymphoma
 - Lymphocyte depleted Hodgkin lymphoma

Table 4. Categories of Post-Transplant Lymphoproliferative Disorders (PTLD)

- Early lesions*
 - Reactive plasmacytic hyperplasia
 - Infectious mononucleosis-like
 - Polymorphic PTLD
 - Polyclonal (rare)
 - Monoclonal
 - Monomorphic PTLD (classify according to WHO classification)
 - B-cell lymphomas
 - Diffuse large B-cell lymphoma
 - Burkitt lymphoma/ atypical Burkitt lymphoma variant
 - Plasma cell myeloma
 - T-cell lymphomas
 - Peripheral T-cell lymphoma, not otherwise categorized
 - Other types (Hepatosplenic, gamma-delta, NK/T-cell)
 - Other types (rare)
 - Hodgkin lymphoma-like lesions (associated with methotrexate & other immunosuppressive therapy)
 - Hodgkin's lymphoma
 - Plasmacytoma-like lesions
- * Not considered a neoplasm.

Table 5. Non Formatted Checklist for the Reporting of Lymphoid Neoplasms

Demographics:

Patient Name:

Age:

Sex:

Race (optional):

Case Number:

Clinical History:

Prior diagnosis:

Presenting sites of disease:

Clinical symptoms:

Findings on physical examination:

Laboratory findings:

Gross Assessment:

Labeling of specimen:

Condition of specimen on receipt:

fresh,

in fixative

intact

previously sectioned

Surgical procedure:

Dimensions of the specimen:

Weight of specimen (if relevant):

Capsule:

Color and consistency:

Focal lesions:

Photography:

Allocation of tissue for special studies:

Frozen tissue for archival storage or other studies

Fresh tissue/ cells for flow cytometry, cytogenetics

Other tissue distribution

Diagnostic Information

Anatomic site:

Tissue (lymph node or other):

Histological tumor type:

WHO classification (see Tables 1-4):

Other classification scheme:

Grading (if relevant, i.e., follicular lymphoma):

Adequacy:

Focal involvement:

Multiple histological types present (composite lymphoma):

Immunophenotypic data:

Genotypic data:

Cytogenetics:

Microbiological studies:

Special Studies:

Flow cytometry:

Immunohistochemistry:

 Frozen sections:

 Paraffin sections:

Molecular genetic studies:

 In situ hybridization

 PCR

 RT-PCR

 Southern blot

Cytogenetic studies:

 Conventional cytogenetics:

 Fluorescence in-situ hybridization

Table 6 - Example of Non Formatted Specimen Report

Specimen:

Right cervical lymph node (excisional biopsy)

Clinical Diagnosis and History:

The patient is a 63 year old female with history of follicular lymphoma in 1993, treated with chemotherapy, and now presenting with an enlarging right cervical node.

Final diagnosis:

LYMPH NODE, RIGHT CERVICAL (EXCISIONAL BIOPSY): DIFFUSE LARGE B-CELL LYMPHOMA (75%) AND FOLLICULAR LYMPHOMA, GRADE 2 of 3 (25%), (SEE COMMENT).

Comment: Slides from the previous lymph node biopsy were reviewed (S93-XXXX) and show follicular lymphoma, grade 1 of 3. The current specimen shows a grade 2 follicular lymphoma in about 25% of the node, but in the remainder there is progression to diffuse large B-cell lymphoma. Molecular and cytogenetic studies were not performed in this case. Immunophenotypic studies are consistent with the histological findings, and show positivity for bcl-2 protein in both follicular and diffuse areas. P53 is positive in the diffuse large B-cell lymphoma component. P53 mutations and overexpression have been associated with histological progression in approximately one-third of follicular lymphomas. (Ref: Sander CA, Yano T, Clark HM, et al. p53 mutation is associated with progression in follicular lymphomas. *Blood* 1993; 82(7): 1994-2004)

Microscopic description:

Nodal architecture is completely effaced with extension beyond the node into the perinodal fat. About 25% of the node is nodular, with follicles comprised of small cleaved cells (centrocytes) as well as large lymphoid cells (centroblasts) with an average of 6-10 large cells per high power field. The remainder of the node is effaced by a diffuse proliferation of large lymphoid cells with two to three basophilic nucleoli, round or oval nuclear outlines, and pale cytoplasm. Mitoses are rare in the follicles, but frequent in the diffuse large cell lymphoma. Necrosis is present in about 10% of the node.

Immunohistochemistry report:

Immunoperoxidase stains were performed on B5 fixed sections with appropriate controls.

The atypical lymphoid cells in both the follicular and diffuse areas were positive for CD45, CD20, CD10, bcl-2 and bcl-6 consistent with a B-cell lymphoma of follicle center origin. Ki67 (proliferation marker) is positive in 30% of the cells in the diffuse areas, and 10% in the follicular areas. CD3 and CD5 stain admixed small lymphocytes, mainly in the interfollicular regions. P53 is focally positive in follicular areas (<10% of follicles stain), but strongly positive in diffuse large cell component (>90% positive cells).

Gross description:

Received fresh from the operating room in normal saline and labeled with the patients name and hospital number is an excisional biopsy of an intact oval lymph node and adjacent adipose tissue which measures 2.3 cm x 1.4 cm x 1.4 cm. The cut surface is tan and fleshy with foci of necrosis. There is no nodularity grossly visible. The lymph node is serially sectioned at 0.3cm intervals and appears homogeneous apart from foci of necrosis. A well-defined capsule is not grossly identified. Imprints are made from the cut surface of the node and air-dried. One slice is snap frozen in isopentane and dry ice, embedded in OCT, for potential molecular or immunohistochemical studies. A portion of sterile node is placed in culture medium for potential cytogenetic studies or flow cytometry. The remainder of the node is submitted in its entirety in three paraffin blocks, after fixation as follows: A - B5, B - formalin, C- formalin.

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