DIAGNOSTIC PATHOLOGY

Lymph Nodes and Extranodal Lymphomas

SECOND EDITION

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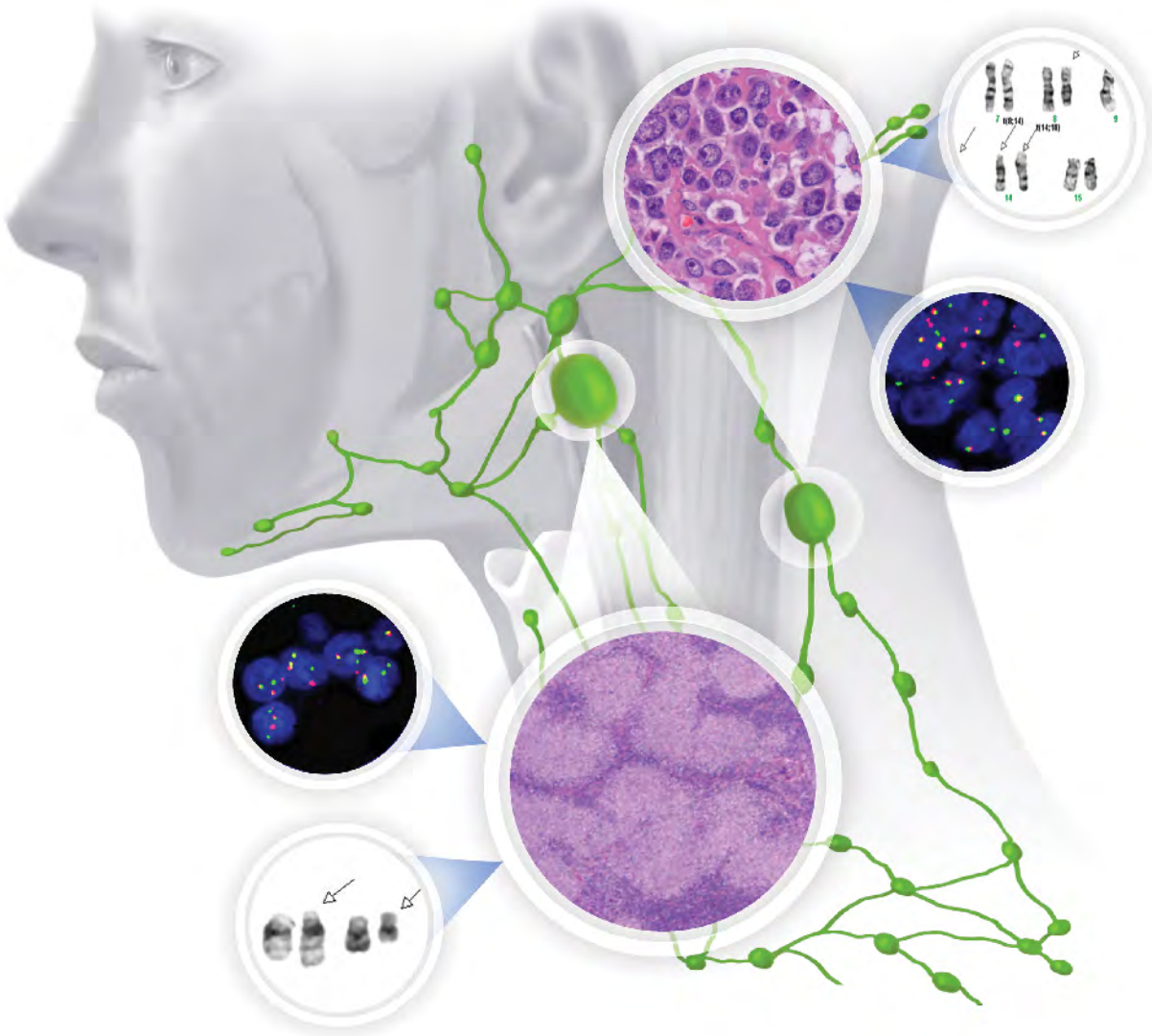

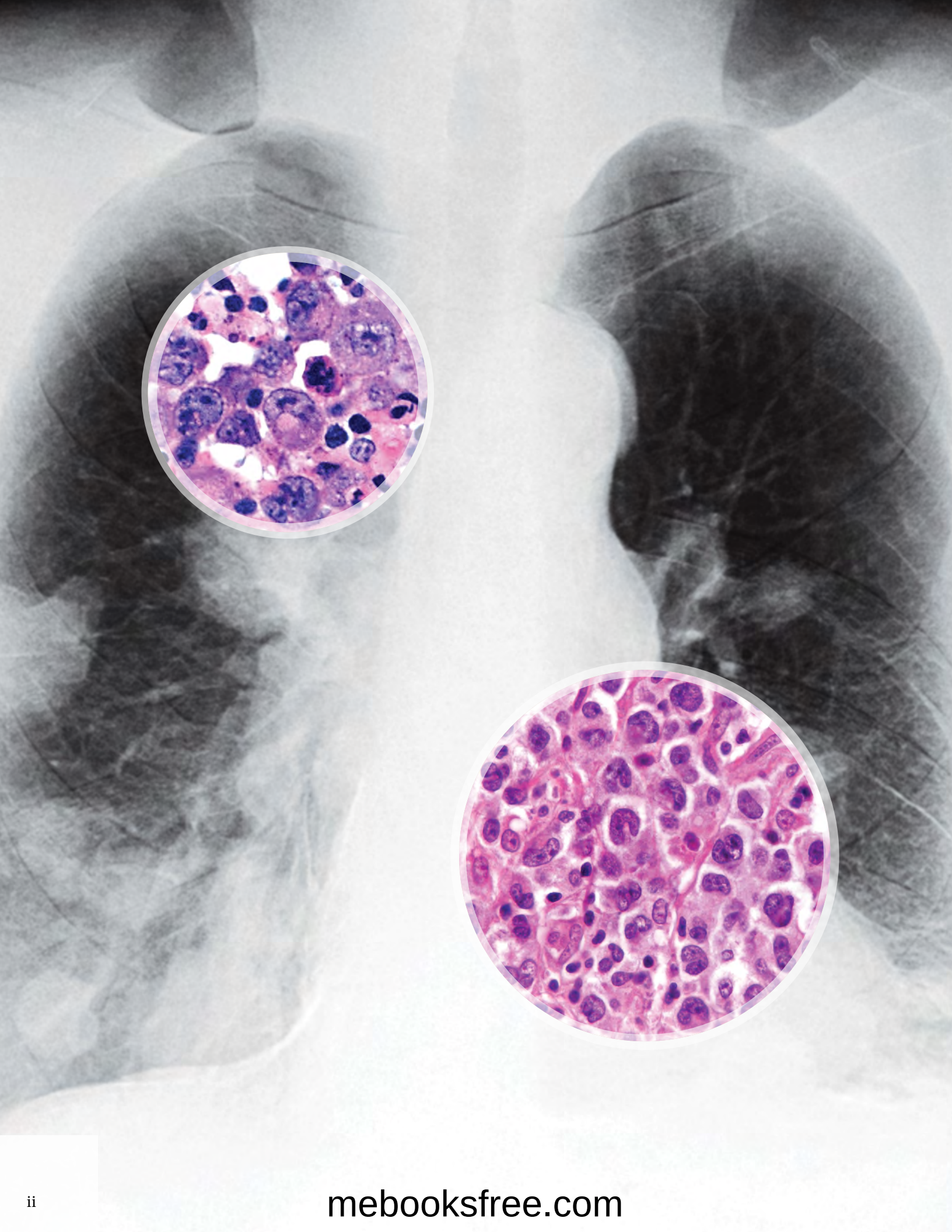

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Lymph Nodes and Extranodal Lymphomas

SECOND EDITION

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Dedications

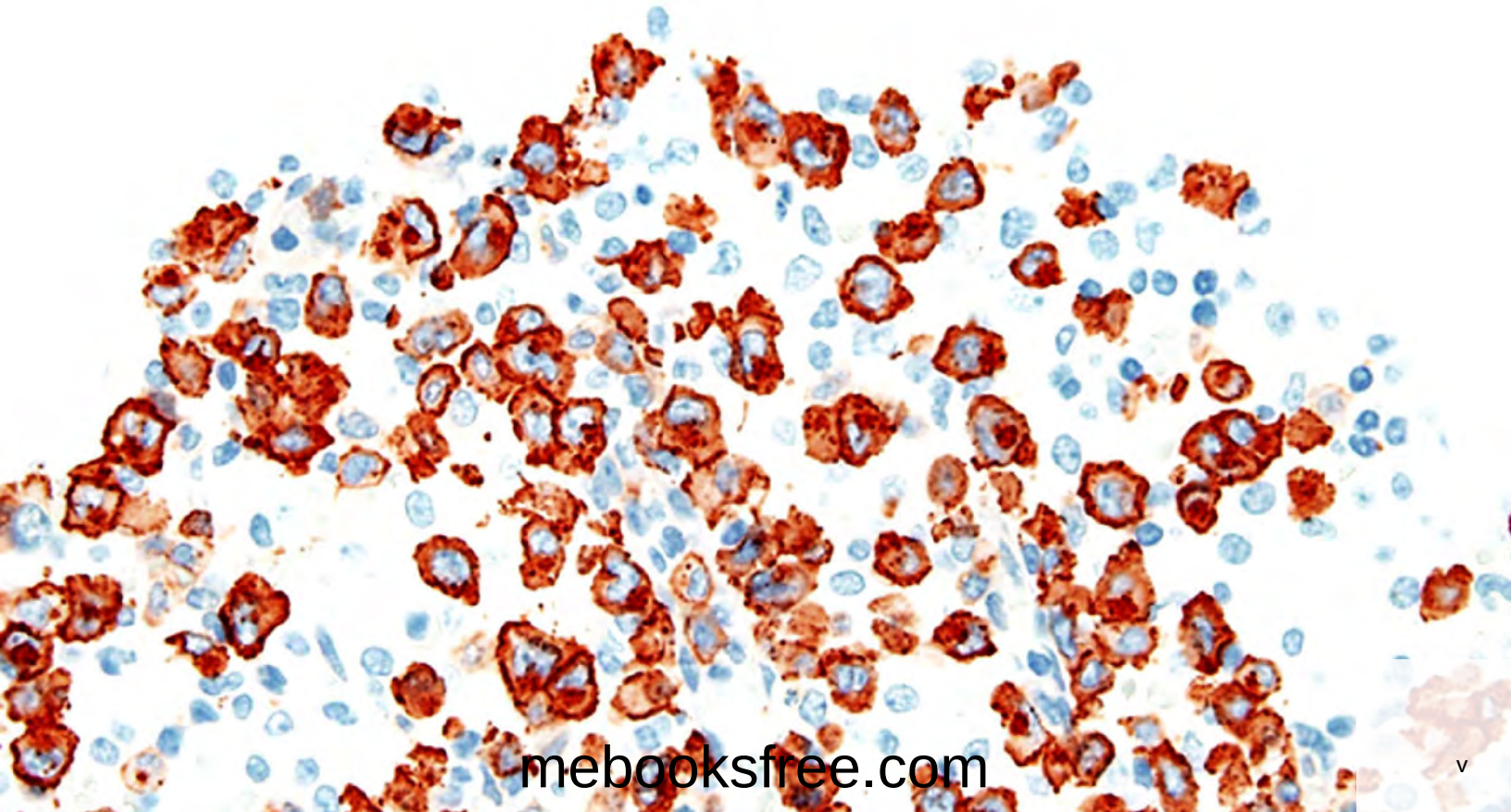
To the women in my life—my mother, Albertina Medeiros, my sister, Deborah Medeiros Stroscio, my wife, Carrie Medeiros, and our daughters, Christina and Caroline.

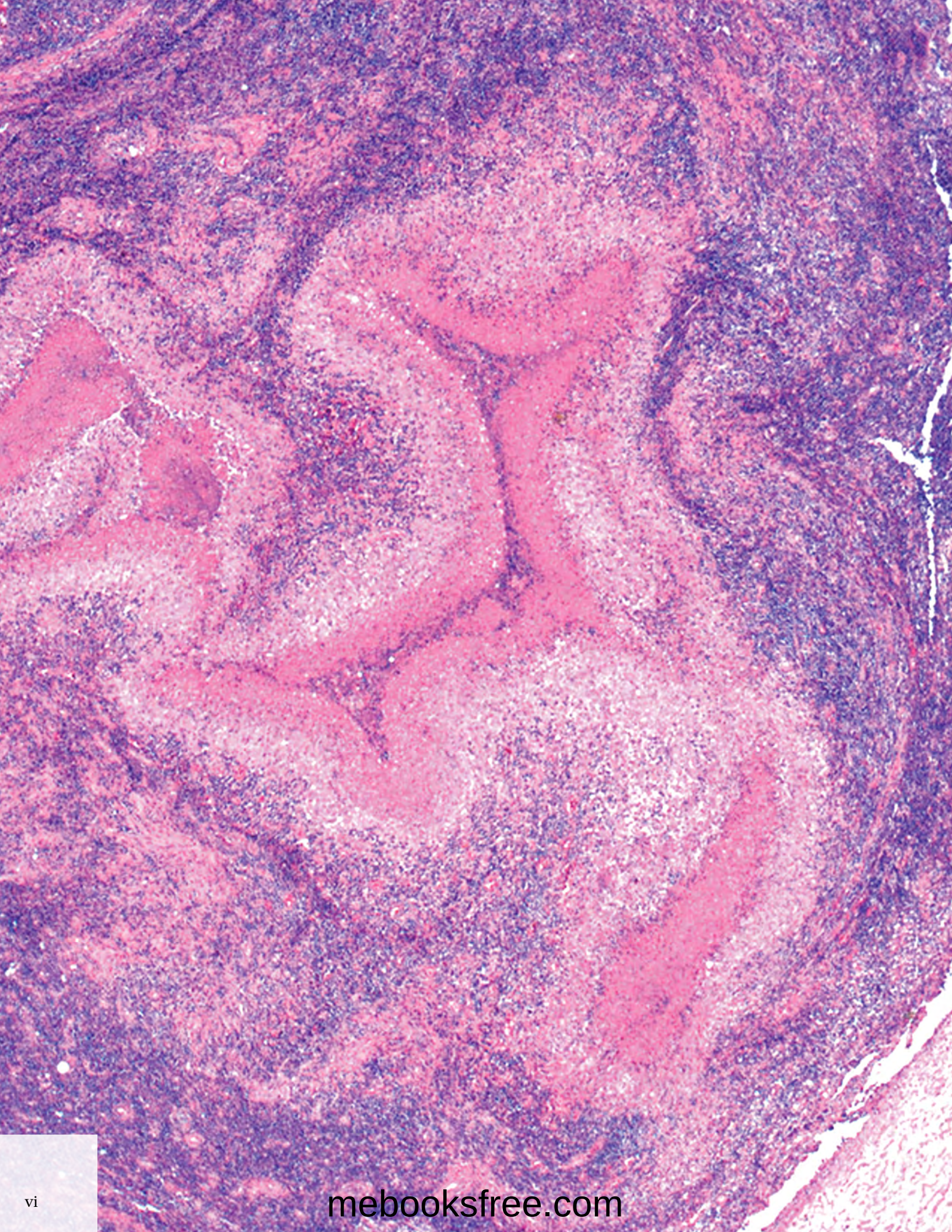
To Mark L. Silverman, MD, retired Chair, department of pathology, Lahey Hospital and Medical Center. Thanks for believing I had potential and patiently teaching me surgical pathology.

LJM

Dedicated to my wife, Norma, and our children, Alonso and Andrea. This work is also dedicated to my mother, Milly, my late father, Hernan, and my siblings, Hernan, Elena, Carina, and Aaron.

RNM





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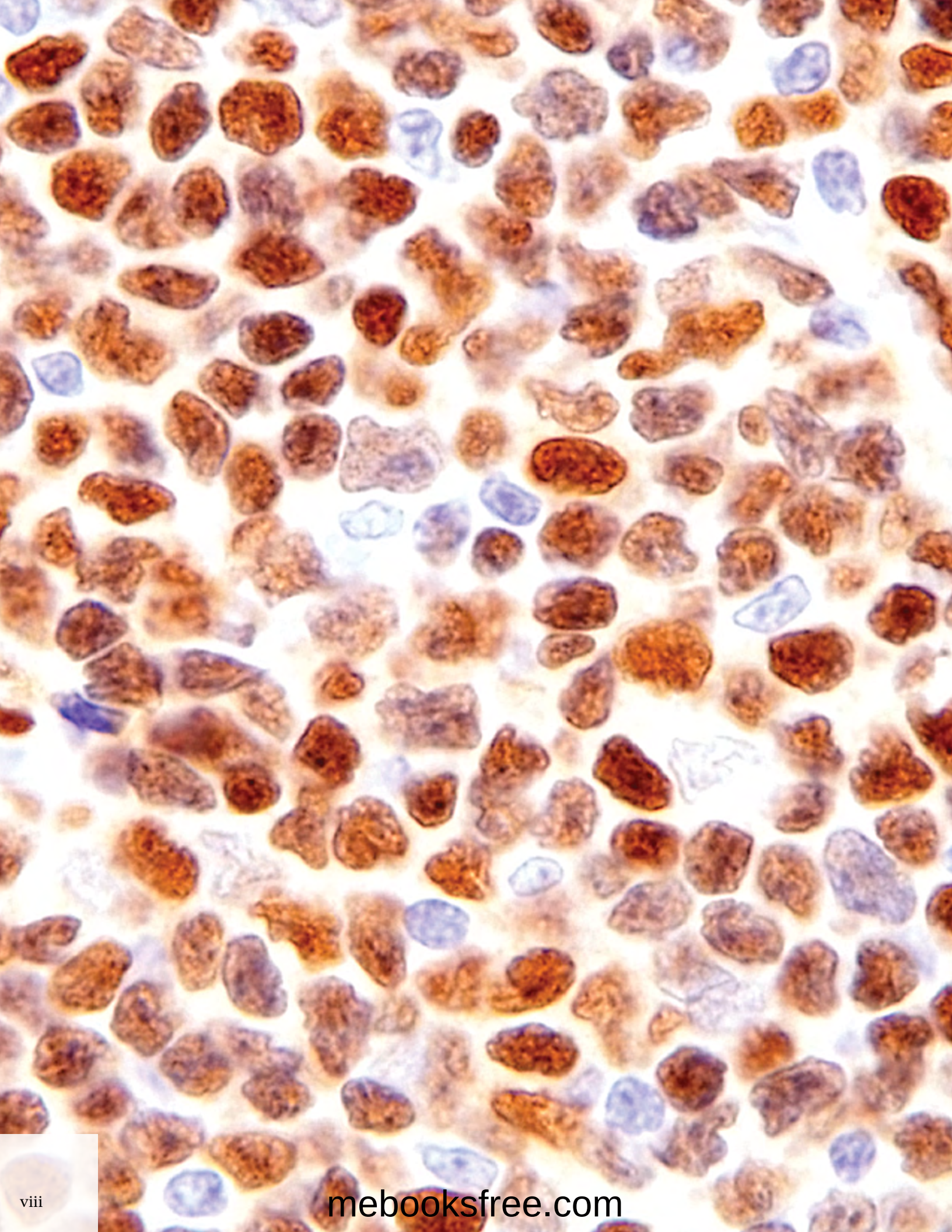

Preface

Most likely, the reader has heard the lament, often said in jest, "All lymphomas look the same to me." Indeed, lymphomas involving lymph nodes and 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 nonhematopoietic 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 and illustrating this book was to create a systematic, easy-to-use reference. The contents of this volume include benign and malignant lesions of lymph nodes as well as extranodal lymphomas. The lymphomas are designated, in large part, using the terminology of the 2016 revision of the 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 and illustrations on the first page of each chapter capture 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.

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

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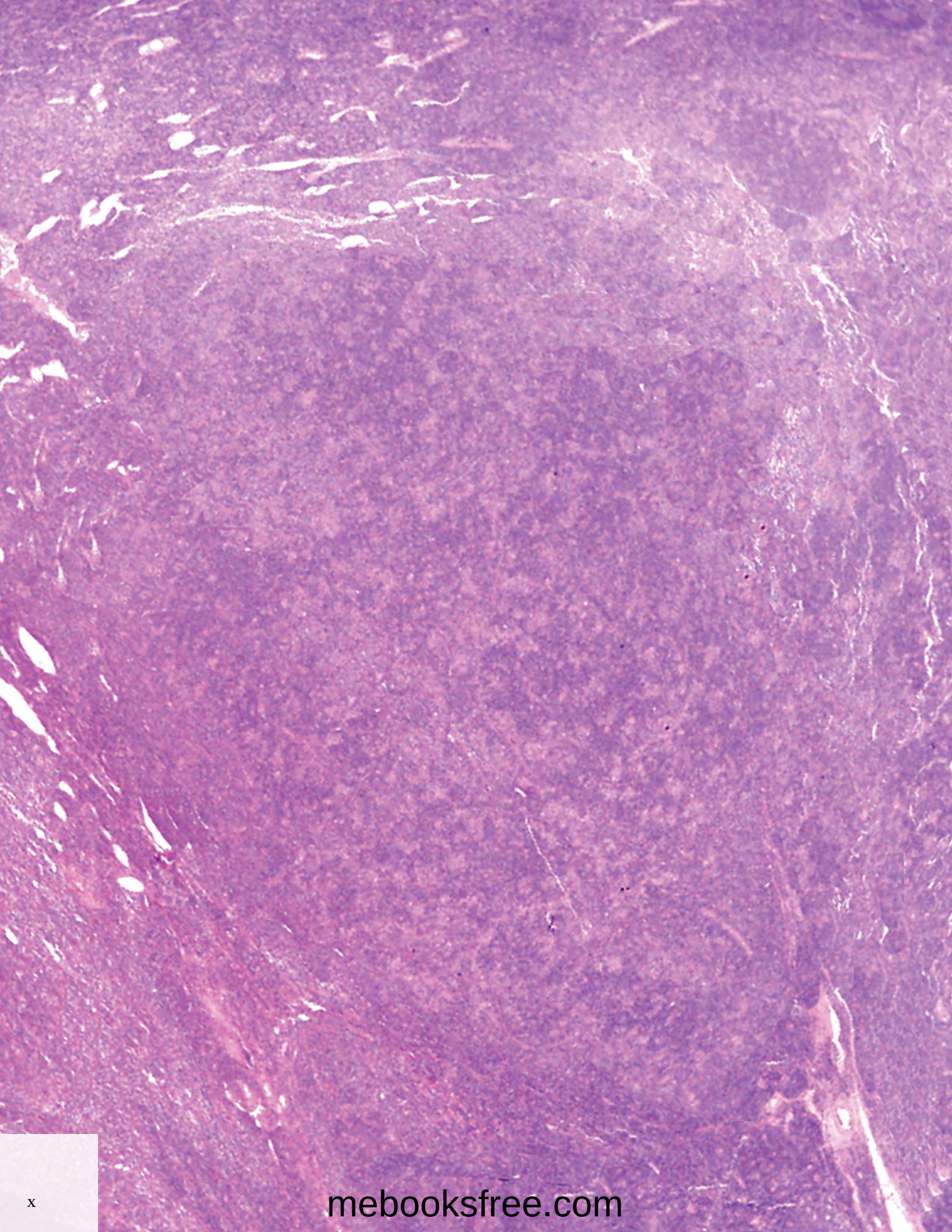

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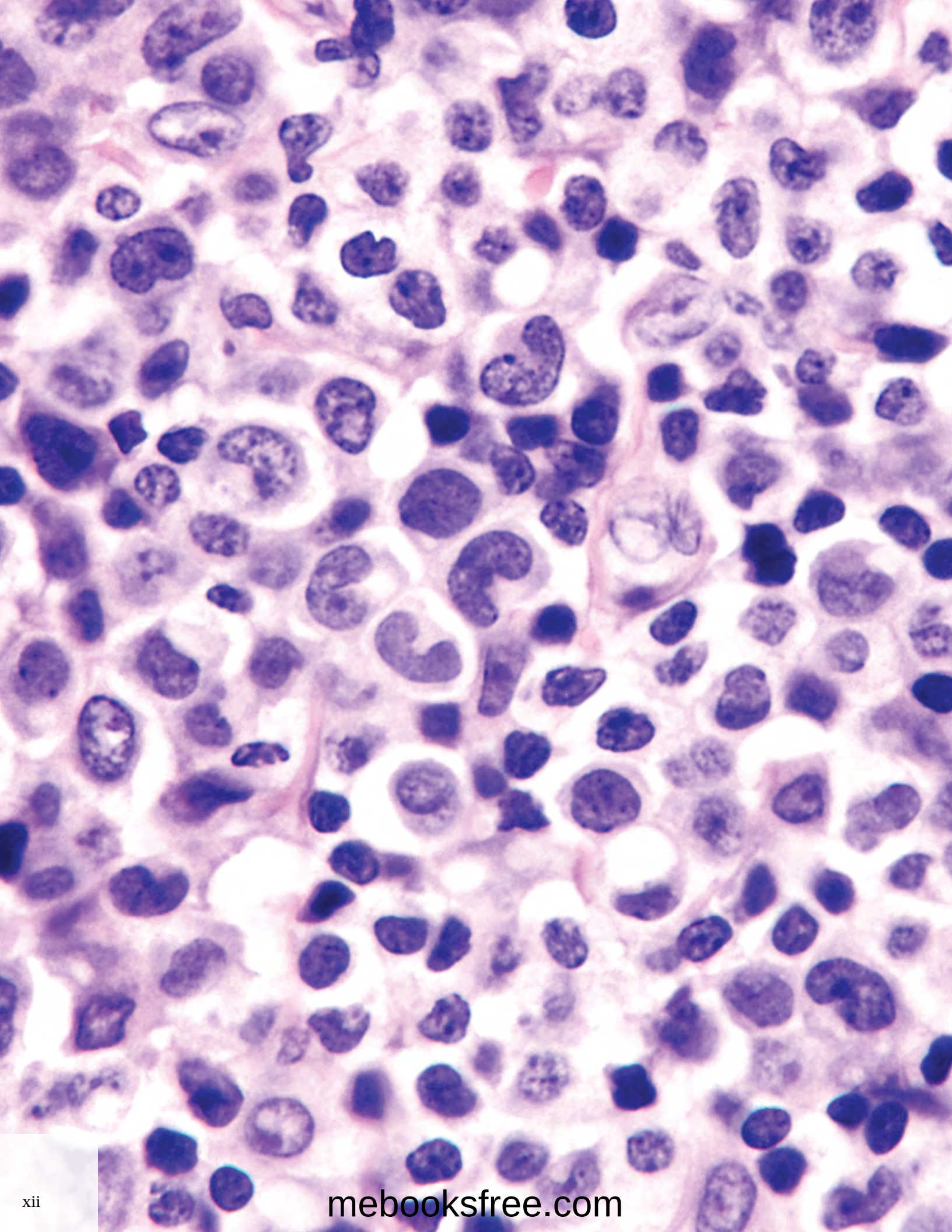

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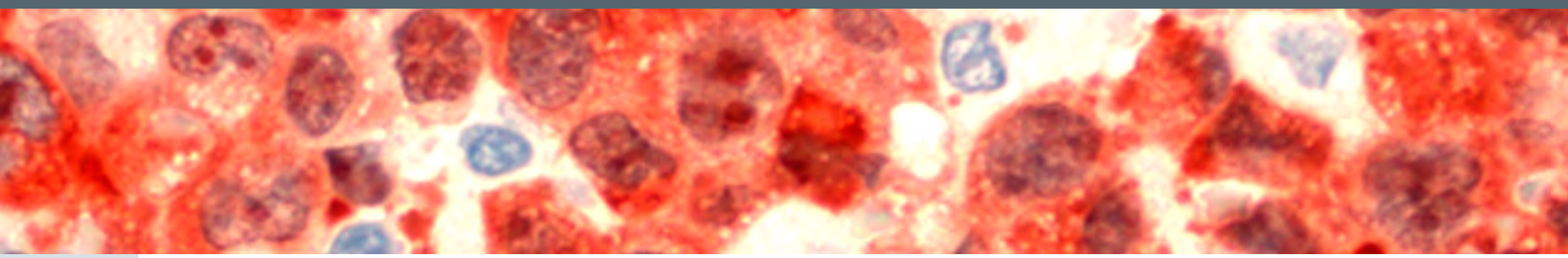

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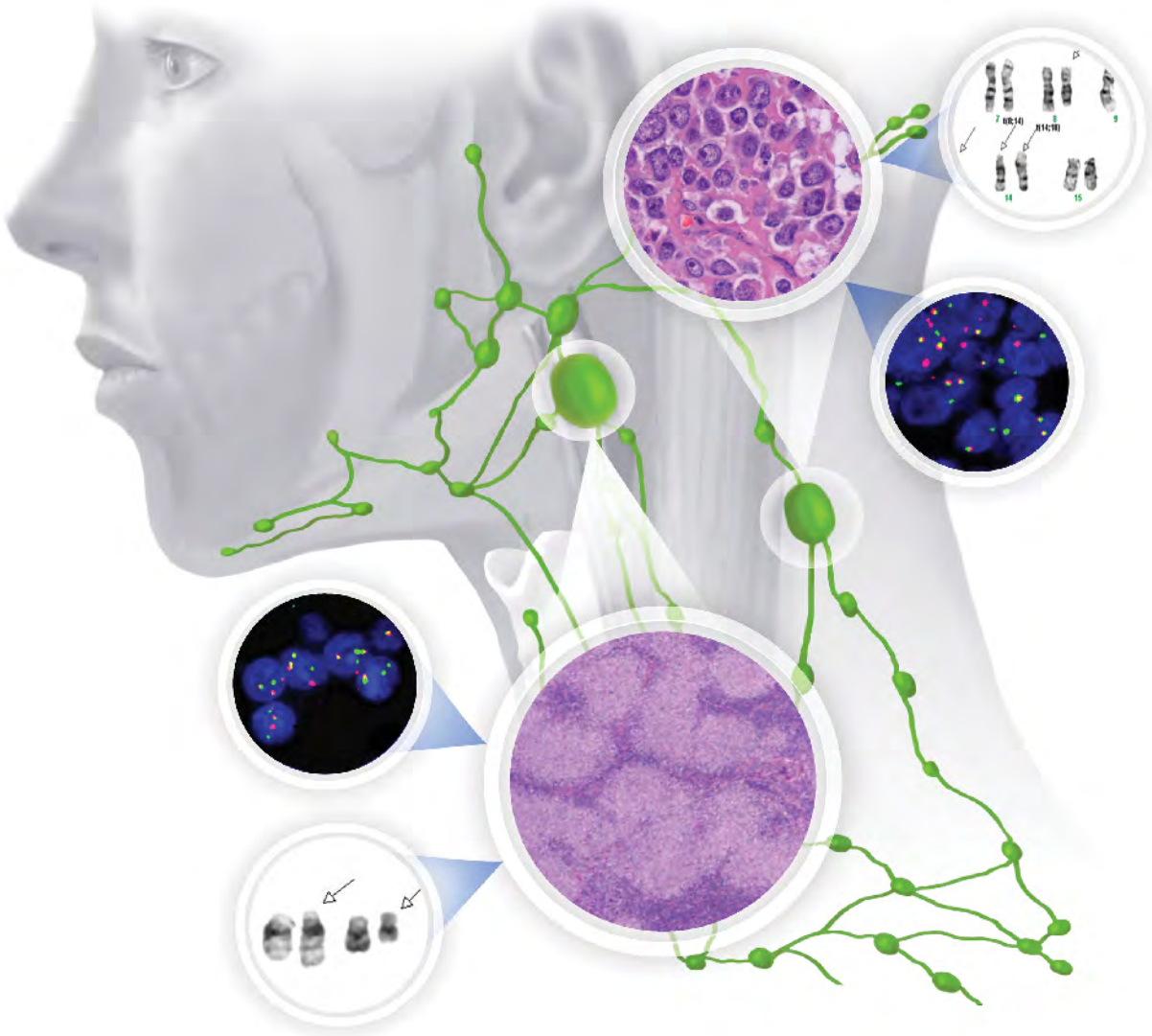

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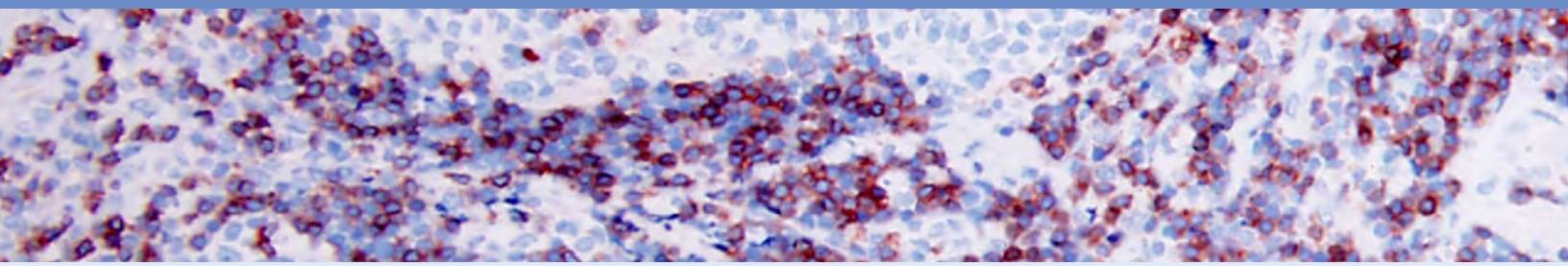
SECTION 1

Reactive Nonspecific Changes



Reactive Follicular Hyperplasia

KEY FACTS

TERMINOLOGY

- Benign, reversible process characterized by hyperplastic follicles with secondary germinal centers

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

- 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
- Germinal centers include predominantly centrocytes and centroblasts, few T lymphocytes and scattered histiocytes
- Germinal centers: Usually organized into dark and light zones (a.k.a. polarization)

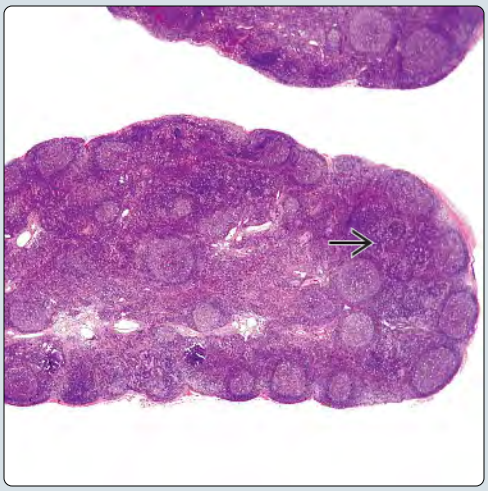
ANCILLARY TESTS

- 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(-)
- Polyclonal *IGH* gene rearrangements
- No evidence of t(14;18)(q32;q21) or *IGH-BCL2* fusion sequences

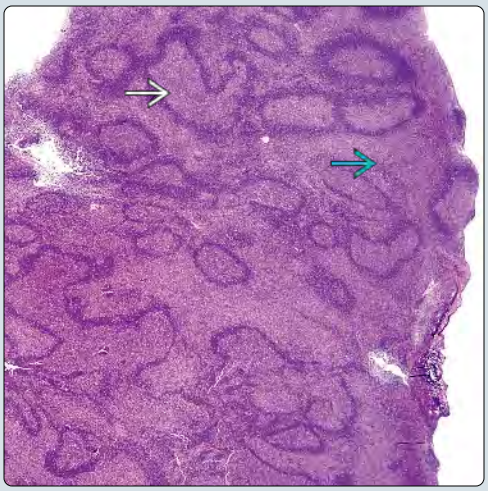
TOP DIFFERENTIAL DIAGNOSES

- Follicular lymphoma
- Atypical follicular hyperplasia
- Progressive transformation of germinal centers
- Nodular lymphocyte predominant Hodgkin lymphoma
- Lymphocyte-rich classic Hodgkin lymphoma, nodular variant

Reactive Follicular Hyperplasia

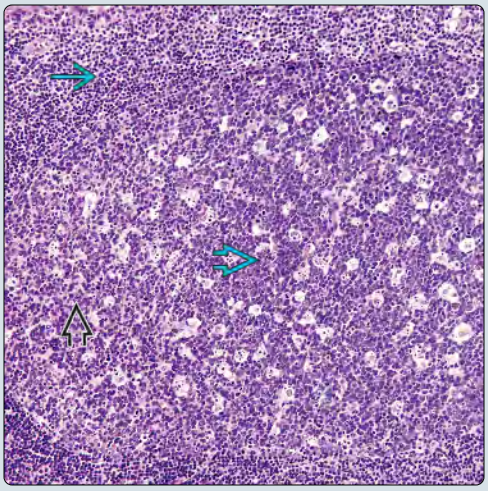


Irregular Hyperplastic Follicles

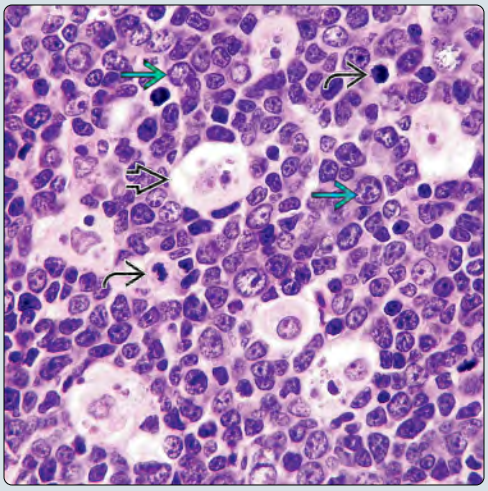


(Left) *Low-power view of a lymph node shows numerous enlarged, round to oval follicles, predominantly distributed in the cortex. Focal paracortical hyperplasia is also present.* **(Right)** *Lymph node with mixed pattern of reactive follicular and paracortical hyperplasia is shown. The hyperplastic follicles exhibit markedly irregular shapes that prompted testing of clonality by polymerase chain reaction. IGH rearrangements were polyclonal, supporting a reactive process.*

Hyperplastic Lymphoid Follicle



Starry-Sky Pattern in Germinal Center



(Left) *A prominent germinal center is surrounded by a sharply demarcated mantle zone. The germinal center is composed of a dark zone with a prominent starry-sky pattern and a light zone with a predominance of small centrocytes.* **(Right)** *High magnification of a germinal center shows centroblasts admixed with histiocytes displaying abundant clear cytoplasm with nuclear fragments, so-called tingible body macrophages. Frequent mitoses are common in the dark zone.*

TERMINOLOGY

Abbreviations

- Reactive follicular hyperplasia (RFH)

Synonyms

- Follicular hyperplasia

Definitions

- Benign, reversible process characterized by hyperplastic lymphoid follicles
  - Predominance of hyperplastic follicles with prominent germinal centers (so-called secondary follicles)
    - Hyperplastic follicles may be part of mixed reactive pattern
- Characteristic of humoral immune reaction involving stimulation and proliferation of B cells
- Usually involves lymph nodes but can affect extranodal sites

ETIOLOGY/PATHOGENESIS

Environmental Exposure

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

Infectious Agents

- Most common cause of RFH is bacterial infection
  - Viruses such as HIV and EBV are also causes

Others

- Autoimmune diseases
- In many cases, etiology of RFH cannot be identified

CLINICAL ISSUES

Presentation

- Patients typically present with enlarged lymph nodes, either localized or generalized
  - Systemic symptoms, such as fever, fatigue, and weight loss may be present
  - Laboratory abnormalities may be detected
    - Leukocytosis, neutrophilia, or lymphocytosis suggest infection
- Lymph node size is important
  - Small, shotty lymph nodes in asymptomatic patients are, as a rule, clinically irrelevant
  - In general, lymph nodes ≥ 1 cm in diameter are abnormal
    - For epitrochlear, significant size is > 0.5 cm and for inguinal is > 1.5 cm
- Painful lymph nodes are more often related to inflammation or hemorrhage
- Lymphadenopathy for > 1 month may be of clinical significance
- Location can suggest the underlying disease
  - Cervical: Infectious mononucleosis
  - Posterior cervical: Toxoplasmosis
  - Parotid, submaxillary, epitrochlear: HIV infection
  - Cervical and axillary: Cat-scratch disease
  - Inguinal: Sexually transmitted diseases
  - Supraclavicular: Malignancy, particularly in older patients
- Consistency
  - 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
  - Persistent lymphadenopathy > 3 or 4 weeks, requires additional investigation
- Generalized lymphadenopathy usually requires investigation for etiology

Prognosis

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

MICROSCOPIC

Histologic Features

- Numerous enlarged follicles, varying in size and shape, with occasional coalescence
  - In lymph nodes, reactive follicles usually prominent in cortex, with lesser involvement of medulla
- Reactive follicles have central germinal centers and peripheral, sharply demarcated mantle zones
- Germinal centers cell composition
  - B lineage: Predominance of centrocytes and centroblasts
    - Immunoblasts and plasma cells less common
  - T lymphocytes: Predominantly follicular T-helper cells
  - Histiocytes and follicular dendritic cells (FDC)
- Centroblasts
  - 3-4x size of small lymphocytes; 1-3 peripheral nucleoli
  - Large vesicular nuclei, frequent mitoses, and rim of cytoplasm
- Centrocytes
  - Small- to intermediate-sized cells with cleaved, hyperchromatic nuclei, with small or absent nucleolus
- T lymphocytes
  - Small, round, hyperchromatic lymphocytes
  - Can be highlighted with CD3 immunohistochemistry
    - T helper cells (Tfh) are CD4(+), CD10(+)
    - T cytotoxic subset are CD8 (+)
- Follicular dendritic cells
  - Few (~ 1%) have 2 square-shaped adjacent nuclei
  - Have long cytoplasmic processes that can be highlighted by CD21, CD23, or CD35 immunohistochemistry
- Histiocytes
  - Display oval or twisted vesicular nuclei; faint or pink cytoplasm
  - Subset has abundant pale cytoplasm with karyorrhectic nuclei
    - So-called tingible-body macrophages and impart a starry-sky pattern when prominent
  - Histiocytes are highlighted with CD68 or CD163
- Germinal centers: Usually organized into dark and light zones (a.k.a. polarization)

- Dark zone contains many centroblasts and mitotic figures
- Light zone contains predominantly centrocytes and follicular dendritic cells

- Mantle zones: Composed of concentric layers of small naive (not antigen-exposed) B lymphocytes
- In some cases, microorganisms can be detected
  - Common histochemical stains to detect microorganisms
    - Acid-fast stain, periodic acid-Schiff, Gomori methenamine silver, 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 pan-B-cell antigens and polytypic immunoglobulins
- Centrocytes and centroblasts are CD10(+), Bcl-6(+), and Bcl-2(-)

Flow Cytometry

- Polytypic B cells; 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

Genetic Testing

- Rare cases of florid hyperplasia with numeric or structural abnormalities need to be better defined

DIFFERENTIAL DIAGNOSIS

Follicular Lymphoma

- Lymph node typically replaced by numerous follicles
  - Minimal variation of size and shapes, commonly closely packed ("back to back")
- Relatively monomorphous population of germinal center cells
- Neoplastic follicles often lack mantle zones
- Few or no tingible-body macrophages
- Few mitoses and low proliferation rate (Ki-67) as opposed to RFH
- Immunophenotyping is very helpful
  - Follicular lymphoma (FL) cells usually express monotypic surface Ig and Bcl-2
  - Some cases of FL lack surface Ig; this is aberrant and supports lymphoma
  - Diagnosis more challenging with pediatric follicular lymphoma since Bcl-2(-)
- 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 often attributable to lack of fresh tissue for ancillary studies

Progressive Transformation of Germinal Centers

- Typically associated with RFH
- Nodules with diameters that are 3-4x larger than reactive follicles
- Most lymphocytes in nodules are small, round to oval, and hyperchromatic
- Remnant centrocytes and centroblasts may be found
  - Reactive centrocytes & centroblasts are Bcl-6(+)/Bcl-2(-)

Nodular Lymphocyte Predominant Hodgkin Lymphoma

- Nodules are typically much larger than reactive follicles
  - Predominance of small lymphocytes, which are mostly reactive B cells
  - Scattered large lymphocyte predominant (LP) cells
    - LP cells are CD20(+), CD45(+), Bcl-2(-)

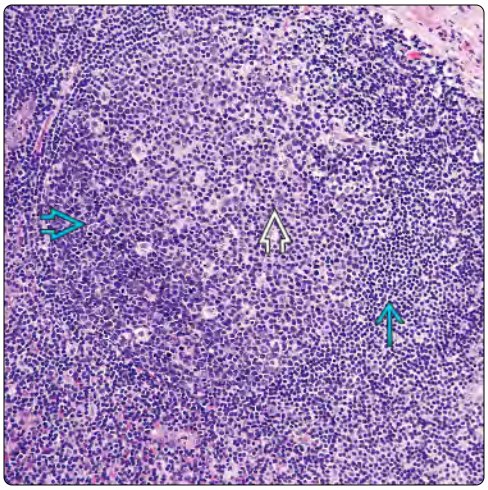
Lymphocyte-Rich Classic Hodgkin Lymphoma

- Nodular variant can closely resemble nodular LP Hodgkin lymphoma
- Neoplastic cells are CD15(+), CD30(+), CD20(-/+), pax-5(+), and CD45(-)
- Small reactive germinal centers can often be observed within neoplastic nodules

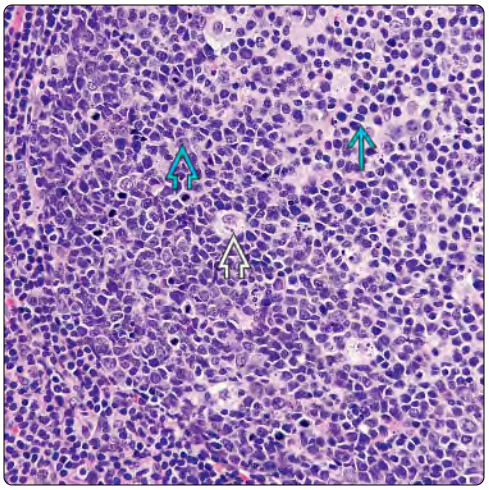
SELECTED REFERENCES

1. Mohseni S et al: Peripheral lymphadenopathy: approach and diagnostic tools. Iran J Med Sci. 39(2 Suppl):158-70, 2014
2. Ingolfsdottir M et al: Evaluation of cervical lymphadenopathy in children: advantages and drawbacks of diagnostic methods. Dan Med J. 60(8):A4667, 2013
3. Sevilla DW et al: Cytogenetic abnormalities in reactive lymphoid hyperplasia: byproducts of the germinal centre reaction or indicators of lymphoma? Hematol Oncol. 29(2):81-90, 2011
4. Weiss LM et al: Immunoglobulin light chain immunohistochemistry revisited, with emphasis on reactive follicular hyperplasia versus follicular lymphoma. Appl Immunohistochem Mol Morphol. 18(3):199-205, 2010
5. Lin P et al: The activation profile of tumour-associated reactive T-cells differs in the nodular and diffuse patterns of lymphocyte predominant Hodgkin's disease. Histopathology. 44(6):561-9, 2004
6. Chang CC et al: Follicular hyperplasia, follicular lysis, and progressive transformation of germinal centers. A sequential spectrum of morphologic evolution in lymphoid hyperplasia. Am J Clin Pathol. 120(3):322-6, 2003
7. Twist CJ et al: Assessment of lymphadenopathy in children. Pediatr Clin North Am. 49(5):1009-25, 2002
8. Nguyen PL et al: Progressive transformation of germinal centers and nodular lymphocyte predominance Hodgkin's disease: a comparative immunohistochemical study. Am J Surg Pathol. 23(1):27-33, 1999
9. Osborne BM et al: Clinical implications of nodal reactive follicular hyperplasia in the elderly patient with enlarged lymph nodes. Mod Pathol. 4(1):24-30, 1991
10. van der Valk P et al: The histology of reactive lymph nodes. Am J Surg Pathol. 11(11):866-82, 1987
11. Nathwani BN et al: Morphologic criteria for the differentiation of follicular lymphoma from florid reactive follicular hyperplasia: a study of 80 cases. Cancer. 48(8):1794-806, 1981

Polarity in Germinal Center

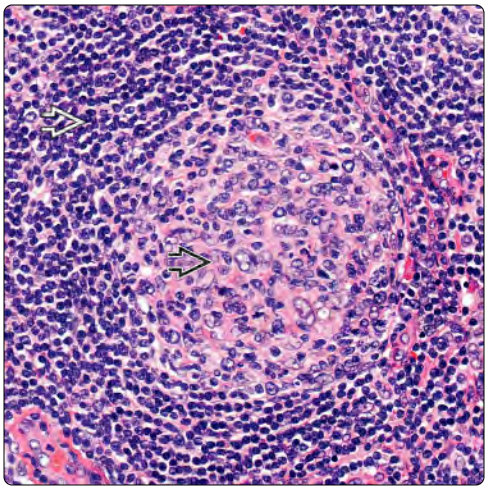


Polarity of Germinal Center

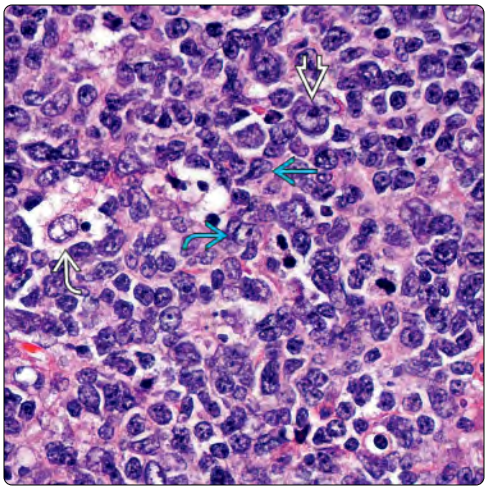


(Left) *A hyperplastic lymphoid follicle displays polarization of the germinal center with a dark zone and light zone. The mantle zone is sharply demarcated. These features are characteristic of a reactive process but require optimal histologic sections.* **(Right)** *High-power magnification of a hyperplastic germinal center shows the dark zone containing many centroblasts and scattered tingible body macrophages. In comparison, the light zone shows a predominance of small centrocytes.*

Lymphoid Follicle

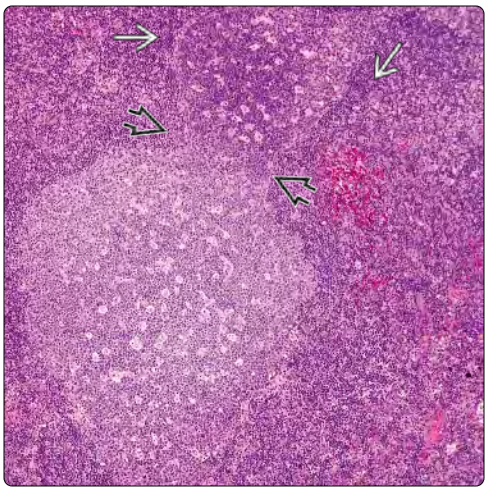


Dark Zone of Germinal Center

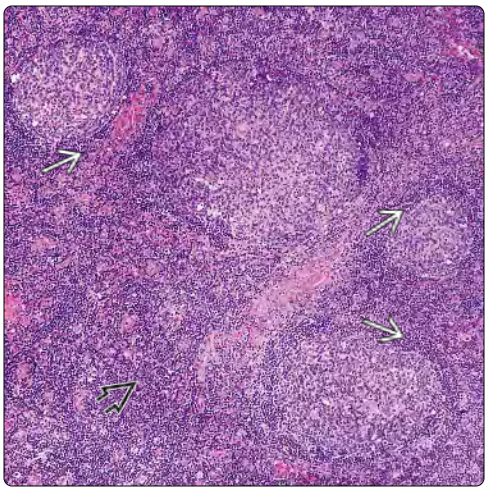


(Left) *A hyperplastic lymphoid follicle is seen with a central germinal center surrounded by a sharply demarcated and expanded mantle zone. The germinal center is composed of small centrocytes and large centroblasts. The mantle zone is composed of small, round lymphocytes.* **(Right)** *The dark zone of a reactive germinal center is composed of a mixed population of numerous centroblasts, few centrocytes, scattered tingible-body macrophages, and occasional follicular dendritic cells.*

Coalescence of Germinal Centers

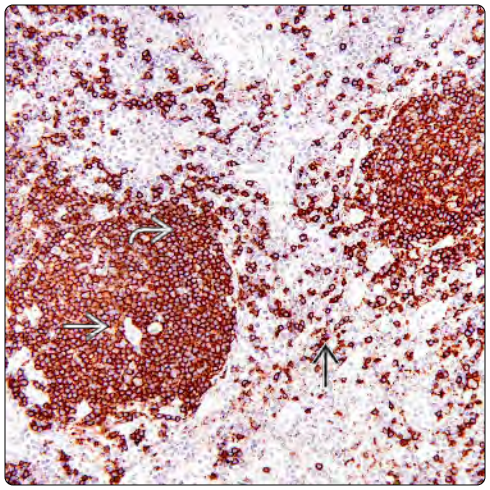


Reactive Lymphoid Follicles

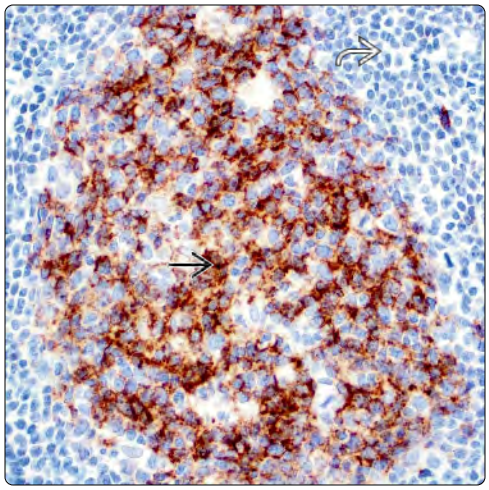


(Left) *Two hyperplastic lymphoid follicles with prominent starry-sky pattern appear to merge or coalesce. Both follicles exhibit polarization and are surrounded by sharply demarcated mantle zones.* **(Right)** *Four hyperplastic follicles of various sizes are seen in this case of reactive follicular hyperplasia. Although they are somewhat crowded, there they are surrounded by sharply demarcated mantle zones and there is a distinct interfollicular region.*

CD20 in Lymphoid Follicle

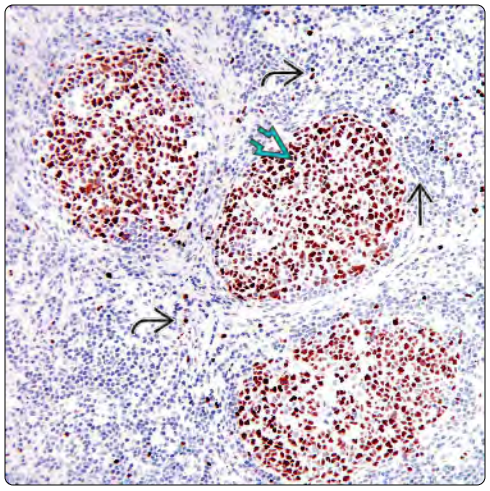


CD10 in Reactive Germinal Center

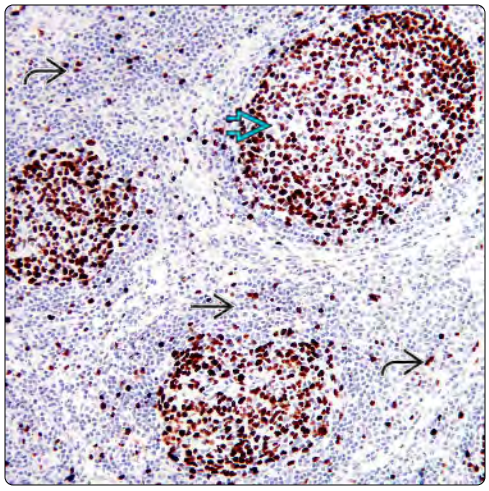


(Left) *Immunohistochemical stain with the pan B-cell marker CD20 highlights most lymphocytes of the germinal center and of the mantle zone. This immunostain shows that germinal center and mantle zone lymphocytes react similarly. Scattered B lymphocytes are normally noted in the interfollicular areas.* **(Right)** *Immunohistochemistry for the germinal center cell marker CD10 shows that most lymphocytes in the germinal center are positive. Lymphocytes in the mantle zone are negative.*

Bcl-6 in Reactive Lymphoid Follicles

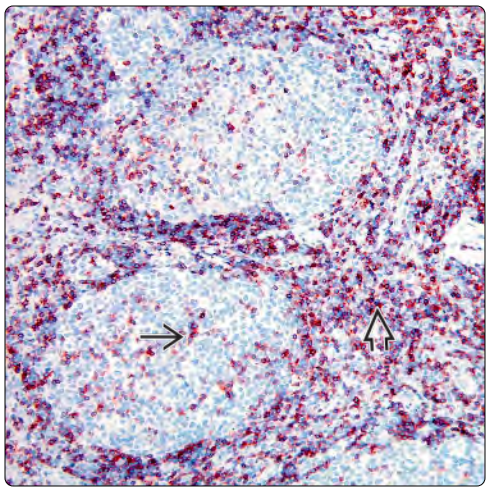


Ki-67 in Reactive Germinal Centers

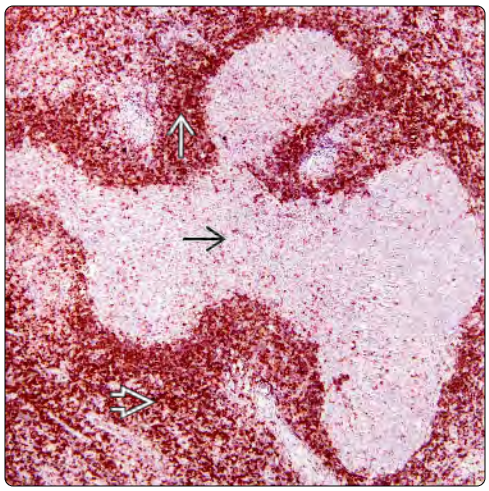


(Left) *Immunohistochemical stain for Bcl-6 highlights centrocytes and centroblasts in the reactive germinal centers. Mantle zone lymphocytes are negative; rare or scattered interfollicular lymphocytes are positive for Bcl-6.* **(Right)** *Immunohistochemical stain for the proliferation marker Ki-67 shows high proliferative rate (~ 100% lymphocytes) in reactive follicles. Only a few lymphocytes are highlighted by Ki-67 in the mantle zones or in the interfollicular region.*

CD3 in Reactive Follicles

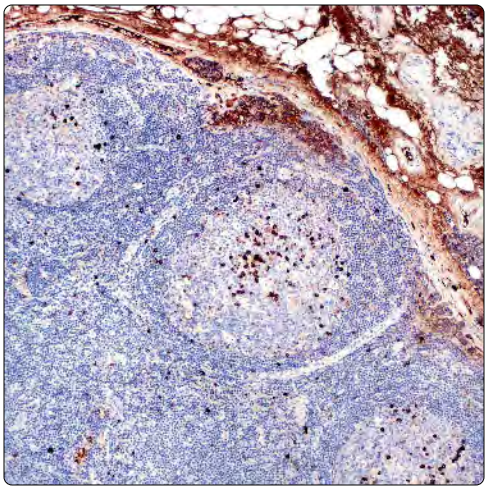


Bcl-2 in Reactive Follicles

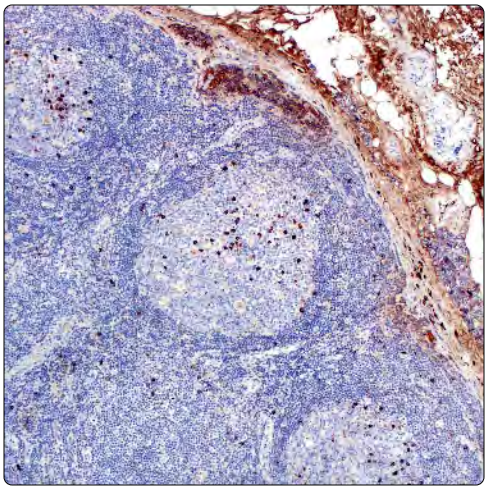


(Left) *Immunohistochemical stain for the pan T-cell marker CD3 highlights scattered small lymphocytes within germinal centers. Many more CD3(+) lymphocytes are noted in the interfollicular region.* **(Right)** *Most lymphocytes in reactive germinal centers do not express Bcl-2, while mantle zone B and T lymphocytes and interfollicular T cells are positive. In contrast, the neoplastic follicles of follicular lymphoma commonly express Bcl-2.*

Immunohistochemistry for κ

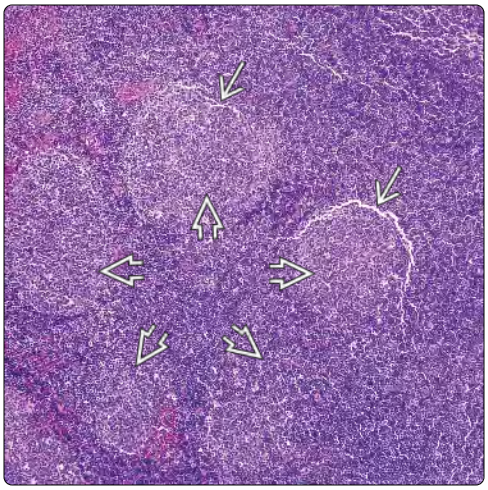


Immunohistochemistry for λ

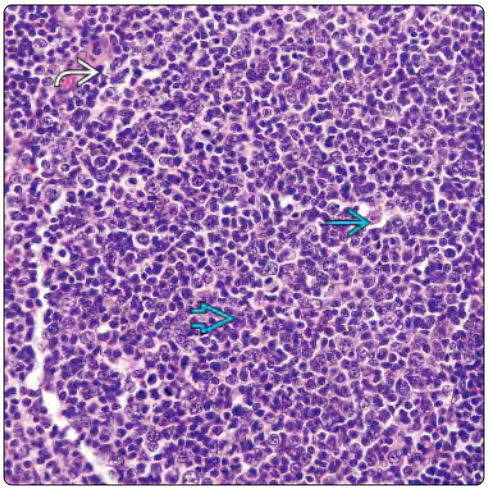


(Left) *Immunohistochemistry for κ-light chain highlights scattered plasma cells in reactive lymphoid follicles and interfollicular region. When tested, similar numbers of plasma cells reacted with λ, indicating a polytypic pattern.* **(Right)** *Immunohistochemistry for λ-light chain highlights scattered plasma cells in reactive lymphoid follicles and interfollicular region. In comparison, similar numbers of plasma cells reacted with κ, indicating a polytypic pattern.*

Neoplastic Follicles in Follicular Lymphoma

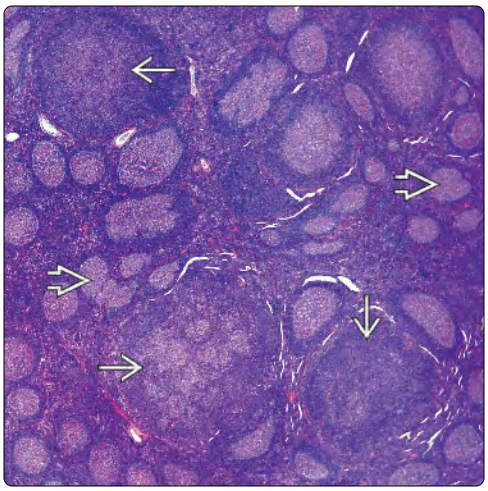


Neoplastic Follicle in Follicular Lymphoma

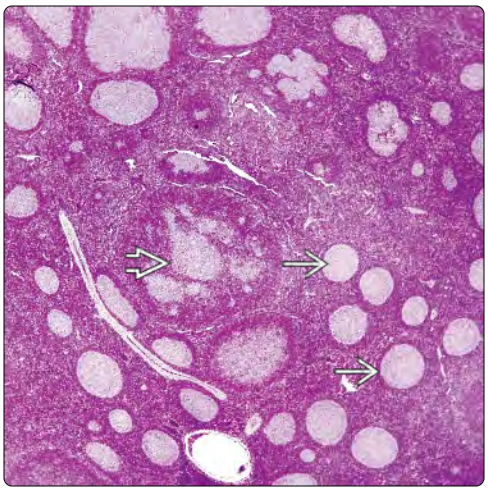


(Left) *In this case of low-grade follicular lymphoma, closely packed neoplastic follicles are present. Cracking artifact is seen and partially surrounds 2 follicles. In contrast with reactive follicular hyperplasia, the neoplastic follicles in follicular lymphoma lack well-formed mantle zones.* **(Right)** *High magnification of a neoplastic follicle of follicular lymphoma grade I shows a monotonous population of small centrocytes with rare tingible-body macrophages. The mantle zone is poorly defined.*

Progressive Transformation of Germinal Centers



Progressive Transformation of Germinal Centers: Bcl-2



(Left) *In this case of progressive transformation of germinal centers, there are 3 progressively transformed follicles. These nodules are 3-4x larger than usual hyperplastic follicles and are composed of reactive germinal centers infiltrated and disrupted by small lymphocytes.* **(Right)** *A progressively transformed germinal center with Bcl-2(-) germinal centers and Bcl-2(+) small lymphocytes is shown. Typical reactive follicles with Bcl-2(-) germinal centers are also present in the field.*

KEY FACTS

ETIOLOGY/PATHOGENESIS

- Predominantly T-cell response commonly seen in viral and drug-related lymphadenopathies
- Variety of environmental pollutants and chemicals can cause paracortical hyperplasia

CLINICAL ISSUES

- Localized or widespread lymphadenopathy
- Systemic symptoms can be present
- Important factors in identifying etiology
  - Size, location, and consistency of lymph nodes
  - Patient's age and duration of lymphadenopathy
- Self-limiting and reversible process with no impact on survival

MICROSCOPIC

- Overall lymph node architecture is preserved
- Paracortical areas are markedly expanded
  - Due to heterogeneous population of cells
    - Small lymphocytes
    - Histiocytes
    - Immunoblasts
- Immunoblasts are large with prominent nucleoli
  - Can resemble Hodgkin-Reed-Sternberg cells
  - CD30(+), CD45(+), CD15(-)
- Eosinophils can be prominent

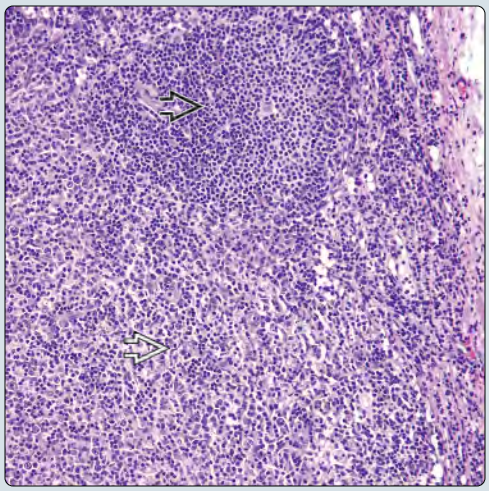
ANCILLARY TESTS

- Mature T-cell immunophenotype
- Polyclonal *IGH, TRG,* or *PKM* gene rearrangements

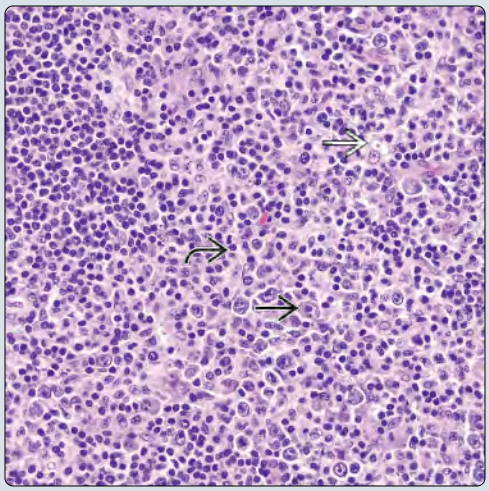
TOP DIFFERENTIAL DIAGNOSES

- Dermatopathic lymphadenopathy
- Drug reactions
- Kikuchi-Fujimoto lymphadenitis
- Anaplastic large cell lymphoma
- Myeloid sarcoma
- Hodgkin lymphoma

Reactive Paracortical Hyperplasia

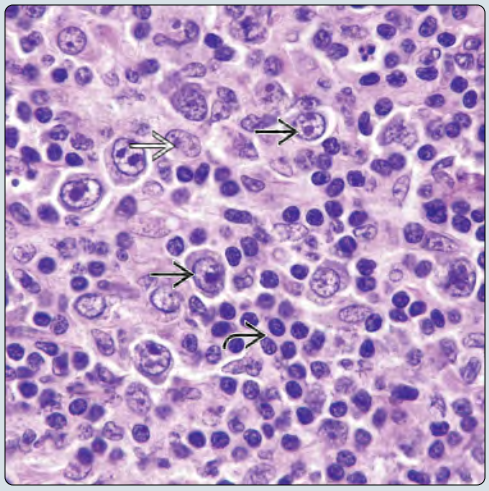


RPH: Heterogeneous Population

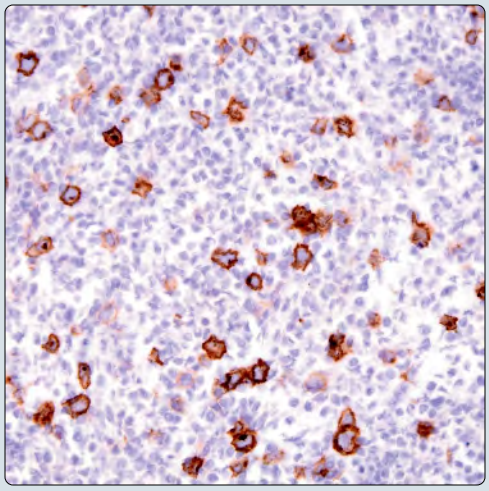


(Left) *Lymph node with reactive paracortical hyperplasia (RPH) demonstrates that the interfollicular area is markedly expanded. A residual follicle is noted.* **(Right)** *This intermediate magnification of the expanded paracortical area shows a heterogeneous cell population of small lymphocytes, immunoblasts, and histiocytes. These histological findings suggest a cell-mediated or T-cell immunologic response but are otherwise nonspecific regarding etiology.*

RPH: Immunoblasts



CD30(+) Immunoblasts



(Left) *This hyperplastic paracortex shows a mixture of small lymphocytes, histiocytes, and large immunoblasts with prominent nucleoli.* **(Right)** *Immunohistochemical stain for CD30 in a lymph node shows RPH. The immunoblasts express CD30 in a membranous and Golgi pattern.*

TERMINOLOGY

Abbreviations

- Reactive paracortical hyperplasia (RPH)

Synonyms

- Diffuse paracortical lymphoid hyperplasia
- Interfollicular hyperplasia, T-zone hyperplasia

Definitions

- RPH is benign reaction, predominantly within paracortical regions of lymph node; manifestation of T-cell immunological response
  - Also occurs in extranodal lymphoid tissues
  - Often occurs along reactive follicular hyperplasia

ETIOLOGY/PATHOGENESIS

Environmental Exposure

- Variety of environmental pollutants and chemicals can cause paracortical hyperplasia
- Therapeutic agents (drugs) are important cause
  - Phenytoin (Dilantin) and other antiseizure medications
- Vaccine administration
  - Vaccinia
  - Measles (live, attenuated)
  - Usually arises 1-3 weeks after vaccination

Infectious Agents

- Viral infection is common cause of RPH
  - Epstein-Barr virus (EBV)
  - CMV
  - Herpes simplex virus (type 1 or 2)
- Necrosis is usually present in viral infection

CLINICAL ISSUES

Presentation

- Localized or widespread lymphadenopathy
- Systemic symptoms can be present
  - Fever, fatigue, and weight loss
- Laboratory abnormalities may be present
  - Leukocytosis, lymphocytosis
- Clues to etiology related to
  - Patient age, duration of symptoms, and site
  - Size and consistency of lymph node(s)

Treatment

- Localized lymphadenopathy in absence of other symptoms can be followed
  - If no resolution after 3-4 weeks, investigation is needed
- Generalized lymphadenopathy should be cause for concern
  - Immediate investigation for etiology is recommended

Prognosis

- Self-limiting and reversible process with no impact on survival
  - Depends, in part, on underlying cause
- Can be associated with other diseases (e.g., autoimmune diseases, malignancy)

IMAGING

Radiographic Findings

- Lymphadenopathy, localized or generalized

MACROSCOPIC

General Features

- Lymph nodes mildly to moderately enlarged
  - No masses; lymph nodes usually not matted
- Tan-white, soft-cut surface
- Focal necrosis may be found

MICROSCOPIC

Histologic Features

- Overall lymph node architecture is distorted but preserved
- Paracortical areas are markedly expanded by heterogeneous cell population
  - There is mixture of
    - Small lymphocytes
    - Immunoblasts
    - Histiocytes
  - Imparts mottled or moth-eaten pattern at scanning magnification
- Immunoblasts are large with vesicular nuclei and central nucleoli
  - Nucleoli are basophilic, often with trapezoidal shape
  - Nucleoli often have thin attachments to nuclear membrane ("spider legs")
  - Can resemble Reed-Sternberg and Hodgkin (RS+H) cells
  - Can be numerous and arranged in sheets and raise concern of large cell lymphoma
- Eosinophils can be prominent
  - Particularly in cases of hypersensitivity, such as drug reactions
- High endothelial venules often present
- Other lymph node components commonly seen, so-called mixed pattern
  - Reactive follicles
  - Monocytoid B-cell hyperplasia in sinuses
  - Nodules of plasmacytoid dendritic cells

Predominant Pattern/Injury Type

- Lymphoid, interfollicular

Predominant Cell/Compartment Type

- Lymphadenopathy

ANCILLARY TESTS

Immunohistochemistry

- Small lymphocytes are usually mature T cells
  - Positive for pan-T-cell antigens: CD3, CD5, CD7, CD43
  - CD4(+) and CD8(+) subsets
- Immunoblasts can be of either T-cell or B-cell lineage
  - CD30(+), CD45(+), CD15(-)
- Evidence of virus in EBV-associated cases
  - Positive for EBV-encoded small RNAs or EBV latent membrane protein

Flow Cytometry

- Numerous T cells with mature T-cell immunophenotype
- Fewer polytypic B cells

In Situ Hybridization

- Evidence of virus in virally induced cases

PCR

- Polyclonal *IGH* or T-cell receptor gene rearrangements

DIFFERENTIAL DIAGNOSIS

Dermatopathic Lymphadenopathy

- Paracortical distribution, nodular pattern
- Increase of interdigitating dendritic cells
  - S100 protein (+)
- Few or numerous Langerhans cells
  - Positive for CD1a and langerin (CD207)

Viral Causes of Reactive Paracortical Hyperplasia

- Histologic findings are similar to RPH, not otherwise specified
- Foci of necrosis are common
- Viral inclusions in CMV and herpes simplex virus infections
- Common viruses: EBV, CMV, herpes simplex

Drug Reactions

- May manifest as RPH or mixed pattern of RPH and follicular hyperplasia
- Eosinophils often present
- May arise suddenly, raising clinical concern for lymphoma
- Lymphadenopathy often resolves after drug is discontinued

Reaction to Vaccine Administration

- Regional lymph nodes 1-3 weeks after vaccination
- Histologic findings show typical RPH ± follicular hyperplasia

Kikuchi-Fujimoto Lymphadenitis

- Paracortical pattern similar to RPH
- Proliferative phase with many monocytes
- Necrotic and xanthomatous phases
  - No neutrophils

Anaplastic Large Cell Lymphoma

- Replacement of architecture in most cases
- Neoplastic cells show cytologic atypia and often exhibit sinusoidal distribution
  - Hallmark cells have horseshoe shape
- Aberrant loss of pan-T-cell antigens
- Usually express cytotoxic markers granzyme B, TIA-1
- ALK-1 expression in cases with rearrangements of ALK
- Monoclonal T-cell receptor gene rearrangement

Peripheral T-Cell Lymphoma, Not Otherwise Specified

- Complete effacement of lymph node architecture
- Cytologically atypical lymphoid cells ± eosinophils or plasma cells
- Aberrant loss of pan-T-cell antigens
- Monoclonal *PKM* or T-cell receptor gene rearrangement

Myeloid Sarcoma

- Complete effacement of lymph node architecture
- Eosinophilic myelocytes in subset (~ 50%)
- Positive for myeloid-associated antigens: Lysozyme, myeloperoxidase, CD43, and CD11c
  - Subsets of cases express CD34 and terminal deoxynucleotidyl transferase (immature) or CD15 (mature)

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

- Replacement of lymph node architecture by vague nodules
- Numerous small lymphocytes and histiocytes similar to RPH
- Large neoplastic lymphocyte-predominant (or "lymphocyte predominant") cells

Classic Hodgkin Lymphoma

- Can have paracortical pattern similar to RPH
- Lymph node architecture usually replaced
- Large neoplastic RS+H cells
  - CD15(+), CD30(+), pax-5 (dim+), CD45-RB/leukocyte common antigen (-)

T-Cell/Histiocyte-Rich Large B-Cell Lymphoma

- Replacement of lymph node architecture
- Scattered, large, neoplastic cells admixed with abundant reactive lymphocytes and histiocytes
- Large neoplastic cells of B-cell lineage

Diffuse Large B-Cell Lymphoma, Not Otherwise Specified

- Sheets of large cells that replace lymph node architecture
  - May occasionally present in paracortical pattern
- Monotypic surface immunoglobulins
- Monoclonal *IGH* rearrangements

DIAGNOSTIC CHECKLIST

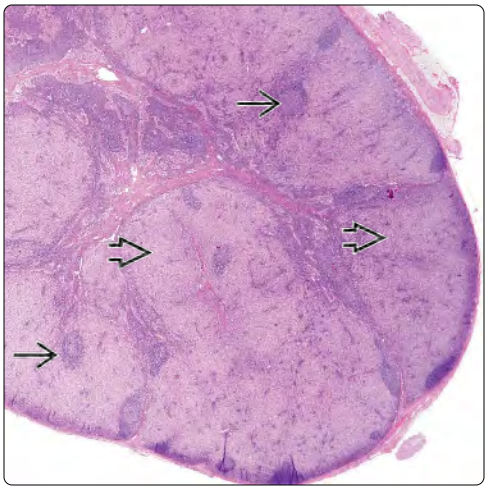
Pathologic Interpretation Pearls

- Overall preservation of architecture
- Paracortical pattern
- Moth-eaten appearance at low magnification
- Large cells are immunoblasts
- Eosinophils suggest hypersensitivity (e.g., drug reaction)
- Ancillary test results do not support lymphoma

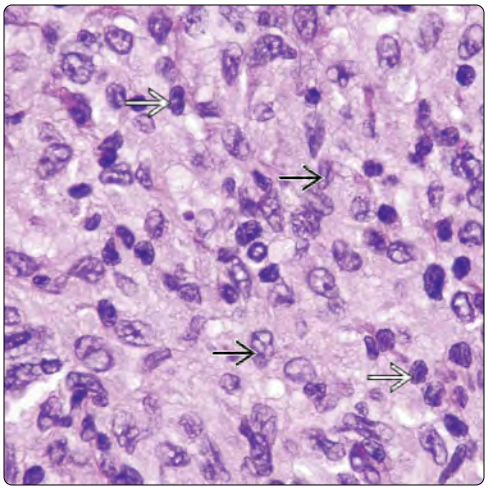
SELECTED REFERENCES

1. Weiss LM et al: Benign lymphadenopathies. Mod Pathol. 26 Suppl 1:S88-96, 2013
2. Pilichowska ME et al: Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease): lesional cells exhibit an immature dendritic cell phenotype. Am J Clin Pathol. 131(2):174-82, 2009
3. Medeiros LJ et al: Reactive lymphoid hyperplasia. In Ioachim H et al: Ioachim's Lymph Node Pathology. 4th ed. Philadelphia: Lippincott Williams & Wilkins. 172-80, 2008
4. Kojima M et al: Clinical implication of dermatopathic lymphadenopathy among Japanese: a report of 19 cases. Int J Surg Pathol. 12(2):127-32, 2004
5. Kojima M et al: Autoimmune disease-associated lymphadenopathy with histological appearance of T-zone dysplasia with hyperplastic follicles. A clinicopathological analysis of nine cases. Pathol Res Pract. 197(4):237-44, 2001
6. Abbondazo SL et al: Dilantin-associated lymphadenopathy. Spectrum of histopathologic patterns. Am J Surg Pathol. 19(6):675-86, 1995
7. Dorfman RF et al: Lymphadenopathy simulating the malignant lymphomas. Hum Pathol. 5(5):519-50, 1974

Dermatopathic Lymphadenopathy

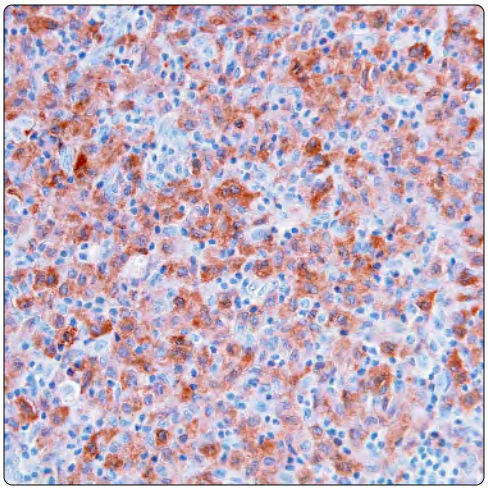


Interdigitating Dendritic Cells

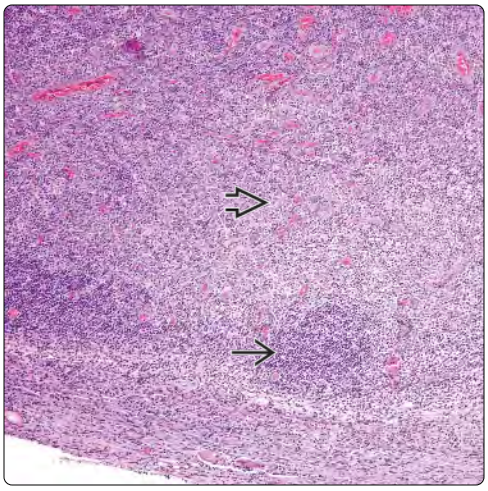


(Left) *This lymph node is involved by dermatopathic lymphadenopathy. The paracortical areas are markedly expanded and appear as pale areas ⇨ surrounding residual lymphoid follicles ⇨.* **(Right)** *In dermatopathic lymphadenopathy, the paracortex is expanded by numerous interdigitating dendritic cells with folded nuclei ⇨ and abundant eosinophilic cytoplasm. Scattered small lymphocytes ⇨ are present.*

Interdigitating Dendritic Cells: S100(+)

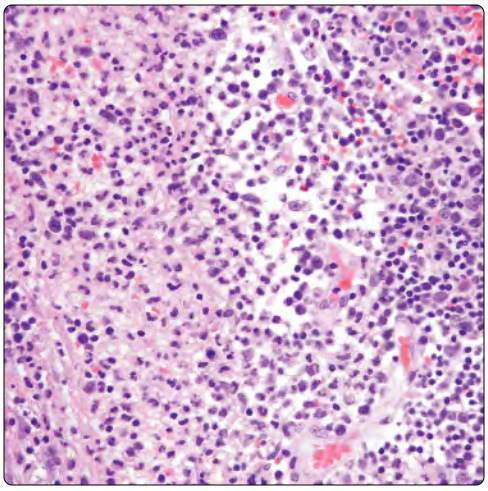


Paracortical Hyperplasia Due to Herpes Simplex Virus

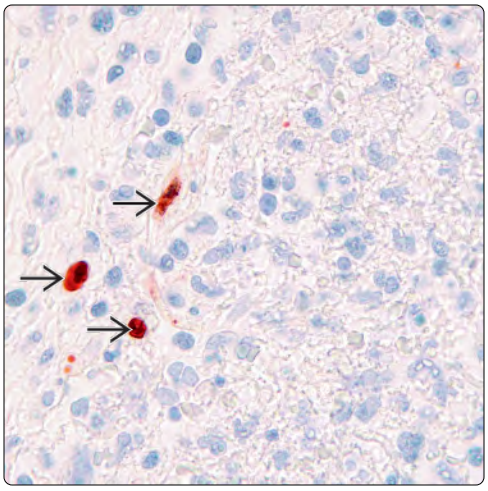


(Left) *Immunohistochemical stain for S100 protein highlights both interdigitating dendritic cells and Langerhans cells in this case of dermatopathic lymphadenopathy. Small lymphocytes are negative for S100.* **(Right)** *This lymph node shows marked expansion of the paracortical region ⇨. In this case, the hyperplasia was caused by herpes simplex virus (HSV) infection. A residual follicle ⇨ is also observed. In this case, HSV was demonstrated by in situ hybridization.*

Herpes Simplex Virus Lymphadenitis

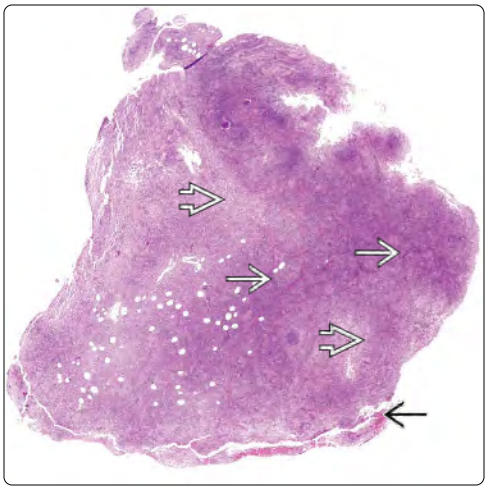


In Situ Hybridization Positive for Herpes Simplex Virus

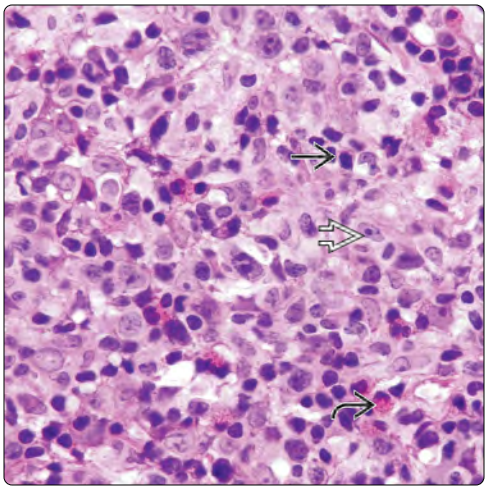


(Left) *This high magnification shows RPH caused by HSV infection. This field shows a small focus of punched-out necrosis commonly seen in lymph nodes infected by HSV. Viral inclusions were not seen in this field, but HSV was demonstrated by in situ hybridization.* **(Right)** *In situ hybridization analysis for HSV shows a case of RPH. These positive nuclei ⇨ were located in a focus of necrosis.*

Drug-Related RPH

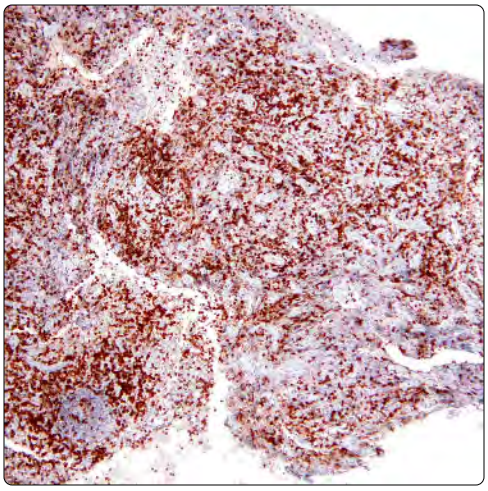


Eosinophilia in Drug-Related RPH

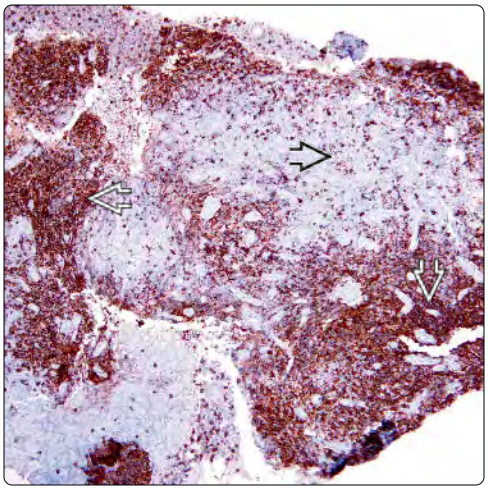


(Left) *This lymph node with drug-related RPH shows a marked expansion of the paracortex. Scattered residual reactive lymphoid follicles are also noted. Note that the inflammatory process extends outside the lymph node boundaries.* **(Right)** *This lymph node with drug-related RPH shows a mixture of small and large lymphocytes and scattered eosinophils.*

RPH: T Cells

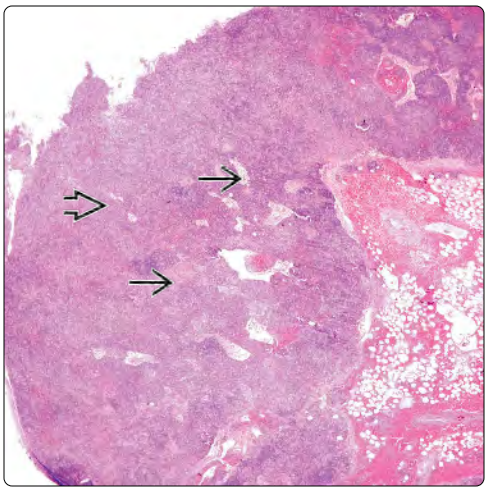


RPH: B Cells

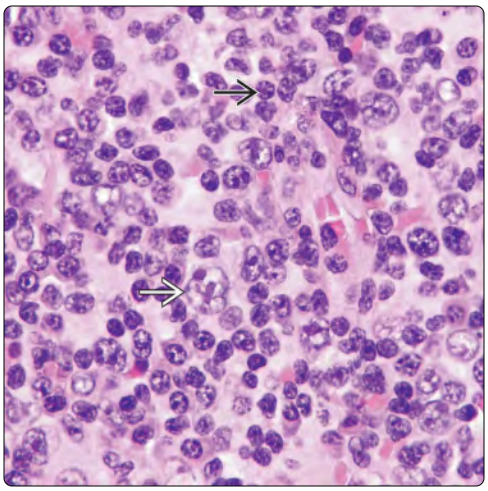


(Left) *Immunohistochemical stain for CD3 of a lymph node with drug-related RPH shows that most of the cells in the paracortical areas are T cells.* **(Right)** *This immunohistochemical stain for the B-cell marker CD20 of a lymph node with drug-related RPH shows relatively few B cells in the paracortical areas. Most B cells are within reactive lymphoid follicles.*

Infectious Mononucleosis

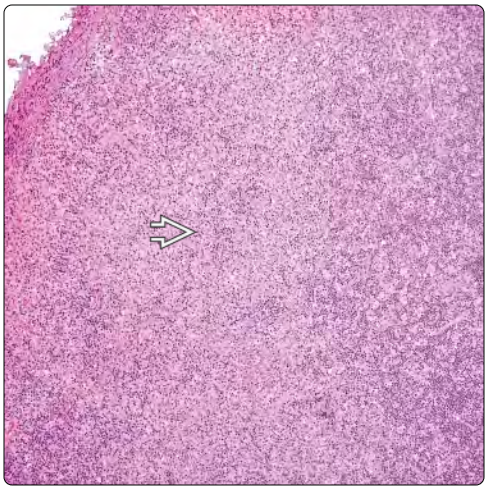


Infectious Mononucleosis: Immunoblasts

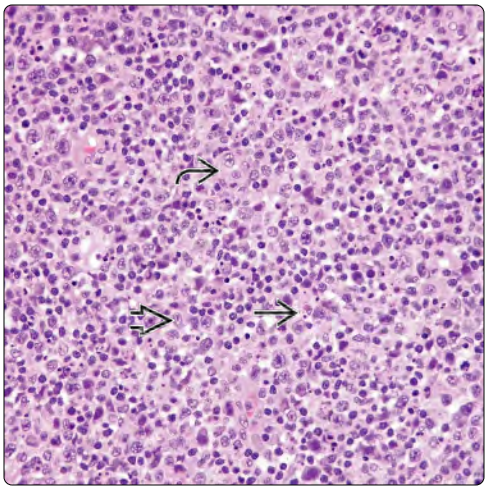


(Left) *This low-power view of a lymph node in a patient with infectious mononucleosis shows marked RPH. Note the patent sinuses, indicating that the architecture is not completely replaced.* **(Right)** *This high magnification of the paracortical region in the lymph node of a patient with infectious mononucleosis shows immunoblasts admixed with small lymphocytes.*

Kikuchi-Fujimoto

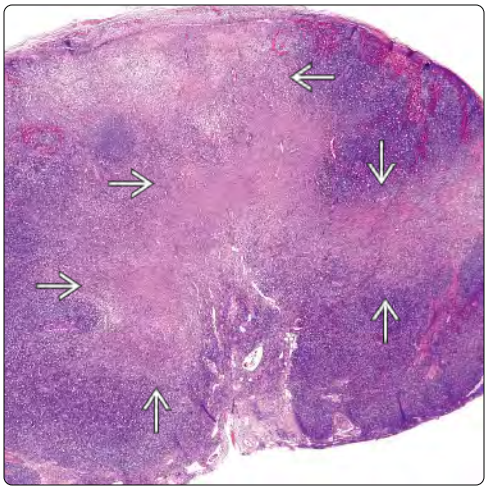


Kikuchi-Fujimoto Lymphadenitis

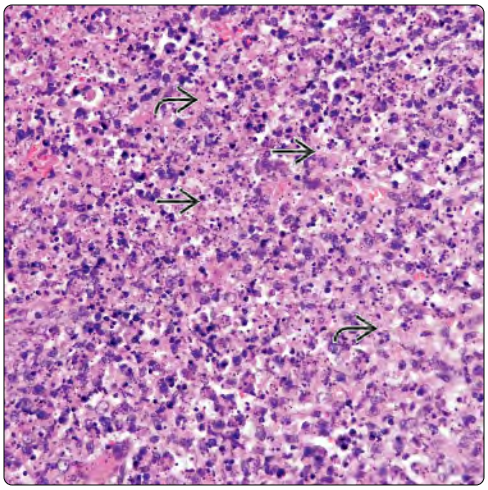


(Left) *This lymph node involved by Kikuchi-Fujimoto shows the proliferative phase, characterized by expansion of the paracortex. The pallor is partially due to the presence of numerous histiocytes with moderately abundant cytoplasm.* **(Right)** *Paracortex in a case of Kikuchi-Fujimoto lymphadenitis shows numerous histiocytes with folded nuclei and abundant cytoplasm, which are admixed with small lymphocytes, immunoblasts, apoptotic bodies, and cell debris.*

Kikuchi-Fujimoto Necrotizing Phase

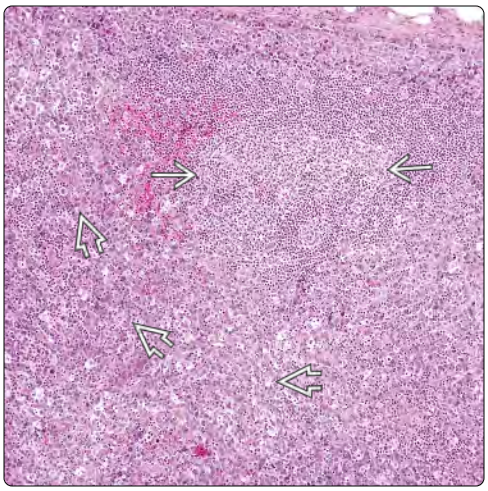


Kikuchi-Fujimoto Necrotizing Phase

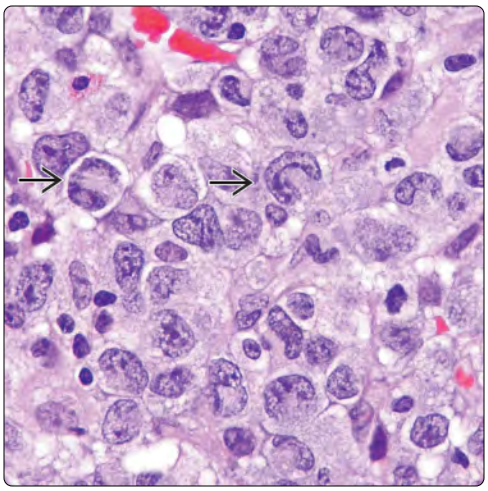


(Left) *This lymph node is involved by Kikuchi-Fujimoto lymphadenitis during the necrotizing phase. The paracortex is expanded by necrosis, outlined by numerous apoptotic cells and debris.* **(Right)** *This lymph node is involved by Kikuchi-Fujimoto lymphadenitis during the necrotizing phase. The paracortical areas are replaced by numerous necrotic cells, apoptotic bodies, and debris. Note that no neutrophils are present.*

Anaplastic Large Cell Lymphoma

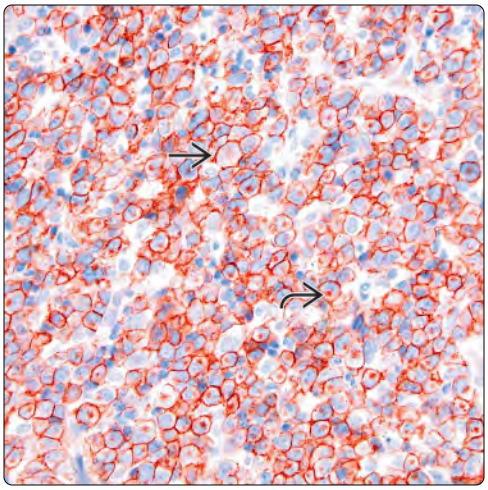


ALCL: Hallmark Cells

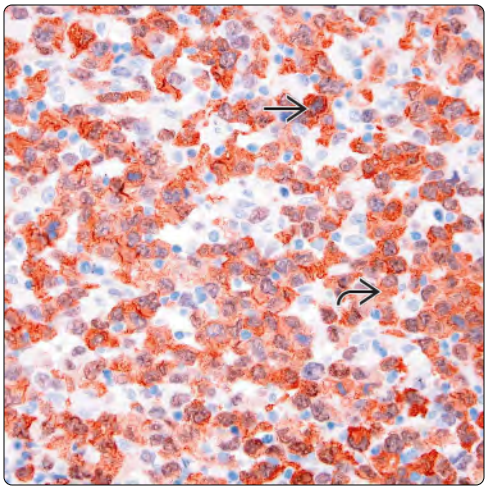


(Left) *This lymph node involved by anaplastic large cell lymphoma (ALCL) shows almost complete effacement of the architecture due to the presence of sheets of lymphoma cells distributed in the interfollicular regions. A residual follicle is highlighted.* **(Right)** *The high magnification of this lymph node involved by ALCL shows numerous large cells. Note the so-called hallmark cells with a horseshoe-shaped nucleus and eosinophilic cytoplasm.*

ALCL: CD30

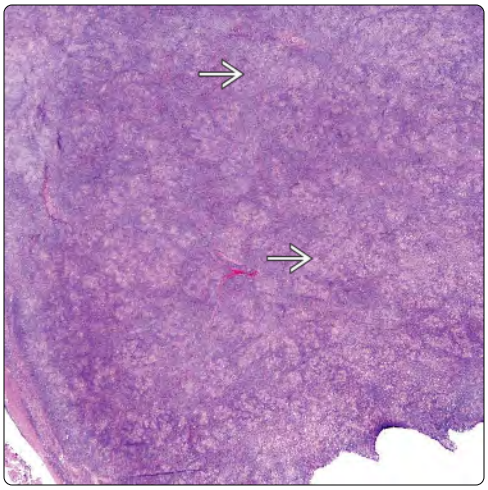


ALCL: ALK-1

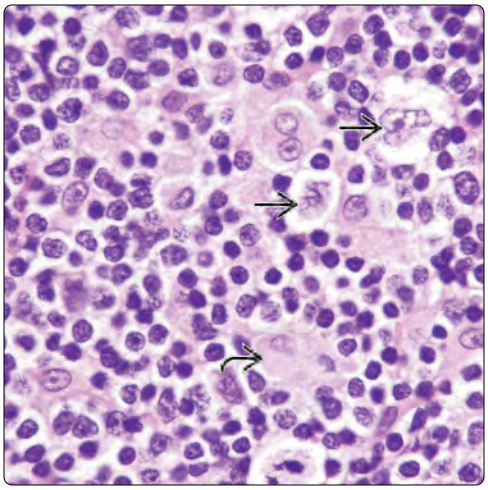


(Left) *The immunohistochemical stain for CD30 in a case of ALCL demonstrates that most cells react strongly and uniformly with a membrane ⇨ and Golgi ⇨ pattern.* **(Right)** *This immunohistochemical stain for anaplastic lymphoma kinase (ALK)-1 in a case of ALCL demonstrates that the neoplastic cells are strongly positive for ALK-1 in a nuclear ⇨ and a cytoplasmic ⇨ pattern, consistent with t(2;5)(p23;q35).*

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

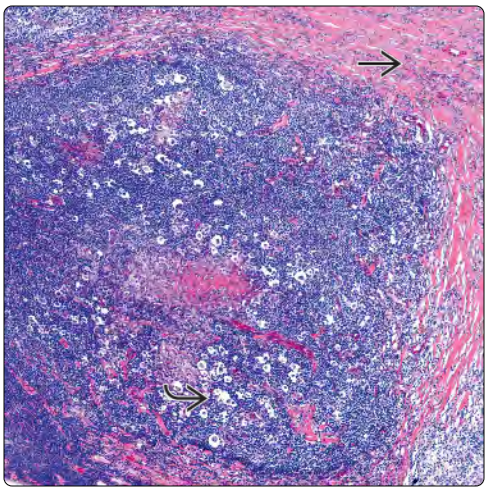


NLPHL: Lymphocyte-Predominant Cells

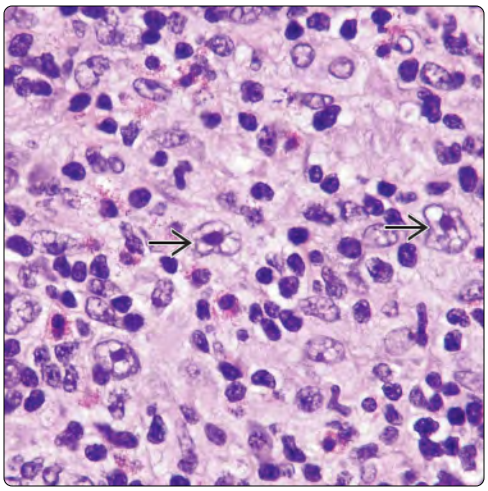


(Left) *The low magnification of this lymph node shows vague nodularity ➡, characteristic of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). The architecture is replaced by vague nodules.* **(Right)** *High-power view of a lymph node involved by NLPHL shows scattered large, neoplastic lymphocyte-predominant cells ⇨ admixed with numerous small lymphocytes and histiocytes ⇨.*

Nodular Sclerosis Hodgkin Lymphoma



NSHL: RS+H Cells



(Left) *This low magnification of a lymph node involved by nodular sclerosis Hodgkin lymphoma (NSHL) shows the thickened fibrous bands ⇨ surrounding cellular nodules that contain the lacunar cells ⇨.* **(Right)** *This high magnification of a lymph node involved by nodular sclerosis Hodgkin lymphoma shows scattered Reed-Sternberg and Hodgkin (RS+H) cells (mononuclear variants) ⇨ admixed with numerous small lymphocytes.*