DIAGNOSTIC PATHOLOGY

LYMPH NODES AND SPLEEN WITH EXTRANODAL LYMPHOMAS

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DIAGNOSTIC PATHOLOGY
LYMPH NODES AND SPLEEN WITH EXTRANODAL LYMPHOMAS

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To the women in my life—my mother Albertina Medeiros, my sister Deborah Medeiros-Stroscio, my wife Carrie Medeiros, and our two precious girls Christina and Caroline.

To my first teacher of hematopathology—Professor Isao Katayama of Japan.

To the coauthors of this book—a marvelous group of colleagues who worked so very hard to complete this project.

LJM

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DIAGNOSTIC PATHOLOGY

LYMPH NODES AND SPLEEN WITH EXTRANODAL LYMPHOMAS

AMIRSYS®

Amirsys, creators of the highly acclaimed radiology series Diagnostic Imaging, proudly introduces its new Diagnostic Pathology series, designed as easy-to-use reference texts for the busy practicing surgical pathologist. Written by world-renowned experts, the series will consist of 15 titles in all the crucial diagnostic areas of surgical pathology.

The newest book in this series, *Diagnostic Pathology: Lymph Nodes and Spleen with Extranodal Lymphomas*, contains approximately 900 pages of comprehensive, yet concise, descriptions of more than 120 specific diagnoses. Amirsys's pioneering bulleted format distills pertinent information to the essentials. Each chapter has the same organization providing an easy-to-read reference for making rapid, efficient, and accurate diagnoses in a busy surgical pathology practice. A highlighted Key Facts box provides the essential features of each diagnosis. Detailed sections on Terminology, Etiology/Pathogenesis, Clinical Issues, Macroscopic and Microscopic Findings, and the all important Differential Diagnoses follow so you can find the information you need in the exact same place every time.

Most importantly, every diagnosis features numerous high-quality images, including gross pathology, H&E and immunohistochemical stains, correlative radiographic images, and richly colored graphics, all of which are fully annotated to maximize their illustrative potential.

We believe that this lavishly illustrated series, with its up-to-date information and practical focus, will become the core of your reference collection. Enjoy!

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PREFACE

Most likely the reader has heard the lament, often said in jest, "All lymphomas look the same to me." Indeed, lymphomas involving lymph nodes, spleen, and other extranodal sites present many diagnostic difficulties to the practicing pathologist.

Distinguishing benign from malignant lesions can be a challenge in and of itself, requiring histologic and often immunophenotypic analysis, as well as molecular studies in a subset of cases. Once the benign nature of a lesion is established, an etiology needs to be suggested. If the lesion is malignant, both hematopoietic and non-hematopoietic tumors must be identified as such. Even after a lesion is recognized as hematopoietic, the possibilities are vast and include neoplasms of B, T, NK, myeloid, and histiocytic lineage. Complicating matters further is the continuous evolution of the concepts and terminology of the field and the large amounts of data being generated via high throughput technologies. How does one sort and apply this information? What is needed to sign out cases, and what is not?

With these questions in mind, the shared goal of the authors in writing this text was to create a quick, easy-to-use reference. The contents of this volume include benign and malignant lesions of lymph node and spleen as well as extranodal lymphomas. The lymphomas are designated, in large part, using the terminology of the 2008 World Health Organization.

As is the style of the Diagnostic Pathology series, clinical and histologic features, the results of relevant ancillary studies, and a differential diagnosis for each entity are provided in an easy-to-read bulleted format. A Key Facts section captures essential aspects of the entity. References are recent and selected for relevance, rather than encyclopedic coverage. Images have been used generously and illustrate the typical and common variant features of each entity. We also have included standard protocols for the examination and reporting of lymphomas. Finally, the Amirsys eBook Advantage™ license included with each printed copy of this book provides fully searchable text and a complete listing of antibodies.

The authors hope that the reader will find *Diagnostic Pathology: Lymph Nodes and Spleen with Extranodal Lymphomas* to be a useful resource.

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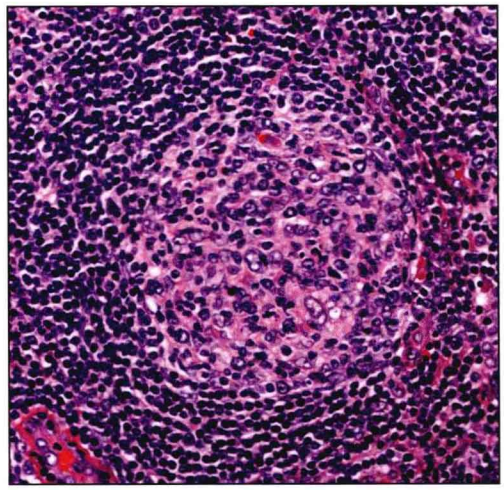
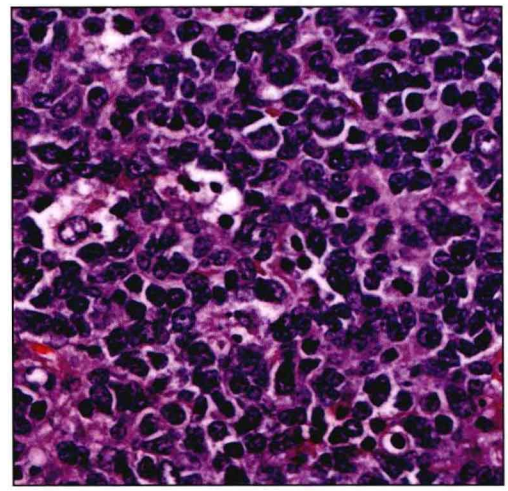
REACTIVE FOLLICULAR HYPERPLASIA



A hyperplastic lymphoid follicle is seen with a central, prominent germinal center and a peripheral, sharply demarcated mantle zone.



A reactive germinal center is composed of a mixed population of centrocytes, centroblasts, follicular dendritic cells, and tingible-body macrophages.

TERMINOLOGY

Abbreviations

- Reactive follicular hyperplasia (RFH)

Synonyms

- Follicular hyperplasia

Definitions

- Benign, reversible process characterized by marked proliferation of hyperplastic lymphoid follicles
  - Hyperplastic follicles have prominent germinal centers (so-called secondary follicles)
  - Characteristic of humoral immune reaction involving stimulation and proliferation of B cells
  - Usually involves lymph nodes but can affect extranodal organs

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Variety of drugs, chemicals, and environmental pollutants can cause RFH

Infectious Agents

- Most common cause of RFH is bacterial infection
  - Fungi, parasites, and viruses also can cause RFH, either pure or as part of mixed reactive pattern

Others

- In many cases, etiology of RFH cannot be identified

CLINICAL ISSUES

Presentation

- Patients typically present with enlarged lymph nodes, either localized or widespread
  - Systemic symptoms, such as fever, fatigue, and weight loss, may be present
  - Laboratory abnormalities, such as leukocytosis, neutrophilia, or lymphocytosis, are common with infections and may be present
- Lymph node size is important
  - Small, shotty lymph nodes in asymptomatic patients are within normal limits
  - Lymph nodes ≥ 1 cm in diameter are abnormal
- Painful lymph nodes are more often related to inflammation or hemorrhage
- Age and duration are important in identifying etiology
- Location and consistency can suggest most likely etiologic agent
  - Location, as related to likely causes of lymphadenopathy
    - Cervical: Infectious mononucleosis
    - Posterior cervical: Toxoplasmosis
    - Parotid, submaxillary, epitrochlear: HIV infection
    - Cervical and axillary: Cat scratch disease
    - Inguinal: Sexually transmitted diseases
    - Supraclavicular: Often associated with malignant diseases, especially in older patients
  - Consistency, as related to likely causes of lymphadenopathy
    - Soft: Inflammatory
    - Fluctuant: Suppurative infection (often bacterial or fungal)
    - Matted: Tuberculosis, lymphogranuloma venereum, cancer
    - Firm to hard: Malignancy, including lymphoma or metastatic carcinoma

Treatment

- Localized lymph node enlargement in absence of other symptoms requires follow-up for 3-4 weeks
  - If lymphadenopathy does not resolve, additional investigation is likely needed
- Generalized lymphadenopathy usually requires immediate investigation for etiology

REACTIVE FOLLICULAR HYPERPLASIA

Key Facts

Terminology
- Benign, reversible process characterized by hyperplastic secondary lymphoid follicles

Clinical Issues
- Enlarged lymph nodes, localized or widespread
- ± systemic symptoms: Fever, fatigue, weight loss
- Age and duration are important clues for etiology
- Lymph node size, location, and consistency can suggest likely etiologic agent

Microscopic Pathology
- Numerous enlarged follicles, varying in size and shape, with occasional coalescence of follicles
- Reactive follicles have central germinal centers and peripheral, sharply demarcated mantle zones

Ancillary Tests
- Germinal center and mantle zone B cells express polytypic Igs and pan-B markers
- Germinal center centrocytes and centroblasts are CD10(+), Bcl-6(+), and Bcl-2(-)
- No monoclonal *IgH* gene rearrangements
- No evidence of t(14;18)(q32;q21) or *IgH-BCL2* fusion sequences

Top Differential Diagnoses
- Follicular lymphoma
- Atypical follicular hyperplasia
- Progressive transformation of germinal centers
- Nodular lymphocyte predominant Hodgkin lymphoma
- Lymphocyte-rich classical HL, nodular variant

Prognosis
- Benign, reversible process with no impact on patient survival
  - Can be associated with other diseases such as autoimmune disease or malignancy

MICROSCOPIC PATHOLOGY

Histologic Features
- Numerous enlarged follicles, varying in size and shape, with occasional coalescence of follicles
  - In lymph nodes, reactive follicles usually prominent in cortex, with lesser involvement of other lymph node compartments
  - In spleen, reactive follicles are located in white pulp
- Reactive follicles: Have central germinal centers and peripheral, sharply demarcated mantle zones
- Germinal centers: Composed of centrocytes, centroblasts, follicular dendritic cells (FDC), T cells, and macrophages/histiocytes
- Centroblasts: 3-4x size of small lymphocytes with large vesicular nuclei, 1-3 peripheral nucleoli, frequent mitoses, and rim of cytoplasm
- Centrocytes: Smaller cells with cleaved nuclei, small nucleoli, rare mitoses, and scant cytoplasm
- Follicular dendritic cells: Few (~ 1%) have 2 square-shaped adjacent nuclei and long cytoplasmic processes
- Histiocytes: Have pale cytoplasm often containing apoptotic cellular debris (so-called tingible body macrophages)
  - Impart "starry sky" pattern when prominent
- Germinal centers: Usually organized into dark and light zones (a.k.a. polarization)
  - Dark zone contains many centroblasts and mitotic figures
  - Lymphocyte proliferation and somatic hypermutation of *IGH* gene occur in dark zone
  - Light zone contains predominantly centrocytes and follicular dendritic cells
  - Centrocytes represent later stage of activation/maturation; interaction with T cells and FDCs occurs
- Mantle zones: Composed of concentric layers of small naive (not antigen-exposed) B lymphocytes
- In some cases, specific microorganisms can be detected in histologic sections
  - Common histochemical stains for this purpose: Acid-fast, PAS, GMS, Gram, and Warthin-Starry

Predominant Pattern/Injury Type
- Lymphoid, follicular

Predominant Cell/Compartment Type
- Lymphadenopathy

ANCILLARY TESTS

Immunohistochemistry
- Germinal center and mantle zone B cells express polytypic immunoglobulins and pan-B-cell antigens
- Germinal center centrocytes and centroblasts are CD10(+), Bcl-6(+), and Bcl-2(-)

Flow Cytometry
- Polytypic B-cell population; CD10(+), CD23(+/-), T-cell antigens(-)

PCR
- No monoclonal immunoglobulin heavy chain gene rearrangement by PCR
- No evidence of t(14;18)(q32;q21) or *IgH-BCL2* fusion sequences

DIFFERENTIAL DIAGNOSIS

Follicular Lymphoma (FL)
- Lymph node typically replaced by numerous follicles of similar size and shape (back to back)
- Neoplastic follicles composed of relatively monomorphous population of germinal center cells
- Neoplastic follicles often lack mantle zones

REACTIVE FOLLICULAR HYPERPLASIA

Differential Diagnosis: Reactive Follicular Hyperplasia (RFH) vs. Follicular Lymphoma (FL)

	Reactive Follicular Hyperplasia	Follicular Lymphoma
Size and shape of follicles	Variable	Similar, back to back
Germinal center cells	Heterogeneous	Monotonous
Tingible-body macrophages	Numerous	Few
Proliferation activity	High	Low
Mantle zone	Sharply demarcated	Absent
Capsule and perinodal invasion	Uncommon	Common
Surface Ig	Polytypic	Monotypic
Bcl-2	Negative	Positive ~ 80-90%
IgH gene rearrangement	Polyclonal	Monoclonal
t(14;18)(q32;q21)	Absent	Present ~ 80-90%

- Tingible-body macrophages are typically decreased compared with RFH
- Mitoses and proliferation rate (assessed by Ki-67) often lower in follicular lymphoma than in RFH
- Neoplastic follicles commonly invade lymph node capsule or extend into perinodal tissues
- Immunophenotyping is very helpful
  - FL cells usually express monotypic surface Ig and Bcl-2
  - Some cases of FL lack surface Ig; this is aberrant and supports lymphoma
- Molecular or cytogenetic studies are also helpful for FL diagnosis
  - Most cases of FL carry monoclonal *IgH* gene rearrangements
  - t(14;18)(q32;q21) or *IgH-BCL2* fusion sequences present in 80-90% of FL

Atypical Follicular Hyperplasia

- Term used for follicular lesions having some histologic features suggestive of FL
- Diagnosis is now uncommon with advent of immunophenotypic and molecular methods
  - Problem can be attributed to lack of fresh tissue for ancillary studies in some cases
- Patients require close clinical follow-up

Progressive Transformation of Germinal Centers (PTGC)

- Typically associated with RFH
- Nodules are 3-4x larger than reactive follicles
- Germinal center cells are Bcl-2(-)

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

- Nodules are typically much larger than reactive follicles
- Neoplastic L&H cells are CD20(+), CD45(+), Bcl-2(-)
- Small cells in tumor nodules are mostly reactive B cells
- CD57(+) T cells are increased in nodules; T cells can form rosettes around LP cells

Lymphocyte-rich Classical HL

- Nodular variant can closely resemble NLPHL
- Neoplastic cells are typically CD15(+), CD30(+), CD20(-/+), and CD45(-)
- Small reactive follicles can often be observed within neoplastic nodules

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