Protocol for the Examination of Specimens From Patients With Hematopoietic Neoplasms Involving the Bone Marrow

Based on AJCC/UICC TNM, 7th Edition
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Procedures
- Bone marrow aspiration
- Bone marrow core (trephine) biopsy

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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 of surgical specimens. 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 this document.

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Surgical Pathology Cancer Case Summary (Checklist)

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BONE MARROW: Aspiration, Core (Trephine) Biopsy

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)
___ Peripheral blood smear
___ Bone marrow aspiration
___ Bone marrow aspirate clot (cell block)
___ Bone marrow core (trephine) biopsy
___ Bone marrow core touch preparation (imprint)
___ Other (specify): _____
___ Not specified

Procedure (select all that apply)
___ Aspiration
___ Biopsy
___ Other (specify): _____
___ Not specified

Aspiration Site (if performed) (select all that apply) (Note B)
___ Right posterior iliac crest
___ Left posterior iliac crest
___ Sternum
___ Other (specify): _____
___ Not specified

Biopsy Site (if performed) (select all that apply) (Note B)
___ Right posterior iliac crest
___ Left posterior iliac crest
___ Other (specify): _____
___ Not specified

Histologic Type (Note C)
Note: The following is a partial list of the 2008 World Health Organization (WHO) classification[1] and includes those neoplasms seen in bone marrow specimens.

___ Histologic type cannot be assessed

Myeloproliferative Neoplasms
___ Chronic myelogenous leukemia, *BCR-ABL1* positive
___ Chronic neutrophilia leukemia
___ Polycythemia vera
___ Primary myelofibrosis
___ Essential thrombocythemia
___ Chronic eosinophilic leukemia, not otherwise specified (NOS)

* 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.

___ Mastocytosis (specify type): _____
___ Myeloproliferative neoplasm, unclassifiable

Myeloid and Lymphoid Neoplasms With Eosinophilia and Abnormalities of *PDGFRA*, *PDGFRB* and *FGFR1*
___ Myeloid or lymphoid neoplasm with *PDGFRA* rearrangement
___ Myeloid neoplasm with *PDGFRB* rearrangement
___ Myeloid or lymphoid neoplasm with *FGFR1* abnormalities

Myelodysplastic/Myeloproliferative Neoplasms
___ Chronic myelomonocytic leukemia
___ Atypical chronic myeloid leukemia *BCR-ABL1* negative
___ Juvenile myelomonocytic leukemia
___ Myelodysplastic/myeloproliferative neoplasm, unclassifiable
___ *Refractory anemia with ring sideroblasts associated with marked thrombocytosis*

Myelodysplastic Syndromes
___ Refractory anemia
___ Refractory neutropenia
___ Refractory thrombocytopenia
___ Refractory anemia with ring sideroblasts
___ Refractory cytopenia with multilineage dysplasia
___ Refractory anemia with excess blasts
___ Myelodysplastic syndrome associated with isolated del(5q)
___ Myelodysplastic syndrome, unclassifiable
___ Refractory cytopenia of childhood

Acute Myeloid Leukemia (AML) With Recurrent Genetic Abnormalities
___ AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
___ AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
___ Acute promyelocytic leukemia with t(15;17)(q22;q12); *PML-RARA*
___ AML with t(9;11)(p22;q23); *MLLT3-MLL*
___ AML with t(6;9)(p23;q34); *DEK-NUP214*
___ AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
___ AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
___ *AML with mutated NPM1*
___ *AML with mutated CEBPA*

Acute Myeloid Leukemia With Myelodysplasia-Related Changes (select all that apply)
___ Multilineage dysplasia
___ Prior myelodysplastic syndrome
___ Myelodysplasia-related cytogenetic abnormalities

Therapy-related Myeloid Neoplasms
___ Therapy-related AML
___ Therapy-related myelodysplastic syndrome
___ Therapy-related myelodysplastic/myeloproliferative neoplasm

* 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.

Acute Myeloid Leukemia, NOS
___ AML with minimal differentiation
___ AML without maturation
___ AML with maturation
___ Acute myelomonocytic leukemia
___ Acute monoblastic/monocytic leukemia
___ Acute erythroid leukemia
___ Acute megakaryocytic leukemia
___ Acute basophilic leukemia
___ Acute panmyelosis with myelofibrosis
___ AML, NOS[#]

Myeloid Proliferations Related to Down Syndrome
___ Transient abnormal myelopoiesis
___ Myeloid leukemia associated with Down syndrome

Acute Leukemias of Ambiguous Lineage
___ Acute undifferentiated leukemia
___ Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*
___ Mixed phenotype acute leukemia with t(v;11q23); *MLL rearranged*
___ Mixed phenotype acute leukemia, B/myeloid, NOS
___ Mixed phenotype acute leukemia, T/myeloid, NOS
___ Mixed phenotype acute leukemia, NOS, rare types (specify type): _____
___ *Natural killer (NK) cell lymphoblastic leukemia/lymphoma*

Other Myeloid Leukemias
___ Blastic plasmacytoid dendritic cell neoplasm

Precursor Lymphoid Neoplasms
___ B lymphoblastic leukemia/lymphoma, NOS[#]
___ B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*
___ B lymphoblastic leukemia/lymphoma with t(v;11q23); *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 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
___ 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

* 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.

___ Plasma cell myeloma
___ Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
___ Follicular lymphoma
___ Mantle cell lymphoma
___ Diffuse large B-cell lymphoma (DLBCL), NOS
___ T cell/histiocyte-rich large B-cell lymphoma
___ Primary cutaneous DLBCL, leg type
___ *Epstein-Barr virus* (*EBV)-positive DLBCL of the elderly*
___ DLBCL associated with chronic inflammation
___ Lymphomatoid granulomatosis
___ Anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma
___ Plasmablastic lymphoma
___ Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
___ 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
___ B-cell lymphoma, NOS
___ Other (specify): _____

<u>Mature T- and NK-cell Neoplasms</u>
___ 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
___ Adult T-cell leukemia/lymphoma
___ Extranodal NK/T-cell lymphoma, nasal type
___ Enteropathy-associated T-cell lymphoma
___ Hepatosplenic T-cell lymphoma
___ Mycosis fungoides
___ Peripheral T-cell lymphoma, NOS
___ Angioimmunoblastic T-cell lymphoma
___ Anaplastic large cell lymphoma, ALK-positive
___ *Anaplastic large cell lymphoma, ALK-negative*

<u>Hodgkin Lymphoma</u>
___ Nodular lymphocyte predominant Hodgkin lymphoma
___ Classical Hodgkin lymphoma

<u>Histiocytic and Dendritic Cell Neoplasms</u>
___ Histiocytic sarcoma
___ Langerhans cell histiocytosis
___ Langerhans cell sarcoma
___ Interdigitating dendritic cell sarcoma
___ Follicular dendritic cell sarcoma
___ Disseminated juvenile xanthogranuloma
___ Histiocytic neoplasm, NOS

* 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.

Posttransplant Lymphoproliferative Disorders (PTLD) [##]
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[###]

___ Other (specify): _____

Note: Italicized histologic types denote provisional entities in the 2008 WHO classification.

[#] An initial diagnosis of "AML, NOS" or "B lymphoblastic leukemia/lymphoma, NOS" may need to be given before the cytogenetic results are available or for cases that do not meet criteria for other leukemia subtypes.

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

[###] Classical Hodgkin lymphoma type PTLD can be reported using either this protocol or the separate College of American Pathologists protocol for Hodgkin lymphoma.[2]

***Additional Pathologic Findings**
*Specify: _____

***Cytochemical/Special Stains (Note D)**
*___ Performed
*Specify stains and results: _____
_____
*___ Not performed

Immunophenotyping (flow cytometry and/or immunohistochemistry) (Note E)
___ Performed, see separate report: _____
___ Performed
Specify method(s) and results: _____
_____
___ Not performed

Cytogenetic Studies (Note F)
___ Performed, see separate report: _____
___ Performed
Specify method(s) and results: _____
_____
___ Not performed

***Fluorescence In Situ Hybridization (Note F)**
*___ Performed, see separate report: _____
*___ Performed
*Specify method(s) and results: _____
_____
*___ Not performed

***Molecular Genetic Studies (Note F)**

*___ Performed, see separate report: _____

*___ Performed

Specify method(s) and results: _____

_____

*___ Not performed

***Comment(s)**

Explanatory Notes

A. Specimen

Complete evaluation of hematopoietic disorders involving the bone marrow requires integration of multiple pieces of data, including the clinical history, pertinent laboratory studies (eg, complete blood count [CBC], serum lactate dehydrogenase [LDH], and beta-2-microglobulin levels, serum protein electrophoresis, and immunofixation results), and a satisfactory peripheral blood smear and bone marrow specimen. In most instances, this requires receiving a peripheral blood smear, bone marrow aspirate specimen, an aspirate clot section (cell block), and a bone marrow core biopsy.[3] Touch preparations (imprints) of the biopsy specimen are also very helpful. The World Health Organization (WHO) classification recommends performing a 200-cell differential count on peripheral blood smears and a 500-cell differential count on bone marrow aspirate specimens in the evaluation of hematopoietic disorders.[1] This will allow adequate evaluation of the cellular elements within the peripheral blood and bone marrow.

In addition, submission of bone marrow (usually aspirate) material for flow cytometry immunophenotyping, cytogenetic studies, fluorescence in situ hybridization (FISH), and molecular studies is often necessary. The guidelines that follow are suggested for handling of bone marrow specimens:

- The number of stained and unstained peripheral blood, bone marrow aspirate, and bone marrow core biopsy touch preparation smears should be recorded.
- The length of the bone marrow core biopsy(s) should be recorded.
- For conventional cytogenetic studies, a bone marrow aspirate specimen received in a sodium heparin tube is ideal, but fresh specimens submitted in saline or RPMI transport medium is sufficient.
- For immunophenotyping by flow cytometry, a bone marrow aspirate specimen received in an ACD tube (yellow top tube) or EDTA tube (lavender top tube) is preferred.
- Bone marrow core biopsy specimens require decalcification, and care must be taken not to under- or over-decalcify the specimen, as it will impact the ability to cut and interpret the histologic sections and may interfere with immunohistochemical staining. Formic acid decalcification procedures can also degrade DNA, whereas EDTA decalcification may allow for preservation of DNA for polymerase chain reaction (PCR) studies. EDTA decalcification, however, is slower than acid decalcification techniques.
- Fixation:
    - Zinc formalin or B5 fixatives produce superior cytologic detail but are not suitable for DNA extraction and impair some immunostains (eg, CD30). B5 has the additional limitation of requiring proper hazardous-materials disposal.
    - Formalin fixation is preferable in many situations, as it allows for many ancillary tests such as molecular/genetic studies, in-situ hybridization, and immunophenotyping.
    - Over-fixation (ie, more than 24 hours in formalin, more than 4 hours in zinc formalin or B5) should be avoided for optimal immunophenotypic reactivity.

Care must be taken to ensure that high-quality specimens and sections are obtained for each bone marrow specimen. Often this requires working hand-in-hand with clinical colleagues to achieve this goal. In addition to being used for the diagnosis of primary hematopoietic disorders, bone marrow examination is often utilized as part of the

pathologic staging of many hematopoietic neoplasms, including Hodgkin and non-Hodgkin lymphomas.[3-5] Bone marrow involvement identified within staging biopsy specimens typically indicates stage IV disease within the Ann Arbor staging system utilized by the American Joint Committee on Cancer (AJCC)[6] and the International Union Against Cancer (UICC).[7] For multiple myeloma, the Durie-Salmon staging system is recommended by the AJCC.[8] Both staging systems are shown below. In pediatric patients, the St. Jude staging system is commonly used.[9]

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 (IIE).[##],[###]
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 (IIIS) 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: eg, II_3. 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 greater than 10.0 g/dL Serum calcium 12 mg/dL or less Normal bone x-rays or a solitary bone lesion IgG less than 5 g/dL IgA less than 3 g/dL Urine M-protein less than 4 g/24 hours
Stage III	One or more of the following are included: Hemoglobin less than 8.5 g/dL

Serum calcium greater than 12 mg/dL
Advanced lytic bone lesions
IgG greater than 7 g/dL
IgA greater than 5 g/dL
Urine M-protein greater than 12 g/24 hours

Stage II Disease fitting neither stage I nor stage III

Note: Patients are further classified as (A) serum creatinine less than 2.0 mg/dL, or (B) serum creatinine 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. These predicted survivals, however, may underestimate expected survival for these patient populations with modern therapy.

B. Aspiration/Biopsy Site

Bone marrow sampling (aspiration and trephine core biopsy) is usually performed at the posterior iliac crest.[3] Aspirations and biopsies may be unilateral or bilateral, depending on the indication for the bone marrow biopsy as well as clinician preference. Rarely, a sternal aspiration may be performed if only a bone marrow aspirate specimen is necessary. Sternal aspirations should only be considered as a last resort and should be performed only by persons with extensive experience with this procedure. Occasionally, the anterior iliac crest or tibia may be the site of the biopsy, depending on patient age and other unique characteristics of the patient.

C. Histologic Type

This protocol recommends assigning histologic type based on the WHO classification of lymphoid neoplasms.[1] Originally published in 2001 and revised and updated in 2008, this classification incorporates the morphologic, immunophenotypic, cytogenetic, and molecular findings into the final diagnosis. Whereas histologic examination remains of paramount importance, many neoplasms will require the use of these ancillary studies to arrive at the correct diagnosis.[10-15] It may not be possible to provide a specific lymphoma diagnosis with bone marrow examination, particularly for patients in whom the bone marrow is the first identified site of involvement. Some of the entities provided in the checklist may be extremely uncommon in the bone marrow or may have not been described but are listed for completeness.

D. Cytochemical/Special Stains

Numerous cytochemical or special stains may be utilized in the diagnosis of hematopoietic neoplasms involving the bone marrow.[3] An iron (Prussian blue) stain is paramount in the evaluation of myelodysplastic syndromes and some myeloproliferative disorders. A reticulin stain is necessary for the diagnosis of some myeloproliferative disorders but may be valuable in evaluation of numerous other disorders such as hairy cell leukemia. Cytochemical stain for myeloperoxidase is rapid, convenient, and helpful for the assessment of myeloid neoplasms. Cytochemical stains for leukocyte alkaline phosphatase, and naphthol-ASD chloroacetate esterase provide information related to cell origin or specific disease states. Cytochemical stains, however, are no longer required for the diagnosis of most disorders.

E. Immunophenotyping by Flow Cytometry and/or Immunohistochemistry

Immunophenotyping of bone marrow specimens can be performed by flow cytometry[10] or immunohistochemistry.[11] Each has advantages and disadvantages. Flow cytometry is rapid (hours), quantitative, and allows multiple antigens to be evaluated on the same

cell simultaneously. Flow cytometry may also allow for the detection of minimal residual disease, especially in situations in which there is a unique expression pattern. Antigen reactivity, however, cannot be correlated with architecture or cytologic features. In patients from whom a dry tap is obtained, an additional bone marrow core biopsy submitted fresh in transport medium can be disaggregated and utilized for flow cytometry immunophenotyping. 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, prognostic, and therapeutic information. Documentation of expression of antigens such as CD20, CD33, and CD52 by the neoplastic population can aid the clinician in selection of potential therapeutic options such as monoclonal antibody therapy. The specific immunophenotypes for individual hematopoietic disorders involving the bone marrow are readily available within the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* as well as many other hematopathology textbooks.[1,3,5]

F. Cytogenetic and Molecular Genetic Studies

Within the WHO classification of hematopoietic disorders, significant emphasis has been placed on cytogenetic and molecular genetic studies. More than ever before, specific cytogenetic findings are helpful for the diagnosis of specific neoplasms and disease states.[12-16] In fact, many acute leukemias are currently defined based upon their specific cytogenetic abnormalities.[1] Given the importance now placed upon knowing the cytogenetic or molecular results (as determined by karyotyping, FISH, or PCR results) it is of paramount importance that care is taken to evaluate the need for these studies at the time of biopsy. FISH studies can be also performed on air-dried unfixed slides, and in some cases DNA can be scraped off air-dried unfixed slides for molecular studies. Since karyotyping requires growing viable cells in culture, it is necessary to submit fresh specimens promptly to help ensure the best opportunity for a successful study.

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