JOSEPH F. TOMASHEFSKI, JR.
PHILIP T. CAGLE
CAROL F. FARVER
ARMANDO E. FRAIRE
EDITORS

Dail and Hammar's Pulmonary Pathology

Volume II
Neoplastic Lung Disease

THIRD EDITION

Springer

Dail and Hammar's Pulmonary Pathology

Third Edition

Dail and Hammar's Pulmonary Pathology

Volume II: Neoplastic Lung Disease

Third Edition

Editor

Joseph F. Tomashefski, Jr., MD
Professor, Department of Pathology, Case Western Reserve University School of Medicine; Chairman, Department of Pathology, MetroHealth Medical Center, Cleveland, Ohio, USA

Associate Editors

Philip T. Cagle, MD
Professor, Department of Pathology, Weill Medical College of Cornell University, New York, New York; Director, Pulmonary Pathology, Department of Pathology, The Methodist Hospital, Houston, Texas, USA

Carol F. Farver, MD
Director, Pulmonary Pathology, Department of Anatomic Pathology, The Cleveland Clinic Foundation, Cleveland, Ohio, USA

Armando E. Fraire, MD
Professor, Department of Pathology, University of Massachusetts Medical School, Worcester, Massachusetts, USA

Springer

Editor:
Joseph F. Tomashefski, Jr., MD
Professor, Department of Pathology, Case Western Reserve University School of Medicine; Chairman, Department of Pathology, MetroHealth Medical Center, Cleveland, OH, USA

Associate Editors:
Philip T. Cagle, MD
Professor, Department of Pathology, Weill Medical College of Cornell University, New York, NY; Director, Pulmonary Pathology, Department of Pathology, The Methodist Hospital, Houston, TX, USA

Carol F. Farver, MD
Director, Pulmonary Pathology, Department of Anatomic Pathology, The Cleveland Clinic Foundation, Cleveland, OH, USA

Armando E. Fraire, MD
Professor, Department of Pathology, University of Massachusetts Medical School, Worcester, MA, USA

Library of Congress Control Number: 2007920839

Volume II ISBN: 978-0-387-72113-2 e-ISBN: 978-0-387-72114-9
DOI: 10.1007/978-0-387-72114-9

Set ISBN: 978-0-387-72139-2

Printed on acid-free paper.

9 8 7 6 5 4 3 2 1

springer.com

To
David H. Dail
Samuel P. Hammar

For their many contributions to pulmonary pathology, and for their conceptual and sustaining vision of this textbook

Joseph F. Tomashefski, Jr.
Philip T. Cagle
Carol F. Farver
Armando E. Fraire

To my dear wife, Cathy, and our children, Amy, Cary, David, Jessica, and Sarah

Joseph F. Tomashefski, Jr.

To my wife, Kirsten

Philip T. Cagle

To the memory of my parents, Albert and Gladys Farver

Carol F. Farver

In memory of Dr. S. Donald Greenberg, dear friend, respected colleague, and superb teacher

Armando E. Fraire

Preface

It is with a great sense of good fortune, humility, and responsibility that we, the editors, have undertaken the task of updating Dail and Hammar's *Pulmonary Pathology*, one of the great modern textbooks not only in the field of lung pathology but also in the wider arena of general pathology as well. Following the publication of its first edition, "Dail and Hammar" rapidly became the standard against which subsequent textbooks of lung pathology were measured.

First published in 1987, *Pulmonary Pathology* provided an alternative to Herbert Spencer's time-honored text, *Pathology of the Lung* which, in its fourth edition at that time, was the reigning tome on the pathology of the respiratory system. The first edition of "Dail and Hammar" was in part dedicated to Dr. Spencer, who graciously penned the foreword for that text. The first edition was also dedicated to Averill Liebow, one of the giants of pulmonary pathology, under whom Dr. Dail had served and been mentored as a fellow. Dr. Liebow's influence was notable in the first two editions, and has continued in this edition in the revised classifications and current understanding of interstitial pneumonias and lung tumors, subjects in which Dr. Liebow played such a defining role. Several of Dr. Liebow's timeless original illustrations continue to grace the pages of the third edition.

In the 13 years since the second edition there have been astounding advances in medicine and pathology. The current edition has been revised and updated to reflect these advances. As much as possible, however, we have striven to remain true to Drs. Dail and Hammar's original goals, "to present the reader with an authoritative yet readable text which hopefully answers questions that might arise in facing problem cases and to offer the reader appropriate review of particular areas within the field of pulmonary pathology." In the face of wide-reaching revisions our intent has been to maintain the unique character of *Pulmonary Pathology*, and retain continuity with previous editions. Dr. Dail and Dr. Hammar have continued to play a major role in the present text, together contributing as author or coauthor to approximately one fourth of the chapters. Nine other chapters have been updated by contributors who were also featured in the second edition. Many, if not the majority, of the illustrations in the text represent the color counterparts of previous black-and-white figures. Electron microscopy, which was emphasized in the previous two editions, continues to have a presence in the third, mainly in the volume on neoplasia, and lays the foundation for a deep understanding of the histological appearances of tumors.

The changes in the current edition, however, are significant. The previous sizable single volume text has been divided into two volumes, covering neoplastic and non-neoplastic lung diseases, to afford the reader more ready access and less strenuous effort when referencing the sections of interest. Entirely new chapters have been added on the pathology of small airways disease (Chapter 25), forensic lung pathology (Chapter 31), molecular genetics of lung and pleural neoplasms (Chapter 33), and preinvasive (neoplastic) disease (Chapter 34). The topics formerly included in the second edition chapters on AIDS and tobacco-related injury have been

dispersed in the third edition, mainly throughout the sections on lung infections and lung cancer, respectively. Similarly the monumental chapters on common and uncommon lung tumors in the previous editions have been divided into seven smaller topical units housed in the second volume. Over 90 percent of the illustrations in the current edition are now presented in vivid color.

Pulmonary Pathology was one of the first pathology textbooks to emphasize the burgeoning field of immunohistochemistry and its application to diagnostic pathology, and the current edition continues to expound on the important diagnostic role of immunohistochemical stains. In this edition, however, we also embrace the molecular age with updated information on molecular pathology. In addition to extensive references to molecular aspects of lung disease, which are integrated within each of the individual chapters, the new edition includes two chapters (Chapters 33 and 34) devoted almost exclusively to molecular pathology. Chapter 33 (Molecular Genetics of Lung and Pleural Neoplasms) is essentially a text-within-a-text, serving as a compendium of information on the molecular pathology of lung tumors as well as a primer on basic molecular pathology for the uninitiated or molecularly challenged pathologist.

Within reason and to the best of our ability we have tried to maintain the reputation of *Pulmonary Pathology* as a comprehensive textbook that not only serves as a diagnostic guide to the "labyrinths of the lung," but also enables the reader to explore the etiology and pathogenesis of lung diseases. The references, both classical and modern, have been greatly increased and, as of the time that the book went to press, are relatively current. The present edition also recognizes the growing importance of electronic information sources. Relevant Internet Web sites have been included among the chapter references, and Chapter 22 on pulmonary drug toxicity is essentially constructed around Web-based resources.

There are numerous individuals to whom we owe a debt of gratitude. Most importantly, we thank the many authors who gave of their time and talent, without

Figure 1. Members of the editorial board with Drs. Dail and Hammar. (From left to right: Carol F. Farver, Philip T. Cagle, David H. Dail, Samuel P. Hammar, Armando E. Fraire, and Joseph F. Tomashefski, Jr.)

financial compensation, to contribute to this book. Their expertise and dedication represent the soul of the work. We also appreciate their patience and understanding as both authors and editors faced the stressful implications of rapidly approaching (and receding) publication deadlines. We recognize and are especially thankful for the wonderful pulmonary pathologists under whom we have trained, who taught us the trade and served as our role models: Dr. S. Donald Greenberg (Drs. Cagle and Fraire); Dr. William Thurlbeck (Dr. Cagle); Drs. Jerome Kleinerman, John D. Reid, Merle Legg, and Lynne Reid (Dr. Tomashefski); and Drs. John Godleski and Les Kobzik (Dr. Farver). Finally, we are grateful to the Springer publishing firm, especially to our executive editor, Melissa Ramondetta and her editorial assistant, Dianne Wuori. A special thanks goes to our developmental editor, Stephanie Sakson, who kept us on track throughout the process, surmounting the hurdles of copyright permits, and the inexorable correlation of images, references, and text.

From the editors' perspective our labors now are ended (for a while at least). We leave it to you, the reader, to evaluate this text. We welcome your comments, positive or negative, which may help to direct future editions.

Joseph F. Tomashefski, Jr., MD
Philip T. Cagle, MD
Carol F. Farver, MD
Armando E. Fraire, MD

Contents

Volume II: Neoplastic Lung Disease

Volume I: Nonneoplastic Lung Disease

Contributors

Patrick A. Adegboyega, MD
Department of Pathology, University of Texas Medical Branch, Galveston, TX 77555, USA

Timothy C. Allen, MD, JD
Chairman, Department of Pathology, University of Texas Health Center at Tyler, Tyler, TX 75708, USA

Roberto Barrios, MD
Attending Pathologist, Department of Pathology, The Methodist Hospital, Houston, TX 77030, USA

Mary Beth Beasley, MD
Department of Pathology, Providence Portland Medical Center, Portland, OR 97210, USA

Kelly J. Butnor, MD
Assistant Professor, Department of Pathology, University of Vermont/Fletcher Allen Health Care, Burlington, VT 05401, USA

Philip T. Cagle, MD
Professor, Department of Pathology, Weill Medical College of Cornell University, New York; *and* Director, Pulmonary Pathology, Department of Pathology, The Methodist Hospital, Houston, TX 77030, USA

Thomas V. Colby, MD
Consultant in Pathology, Mayo Clinic Scottsdale, Scottsdale, AZ 85259, USA

Carlyne D. Cool, MD
Department of Pathology, University of Colorado Health Sciences Center, Denver, CO 80262, USA

David H. Dail, MD
Staff Pathologist, Department of Pathology, Virginia Mason Medical Center, Seattle, WA 98101, USA

Louis P. Dehner, MD
Professor and Director, Division of Anatomic Pathology, Washington University School of Medicine, St. Louis, MO 63122, USA

Ronald F. Dodson
ERI Consulting, Inc., 2026 Republic Drive, Ste A, Tyler, TX 75701, USA

Carol F. Farver, MD
Director, Pulmonary Pathology, Department of Anatomic Pathology, The Cleveland Clinic Foundation, Cleveland, OH 44195, USA

Douglas B. Flieder, MD
Chief of Surgical Pathology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA

Armando E. Fraire, MD
Professor, Department of Pathology, University of Massachusetts Medical School, Worcester, MA 01655, USA

Anthony A. Gal, MD
Professor, Department of Pathology and Laboratory Medicine, Emory University Hospital, Atlanta, GA 30322, USA

Michael A. Graham, MD
Professor, St. Louis University School of Medicine; *and* Chief Medical Examiner, City of St. Louis, Division of Forensic and Environmental Pathology, St. Louis, MO 63104, USA

Steve D. Groshong, MD, PhD
Instructor, Department of Pathology, University of Colorado Health Sciences Center, Denver, CO 80262, USA

Donald G. Guinee, Jr., MD
Pathologist, Department of Pathology, Virginia Mason Medical Center, Seattle, WA 98111, USA

Samuel P. Hammar, MD
Harrison Medical Center, Pathology Associates of Kitsap County, Bremerton, WA 98310, USA

Abida K. Haque, MD
Medical Director, Department of Pathology, San Jacinto Methodist Hospital, Baytown, TX 77521, USA

Philip Hasleton, MD, FRCPath
Professor, Department of Histopathology, Clinical Sciences Block, Manchester Royal Infirmary, Manchester M13 9WL, UK

Douglas W. Henderson, MB, BS, FRCPA, FRCPath, FHKCPath (Hon)
Professor and Senior Consultant, Departments of Pathology and Anatomical Pathology, Flinders Medical Centre, Bedford Park 5042, Adelaide, South Australia

Elise R. Hoff, MD
Department of Pathology, University of Pittsburgh Medical Center—Presbyterian, Pittsburgh, PA 15213, USA

Aliya N. Husain, MB, BS
Professor, Department of Pathology, University of Chicago, Chicago, IL 60637, USA

Jaishree Jagirdar, MD
Department of Pathology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78284, USA

Keith M. Kerr, BSc(Hons) MB ChB FRCPath
Consultant, Pathologist and Clinical Senior Lecturer, Department of Pathology, Aberdeen Royal Infirmary and Aberdeen University School of Medicine, Foresterhill, Aberdeen, AB25 2ZD, UK

Andras Khoor, MD
Department of Pathology, Mayo Clinic Jacksonville, Jacksonville, FL 32224, USA

Sonja Klebe, MD, PhD, FRCPA
Senior Lecturer in Anatomical Pathology, Flinders University and Consultant in Anatomical Pathology, Flinders Medical Centre, Bedford Park 5042, Adelaide, South Australia

Les Kobzik, MD
Associate Professor, Department of Environmental Health, Harvard School of Public Health, Boston, MA 02115, USA

P. Rocco LaSala, MD
Fellow, Medical Microbiology, Department of Pathology, University of Texas Medical Branch, Galveston, TX 77555, USA

Kevin O. Leslie, MD
Consultant and Professor, Mayo Clinic College of Medicine, Rochester, MN; *and* Department of Laboratory Medicine and Pathology, Mayo Clinic Scottsdale, Scottsdale, AZ 85259, USA

Aileen M. Marty, MD, FACP
Senior Scientific Advisor to the Undersecretary for Science and Technology Directorate, DHS, Department of Homeland Security, National Defense University, North Bethesda, MD 20852, USA

Michael R. McGinnis, PhD
Professor, Department of Pathology, University of Texas Medical Branch, Galveston, TX 77555, USA

William George Morice, MD, PhD
Consultant, Associate Professor of Medicine, Departments of Hematopathology and Anatomic Pathology, Mayo Clinic, Mayo Medical School, Rochester, MN 55905, USA

Andrew G. Nicholson, FRCPath DM
Professor of Respiratory Pathology, National Heart and Lung Institute Division of Imperial College School of Medicine and Consultant Histopathologist, Royal Brompton Hospital, Department of Histopathology, Sydney Street, London SW3 6NP, UK

N. Paul Ohori, MD
Medical Director of Cytopathology, Department of Pathology, University of Pittsburgh Medical Center—Presbyterian, Pittsburgh, PA 15213, USA

Christopher D. Paddock, MD, MS, MPHTM
Staff Pathologist, Department of Infectious Disease Pathology Activity, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA

Helmut H. Popper, MD, Prof. Pathol.
Department of Pathology, University of Graz, Auenbruggerplatz 25, Graz A-8036, Austria

Gary W. Procop, MD, MS
Section Head, Clinical Microbiology, Division of Pathology and Laboratory Medicine, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195

Victor L. Roggli, MD
Department of Pathology, Duke University and Durham VA Medical Centers, Durham, NC 27705, USA

Thomas A. Sporn, MD
Department of Pathology, Duke University and Durham VA Medical Centers, Durham, NC 27710, USA

J. Thomas Stocker, MD
Professor of Pathology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814

Joseph F. Tomashefski, Jr., MD
Professor, Department of Pathology Case Western Reserve University School of Medicine; Chairman, Department of Pathology MetroHealth Medical Center Cleveland, OH 44109, USA

William D. Travis, MD
Attending Thoracic Pathologist, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY 10021, USA

David H. Walker, MD
Department of Pathology, University of Texas Medical Branch, Galveston, TX 77555, USA

Washington C. Winn, Jr., MD
Fletcher Allen Health Care, University of Vermont College of Medicine, Burlington, VT 05482, USA

Sherif R. Zaki, MD, PhD
Chief, Infectious Disease Pathology Activity, Department of Infectious Disease Pathology Activity, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA

Dani S. Zander, MD
Professor and Chair, Department of Pathology, Penn State Milton S. Hershey Medical Center, Hershey, PA 17033, USA

32
Lymphoproliferative Diseases

William George Morice and Thomas V. Colby

Lymphoreticular diseases affecting the lung include primary and secondary lymphomas and related disorders, leukemias, and a number of lesions that are generally considered benign and hyperplastic processes. Distinguishing neoplastic disorders such as low-grade B-cell lymphomas from reactive conditions associated with prominent lymphoid infiltrates such as lymphocytic interstitial pneumonia has long been difficult for pathologists.[1–4] This difficulty is typified by the colorful history of pseudolymphoma (see below) and by lymphomatoid granulomatosis, with all its synonyms,[5–7] which has been considered by some to be a peculiar vasculitis and by others a lymphoproliferative disorder, although the weight of evidence suggests that most cases represent the latter.[8]

Classically, lymphomas involving pulmonary tissues were recognized histologically by the presence of a monomorphous population of atypical lymphoid cells and clinically by manifesting as aggressive neoplasms. However, the advent of antibody and molecular genetic reagents has allowed for a more precise definition of lymphoid malignancies as a clonal proliferation of hematolymphoid cells. This, in turn, has led to the generation of a classification scheme of these disorders based on both the cell lineage (B cell, T cell, or true histiocytic) and the putative immunologic compartment from which these neoplasms arise.[9] These tools have also enabled the recognition of a broader clinical and histologic spectrum of lymphoproliferative disorders involving the lung, including lesions that pursue a very indolent clinical course and those with a polymorphous cellular composition.

Normal Lymphoid Tissue and Lymphatic Routes of the Lung

Understanding the histology of lymphoreticular infiltrates in the lungs requires knowledge of the normal lymphatic routes and lymphoid tissue of the lung. The lymphatic routes (listed in Table 32.1) are found along the bronchovascular bundles, the pulmonary veins, and in the septa and pleura.[10,11] The lymphatics themselves are barely discernible in normal lungs but are easily recognized in pathologic states such as pulmonary edema. Lesions that tend to show a distribution along the lymphatic routes include lymphoreticular infiltrates (Fig. 32.1), lymphangitic carcinoma, sarcoidosis, and some pneumoconioses, the last reflecting lymphatic drainage of the inhaled dust.

Hilar and peribronchial lymph nodes are present in all individuals, but intrapulmonary lymph nodes are uncommon. *Intrapulmonary lymph nodes* (Fig. 32.2) are usually incidental findings encountered during computed tomography (CT) scanning of the chest, in lobectomy specimens, or at autopsy. Radiologic and pathologic studies have demonstrated that these lymph nodes most often occur singly below the level of the carina, although in some instances they may be multiple and be present in the upper lungs. Radiologically these usually appear as small (less than 2 cm), oval, smooth lesions that are either immediately subpleural or within close proximity (1 cm or less).[12] Intrapulmonary lymph nodes appear to be most commonly encountered in adult males, and an autopsy study suggested an association with smoking.[13]

Table 32.1. Lymphatic routes of the lung

Pleura
Interlobular septa
Bronchovascular bundles and along large intralobular veins

Note: Lymphatics are not found in alveolar septa.

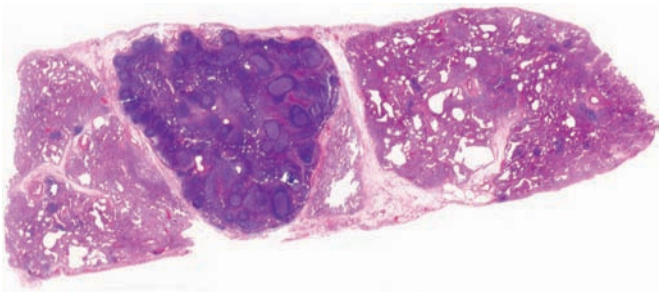


Figure 32.2. Intrapulmonary lymph node. This wedge biopsy shows an intrapulmonary lymph node located in an interlobular septum. Reactive follicles are apparent even at scanning power microscopy. Most intrapulmonary lymph nodes are located in or along the pleura or interlobular septa.

On histologic examination they are usually anthracotic, and may contain or coexist with silicotic nodules.[13] The primary importance of intrapulmonary lymph nodes for the pathologist is that they may be detected during high-resolution CT scanning of the chest for cancer screening or staging. As the radiologic features of these lymph nodes are not sufficiently distinctive to reliably distinguish them from potential early malignancies, biopsy may be required for their accurate identification.[12,14]

Bienenstock et al.[15–18] and others[19] have drawn attention to a relatively extensive system of pulmonary lymphoid tissue termed bronchus-associated lymphoid tissue (BALT). BALT represents lymphoid aggregates found along airways, particularly at bifurcations, as well as those along other lymphatic routes of the lung, and is thought to be part of a more generalized immunologic compartment of mucosa-associated lymphoid tissue (MALT). MALT is specialized lymphoid tissue that is distinguished from peripheral somatic (nodal) lymphoid tissue by its ability to combat pathogens at mucosal sites through the production of immunoglobulin A (IgA) and other factors.[18,19] As might be expected from the functional role of the MALT compartment, this tissue is intimately associated with the adjacent epithelium and may even percolate between individual epithelial cells (Fig. 32.3C,D). This tropism for epithelial cells can be particularly prominent in lymphomas derived from MALT tissues, which have a proclivity to invade adjacent epithelial structures.[20–22] Lymphocytes in this system also have the ability to circulate and to "home" to other MALT organs such as the salivary glands, intestinal tract, thyroid, cervix, endometrium, and breast.[15–18,20,21,23–25]

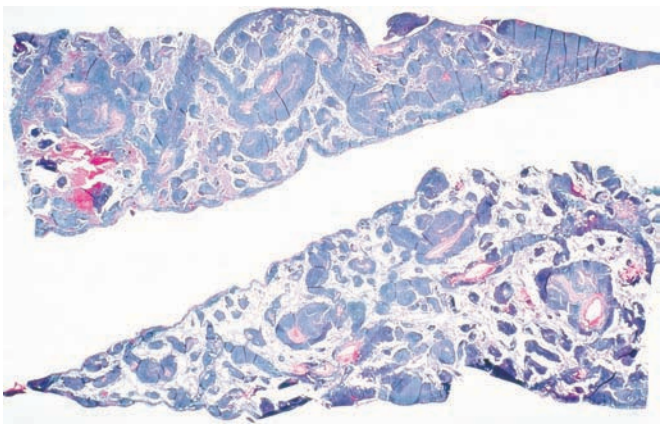


Figure 32.1. The lymphatic routes of the lung are illustrated in this lymphoma. The lymphomatous infiltrate is found in the pleura, septa, and along bronchovascular bundles, with relative sparing of the alveolar portions of the lung that do not have lymphatics.

The radiologic manifestations of lymphoreticular infiltrates include a broad and nonspecific spectrum of changes.[26–28] The radiographic patterns of disease can often be correlated with the histologic findings: lesions that are characterized histologically by diffuse infiltrates along lymphatic routes without extensive nodular expansions produce a diffuse interstitial pattern radiologically, whereas mixed interstitial and nodular or frankly nodular patterns are associated with progressively larger nodules along the lymphatic distribution. Massive infiltration with spillover into air spaces produces a pneumonic or alveolar pattern. Combinations of these patterns are common.[26–28]

A wide variety of abnormalities may also be observed by CT examination including ground-glass opacification of pulmonary parenchyma and reticulonodular infiltrates along bronchovascular bundles. In comparison to routine chest radiology, CT scanning may be more sensitive in detecting micronodular infiltrates and peribronchovascular thickening and also may provide more detailed information regarding the character of the infiltrate, particularly in low-grade lesions. The radiologic features of lymphoreticular processes are usually not sufficiently distinctive to allow them to be distinguished from other disorders such as bronchioloalveolar carcinoma, granulomatous processes, and organizing pneumonia.[29,30] The radiologic features of specific entities are discussed in greater detail throughout the chapter.

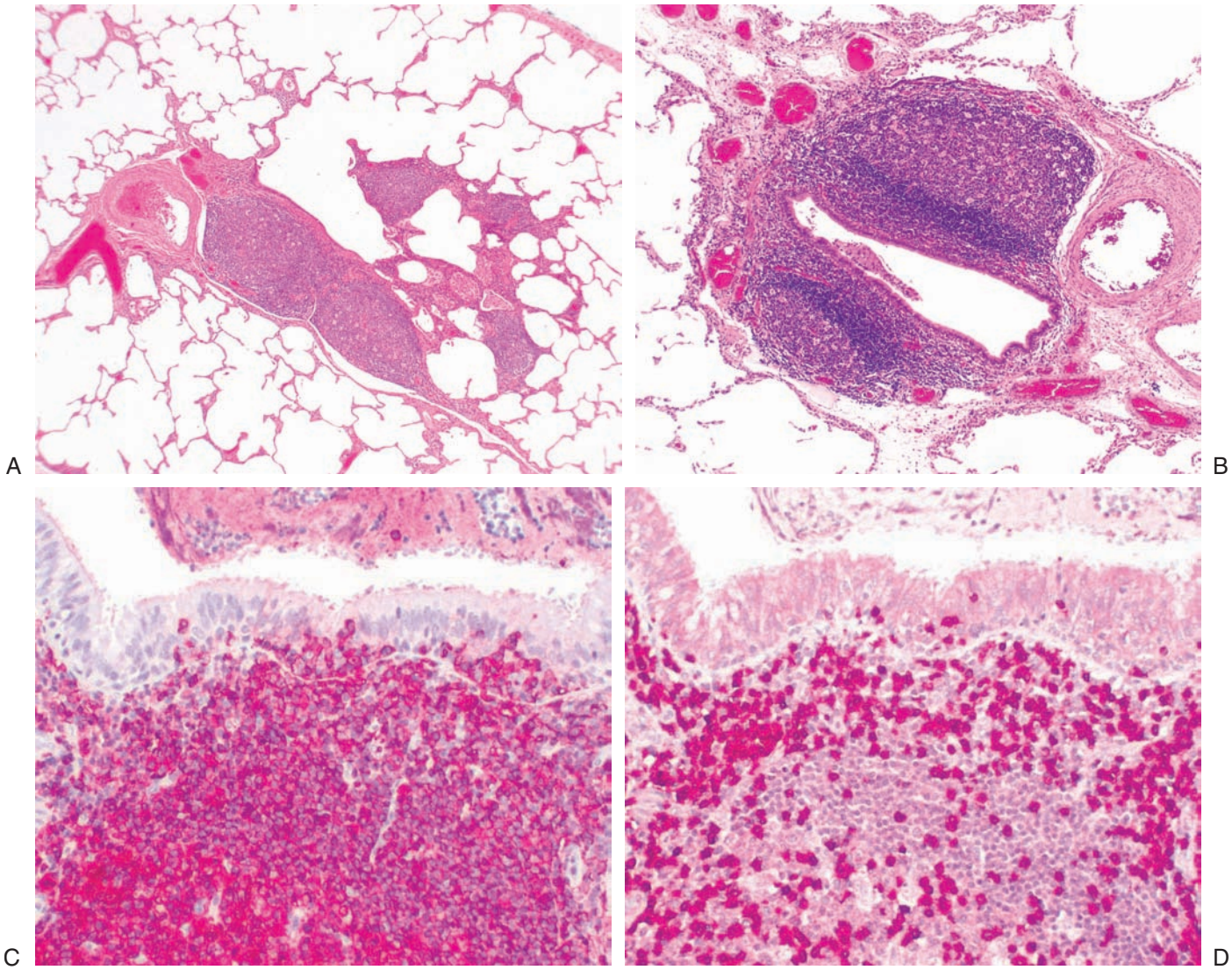


FIGURE 32.3. **(A,B)** Bronchus-associated lymphoid tissue. This case of follicular bronchiolitis shows reactive germinal centers along a small bronchiole. Immunostaining for CD20 **(C)** and CD3 **(D)** illustrates the close approximation of the lymphoid tissue to the epithelium and the extension of B cells as well as a few T cells into the epithelium.

Lymphoid Hyperplasias, Benign Lymphoid Infiltrates, and Related Lesions

Hyperplasia of lymphoid tissue in the lung is similar to lymphoid hyperplasia of other sites, with the production of germinal centers distributed along the normal locations of lymphatic tissue, specifically the pulmonary lymphatic routes. Exuberant lymphoid hyperplasia along the airways is termed follicular bronchitis or follicular bronchiolitis (Fig. 32.3), depending on the size of airway involved.[31] Lymphoid hyperplasia may also involve the septa and pleura.

In healthy children one may see a few lymphocytes and a rare germinal center in the lung. Adults generally do not have significant quantities of lymphoid tissue in parenchymal biopsy material.[19] Studies have shown the presence of small lymphoid aggregates in some bronchial biopsies from otherwise normal individuals,[32] when pulmonary lymphoid tissue is prominent; however, a pathologic condition is usually present. Hyperplasia of lymphoid tissue in the lung is most commonly a manifestation of chronic infections, chronic bronchitis, bronchiectasis, or cystic fibrosis, or is a reaction around chronic inflammatory processes such as granulomatous infections or abscesses.[33] Primary and secondary neoplasms can also have an associated lymphoid reaction including germinal

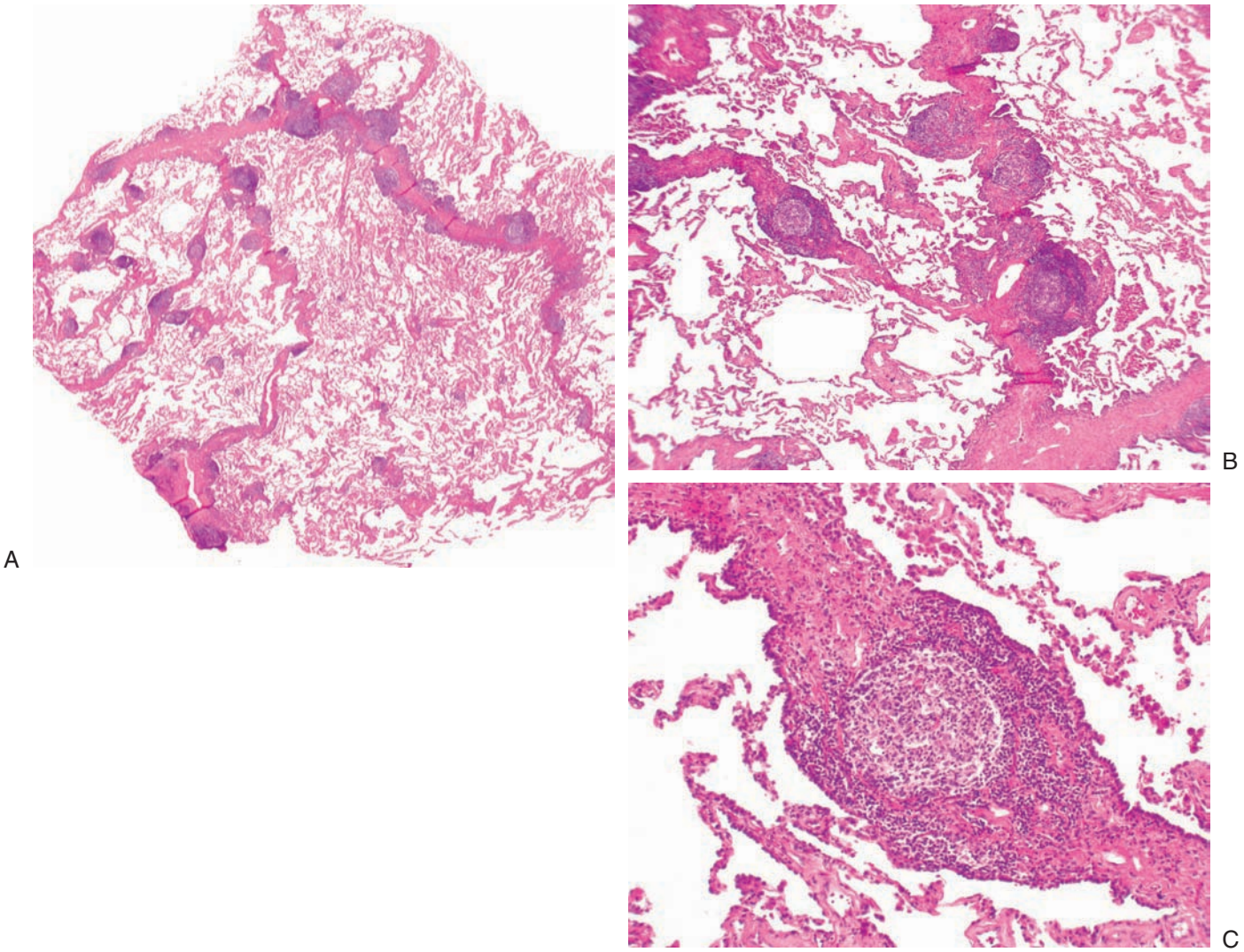


FIGURE 32.4. **(A–C)** Diffuse lymphoid hyperplasia in rheumatoid arthritis. There is a proliferation of germinal centers most prominent along interlobular septa **(A,B)**.

centers, sheets of plasma cells, or granulomas, especially in foci of obstructive pneumonia. Metastases from the lymphoepithelial variant of nasopharyngeal carcinoma and primary lymphoepithelioma-like carcinomas of the lung represent particularly florid examples.

Diffuse lymphoid hyperplasia (Fig. 32.4) producing bilateral pulmonary infiltrates on chest radiographs may sometimes be an isolated histologic finding, particularly in collagen vascular diseases (e.g., rheumatoid arthritis, Sjögren's syndrome), congenital and acquired immunodeficiency states (including HIV infection; Fig. 32.5), and systemic hypersensitivity reactions.[31,34–36] This is one of the patterns that has also been encompassed by the term *lymphocytic interstitial pneumonia* (see below). In collagen vascular diseases, this lymphoid proliferation is the lung's correlate of the exuberant lymphoid hyperplasia, which may be seen in lymph nodes in this group of disorders.[37] The lymphoid hyperplasia may at times be most prominent along airways (follicular bronchitis/bronchiolitis) and associated with clinical evidence of interstitial *or* airflow obstructive disease.[31]

When first described, *angioimmunoblastic lymphadenopathy* was thought to represent a peculiar autoimmune reaction with a syndromic clinical presentation and relatively frequent pulmonary involvement. Signs and symptoms associated with the condition included generalized lymphadenopathy, hepatosplenomegaly, Coombs-positive hemolytic anemia, skin rash, polyclonal hypergammaglobulinemia, and anemia.[38–41] While some reactive conditions with these features may occur, most cases are now recognized as being representative of a unique type of peripheral T-cell lymphoma termed angioimmunoblas-

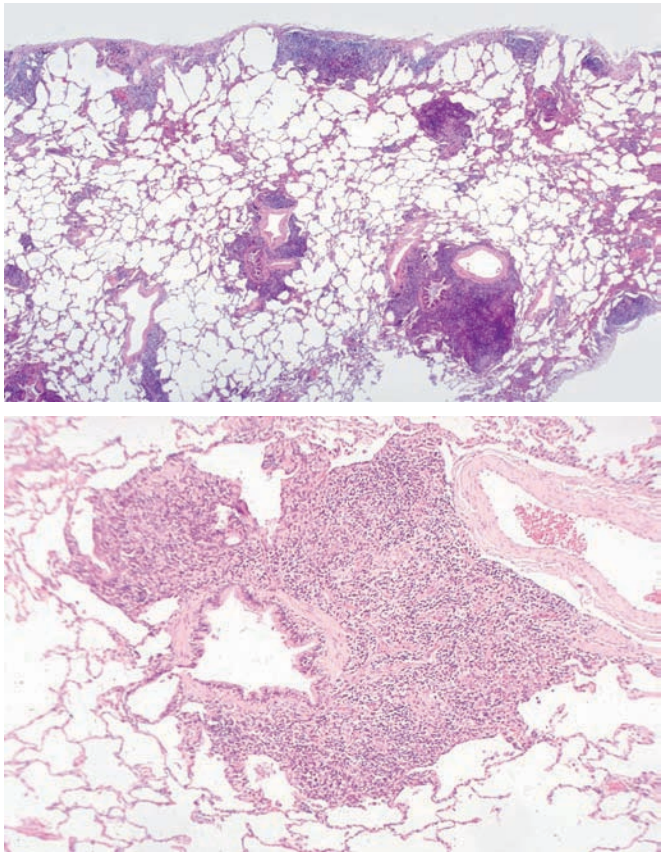


FIGURE 32.5. **(A,B)** Diffuse lymphoid hyperplasia in AIDS. Scanning power shows nodular lymphoid infiltrates along lymphatic routes, which at higher power show some features of reactive follicles **(B)**.

tic T-cell lymphoma.[42] For this reason this entity is discussed in greater detail below (see Lymphomas with Secondary Lung Involvement).

Lymphocytic Interstitial Pneumonia

Lymphocytic (*lymphoid*) *interstitial pneumonia* (*LIP*) (Fig. 32.6) is a chronic interstitial pneumonia characterized by a dense and diffuse polymorphous interstitial infiltrate composed of cells that are histologically benign and immunophenotypically polyclonal.[2,4,35,43,44] LIP is usually diffuse in its involvement of alveolar walls, another feature that distinguishes it from most malignant lymphomas. Lymphoid follicles are often present and there is overlap of this pattern with diffuse lymphoid hyperplasia (Fig. 32.7), although the latter is primarily related to the lymphatic routes. In the literature, both of these patterns have often been collectively referred to as lymphocytic interstitial pneumonia. However, when lymphoid follicles with germinal centers distributed along the lymphatic routes are the dominant features (Figs. 32.4 and 32.5), the term *diffuse lymphoid hyperplasia* is appropriately descriptive.[35]

With the description of the cellular pattern of nonspecific interstitial pneumonia (NSIP), many cases that might formerly have been called LIP are now called NSIP.[45] There are no precise criteria to distinguish LIP and NSIP, but most observers include as LIP only those cases with *dense* infiltrates of lymphoid cells. The following description is derived primarily from the older literature, which probably included cases that now would be called NSIP.

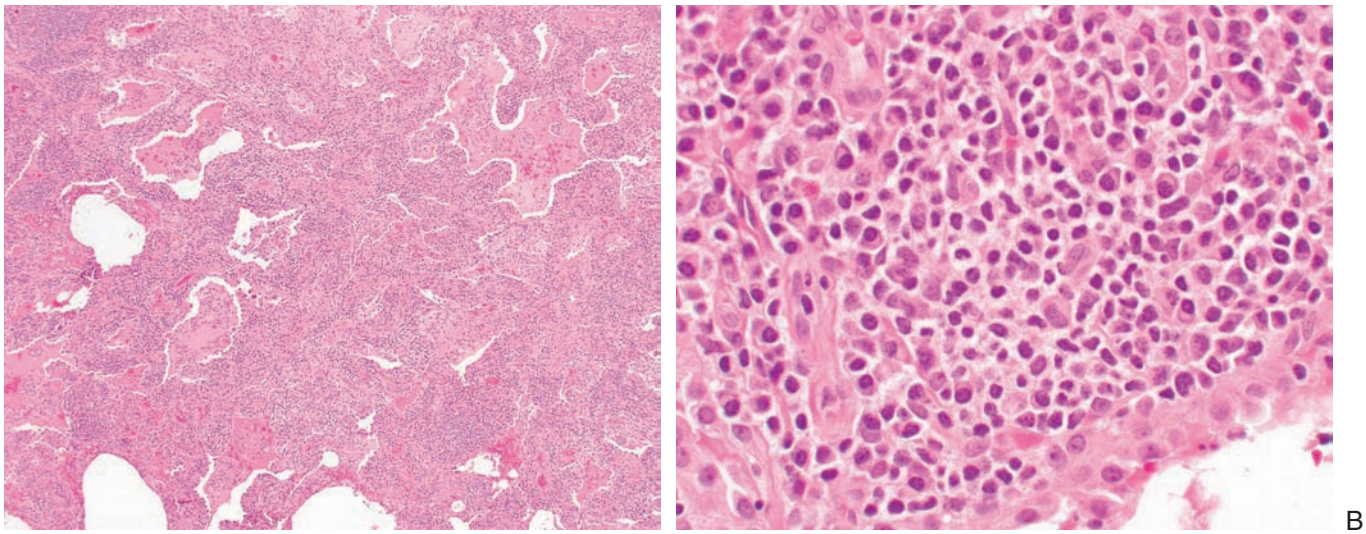


FIGURE 32.6. Lymphocytic interstitial pneumonia (LIP). There is a dense diffuse interstitial infiltrate of mononuclear cells **(A)**, which at higher power are polymorphous and include lymphocytes and plasma cells **(B)**. Immunophenotyping, including molecular studies for gene rearrangements, were negative in this case of LIP associated with Sjögren's syndrome.

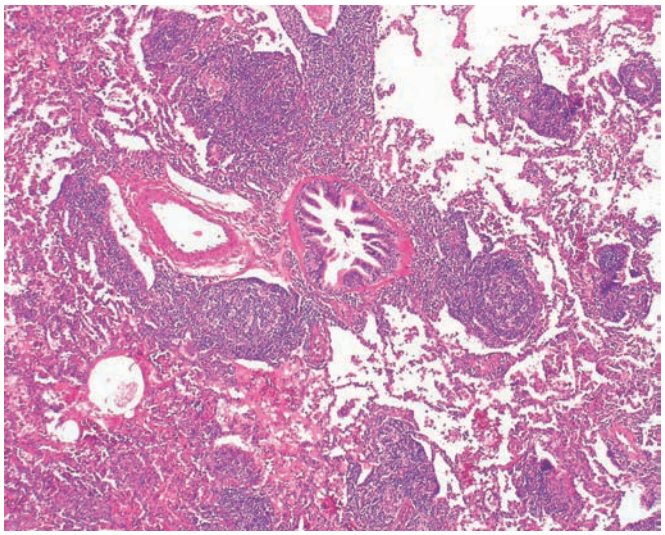


FIGURE 32.7. Diffuse lymphoid hyperplasia. There is a proliferation of germinal centers, which in this field, is predominantly along a bronchovascular structure. Diffuse lymphoid hyperplasia is one of the patterns associated with LIP. In this case there was an underlying congenital IgG deficiency.

The majority of reported cases of LIP occur in adults and have symptoms similar to other chronic interstitial pneumonias, including cough, dyspnea, weight loss, and progressive shortness of breath.[4,43,44] Children may also be affected.[46] Chest radiographs show bibasilar infiltrates. Pulmonary functions reflect infiltrative lung disease with restriction and abnormal gas exchange. Dysproteinemias are a common laboratory finding, and either hyper- or hypogammaglobulinemia may be identified. A number of conditions have been associated with LIP and diffuse lymphoid hyperplasia; they are listed in Table 32.2.[36,43,44,46–52] An example of LIP associated with bone marrow transplantation is shown in Figure 32.8. These associated conditions should be excluded before considering a diagnosis of idiopathic LIP, which is very rare.[45]

The histopathologic and immunophenotypic features of LIP are outlined in Table 32.3. The histology of LIP is characterized by a marked interstitial infiltrate of lymphocytes, plasma cells, and histiocytes (Fig. 32.6B). Some cases have giant cells, granulomas, or reactive lymphoid follicles. Interstitial fibrosis and honeycombing may be present. In contrast to lymphomas, LIP lacks large monomorphous foci of small lymphocytes or plasmacytoid lymphocytes and fails to show an overwhelming lymphatic distribution. A number of cases previously reported as LIP represented examples of diffuse bilateral small lymphocytic lymphomas presenting in the lung.[22,53,54] Immunophenotypic and molecular studies of LIP fail to show a clonal population of lymphoid cells.[43,55] T or B lymphocytes may predominate.[43,52,55]

TABLE 32.2. Conditions associated with lymphoid interstitial pneumonia/diffuse lymphoid hyperplasia

Autoimmune diseases
Sjögren's syndrome, primary biliary cirrhosis, myasthenia gravis, Hashimoto's thyroiditis, pernicious anemia/agammaglobulinemia, autoimmune hemolytic anemia, systemic lupus erythematosus, celiac disease
Immunodeficiency syndromes
Common variable immunodeficiency, acquired immunodeficiencies, unexplained childhood immunodeficiency, acquired immunodeficiency (AIDS)
Viral-associated (excluding HIV infection)
Epstein-Barr virus, chronic hepatitis
Other infections
Drug-induced
Bone marrow transplantation
Hypersensitivity pneumonitis
Miscellaneous
Familial

Modified from Colby TV, Koss MN. Travis WD. Atlas of tumor pathology. Tumors of the lower respiratory tract. Washington, DC: Armed Forces Institute of Pathology, 1994.

The differential diagnosis of LIP includes nonspecific reactive changes, extrinsic allergic alveolitis, and small lymphocytic and lymphoplasmacytic lymphomas. In immunosuppressed patients, pneumocystis should be excluded. The treatment of lymphocytic interstitial pneumonia is not resolved, but a number of patients, even those with immunodeficiency states, respond to steroids.[44,52]

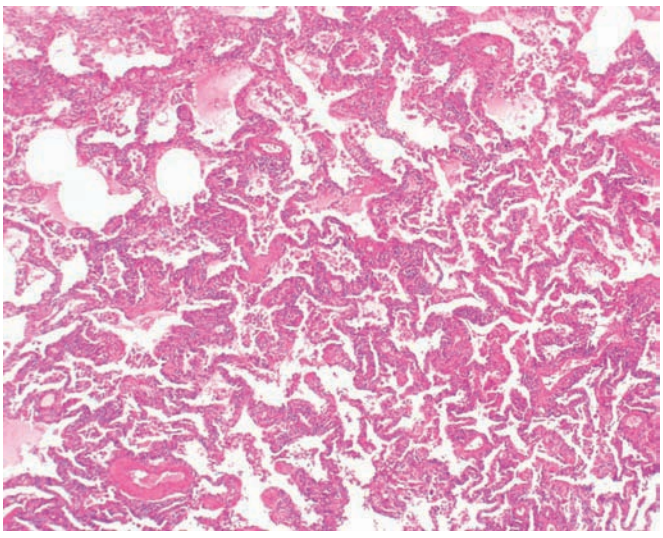


FIGURE 32.8. Lymphocytic interstitial pneumonia associated with bone marrow transplantation. This case shows a relatively dense diffuse mononuclear interstitial infiltrate. This case is right at the borderline between the degree of infiltrate expected for LIP and that expected for cellular nonspecific interstitial pneumonia (NSIP).

TABLE 32.3. Extranodal marginal zone B-cell lymphoma vs. nodular lymphoid hyperplasia and lymphocytic interstitial pneumonia

Feature	Extranodal marginal zone B-cell lymphoma	Nodular lymphoid hyperplasia	Lymphocytic interstitial pneumonia
Presentation	Single or multiple nodules consolidation, diffuse infiltrates	Localized mass/consolidation	Diffuse interstitial process
Distribution	Mass lesions with lymphatic tracking at the edges or diffuse process along lymphatic routes	Mass lesion with variable destruction of lung architecture; some lymphatic tracking of hyperplastic-appearing tissue	Diffuse proliferation of hyperplastic lymphoid tissue along lymphatic routes or dense diffuse infiltrates of interstitium
Germinal centers	Usually present with thick cuff of lymphoid tissue; colonization of germinal centers by monocytoid or centrocytic cells	Normal-appearing germinal centers present	Germinal centers are normal appearing when present
Cellular composition around germinal centers	Mixed including variable numbers of lymphocytes, monocytoid/centrocytic cells, transformed lymphocytes, plasma cells, often with Dutcher bodies	Polymorphous cellular composition, usually lymphocytes and plasma cells without Dutcher bodies	Polymorphous cellular composition, usually lymphocytes and plasma cells without Dutcher bodies
Epithelial infiltration by lymphoid cells (highlighted with cytokeratin staining)	Lymphoepithelial lesions often prominent	Lymphoepithelial lesions inconspicuous	Lymphoepithelial lesions inconspicuous
Immunophenotype	Predominant population of CD20 positive B cells (CD5, CD10, CD23 negative) with appreciable background population of CD3-positive T cells; T cells may appear predominant in some foci; plasma cells may be monotypic or polyclonal	CD20 positive B cells usually confined to follicular and immediate perifollicular regions with the remainder of the cells being predominantly T cells; polytypic plasma cells	CD20-positive B cells usually confined to follicular and immediate perifollicular regions with the remainder of the cells being predominantly T cells; polytypic plasma cells
Additional findings in some cases	Granulomas, hyaline sclerosis, amyloid deposition, crystal storing histiocytosis	Granulomas, hyaline sclerosis	Granulomas, hyaline sclerosis
Flow cytometry, molecular studies	Clonal population identified in most cases (note: these are sample dependent and false negatives may be encountered)	No clonal population identified	No clonal population identified

Note: All of the features encountered in nodular lymphoid hyperplasia and lymphocytic interstitial pneumonia may be encountered in extranodal marginal zone B-cell lymphomas and thus it is often difficult to absolutely exclude the possibility of an extranodal marginal zone B-cell lymphoma in which diagnostic tissue has not been evaluated.

Pseudolymphoma or Nodular Lymphoid Hyperplasia

Pseudolymphoma is a term that has historically been used to describe localized lymphoid proliferations in the lung presenting as a single nodule or region of consolidation confined to one lobe.[35,53,56] This moniker was coined as these lesions did not fulfill the early accepted clinical and pathologic criteria for the diagnosis of lymphoma due to lack of clinically aggressive behavior and the mixture of lymphoid elements present, respectively. The number of cases in which this descriptive category applies has dramatically diminished as most of the lesions that had been called pulmonary pseudolymphoma (synonym: nodular lymphoid hyperplasia[35]) have been reinterpreted as low-grade B-cell lymphomas.[22,53,54,56–61] Of all cases that the surgical pathologist encounters with massive accumulations of lymphocytes in the lung, roughly four of five (80%) were previously interpreted as pseudolymphomas,[62] whereas at least four of five (80%) are now interpreted as low-grade B-cell lymphomas.[56] In light of the controversy and confusion surrounding the term *pulmonary pseudolymphoma*, the term *nodular lymphoid hyperplasia* first proposed by Kradin and Mark[35] is likely a more appropriate and accurate diagnostic appellation. Regardless of whether pseudolymphoma or nodular lymphoid hyperplasia is used, this diagnosis should be restricted to those tumefactive lesions in which there is a prominent lymphoid infiltrate that by routine morphology appears reactive and that by ancillary immunophenotypic and molecular genetic analysis lacks evidence of clonality. In many cases one is left with a descriptive

diagnosis (e.g., "atypical lymphoid proliferation"), since definitive characterization of a lesion may not be possible, particularly in small biopsy specimens.

Reported cases of pulmonary "pseudolymphomas" occur in adults; in a minority of cases there is a history of a prior pneumonia at the site. These lesions are most often encountered in asymptomatic patients in whom a localized mass or infiltrate is detected on routine chest radiography. Laboratory studies are generally noncontributory, but four cases in the series of Koss et al.[56] had a polyclonal hypergammaglobulinemia.

Grossly, nodular lymphoid hyperplasias are tan and well circumscribed from the surrounding tissue.[35] Fibrosis within the lesion may cause retraction of tissue toward the center of the mass. The pathologic findings in nodular lymphoid hyperplasia are described in brief in Table 32.3. A hallmark microscopic feature is the heterogeneity in cellular composition and variation from field to field. The cellular infiltrate is mixed and generally includes lymphocytes, plasma cells, and occasional histiocytes that may form nonnecrotizing granulomas; approximately one third of cases contain giant cells. Reactive germinal centers with intact mantle zones that are separated by plasma cells containing Russell bodies may be prominent, but Dutcher bodies should not be seen. There is a variable amount of scarring that may be cellular and fibroblastic or acellular and hyaline in appearance. When fibroblastic proliferation is marked, *focal* or *chronic organizing pneumonia* may be more appropriate terms.[63] Confusion with the entity *pulmonary hyalinizing granuloma* should not occur (see Chapter 21). Amyloid-like material may be present in lymphoid hyperplasias. At the edge of the lesion, one does not see prominent lymphangiitic tracking or invasion of bronchial cartilage, features that characterize lymphomas. Necrosis was found in one case reported by Koss et al.[56]

Extranodal marginal zone B-cell lymphomas of MALT involving the lung can show many similar, if not identical, histologic features to those of pseudolymphoma/nodular lymphoid hyperplasia. The pathologic features of these entities and LIP are compared in Table 32.3. For this reason the ancillary immunophenotypic and molecular genetic studies are critical in the evaluation of potential pseudolymphomas/nodular lymphoid hyperplasias. These studies should fail to reveal evidence of a clonal B-cell population in all cases in which this diagnosis is rendered.[56]

Castleman's disease (giant lymph node hyperplasia), particularly the hyaline vascular type, may involve nodes that are partially or completely intrapulmonary in location.[64]

In summary, much is made of distinguishing low-grade, indolent lymphomas from either nodular lymphoid hyperplasia or lymphocytic interstitial pneumonia. In practical terms, the distinction of nodular lymphoid hyperplasia from low-grade MALT lymphoma may be largely academic as many of these lesions may be resected for diagnosis. Solitary low-grade lymphomas managed in this way rarely recur and often lack extrapulmonary involvement, and therefore do not require further therapy.

Malignant Lymphomas Presenting in the Lung

Definitions of a primary lymphoma occurring in an extranodal site, including the lung,[65] are somewhat arbitrary, and cases that have evidence of disseminated disease are generally excluded. From a practical management point of view, it is useful to divide pulmonary lymphomas into those cases in which the lung is the major (or only) site of involvement at presentation and those in which the lung is involved in disseminated disease or is a site of relapse in a patient with a previously diagnosed lymphoma at another site.[66] Table 32.4 provides an abbreviated listing of the types of lymphoproliferative disorders that can occur as primary pulmonary disorders.

A lymphatic distribution of involvement can often be recognized histologically in pulmonary lymphomas whether they present in the lung or involve it secondarily.[53,54,66] A spectrum is encountered from diffuse infiltrates along lymphatic routes without mass formation to large necrotic masses with no discernible distribution, although in most cases with large nodules tracking of the infiltrates along lymphatic routes at the edge of the masses is often present. The lymphatic distribution is best appreciated at low power or even with naked-eye examination of the glass slide (Fig. 32.1). This distinctive distribution of lymphoreticular infiltrates has also been appreciated radiologically, particularly with high-resolution CT scanning.

Traditionally, the absence of hilar lymph node involvement has been used as evidence against a diagnosis of lymphoma when evaluating a pulmonary lesion.[62,67] Later studies emphasized that the absence of hilar lymph node involvement is a relatively frequent occurrence in primary

Table 32.4. Lymphomas presenting in the lung

Extranodal marginal zone B-cell lymphomas: most common (approx. 75%)
Lymphomatoid granulomatosis: next to most common
Other non-Hodgkin's lymphomas: rare
Distinct subsets: intravascular lymphomatosis, anaplastic large cell lymphoma
Hodgkin's lymphoma: rare
Lymphoproliferative disorders associated with an immunosuppressed state
Immune system dysfunction may be iatrogenic (posttransplant, methotrexate related), acquired (HIV), or congential (e.g., Wiskott-Aldrich syndrome): rare

pulmonary lymphomas and that this parameter should be considered unreliable in distinguishing benign lesions from malignant ones.[54,56,61]

If a pulmonary lymphoid lesion is suspected at the time of frozen section, the surgeon should be asked to sample hilar nodes, as they may be helpful both in establishing a diagnosis and in staging.

Practically speaking, the pathologist is often confronted with the challenge of appropriately utilizing the myriad of ancillary tests that are available to evaluate lesions composed of hematolymphoid cells. These ancillary methods are outlined and compared in Table 32.5, and they are further discussed as they pertain to specific disease entities discussed below. Many of the antibodies

Table 32.5. Comparison of various ancillary methods used in evaluating hematolymphoid neoplasms

Method	Reagent	Tissue required	Advantages	Shortcomings	Useful for:
Paraffin immunohistochemistry	Antibody	Paraffin embedded	Allows for optimal histopathologic correlation	Not all antigens can be detected	Evaluating all lymphoid processes
Frozen immunohistochemistry	Antibody	Frozen	Allows for some histopathologic correlation; can detect some antigens that cannot be tested in paraffin	Histology suboptimal Limited availability	Evaluating lymphoid processes composed of small lymphocytes
Flow cytometry	Fluorochrome Conjugated antibody	Fresh tissue	Allows for wide range of antigens to be detected; can examine antigen coexpression on specific cell subsets	Requires significant amounts of fresh tissue (approx. 1 cm^2) no longer available for histologic review	Evaluating lymphoid processes composed of small lymphocytes; evaluating acute leukemias and myeloid neoplasms
T-cell receptor (TCR) polymerase chain reaction (PCR)	Multiplexed PCR Primers (usually to TCR gamma chain genes)	Paraffin-embedded, fresh, or frozen	Rapid; widely available	False-positive results occur with some frequency	Evaluating potential T-cell malignancies
Immunoglobulin (Ig) PCR	Multiplexed PCR Primers (to Ig heavy and light chain genes)	Paraffin-embedded, fresh, or frozen	Rapid; widely available	False-negative results can occur, particularly in postfollicular center cell neoplasms (including mucosa-associated lymphoid tissue [MALT] lymphoma)	Evaluating potential B-cell malignancies, particularly those composed of small lymphocytes and PTLDs
TCR, Ig, and EBV Southern blot	Labeled DNA probes to TCR and Ig genes and Epstein-Barr virus (EBV) terminal repeats	Fresh or frozen	Higher specificity (TCR) and sensitivity (Ig); can confirm clonality of EBV positive processes	Labor intensive; limited availability	Evaluating potential B-cell and T-cell neoplasms; evaluating EBV-positive lymphoid disorders
In Situ Hybridization	RNA-specific DNA probes	Paraffin-embedded	Can detect RNA expression	Limited number of probes available; expensive	High sensitivity and specificity in detecting EBV positivity in lymphoid neoplasms
Fluorescence in-situ hybridization (FISH)	Fluorescently labeled DNA probes	Paraffin-embedded fresh	Detecting specific chromosomal translocations	Limited number of probes available; expensive	Evaluating for malignancies with known chromosomal translocations such as mantle cell lymphoma

used in evaluating hematolymphoid tumors are reactive in paraffin-embedded tissue.[68] Hence, obtaining well-fixed, representative paraffin blocks of the sampled tissue is of paramount importance, as paraffin immunohistochemistry may be helpful in confirming a light microscopic impression.[61] If there is sufficient tissue, some of the tumor should also be saved frozen both to allow for more detailed immunophenotyping analysis and to provide large amounts of high-quality DNA for ancillary molecular genetic studies, if needed. Flow cytometry is a powerful immunophenotyping technique. This method, however, requires the use of significant amounts of biopsy tissue that can not then be used for histologic examination; therefore, this technique should be employed only when there is an abundance of evaluable tissue.

Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue

Review of this category is complicated by the evolution of both the classification of lymphomas in general and of the understanding of low-grade lymphomas in the lung in particular. As discussed above, prior to the advent of advanced immunophenotyping and molecular genetic techniques, many of these cases were inappropriately categorized as "pseudolymphomas." As most of these lesions came to be recognized as lymphomas, a variety of diagnostic labels were applied, largely reflecting the contemporaneous terminology used in lymphoma classification schemes. As such, entities in this category have been termed small (well-differentiated) lymphocytic lymphomas with or without plasmacytoid features, lymphocytic lymphomas of intermediate differentiation, and small cleaved-cell lymphomas. This confusing drift in nomenclature also reflects the historic difficulty in classifying lymphomas of MALT.[20] However, as the quintessential features of extranodal marginal zone B-cell lymphomas of the MALT type have been elucidated, it has come to be recognized that the vast majority of low-grade pulmonary lymphomas are of this type.

Multiple studies of pulmonary extranodal marginal zone B-cell lymphomas of the MALT type have revealed similar clinical, radiologic, and pathologic features. The following description is a summary of nine series.[54,56–60,69–71] Most patients are older than 20 (mean age, approximately 60 years), although patients as young as 12 have been observed. A variety of medical diseases/disorders may precede the diagnosis; most frequently described are autoimmune disorders that are present in approximately 30%. Slightly more than half are asymptomatic, with the lesion being discovered on chest radiographs. When present, the symptoms are usually relatively nonspecific and include cough, chest pain, dyspnea, hemoptysis, and fatigue. B-symptoms such as weight loss, fever, and night sweats are relatively uncommon. Pulmonary MALT lymphomas appear to occur slightly more often in females; however, the degree of female predominance varies among studies.

The abnormal laboratory findings in pulmonary MALT lymphoma, like the clinical abnormalities, are generally nonspecific. Up to one third of patients have a monoclonal serum gammopathy either at presentation or subsequently, irrespective of the presence or absence of marrow involvement. The light chain type of the monoclonal serum protein always matches that expressed by the monoclonal tumoral B cells, and is usually IgM class. The amount of serum monoclonal protein is usually low (less than 3 g/dL), in contrast to cases of lymphoplasmacytic lymphoma associated with Waldenström's macroglobulinemia, although cases of pulmonary involvement by low-grade B-cell lymphomas associated with the clinical and laboratory features of Waldenström's macroglobulinemia may occur.[72–74] Cryoglobulinemia with associated vasculitis has also been reported.[70] Pulmonary function studies are rarely recorded because the majority of patients have radiographically localized disease. In the minority of patients who have diffuse bilateral disease

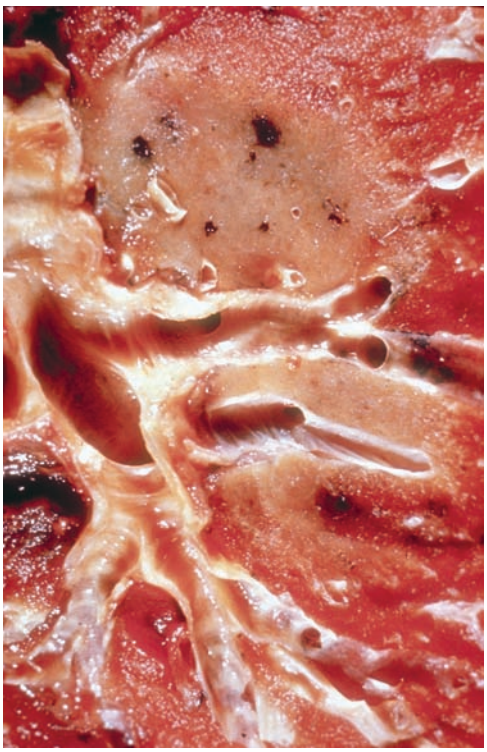


FIGURE 32.9. Low-grade extranodal marginal zone B-cell lymphoma. There is nodular consolidation without necrosis and with growth around, but not destroying, the underlying lung architecture.

radiographically, pulmonary function abnormalities of restriction and decreased diffusing capacity may be present.

The chest radiographic findings are quite variable, and any combination of the following may be seen: single or multiple nodules; unilateral or bilateral disease; localized alveolar or interstitial infiltrates; or diffuse bilateral alveolar or interstitial infiltrates. The most common presentation on routine chest radiology is a solitary, noncalcified nodule that may be 20 cm or more in diameter. Air bronchograms are frequent; cavitation and hilar adenopathy are rarely observed. In a study by Wislez and colleagues,[30] the radiologic and CT features of 13 cases of primary pulmonary MALT lymphoma were compared. In this study CT examination was found to be more sensitive in detecting multiple nodules, particularly small (<7 mm) nodules. The CT studies also appeared to be of greater utility in characterizing the detailed features of the infiltrates including the presence of ground-glass opacities, and a peribronchovascular growth pattern of interstitial thickening and entrapment of airways. Interestingly, dilation of the entrapped airways was seen in three cases; all lacked mucous plugging and in all the dilation resolved with treatment of the tumor.

Like other hematolymphoid neoplasms involving the lung, low-grade extranodal marginal zone lymphomas of the MALT type may form consolidative pulmonary masses (Fig. 32.9). On microscopic examination infiltration of the malignant cells along lymphatic routes can be appreciated (Fig. 32.10A,B) and these infiltrates may

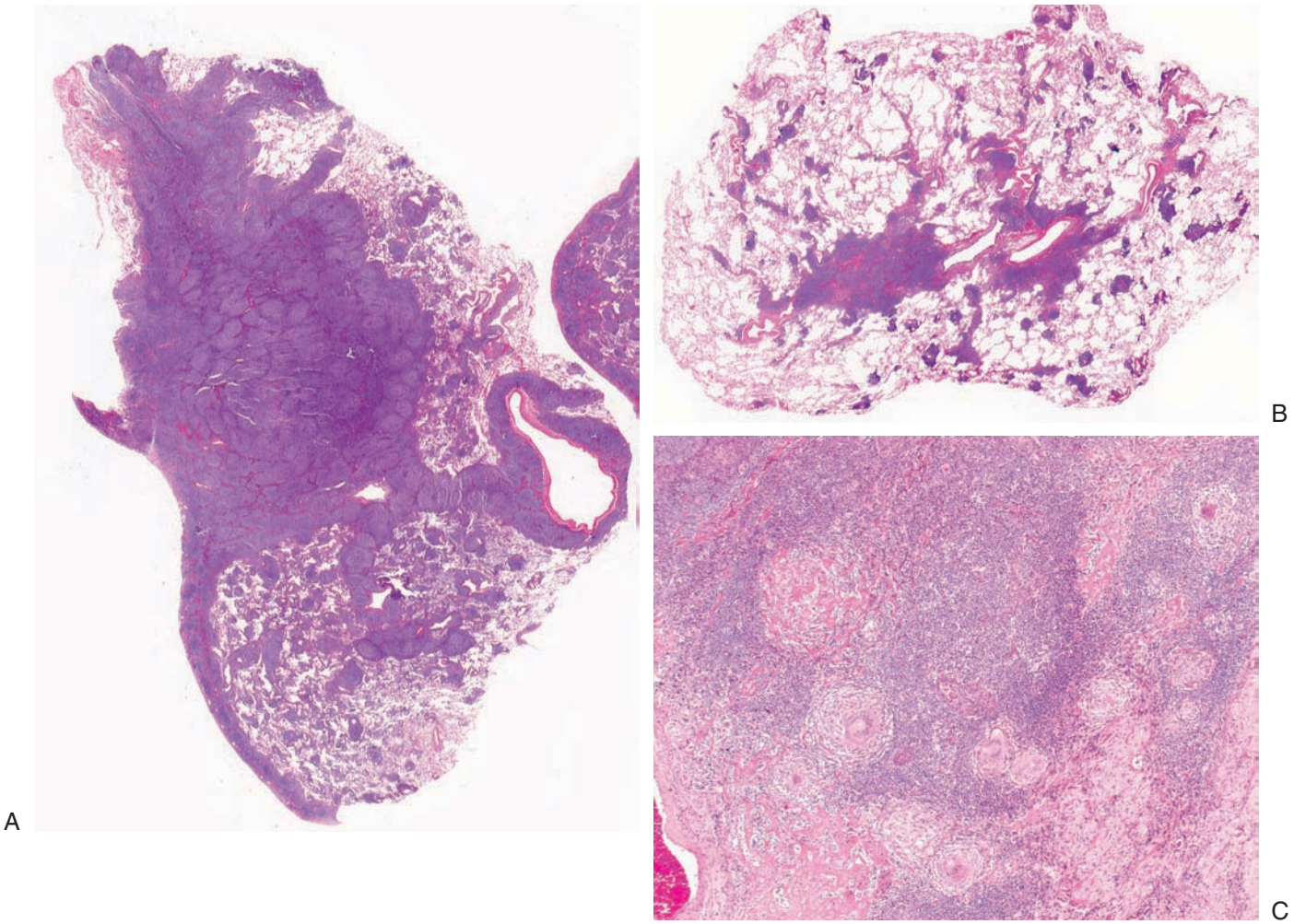
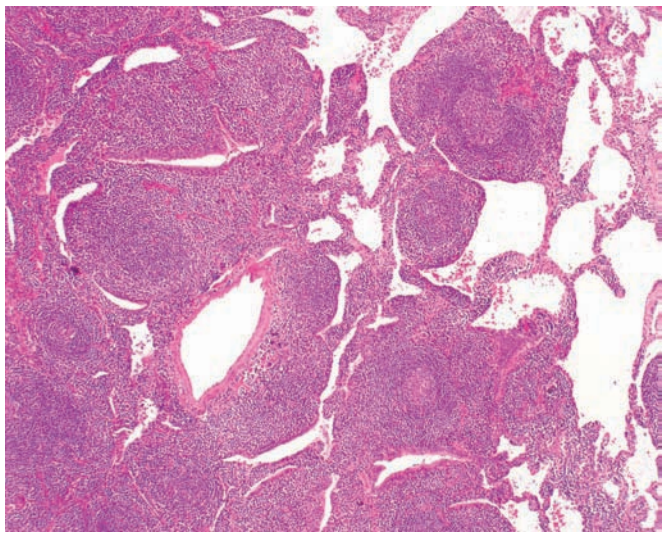


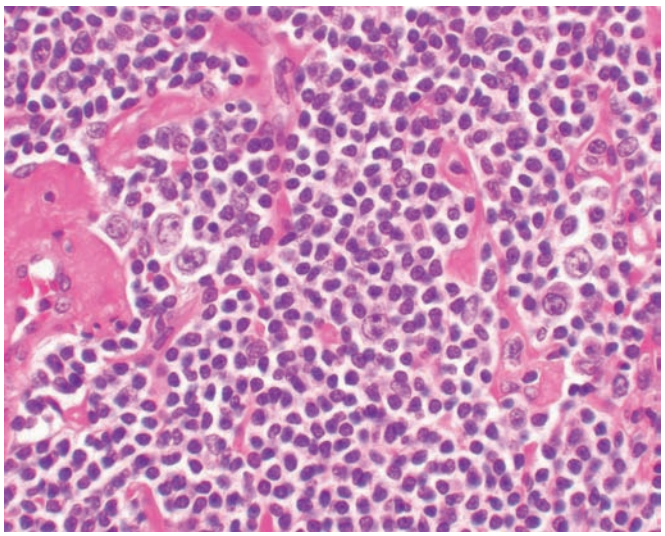
FIGURE 32.10. Low-grade of extranodal marginal zone B-cell lymphoma, low magnification features. **(A)** This whole mount illustration shows marked reactive follicular hyperplasia associated with a lesion that shows a definite tracking along perivascular and pleural lymphatic routes. **(B)** There is a nodular central zone of dense lymphoid infiltrate. There are small nodular aggregates in the surrounding lung tissue that are part of the lymphomatous process but which, in and of themselves, would be difficult to recognize as lymphoma. **(C)** This case illustrates heterogeneity with zones of sclerosis, reactive germinal centers, lymphoepithelial lesions (just below center), and granulomatous inflammation (at the 8 o'clock position).

coalesce with effacement of the normal lung architecture (Fig. 32.10B,C). The distribution may not be readily discernible in large masses, but tracking of the infiltrate along lymphatic routes may be seen at their edge, and smaller satellite lesions may be found distributed along lymphatic routes. The histopathologic findings in pulmonary MALT lymphomas are detailed in Table 32.3. Cytologically, these tumors are composed predominantly of three cell types that are present in varying proportions in each case: small lymphocytes with minimally irregular nuclear contours and sparse cytoplasm; monocytoid B cells with small irregular nuclei, abundant clear cytoplasm, and distinct cytoplasmic membranes; and cells with plasmacytoid or plasmacytic features (Fig. 32.11). When a plasma cell component is present, Dutcher bodies may be found in up to one half of cases. Interspersed among these cell populations are isolated, singly distributed "transformed" lymphocytes with large nuclei, open chromatin, and visible nucleoli.

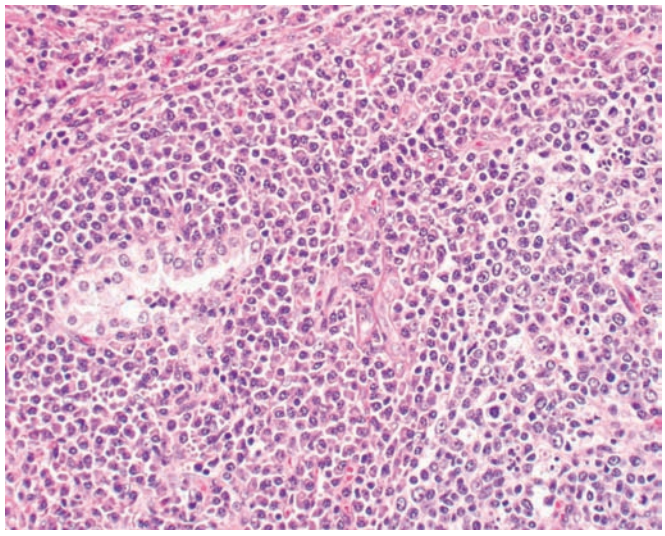
Ideally immunologic evaluation of all suspected MALT lymphomas of the lung should be performed. In some instances this may not be possible; in such cases a diagnosis of MALT lymphoma may be proposed if morphologic features invariably associated with malignancy such as Dutcher bodies are identified. Other features such as invasion of bronchial cartilage may also suggest the diagnosis; the presence or absence of lymphoepithelial lesions does not aid in distinguishing benign and malignant processes. Given the significant histologic and radiologic overlap between MALT lymphoma and nodular lymphoid hyperplasia (the comparative features are outlined in Table 32.3), a definitive diagnosis should be deferred to immunologic and molecular evaluation unless the morphologic features are compelling. Immunophenotyp-



A



B



C

FIGURE 32.11. Low-grade extranodal marginal zone B-cell lymphoma, high magnification features. **(A)** Higher power microscopy from Figure 32.10A shows the presence of germinal centers with a dense surrounding cuff of lymphoid cells. The perifollicular cells represent the neoplastic element in this condition. **(B)** Detail shows predominantly small lymphocytes with scattered immunoblasts. Background shows hyaline stromal fibrosis. **(C)** This case shows foci with dense aggregates of plasma cells, which proved to be clonal.

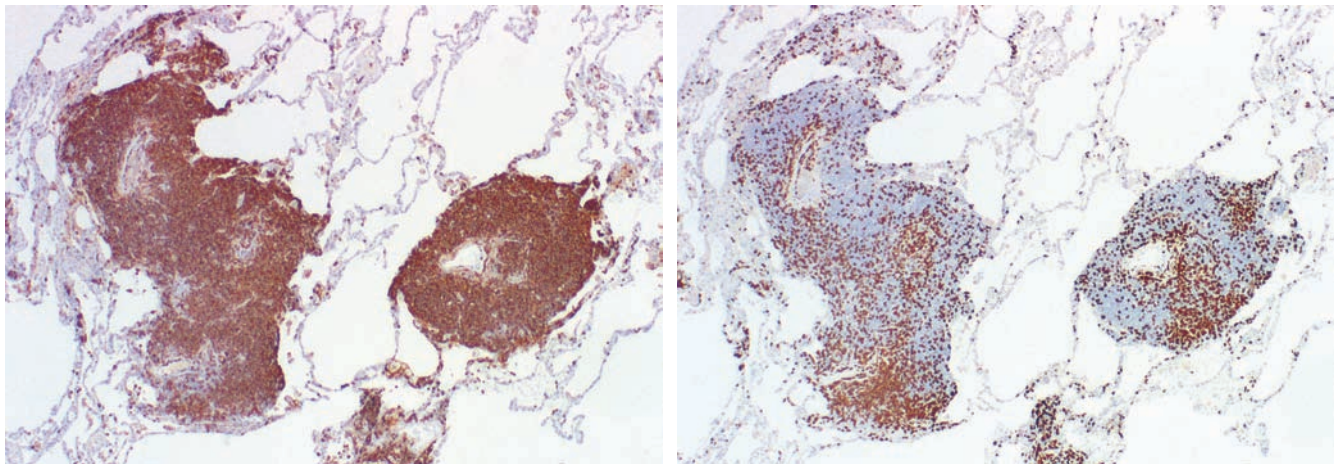


FIGURE 32.12. Low-grade extranodal marginal zone B-cell lymphoma. CD20 **(A)** and CD3 **(B)** staining shows a marked density of the B-cell infiltrate in a perivascular distribution. Although less in number, appreciable T cells are present.

ing and molecular genetic studies should demonstrate a neoplasm predominantly composed of clonal B cells (Fig. 32.12A) in all cases. T cells are also present, although they typically represent a relatively minor component of the lymphoid infiltrate (Fig. 32.12B). Immunoperoxidase staining for kappa and lambda light chains can be additionally useful in highlighting the presence of a clonal plasma cell component, which can be found in about one third of cases (Figs. 32.13 and 32.14). The presence of polyclonal plasma cells does not exclude a MALT-type lymphoma.

As in MALT lymphomas in other sites, the tumoral lesions frequently contain reactive germinal centers (Fig. 32.11A). A mixture of centrocytes and centroblasts usually populates these germinal centers, although in rare instances regressive transformation of germinal centers may be present. Colonization of these reactive germinal centers by immunoglobulin light chain restricted neoplastic plasma cells can sometimes be seen by immunoperoxidase staining.[75] Infiltration of adjacent airway and alveolar epithelium with formation of lymphoepithelial lesions is common (Fig. 32.15). The neoplastic B-cell infiltrate and the associated reactive germinal centers and lymphoepithelial lesions form an architectural unit that recapitulates the architecture seen in normal, nonneoplastic MALT tissues such as Peyer's patches. This archi-

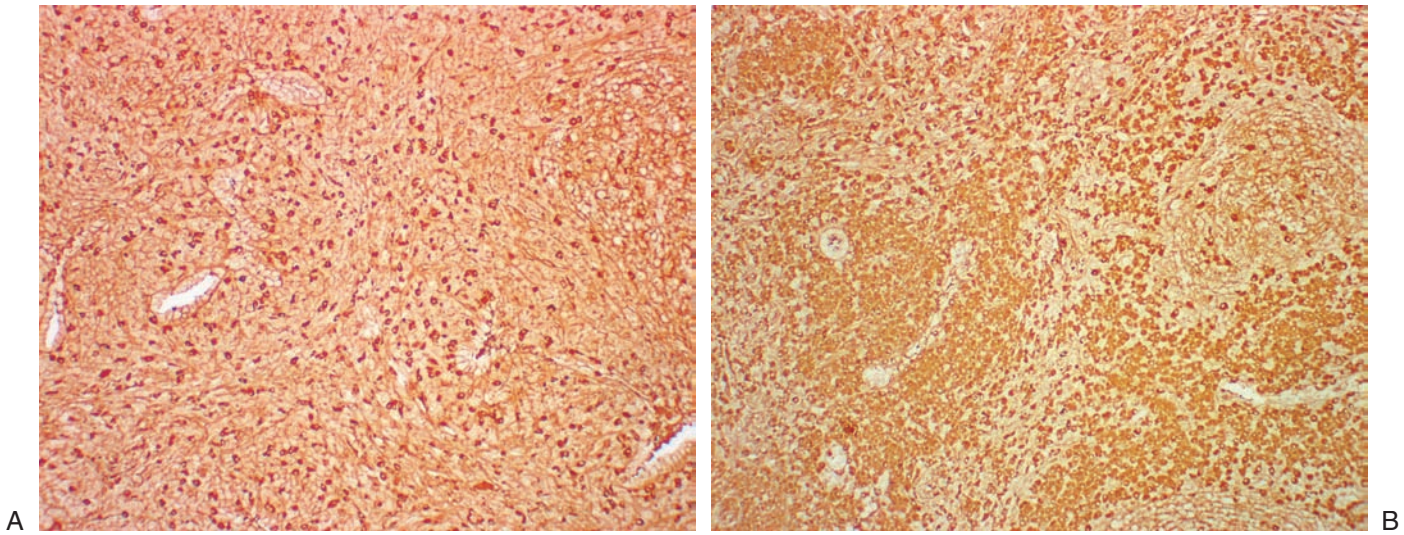


FIGURE 32.13. Low-grade extranodal marginal zone B-cell lymphoma, immunoperoxidase staining with antiimmunoglobulin light chain antibodies. Only scattered nonneoplastic kappa light chain–positive plasma cells are present **(A)**. In contrast, the neoplastic plasma cell component of the extranodal marginal zone B-cell lymphoma show strong, uniform lambda light chain restriction **(B)**.

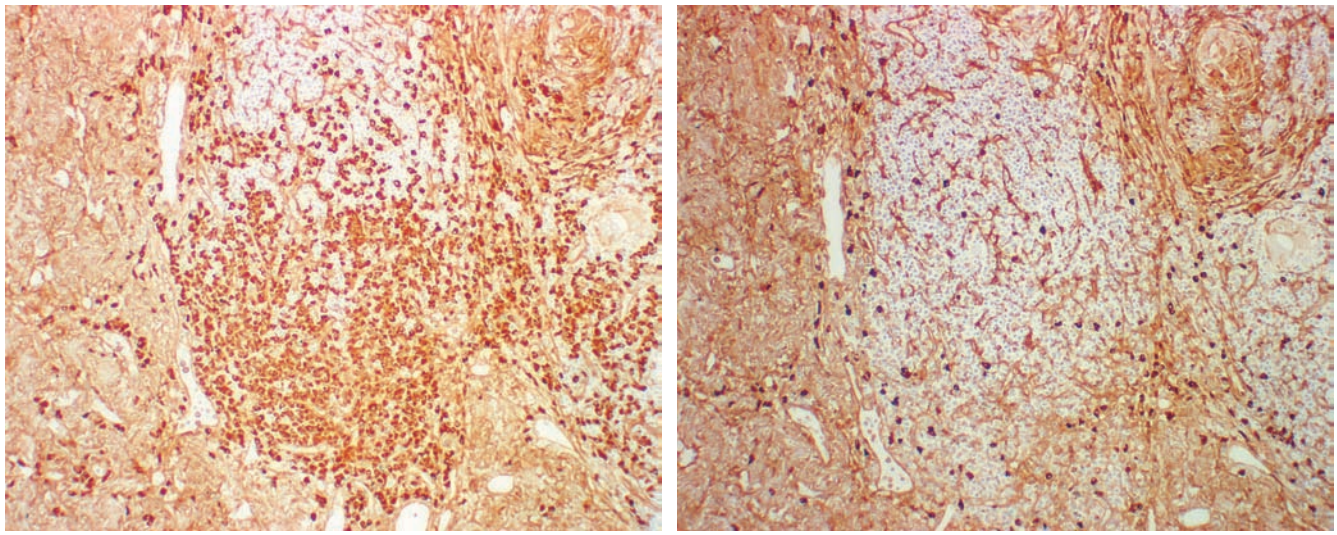


FIGURE 32.14. Low-grade extranodal marginal zone B-cell lymphoma. In some cases clonal plasma cells may be seen as focal aggregates as illustrated in this case showing kappa restriction. **(A)** Kappa. **(B)** Lambda.

tecture is characterized by subepithelial germinal centers with crescenteric accumulations of monocytoid B cells at their periphery polarized toward the overlying epithelium. When a plasma cell component is present, this also is typically polarized toward the overlying epithelium with accumulation of plasma cells in the submucosa. Accumulation of plasma cells may also be found at the periphery of small vessels if they are present within the tumor.

Some vascular infiltration (Fig. 32.16) by malignant cells, cytologically benign cells, or a mixture, is common in pulmonary MALT lymphomas. This infiltration is not typically angiodestructive and not associated with coagulative necrosis. Invasion of airways also occurs and may produce a secondary bronchiolitis or bronchiolitis obliterans with more distal obstructive changes, including foamy macrophages in alveoli and inflammatory infiltrates in alveolar walls.

At the edge of tumor masses one may find admixed plasma cells and histiocytes or a nonspecific intraalveolar accumulation of inflammatory cells. These foci may show a polyclonal immunostaining pattern for immunoglobulin light chains (Fig. 32.17). Granulomas, giant cells, dense sclerosis, and hyalinized material (which may or may not stain positively for amyloid) are sometimes seen.[76,77] A few cases mimic nodular amyloidosis. In addition, amyloid deposition with the tumor may be seen in a small subset of cases; this amyloid is composed of immunoglobulin light chains of the same type expressed by neoplastic B cells. Although this finding is not indicative of systemic amyloid deposition disease, it may be associated with an adverse prognosis. A relatively common appearance is bands of dense sclerosis surrounding islands of

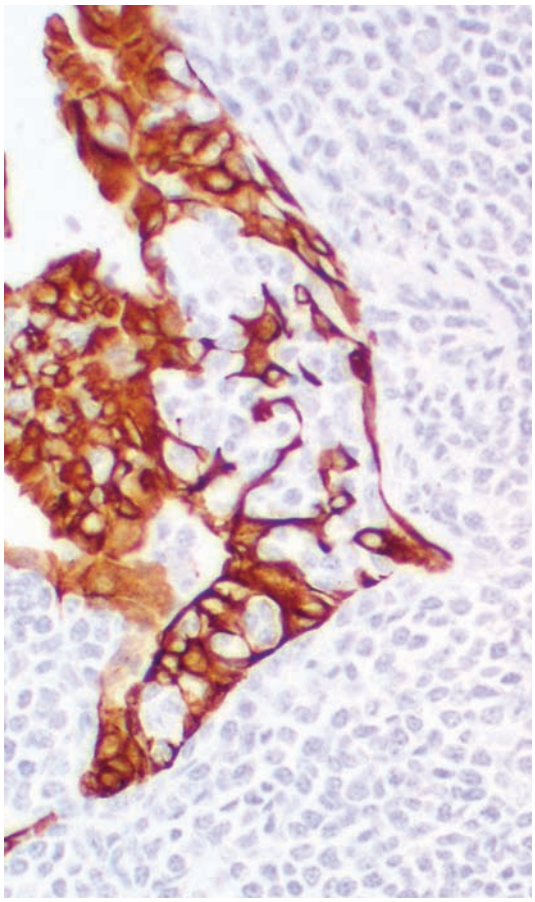


FIGURE 32.15. Low-grade extranodal marginal zone B-cell lymphoma. Lymphoepithelial lesions are highlighted with cytokeratin staining; cytokeratin-negative lymphoid cells infiltrate epithelial structures.

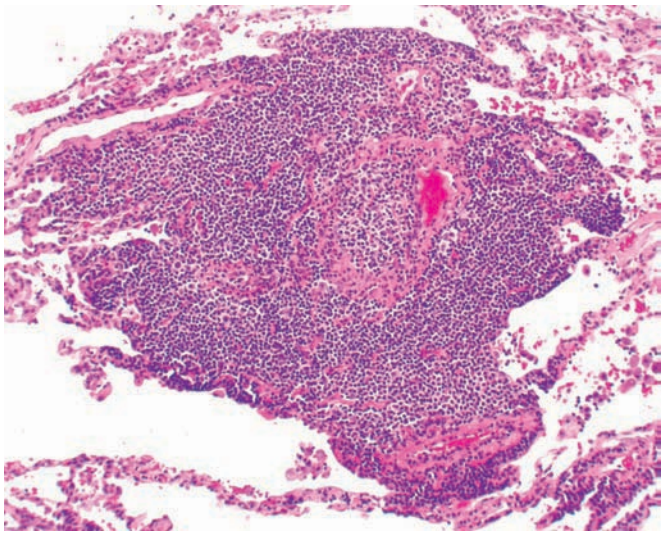


FIGURE 32.16. Low-grade extranodal marginal zone B-cell lymphoma. The lymphoid infiltrate is dense and shows some vascular infiltration, although classic features of vasculitis, including necrosis and fibrinoid change, are not seen.

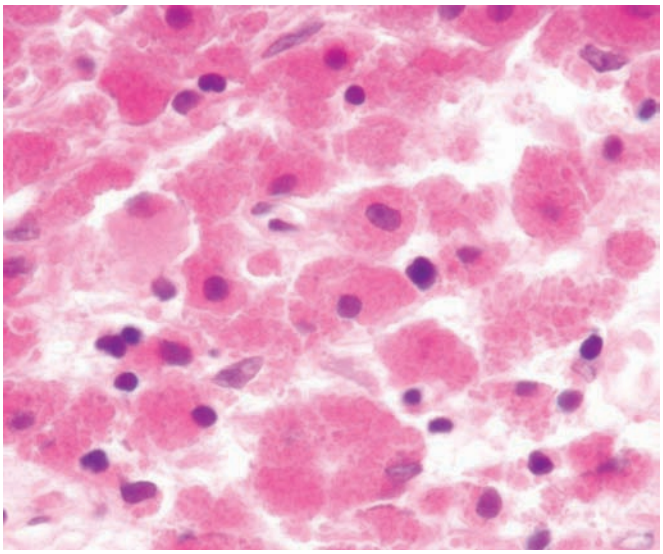
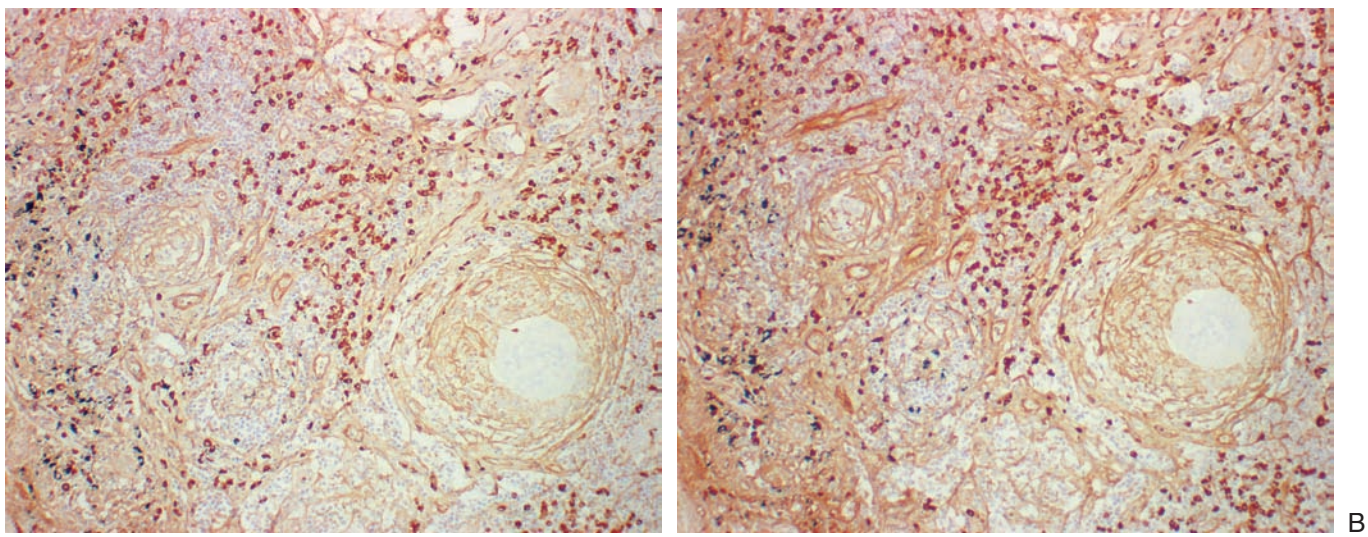


FIGURE 32.18. Low-grade extranodal marginal zone B-cell lymphoma with formation of immunoglobulin crystals in histiocytes.

small lymphocytes with occasional plasma cells. Immunoglobulin crystal deposition has also been described (Fig. 32.18).[78–80]

The differential diagnosis includes LIP, diffuse lymphoid hyperplasia, nodular lymphoid hyperplasia (pseudolymphoma), and other systemic low-grade lymphomas that may involve the lung, including follicular lymphoma and B-cell small lymphocytic lymphoma.

Cytogenetic abnormalities are often present in MALT lymphomas of the lung and other tissues; these abnormalities include aneuploidy and structural anomalies.[81–83] The most frequent aneuploidy in pulmonary MALT lymphomas are trisomies of chromosomes 3 and 18, which may occur singly or in combination. Trisomy of chromosome 12 may also occur, although less often.[84] Structural chromosomal abnormalities have been described. The most common structural abnormality in primary pulmonary MALT lymphoma is a reciprocal translocation involving the *API2* gene on chromosome 11q21 and the *MALT1* gene on chromosome 18q21



A B

FIGURE 32.17. Low-grade extranodal marginal zone B-cell lymphoma. In some proven cases kappa **(A)** and lambda **(B)** staining shows that the plasma cells are polyclonal.

[t(11;18)(q21;q21)].[85,86] This abnormality is present in approximately one quarter to one half of pulmonary MALT lymphomas and appears to be mutually exclusive of aneuploidy.[87,88] In larger series of low-grade gastric MALT lymphomas, this translocation has been associated with more aggressive disease traits; however, its prognostic significance in pulmonary MALT lymphomas remains unclear.[89] A second, less common translocation involving the *MALT1* gene and the *IGH* gene on chromosome 14q32, results in an abnormal chromosome that may be confused with t(14;18)(q32;q21). *BCL2–IGH* fusion of follicular lymphoma has also been described.[90] Both of these translocations appear to result in constitutive activation of the B-cell transcription factor NF-κB through *MALT1*-induced phosphorylation and inactivation of its inhibitor I-κB.[91]

The vast majority of pulmonary MALT lymphomas are indolent and may be cured by surgery alone if they are localized.[21,23,24,54,56–60,69,71] Those that recur may do so within months or up to decades after initial recognition. At presentation, a minority, probably less than one fourth, are found to have evidence of extrapulmonary lymphoma.[54] Transformation into a large-cell lymphoma, may occur.[53,57,71] This transformation is characterized histologically by sheet-like accumulation of large transformed cells either in a biopsy also containing a low-grade MALT lymphoma or in a separate biopsy from a patient in whom a diagnosis of low-grade pulmonary MALT lymphoma has been biopsy proven either contemporaneously or previously.

Therapy and staging procedures should be tempered by the indolent nature of these lesions and the fact that resection alone may cure a significant number of patients. The indolent behavior of these lymphomas is thought to reflect lymphomas of MALT in general.[21,92] A distinctive feature of MALT lymphomas is their proclivity to disseminate to other MALT sites such as the gastrointestinal tract, thyroid, salivary glands, and lacrimal glands. For this reason, particular attention should be paid to these areas during clinical and radiologic staging procedures.[92]

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) was originally described in the early 1970s as an angiocentric and angiodestructive process composed of "lymphoreticular" cells that showed a propensity to infiltrate blood vessels.[3] It was not clear whether it was primarily a disease of the lymphoid system, a peculiar vasculitis, or a hybrid.[3] Much of the controversy regarding the nature of LYG was related to the polymorphous nature of the inflammatory infiltrate, which did not meet widely accepted morphologic criteria for the diagnosis of lymphoma. Another confounding feature of LYG as compared to lymphomas recognized at the time of its initial description was its propensity to involve other extranodal sites such as the nervous system, kidney, and skin rather than the lymph nodes and spleen.

A challenge in understanding the histopathology of LYG is that it is in essence a morphologically defined entity that therefore may be expected to encompass a number of lymphoproliferative diseases as defined by ancillary immunophenotyping and molecular genetic methods. Early frozen-section immunohistochemical studies of LYG indicated that it was a lymphoproliferative disorder in which the majority of the lymphoid cells were T cells.[93,94] This finding was similar to that seen in aggressive angiodestructive lymphoproliferative lesions associated with necrosis occurring in the nasopharynx, so-called lethal midline granuloma or polymorphic reticulosis, and the term *angiocentric immunoproliferative lesion* (AIL) was coined to describe these apparently related diseases.[5,6] However, seminal studies using paraffin-based immunohistochemical and in-situ hybridization methods revealed fundamental differences between these two groups of cases. The majority of LYG cases were demonstrated to contain variable numbers of large Epstein-Barr virus (EBV)-positive B cells that often could be proven to be clonal, in a background of reactive small CD3 positive T cells.[95,96] In contrast, while the lesions occurring in the head and neck also contained EBV-positive atypical cells, in these cases the neoplastic cells were not B cells but rather cytotoxic lymphocytes (most often natural killer [NK] cells).[97] Hence, in the most recent World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues these lesions are now recognized as distinct entities called lymphomatoid granulomatosis and extranodal NK/T-cell lymphoma, nasal type, respectively.[9] Interestingly, the presence of EBV infection in these distinct lymphoproliferative lesions may lead to the common histologic findings of angiodestruction and necrosis in part through the EBV-induced elaboration of cytokines such as IP-10 and Mig.[98]

The relative biologic homogeneity of the morphologically defined entity LYG speaks to the perspicacity of the authors by whom it was initially described. However, some pathologic variability remains even within cases that fulfill the histologic criteria for the diagnosis and in which alternative diagnoses have been excluded. In the current WHO classification, LYG is included under the heading of "B-cell proliferations of uncertain malignant potential" as a disorder of EBV-positive B cells that varies in histologic grade and clinical aggressiveness in proportion to the number of EBV-positive B cells present.[9] However, rare cases in which there is no evidence of EBV positivity in the B cells have been described. Furthermore, in a small subset of cases the cytologically atypical cells are CD3–positive T cells, and B cells are virtually absent.[95] In these latter cases the

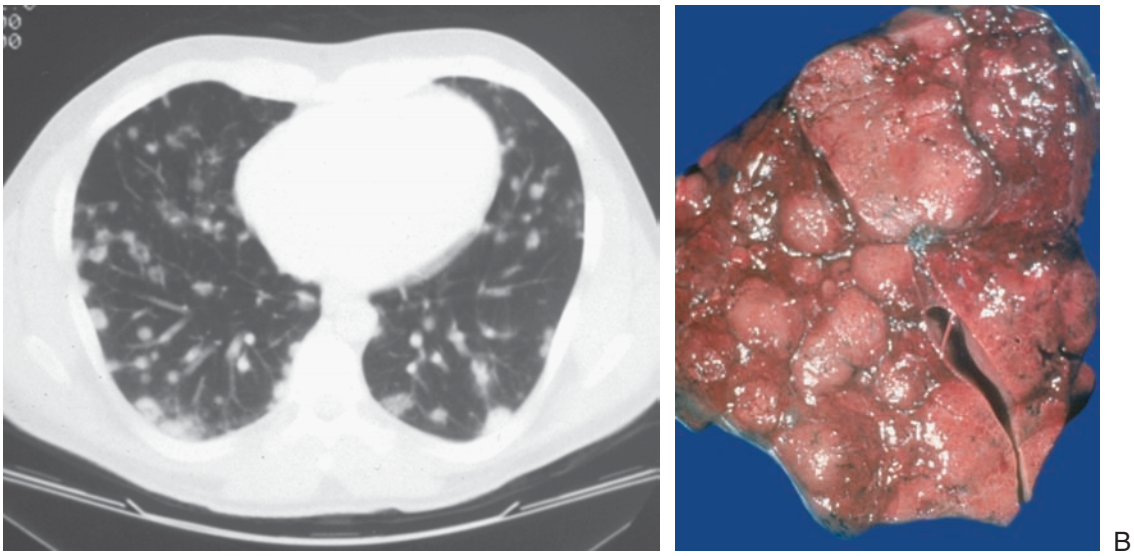


FIGURE 32.19. Lymphomatoid granulomatosis. **(A)** Typical radiologic findings with nodules, some showing cavitation. **(B)** Gross appearance with bulging, fish flesh–like nodules replacing much of the lung parenchyma. Necrosis is not prominent in this case.

atypical T cells are negative for EBV and cytotoxic granule proteins such as TIA-1 and granzyme B, features that distinguish them from extranodal NK/T-cell lymphomas of the nasal type.[99] Some contend that these "T-cell LYG" cases may be undersampled typical LYG cases, and indeed the detection of EBV-positive B cells in LYG may require studying multiple tissue blocks. However, rare cases with histologic features of LYG and the unusual attributes noted above do occur. The relationship of these cases to the entity LYG as now recognized by the WHO is unclear.

Since the initial description of lymphomatoid granulomatosis, several sizable series have been published.[100–103] Lymphomatoid granulomatosis most commonly occurs in adults with a slight male predominance. Cases have been reported in all age groups, however, including children.[104,105] Young patients affected by LYG usually have an underlying immune deficiency such as Wiskott-Aldrich syndrome, which is discussed in greater detail below. Lymphomatoid granulomatosis most commonly involves the lungs; cough as well as generalized systemic complaints such as fever and weight loss are the most common presenting symptoms. Other disease-associated clinical features in LYG are attributable to its propensity to involve other organ systems. In particular, global or localized neurologic symptoms due to involvement of the central and peripheral nervous system and rash secondary to skin involvement often occur, as these are the more frequent extrapulmonary sites of disease.[8] Although renal involvement is not uncommon, it usually is not clinically evident.[100] The laboratory findings in LYG are generally nonspecific, although patients frequently show serologic evidence of acute or prior EBV infection.[106]

Chest radiographs in LYG typically reveal both multiple nodules and/or masses, often involving both lungs, as well as linear reticulonodular infiltrates.[107,108] The nodules or masses have ill-defined borders; cavitation is infrequent and is usually found only in larger mass lesions. Multiple, bilateral pulmonary nodules can be detected along the bronchovascular structures and interlobular septa by CT and magnetic resonance imaging (MRI) scans.[109] These methods appear to be more sensitive in detecting central cavitation in smaller nodular lesions (Fig. 32.19A). CT and MRI scanning may also detect coarse linear abnormalities along bronchovascular bundles, involvement of larger bronchovascular structures in the hilum and mediastinum, and cystic lesions in the pulmonary parenchyma.[109] As would be expected from the pattern of LYG spread, mediastinal adenopathy is not commonly detected.

The gross features parallel the radiologic findings with multiple fish-flesh–like masses having varying amounts of central necrosis, which is usually more prominent in larger masses (Fig. 32.19B). The histologic features (summarized in Table 32.6 and reviewed by Jaffe and Wilson[8]) of lymphomatoid granulomatosis are distinctive (Fig. 32.20). Typically there are polymorphous nodular lymphohistiocytic infiltrates that, when small, are seen to center on or be adjacent to vascular structures (Fig. 32.20B). Less often diffuse infiltrates along vascular structures and within septa are present. Vascular infiltration by the lymphoid infiltrate with luminal narrowing is a

TABLE 32.6. Lymphomatoid granulomatosis: summary

Histologic findings	Immunohistochemical findings
Nodular infiltrates with central necrosis	Predominantly CD3-positive T cells, many of which show additional staining for cytotoxic granule proteins TIA-1 and granzyme B
Prominent vascular infiltration	Lesser population of CD20-positive B cells comprising the immunoblastic cells
Heterogeneous cell population	Appreciable numbers of CD68-positive histiocytes in some cases
Variable numbers of immunoblasts	EBV identified in B cells by immunohistochemistry or in-situ hybridization
Lack of sarcoid-like granulomas	
Lack of multinucleated giant cells	
Lack of significant numbers of neutrophils	
Lack of eosinophils	
Lack of lymphoepithelial lesions	
Lack of hyaline sclerosis	
Lack of amyloid production	
No or inconspicuous germinal centers	

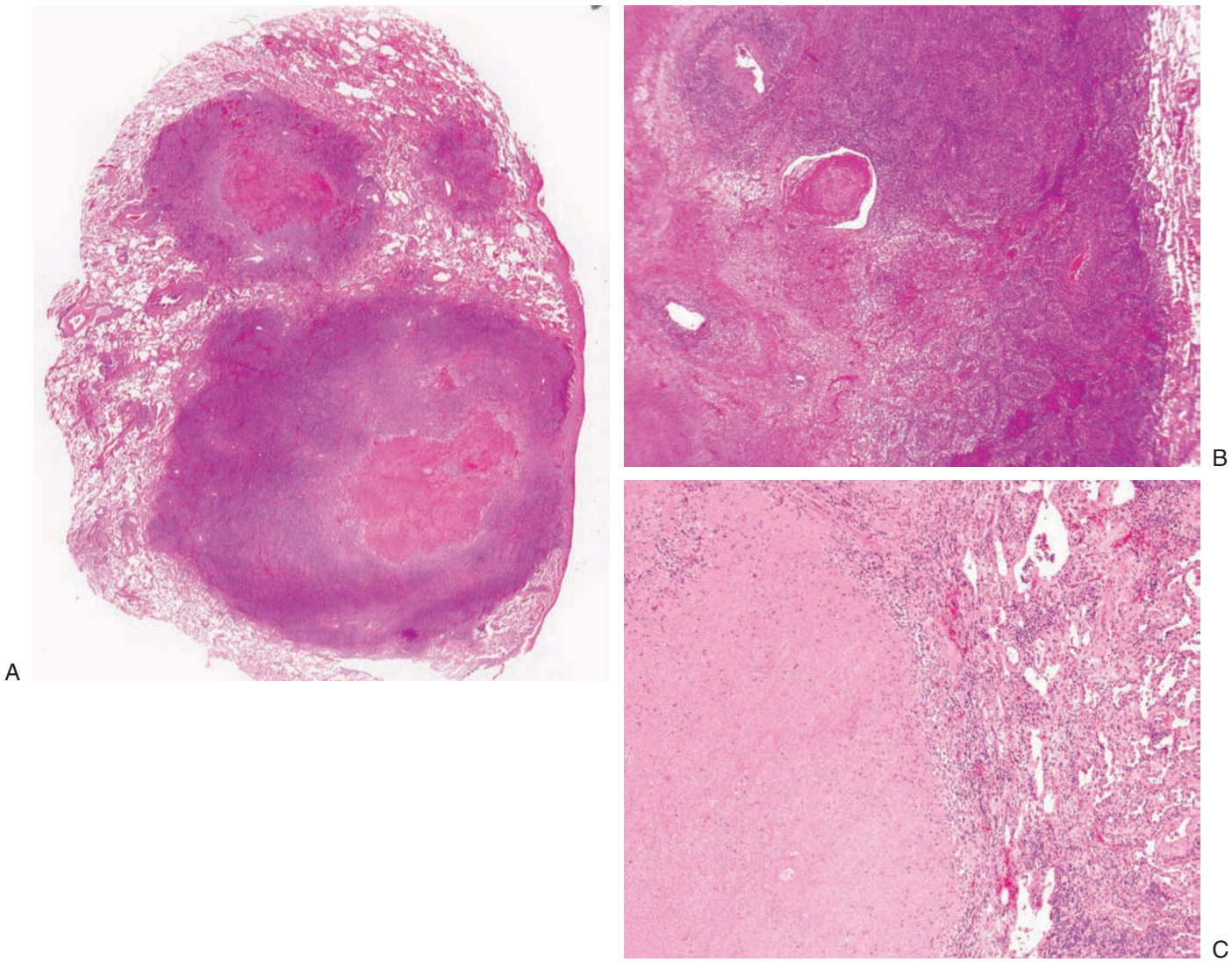


FIGURE 32.20. Lymphomatoid granulomatosis. **(A)** There are nodular infiltrates with central necrosis. The necrosis is "tumor like" and in the centers of the nodules rather than wedge-shaped as seen in infarcts. **(B)** There is a heterogeneous lymphoid infiltrate at the periphery of the necrotic nodules. Vascular infiltration may be present in the necrosis or in the viable regions (at the 11 o'clock position). **(C)** This case had some necrotic nodules in which no B cells were identified in the viable lymphoid infiltrate at the edge. Many of the necrotic cells (left) showed CD20 positive staining suggesting that the B cells had become necrotic.

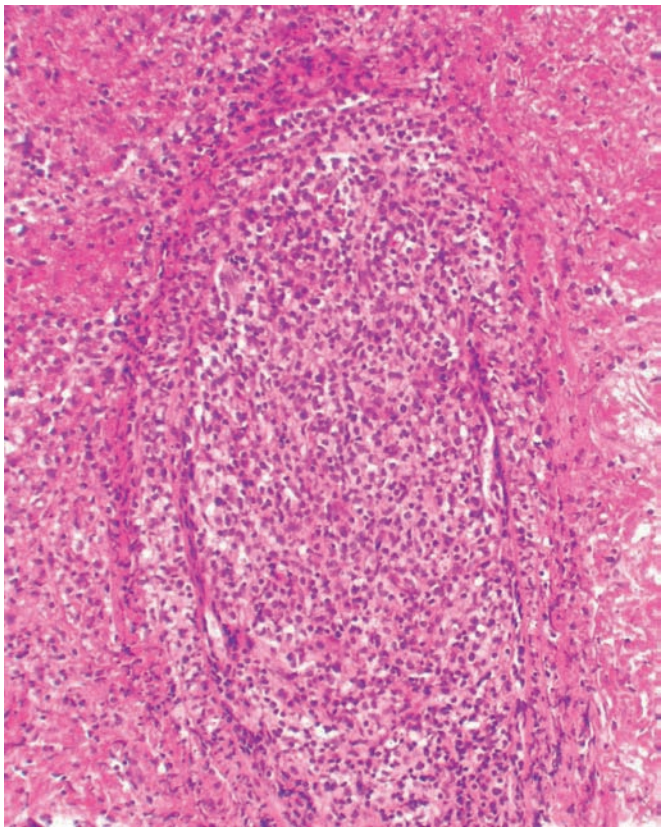


FIGURE 32.21. Lymphomatoid granulomatosis. There is vascular infiltration adjacent to the necrosis (top). Classic features of vasculitis including acute inflammatory necrosis of the vessel wall and fibrinoid change are not prominent.

quintessential feature (Fig. 32.21), but is not seen in all sites of involvement and may not involve all vessels. The vascular infiltration may be by cytologically benign cells, cytologically malignant cells, or a mixture of the two. The nodular lesions may vary in size, and as they enlarge there is a central fibrinous exudation into air spaces (Fig. 32.20A) and eventually central necrosis with a rim of viable tissue (Fig. 32.20B). Extremely large nodules can develop. These lymphohistiocytic infiltrates are composed of a mixture of lymphocytes, histiocytes that may form small epithelioid clusters, plasma cells, and rarely giant cells. Associated secondary changes in the air spaces including accumulation of pulmonary alveolar macrophages that may be foamy, and prominent type II cells are typical.

The lymphoid component of LYG is composed of a mixture of cells with small to intermediate-sized, angulated nuclei and variable numbers of cells with large vesicular nuclei and visible nucleoli (Fig. 32.22). The cytologic atypia in the large cells may be pronounced and in some instances they may resemble the Reed-Sternberg cells of Hodgkin's lymphoma. The number

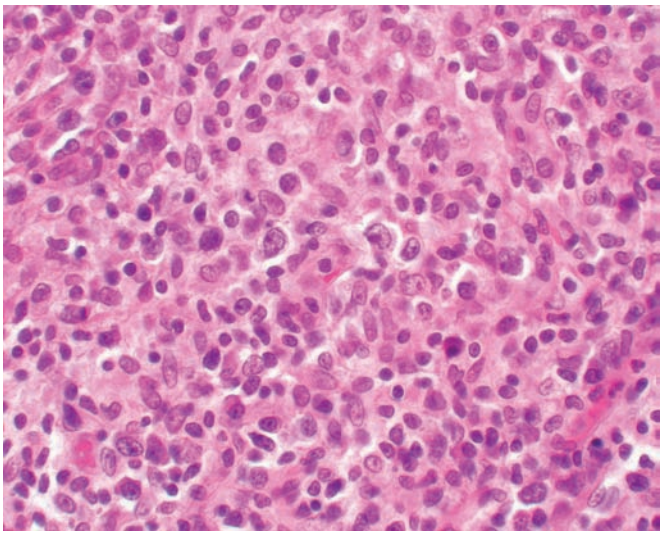


FIGURE 32.22. Lymphomatoid granulomatosis. This case shows a polymorphic cellular background including occasional immunoblasts and a mixed population of lymphocytes, plasma cells, and histiocytes.

of large atypical cells varies from field to field (Fig. 32.20C), and one should search out the most atypical field in order to classify a given case. Not uncommonly, biopsies that show several nodules may reveal monomorphous foci of atypical large cells in only one of the nodules (Fig. 32.23). The large cells are often most readily detected in larger nodules and bordering areas of coagulative necrosis.

In the vast majority of LYG cases ancillary immunoperoxidase and in-situ hybridization studies reveal

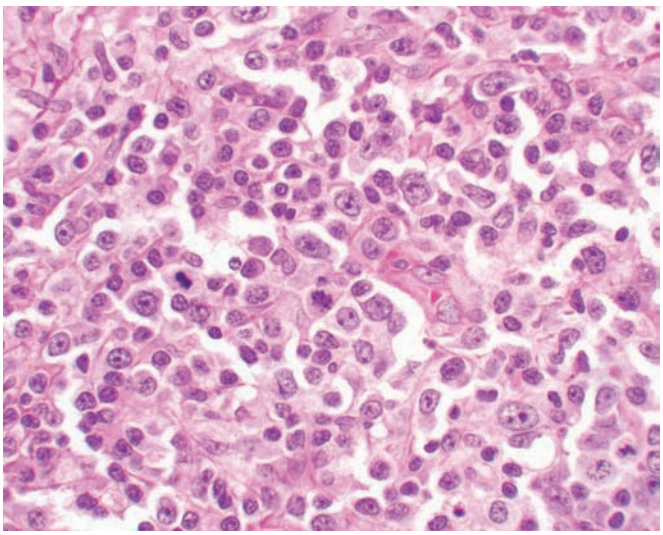


FIGURE 32.23. Lymphomatoid granulomatosis. This case shows larger numbers of immunoblasts with readily recognizable mitotic figures (center).

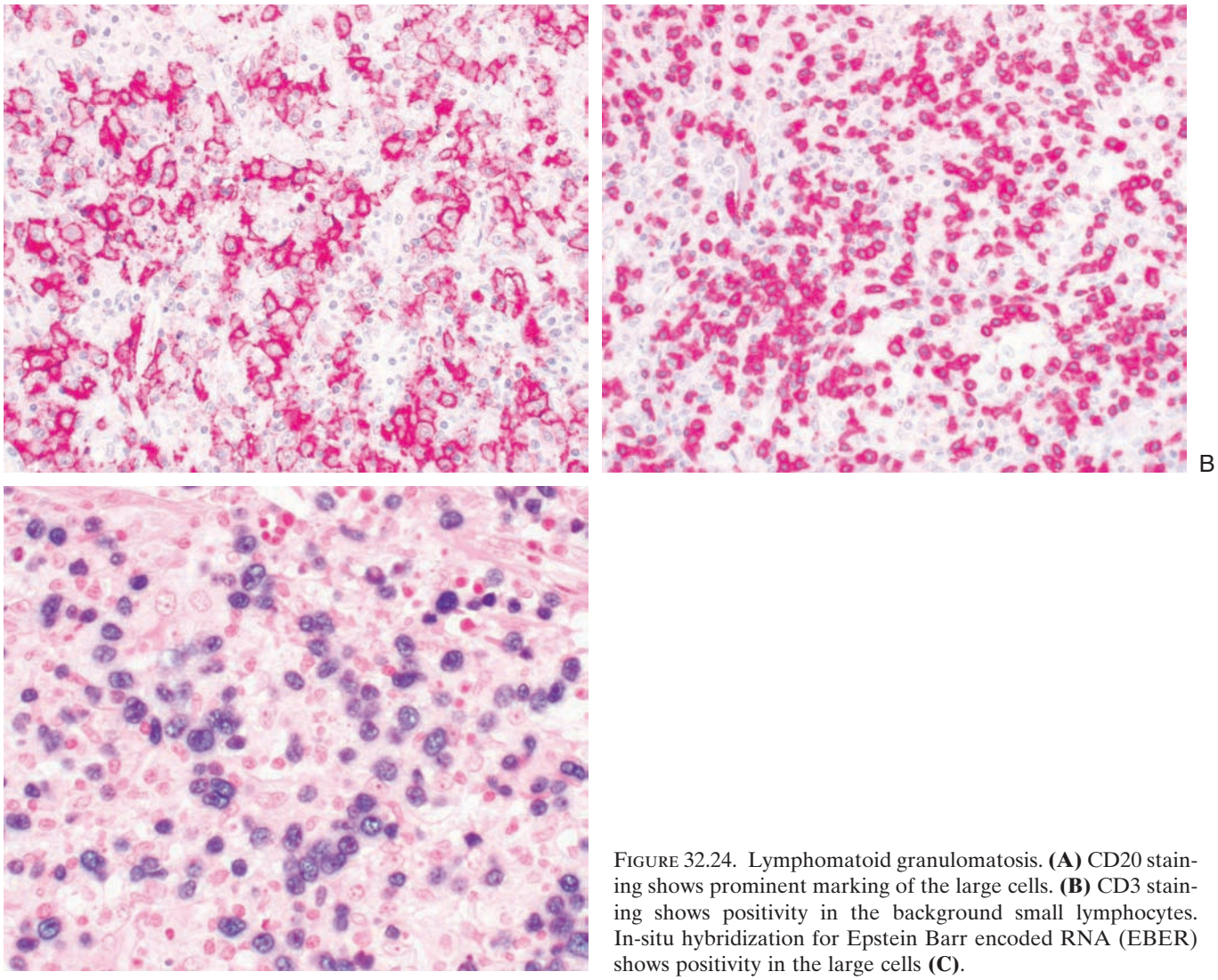


FIGURE 32.24. Lymphomatoid granulomatosis. **(A)** CD20 staining shows prominent marking of the large cells. **(B)** CD3 staining shows positivity in the background small lymphocytes. In-situ hybridization for Epstein Barr encoded RNA (EBER) shows positivity in the large cells **(C)**.

the large atypical lymphoid cells to be CD20–positive, EBV-positive B cells (Fig. 32.24A,B).[95,96] CD3–positive T-cells constitute most of the small lymphocytes (Fig. 32.24B). The results of early studies suggested that most of these T cells coexpressed CD4.[5] Subsequent analysis using a more extensive panel of immunohistochemical reagents revealed a high proportion of the small lymphocytes to express the cytotoxic granule protein TIA-1 with lesser numbers of cells positive for granzyme B, a cytotoxic granule protein expressed in T cells after cellular activation.[99] These findings are similar to those observed in large B-cell lymphomas with a prominent reactive T-cell component.[110] The results of the earlier studies suggesting a predominance of CD4 positive T cells may be attributable to detection of CD4 expression by the admixed histiocytes. Clonality can frequently be detected by EBV terminal repeat Southern blot analysis.[111] Clonal immunoglobulin gene rearrangements can often be detected by polymerase chain reaction (PCR) analysis, whereas these same studies performed using Southern blot methods are usually negative. This disparity is presumably due to the differing sensitivities of these methods.[8,112] Clonal T-cell receptor gene rearrangements are not typical in LYG, and if present, one must strongly consider the possibility of pulmonary involvement by a T-cell lineage lymphoproliferative disorder with overlapping histologic features such as extranodal NK/T-cell lymphoma of the nasal type.

When the term *angiocentric immunoproliferative lesion* was promulgated as a unifying category for what were thought to be related lymphoproliferative disorders, a three-tiered grading system was proposed.[5] In this system, the grade of the lesion increased with increasing numbers of large, cytologically atypical cells and with increased atypia in the background small lymphocytes. The complexity of this grading scheme was likely increased by the

inclusion of extranodal NK/T-cell lymphomas of nasal type. If one considers as LYG the WHO-accepted lesion, a two-grade system with low-grade and high-grade categories based on the number of large B cells has proved most practical. At the low-grade end, one has difficulty believing that a neoplastic lymphoproliferative process is present. Because perivascular infiltrates are common in many conditions, a key feature is the density and mass-like character of the process; expansile nodules, central necrosis, and vascular infiltration are less common in benign lesions. At the high-grade end of the spectrum, recognition of the lymphomatous process is easy. This grading system remains relevant as it has practical implications for the treatment of these disorders. Low-grade lesions may spontaneously resolve or may respond to immunomodulatory regimens with relatively minimal cytotoxicity such as interferon-α_{2b}.[106] In contrast, high-grade lesions should in most instances be clinically approached as diffuse large B-cell lymphomas.[8] Early series of lymphomatoid granulomatosis suggested a poor prognosis despite chemotherapy,[3,100] with less than half of the patients living 2 years. Later studies suggested a more favorable prognosis with aggressive chemotherapy for high-grade lesions, with more than 50% long-term remissions.[5]

Posttransplant Lymphoproliferative Disorders

Lymphoproliferative disorders that occur following organ transplantation are, by definition, considered posttransplant lymphoproliferative disorders (PTLDs). In the case of solid organ transplantation, the frequency of these disorders varies with the type of organ transplant and the type of immunosuppressive therapy employed.[113] Increased degrees of immunosuppression are thought to incur increased risk for the development of a PTLD, as these neoplasms likely arise due to decreased T-cell–mediated immune surveillance. The vast majority of PTLDs are EBV-associated B-cell lineage lymphoproliferative processes that may be either polyclonal or monoclonal in nature. Monoclonality in PTLD may be demonstrated either through documentation of B-cell immunoglobulin light chain restriction or EBV Southern blot analysis.[111,114] The monoclonal PTLDs are further subdivided histologically into polymorphous and monomorphous types with the polymorphous type containing a mixture of plasmacytoid cells, smaller lymphocytes, and large transformed lymphocytes, and the monomorphic types containing a histologically malignant cell population with features of large cell lymphoma, Burkitt lymphoma, or plasmacytoma.[9]

There have been relatively few extensive studies of PTLD in the setting of pulmonary transplantation.[115–118] The reported frequency of PTLD following pulmonary transplantation varies, although more recent studies indicate that it is an uncommon complication of this procedure, occurring in approximately 5% or less of cases. As in other solid organ transplants, increasing age at transplantation appears to be associated with an increased risk for the development of PTLD. A seronegative EBV status in the transplant recipient prior to the procedure may also be a risk factor for the subsequent development of a PTLD.

The latency period between transplantation and the occurrence of PTLD in pulmonary transplants is relatively short, with many cases occurring within the first year after the procedure. These early-onset PTLDs most often occur in the allografted organ. Other sites including the gastrointestinal (GI) tract and skin may be involved in addition to, or instead of, the engrafted lung, particularly in cases that arise after the first year posttransplant.[115,116] The proclivity of early-occurring PTLDs to arise in the allografted organ raises the possibility that they may actually be derived from donor, rather than recipient, lymphocytes.[119,120] However, some pulmonary PTLDs involving the allografted organ are of host origin.[121] Most patients are either asymptomatic or have nonspecific systemic complaints.

The PTLDs typically present radiologically as single or multiple nodules, usually in the transplanted lung. Although these lesions may be detected by routine chest radiography, features seen by CT scanning such as the presence of an invasive rather than a smooth-walled border may help distinguish these lesions from other nonneoplastic causes of pulmonary nodules in transplanted lungs such as invasive pulmonary aspergillosis.[122] Definitive characterization of these lesions, however, requires tissue sampling.[123]

Pathologic studies of pulmonary PTLD suggest that the vast majority are disorders of EBV-infected B cells (Fig. 32.25). The histologic subtype varies with both polymorphous (Fig. 32.26) and monomorphous (Fig. 32.27) types described. Epstein-Barr virus–associated lesions with histopathologic features of lymphomatoid granulomatosis may also be found in this setting.[124] In most of the monomorphous PTLDs arising after transplantation, the morphologic features are those of diffuse large B-cell lymphoma.[118] However, one monomorphous PTLD arising in the colon after pulmonary transplantation was composed of atypical plasma cells and therefore was considered a plasmacytoma-like lesion. In those cases of both polymorphous and monomorphous pulmonary PTLD in which there was sufficient material for molecular genetic studies, evidence of B-cell clonality was detected by PCR or Southern blot analysis of immunoglobulin gene rearrangements.[118]

The treatment approaches to PTLD vary and may include one or more of the following: reduction of immunosuppression, surgical resection, radiation, and

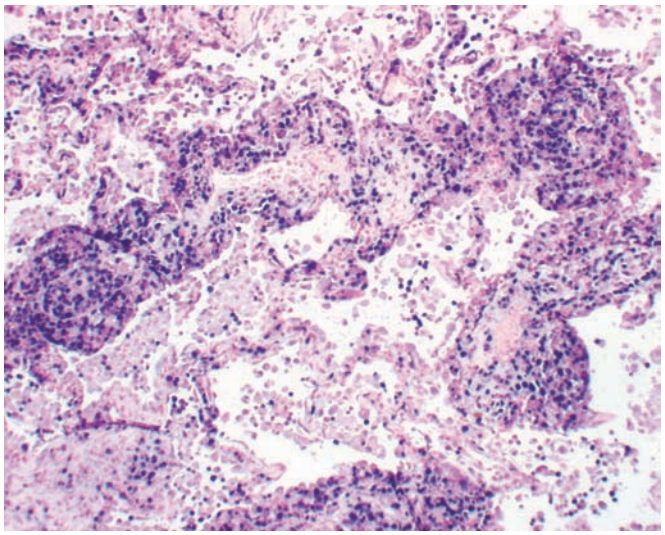


FIGURE 32.25. Primary pulmonary posttransplant lymphoproliferative disorder (PTLD). In-situ hybridization for EBER shows prominent positive staining of the lymphoid cells infiltrating a septum.

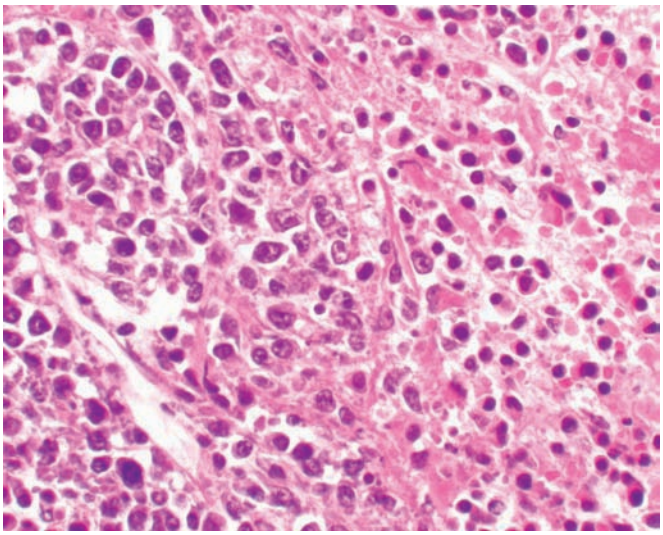
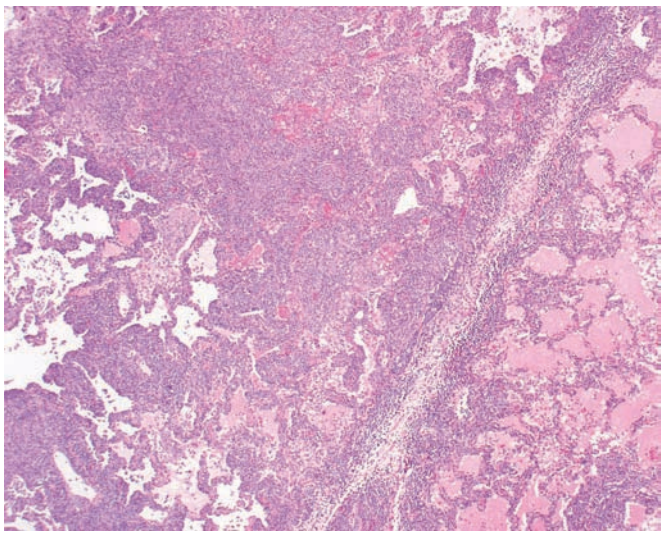


FIGURE 32.27. Primary pulmonary PTLD. This case shows features indistinguishable from large-cell lymphoma with viable lymphoid cells on the left and an area of necrosis on the right.

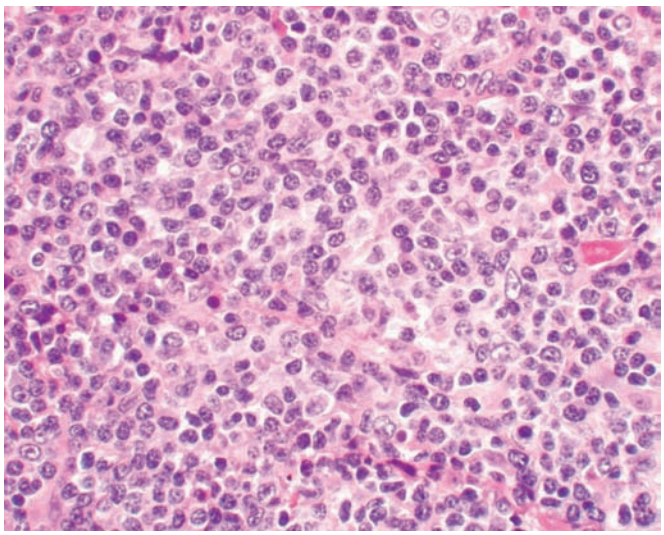
chemotherapy. In some cases even clonal PTLDs may regress with the lessening of immunosuppression; however, this may not be a practical approach due to the risk of allograft rejection. Some reports suggest a dire prognosis in pulmonary PTLD as compared to PTLD occurring in other settings, with a median survival time of less than 1 year.[118] Patients in whom PTLD arises in the first year after treatment tend to have disease confined to the allografted lung and may show a better response to treatment.[115,116] Also, some evidence suggests that anti-CD20 monoclonal antibody immunotherapy may be effective in treating B-cell lineage pulmonary PTLD.[117] (See also discussion in Chapter 23).

Lymphoproliferative Disorders in the Setting of Human Immunodeficiency Virus Infection and Acquired Immune Deficiency Syndrome

Acquired immunodeficiency due to HIV infection is associated with increased risk for the development of



A



B

FIGURE 32.26. Primary pulmonary PTLD. There is a dense lymphoid infiltrate that shows some predilection for lymphatic routes, particularly involving a septum **(A)**; cytologically there is a polymorphic process with lymphocytes, plasma cells, and occasional immunoblasts **(B)**.

lymphoproliferative disorders. As in lymphomas arising in the setting of iatrogenic immune suppression, decreased T-cell function is thought to play a central role in the development of these disorders. Inappropriately exuberant and prolonged immune responses may also play a role in the development of lymphomas in these patients.[125]

A variety of lymphoproliferative disorders have been described as arising with increased frequency in HIV-positive patients; overall about 5% to 10% develop malignant lymphoma at some point in the disease course. Approximately 5% of HIV patients with systemic lymphoma develop clinically evident pulmonary involvement. Some studies suggest, however, that the advent of more effective highly active antiretroviral therapies (HAARTs) may have increased the proportion of lymphoma cases among HIV-positive patients referred to pulmonologists for evaluation of respiratory complications.[126] The incidence of pulmonary involvement by systemic lymphoma in HIV appears to be higher in autopsy studies, with reported frequencies as high as 70%.[127] Human immunodeficiency virus–associated primary pulmonary lymphomas are rare, occurring in less than 1% of patients.[128] Both primary and secondary pulmonary lymphomas tend to occur in advanced-stage disease in patients with low CD4 counts.

Human immunodeficiency virus–positive patients with pulmonary involvement by lymphoma tend to have nonspecific systemic and respiratory signs and symptoms including fever, cough, dyspnea, and tachypnea.[127] A variety of radiologic patterns of lung involvement may be seen in cases of systemic lymphoma with pulmonary involvement, including consolidating lobar infiltrates, nodules, and masses.[129] Multiple pulmonary nodules, usually in the lower lobes, appear to be the most common radiologic pattern in primary pulmonary lymphoma.[130,131] Hilar or mediastinal adenopathy may be observed in lymphomas with secondary lung involvement, whereas these are, by definition, absent in primary pulmonary lymphomas. Pleural effusions also may be present more often in secondary, as opposed to primary, pulmonary lymphomas in HIV patients.

Despite the variety of Hodgkin's and non-Hodgkin's lymphomas that have been described in HIV-positive patients, the vast majority of primary and secondary pulmonary lymphomas appear to be EBV-associated B-cell lymphomas of large cell or high-grade Burkitt or Burkitt-like types.[128] Lymphomatoid granulomatosis has also been described in this setting.[132] Apart from the latter, these lymphomas can usually be readily recognized as malignant processes on histologic grounds, and limited sampling procedures such as transbronchial or transthoracic needle biopsies may be sufficient for establishing the diagnosis.[128] Both primary pulmonary lymphomas and widespread systemic lymphomas with pulmonary involvement in HIV-positive patients have a poor prognosis, with many patients surviving less than 1 year after the diagnosis despite multiagent chemotherapy.[125,127,128]

Primary Effusion Lymphoma

In addition to these patterns of parenchymal lung involvement by HIV-associated lymphoma a rare type of lymphoma with preferential involvement of the pleural, pericardial, and peritoneal spaces has also been described as occurring almost exclusively in this population. This disease has been termed *primary effusion lymphoma* or body cavity–based lymphoma, as this disease usually involves only one of the sites mentioned above and rarely forms tumefactive tissue masses. Primary effusion lymphoma is a rare disorder, even in HIV-positive patients.

As one may surmise from the name given to this lymphoma, most patients present with unexplained isolated pleural, pericardial, or peritoneal effusions. The pathologic features of primary effusion lymphoma are similar, regardless of the body cavity involved.

Cytologic evaluation reveals the presence of malignant-appearing cells with large nuclei and prominent nucleoli; anaplastic nuclear features may be present. These cells often have dense, vacuolated cytoplasm and a perinuclear clearing or hof. These cells may also be identified in pleural biopsies adherent to the pleural surface with associated fibrin deposition. Leukocyte common antigen (CD45) is invariably expressed; these cells often also express the activation-associated antigens CD30 and CD38 as well as the plasma cell–associated antigen CD138.[133,134] These cells usually lack B-cell– and T-cell–associated antigens, and therefore lineage assignment can be problematic. Molecular genetic studies, however, usually reveal clonally rearranged immunoglobulin genes that when analyzed in detail are found to have undergone the somatic hypermutation process that occurs while B cells are responding to antigen in the environment of the lymphoid follicle.[135] On this basis, as well as the expression of CD138, primary effusion lymphomas are generally regarded as B-cell lymphomas derived from postfollicular center B cells. In some instances, T-cell receptor gene rearrangement may also be seen.[134,136]

In all cases of primary effusion lymphoma the neoplastic cells are positive for the human herpes virus-8/Kaposi sarcoma herpes virus (HHV-8/KSHV).[137,138] In most cases the neoplastic cells are co-infected by and therefore positive for EBV.[134,136] HHV-8/KSHV is also associated with Kaposi's sarcoma and multicentric Castleman's disease, and quite often the former and rarely the latter may also be present.[139] Primary effusion lymphomas may also be found in HIV-negative patient populations in

whom other HHV-8–associated neoplasms have been described, including elderly Mediterranean men.[138] Primary effusion lymphomas arising in this setting tend to be EBV negative.[140]

The prognosis in primary effusion lymphoma is poor, with most patients dying within a year of the diagnosis, regardless of the therapeutic intervention employed.

As mentioned above, HIV infection is also associated with chronic B-cell stimulation. This may account for the prominent reactive pulmonary lymphoid proliferations associated with acquired immunodeficiency syndrome (AIDS); there is also evidence to suggest that the altered T-cell immune system may play a role in allowing these proliferations to occur.[141,142] Lymphocytic interstitial pneumonia (Fig. 32.5) may be encountered either as diffuse dense infiltration of alveolar septa by a mixed population of inflammatory cells or diffuse lymphoid hyperplasia. Lymphocytic interstitial pneumonia in AIDS is more common in children than in adults.[36,50] In isolated cases the B cells in these lesions have been proven to be clonal by immunoperoxidase staining and by molecular genetic analysis, and on this basis the lesions were categorized as MALT lymphomas. The few described cases of HIV-associated pulmonary MALT lymphoma have mostly been in pediatric patients,[143] although an instance of pulmonary MALT lymphoma with an associated *Aspergillus* fungal ball in an HIV-positive man has been described.[144]

It is important to note that some of the pulmonary lymphoid infiltrates encountered in AIDS patients are very difficult to classify into recognized disease categories. This likely reflects the varying cytology of EBV-associated lymphoproliferative diseases, as detailed in the section on PTLD. In some instances these cases may be categorized as HIV-associated polymorphic B-cell lymphoma (PTLD-like) by the WHO criteria, and in other cases it is best to consider the lesions unclassifiable and to reflect this in the diagnosis. One must always bear in mind that immunoblastic reactions, some of which may be EBV associated, can occur in the setting of HIV. Given this, and the poor prognosis associated with higher grade lymphomas in AIDS patients, it is critical that ancillary immunoperoxidase and molecular genetic studies be performed to confirm a diagnosis of lymphoma and exclude a florid reactive process in cases where there is any uncertainty regarding the histologic diagnosis. Kaposi's sarcoma of the lung is sometimes an associated lesion (see Chapter 40).

Lymphoproliferative Disorders Associated with Primary Immunodeficiency States

Numerous primary immunodeficiency syndromes caused by defects in humoral and cellular immune responses have been described.[145] In many of these disorders there are increased rates of pulmonary infection, and changes secondary to chronic infection such as bronchiectasis, may be found (see Chapter 5).[146,147] In addition, in some forms of primary immunodeficiency, especially ataxia telangiectasia and Wiskott-Aldrich syndrome, the affected individuals are at increased risk for the development of malignant lymphoma.[148,149] A variety of lymphoproliferative diseases have been described in these disorders including diffuse large B-cell lymphoma. Although the rarity of these immunodeficiency states precludes systematic study of large numbers of patients, the literature suggests that pulmonary involvement by lymphoproliferative diseases may be particularly associated with Wiskott-Aldrich syndrome (WAS),[104] which is an X-linked disease characterized by eczema, recurrent infections, and thrombocytopenia with small platelets, leading to complications secondary to a bleeding diathesis.[146] This disorder, which is due to abnormalities in the gene on the X-chromosome that encodes the Wiskott-Aldrich syndrome protein (WASP),[150] has been associated with the development of EBV-associated B-cell lymphomatoid granulomatosis-like lesions in the lung and skin.[104] Florid reactive lymphoproliferations/LIP may also be encountered in these patients as well as in patients with common variable immunodeficiency, an autosomal recessive disease of various underlying genetic abnormalities that leads to abnormalities in humoral immunity.[52] As most of these disorders become manifest early in life, in cases of HIV-negative pediatric patients with massive accumulations of small lymphocytes in the lung the possibility of primary immunodeficiency should be considered and clinically excluded. Furthermore, caution must be exercised in overinterpreting these lesions as MALT lymphomas in this setting, as in some cases of primary immunodeficiency states self-limited clonal B-cell expansions have been described, albeit in the gastrointestinal tract.[151]

Hodgkin's Lymphoma Presenting in the Lung

Hodgkin's lymphoma (formerly Hodgkin's disease) is broadly categorized into the classic type containing neoplastic Hodgkin cells and Reed-Sternberg cells and the lymphocyte predominant type containing lymphocytic and histiocytic (L&H) Reed-Sternberg cell variants. The vast majority of Hodgkin's lymphomas involving the lung are of classical type and therefore the discussion focuses on this entity.

Classic Hodgkin's lymphoma is characterized by the presence of large mononucleated Hodgkin cells and multinucleated Reed-Sternberg cells in a polymorphous background containing variable proportions of small lymphocytes, plasma cells, histiocytes, and eosinophils.[9] Hodgkin and Reed-Sternberg (HRS) cells lack most B-cell– and T-cell–associated antigens and rather express

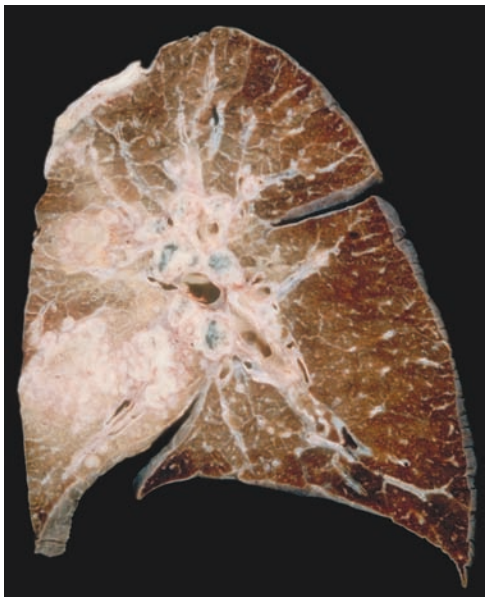


FIGURE 32.28. Pulmonary Hodgkin's lymphoma. There are nodular and linear infiltrates including some plaque-like involvement of the pleura. There is a predilection for lymphatic routes and the infiltrates extend along bronchovascular bundles from the hilum. Hilar lymph nodes are involved. This is from an autopsy in a patient who had initially presented with lymph node disease.

antigens not often expressed by lymphocytes such as CD15 and the activation-associated antigen CD30. For this reason the cellular origin of these cells was unclear. Detailed molecular genetic and immunophenotypic analyses have revealed that in most cases of classic Hodgkin's lymphoma (>95%) the HRS cells are derived from post-germinal center B cells, and in the remainder they are derived from T cells. Gene expression profiling data indicate that HRS cells are all closely related, however, regardless of their cellular origin. A unifying feature of HRS cells is their ability to "turn off" the expression of lineage-specific genes such as productively rearranged immunoglobulin genes in the B-cell type. The mechanism by which this occurs is unknown; however, in normal B cells this would be a lethal event inducing apoptosis (programmed cell death). The HRS cells, in contrast, do not undergo apoptosis in response to these abnormalities, possibly due to the expression of antiapoptotic proteins such as cFLIP and cIAP2 (reviewed by Diehl et al.[152]).

Systemic classic Hodgkin's lymphoma (not the lymphocyte predominance type) frequently involves the lung or pleura. This is especially with relapsed systemic disease where the lung is involved in approximately 40% of cases.[153] In contrast, primary pulmonary Hodgkin's lymphoma is considered rare, and some have disputed its existence. Nevertheless, case reports and small series of primary pulmonary Hodgkin's lymphoma have appeared for many years,[154–156] and 61 cases in the literature were reviewed.[157]

Primary pulmonary Hodgkin's lymphoma occurs more frequently in women (2:1), and patients are older than those with primary nodal disease; the average age is 33 years for men and 51 years for women.[91] The majority were symptomatic, and the symptoms were (in decreasing order of frequency) cough, fever, weight loss, dyspnea, fatigue, anorexia, chest pain, and pruritis.[156] Radiographically, reticulonodular infiltrates and single or multiple nodules are described.[155,156] Cavitation is not uncommon. These findings are similar to those in systemic Hodgkin's lymphoma with pulmonary involvement, where poorly marginated nodules and parenchymal infiltrates have been described.[158] Cavitation, however, is not often encountered in this setting. In Hodgkin's lymphoma, CT appears to be superior to standard radiology in both detecting and characterizing the pulmonary nodules.[158,159]

The gross findings parallel the radiologic findings (Fig. 32.28). The histologic findings of pulmonary Hodgkin's lymphoma are identical to those in lymph nodes (Figs. 32.29 to 32.32): diagnostic Reed–Sternberg cells with large multilobate nuclei with inclusion-like macronucleoli are present in the appropriate polymorphous cellular milieu composed of varying proportions of small lymphocytes, eosinophils, plasma cells, and histiocytes (Fig. 32.32B). It is worthwhile to bear in mind that many cases of primary (and secondary) pulmonary Hodgkin's lymphoma are the nodular sclerosis subtype, and therefore the majority of the Reed-Sternberg cells are lacunar variants, and the classic bilobed Reed-Sternberg cells may be few in number. The diagnosis of

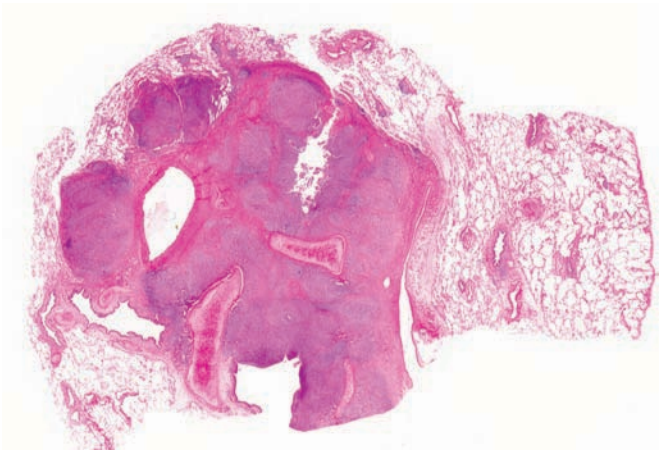


FIGURE 32.29. Primary pulmonary Hodgkin's lymphoma. In this case there is a nodular infiltrate involving a segmental bronchus. Even at scanning power magnification the nodular and sclerotic character of the process typical of the nodular sclerosing variant is apparent.

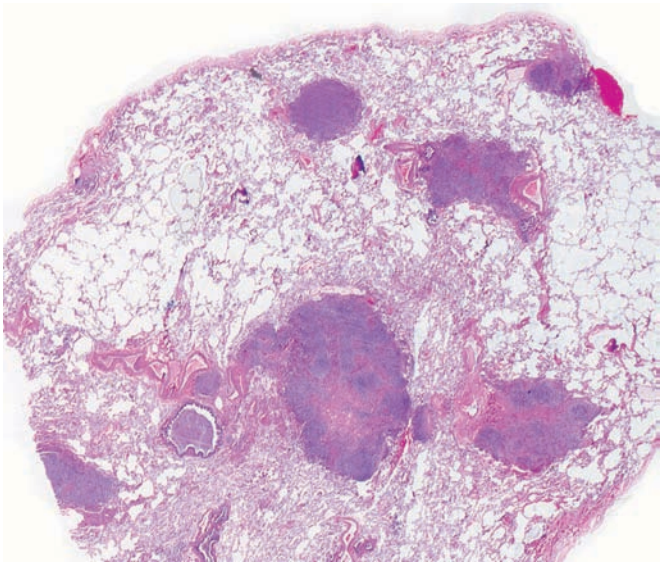


FIGURE 32.30. Primary pulmonary Hodgkin's lymphoma. This case presented as multiple small nodules, which, in most instances, can be traced to lymphatic routes in their distribution.

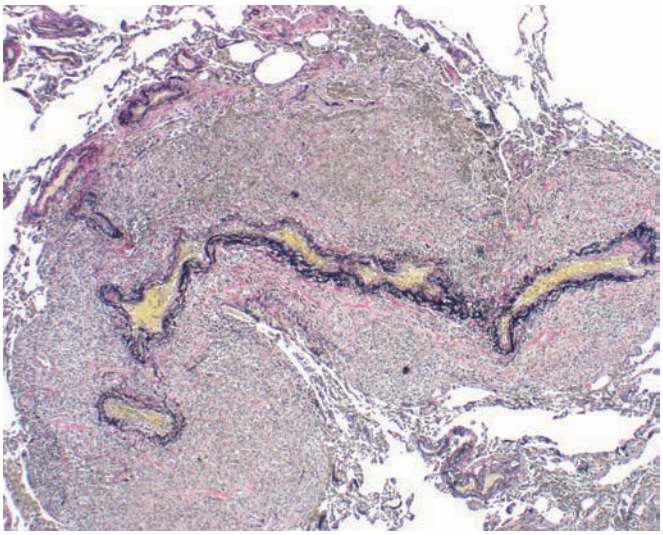
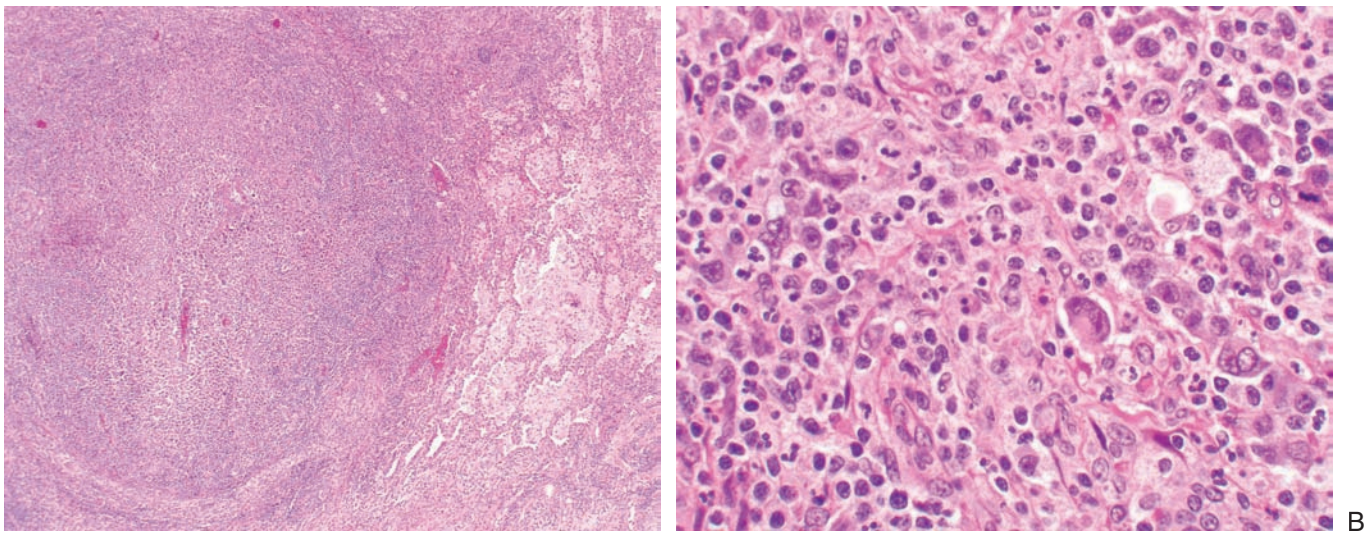


FIGURE 32.31. Pulmonary Hodgkin's lymphoma. This patient presented with lymph node disease and was found to have concurrent pulmonary infiltrates, which were confirmed to represent Hodgkin's lymphoma. The predilection for the process to infiltrate along and sometimes into vessels is apparent on elastic tissue staining.

Hodgkin's lymphoma is usually confirmed by demonstrating the appropriate immunophenotype (CD30 and CD15 positive, CD45 negative) in the Reed-Sternberg cells and variants. In small nodules and diffuse infiltrates, a lymphatic distribution of infiltration can be discerned; vascular infiltration occurs. Other patterns include a pneumonic growth pattern (in which the infiltrate fills alveoli in a consolidative fashion), endobronchial lesions, and extensive subpleural or pleural involvement.[155,156,160] Some cases may show a dramatic sarcoid-like granulomatous reaction.[161]

The patients in Yousem et al.'s[156] series were treated with conventional chemotherapeutic protocols for Hodgkin's disease. Approximately half showed a favorable



A B

FIGURE 32.32. Primary pulmonary Hodgkin's lymphoma. The cytologic features of primary pulmonary Hodgkin's lymphoma are identical to those in lymph nodes. There are nodular infiltrates in the lung parenchyma **(A)**, which show cytologic features identical to Hodgkin's lymphoma presenting in lymph nodes **(B)**. A Reed-Sternberg cell **(B)** is apparent at the 4 o'clock position.

response to combination chemotherapy with long-term remissions. Unfavorable prognosis was linked to B-symptoms, age greater than 60 years, and bilateral disease.

Anaplastic Large Cell Lymphoma Presenting in the Lung

Anaplastic large cell lymphoma (ALCL) is a lymphoproliferative disorder with both morphologic and immunophenotypic features that overlap with those of classic Hodgkin's lymphoma. This entity has been given various names over time, with early names revolving around "histiocytoid" cytology of the neoplastic cells and more recent ones reflecting the uniform strong expression of the activation-associated antigen CD30 by the malignant cells. For a time, B-cell, T-cell and "null"-cell types of CD30–positive ALCL were accepted. However, studies in the 1990s elucidated that a cytogenetic translocation involving the anaplastic large cell lymphoma tyrosine kinase *(ALK)* gene on the short arm of chromosome 2 and the nucleophosmin gene on chromosome 5 was present in a significant subset of the CD30–positive large cell lymphoma cases of T-cell or "null"-cell types (reviewed by Stein et al.[162] and Morris et al.[163]). This translocation, which is associated with a relatively favorable prognosis, was not found in large B-cell lymphomas with CD30 expression, and furthermore this latter group exhibited a behavior more akin to diffuse large B-cell lymphoma.[164] Therefore, in the most recent WHO classification, the T-cell and "null"-cell types of ALCL are recognized and the phrase *CD30-positive* has been dropped from the name.[9] Cases of CD30–positive large B-cell lymphoma are now merely considered large B-cell lymphoma with an activated immunophenotype. It is noteworthy, however, that rare cases of large B-cell lymphoma express the *ALK* gene product through a mechanism distinct from the 2;5 chromosomal translocation of ALCL.[165,166]

When ALCL is encountered in the lung, it is most often a manifestation of widespread systemic disease[167]; however, sporadic cases of primary pulmonary ALCL have been described. A series of five cases of primary pulmonary ALCL was reported by Rush and colleagues.[168] The patients had nonspecific systemic symptoms; four of the five cases presented with isolated pulmonary nodules, one of which formed an endobronchial mass and another of which was hilar with tracheal invasion and spread into the mainstem bronchi. Histologically, these cases were all characterized by destructive infiltrates, some of which spilled into alveolar spaces, composed of large neoplastic cells with variable degrees of nuclear polymorphism (Fig. 32.33). The neoplastic cells showed strong, uniform CD30–positivity, were negative for CD15, and showed variable positivity for CD45 (leucocyte common antigen [LCA]) quintessential immunophenotypic features of ALCL. Three of the cases expressed T-cell–associated antigens; the remainder had a null cell phenotype. None of the tested cases showed evidence of the 2;5 chromosomal translocation by reverse-transcriptase (RT)-PCR analysis.

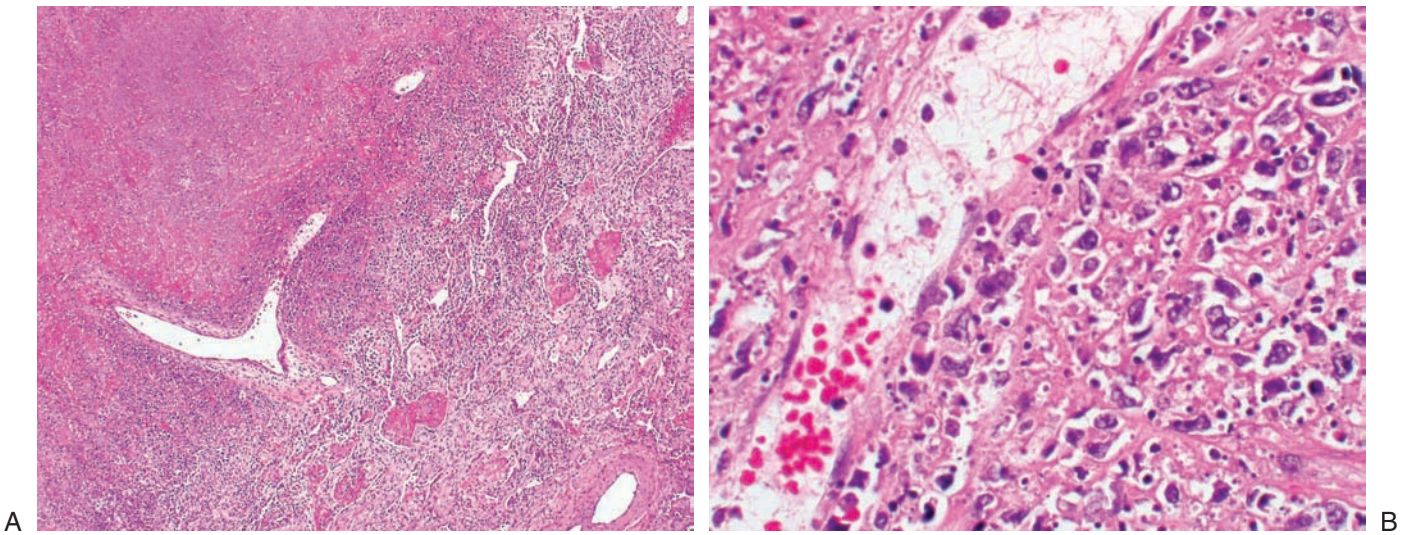


FIGURE 32.33. Primary pulmonary anaplastic large cell lymphoma. **(A)** This case presented as a single large nodule with necrosis and extensive vascular infiltration at the edge of the necrosis evident on low magnification (center left). **(B)** On higher magnification there are atypical large lymphoid cells with cytologic typical features of anaplastic large cell lymphoma. Immunophenotypically these were CD3-positive T cells, which also expressed CD30 and CD45 and were negative for CD20 and Epstein-Barr virus (EBV) (not shown).

A single case in the series of Rush et al. occurred in an HIV-positive individual. Interestingly, a review of the literature reveals other isolated instances of primary pulmonary ALCL arising in immunosuppressed patients, including one case as a PTLD following pulmonary transplantation[117] and two other cases arising in association with HIV.[128,167] This may be in keeping with the propensity for HIV-associated T-cell lymphomas to present with extranodal disease.[169] In a comparative analysis of CD30 positive and CD30 negative non-Hodgkin's lymphomas in HIV-positive patients, Nosari and colleagues[170] found a greater frequency of primary pulmonary involvement in CD30-positive cases. Lymphomas with anaplastic cytologic features occurring in AIDS patients tend to be associated with HHV-8 positivity.[171] It is difficult to glean outcome data from the literature given the rarity of primary pulmonary ALCL. However, cases occurring in immunocompromised individuals were universally associated with a poor outcome.

Other Lymphomas Presenting in the Lung

Pulmonary MALT lymphomas, lymphomatoid granulomatosis, and the other entities discussed above account for the vast majority of lymphomas that present in the lung. Once these disorders are excluded, what remains are a heterogeneous group that includes large cell B-cell lymphomas and other unclassifiable B-cell lymphomas. Follicular lymphomas, high-grade B-cell lymphomas, ALCL, and lymphoblastic lymphomas rarely involve the lung.

Most large descriptive series of pulmonary lymphoma cases predate the recognition of MALT lymphoma as a distinct entity, and therefore it is somewhat difficult to glean the distinctive clinical and radiologic features of non-MALT pulmonary B-cell lymphomas from the literature. Most patients affected by other non-Hodgkin's pulmonary lymphomas, as with MALT lymphoma, are adults, although there is a wide age range, and children may be affected, particularly in immunodeficiency states as discussed above. In contrast to MALT lymphomas, the majority have cough, shortness of breath, fever, and a variety of other systemic complaints. The radiologic and gross pathologic features vary; however, unlike with pulmonary MALT lymphomas, necrosis and cavitation are relatively common in this group. In some instances a single cavitary lung mass simulating tuberculosis may be seen. Either at presentation or during the course, patients may develop a variety of extrapulmonary lesions, including involvement of multiple other organ systems as well as paraneoplastic syndromes.

The presence of pulmonary lymphoma can be histologically obscured by a variety of factors. Like lymphomas presenting at other extranodal sites, lymphomas presenting in the lung may have an associated cytologically benign infiltrate. This infiltrate is usually at the periphery of the mass and can be remarkably extensive as compared to the foci recognizable as lymphoma.[172,173] An intraalveolar exudate and hyperplasia of type II pneumocytes is also common in the parenchyma adjacent to lymphomatous infiltrates. Reactive granulomatous inflammation and vasculitis, changes suggesting Wegener's granulomatosis, have also been described. Furthermore, extensively necrotic lesions often have a rim of viable cytologically benign cells, and one may need to search several blocks to find foci of recognizable lymphoma.

The majority of primary pulmonary lymphomas in this "wastebasket" category are large B-cell lymphomas. Histologically, these lymphomas are recognized by tumefactive lesions composed of sheets of lymphoid cells with large, atypical nuclei; however, the reactive changes described above may obfuscate the presence of lymphoma. Owing to the cytologic atypia of the neoplastic cells the differential diagnosis in the cases usually revolves around distinguishing it from other nonlymphoid malignancies such as carcinoma. The diagnosis of large B-cell lymphoma is usually confirmed by immunoperoxidase stains, which demonstrate the neoplastic cells to react with antibodies to B-cell–associated antigens such as CD20 and CD79a.

Intravascular large B-cell lymphoma is a unique subtype of large B-cell lymphoma in which the neoplastic cells are exclusively confined to the lumina of small vessels.[174–177] The neoplastic cells in this disease may remain in vascular structures due to the lack of expression of adhesion molecules required for tissue homing.[178] This unusual distribution of lymphomatous cells leads to protean clinical manifestations related to impaired blood flow such as mental status changes, nephrotic syndrome, and shortness of breath. Diffuse interstitial pulmonary infiltrates may be present on chest radiographs, and this, in combination with the presence of respiratory complaints, can lead to lung biopsy as an initial diagnostic procedure.[179,180] Histologically, this disease is characterized by the presence of large, cytologically atypical lymphoid cells within vessels, which, at low-power examination, may mimic an interstitial pneumonia (Fig. 32.34). Distinguishing these neoplastic lymphocytes from endothelial cells or intravascular infiltration by carcinoma cells on histologic grounds alone is difficult, a fact reflected by the previously used descriptive diagnosis of malignant angioendotheliomatosis. As a result, immunoperoxidase stains are instrumental in documenting that the neoplastic cells are B lymphocytes (Fig. 32.34C). Caution should be exercised, however, in rendering this diagnosis, as prominent intravascular infiltration can be seen in disseminated large B-cell lymphomas distinct from intravascular

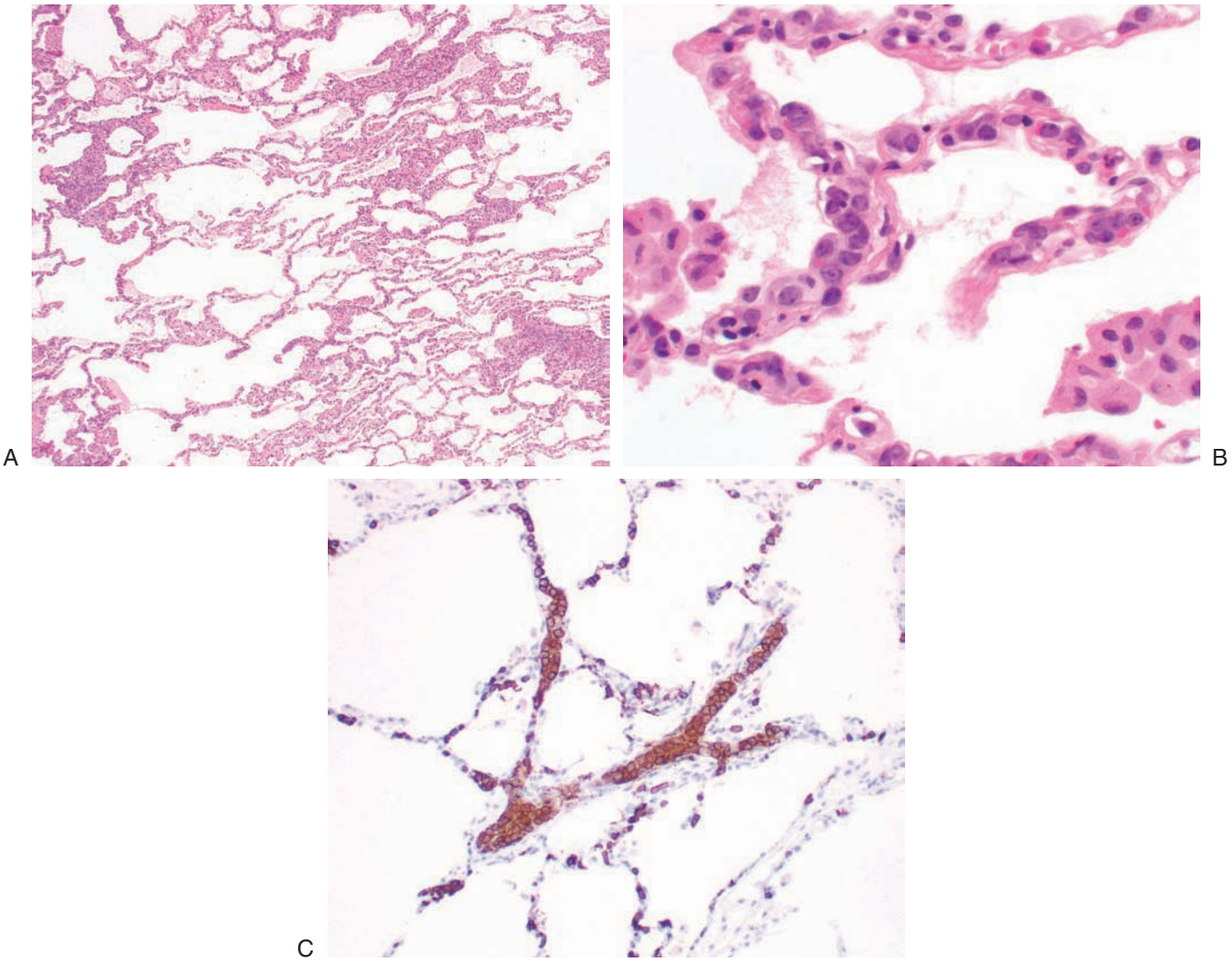


FIGURE 32.34. Intravascular lymphomatosis. Intermediate power microscopy shows some resemblance to an interstitial pneumonia **(A)**, but cytologic evaluation of the cellular areas shows atypical large lymphoid cells within capillaries in the alveolar wall **(B)**. These were confirmed as CD20-positive B cells **(C)**.

large B-cell lymphomas.[181] The latter diagnosis should only be rendered in cases in which the clinical features are typical, and clinical and radiologic examination fail to reveal evidence of lymph node, splenic, or other tissue involvement.

The remaining cases of lymphomas presenting in the lung not encompassed by the preceding discussion are few and poorly described. They are largely composed of B-cell lymphomas that cannot be further subclassified and a few T-cell lymphomas (Fig. 32.35). In cases that present as diffuse infiltrates along lymphatic routes without mass formation, the cellular heterogeneity may be so great that one is extremely reluctant to make a diagnosis of lymphoma. In such cases, cytologic atypia should be sought in infiltrates along pulmonary veins and in plaques of tumor in the pleura, because the peribronchial and peribronchiolar infiltrates tend to be the most polymorphous. The diagnosis of lymphoma should be confirmed by ancillary immunophenotyping and (when necessary) molecular genetic studies.

As with low-grade MALT lymphomas, a localized lymphoma in this group that is entirely resected may be cured.[59,182] However, the majority of patients have extensive bilateral disease, are clinically ill, and require aggressive chemotherapy that may result in either temporary or long-term remissions.[61,66,183]

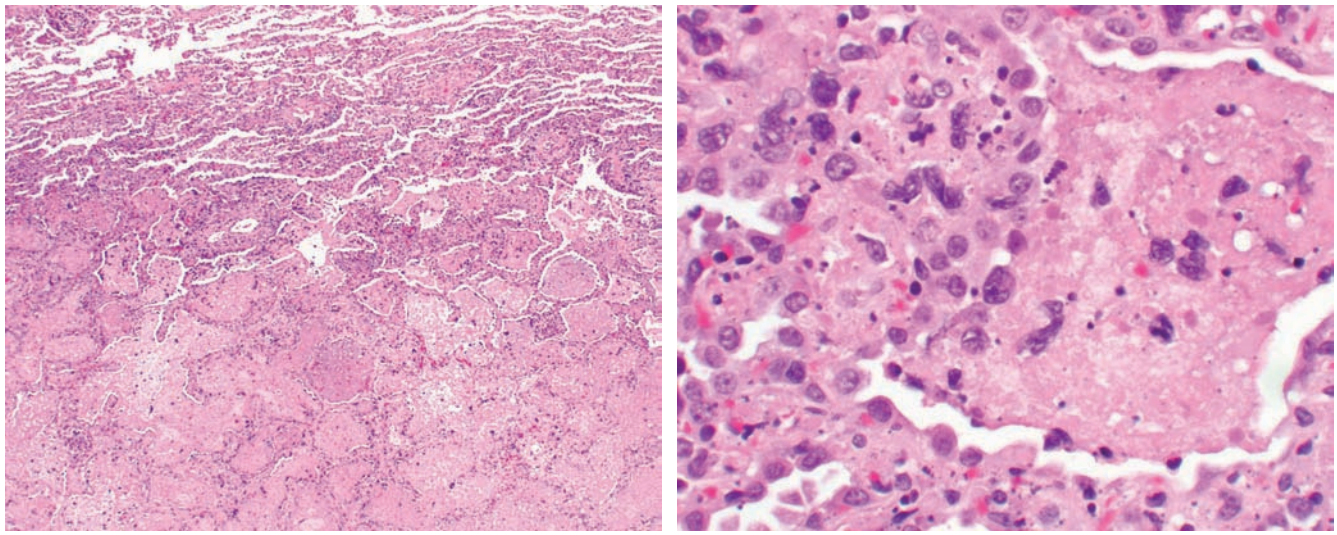


FIGURE 32.35. Primary pulmonary T-cell lymphoma. This case showed nodules with extensive necrosis **(A)** resembling lymphomatoid granulomatosis with obvious cytologic features of lymphoma **(B)**. Immunohistochemistry and molecular studies confirmed T-cell lineage. The EBV studies were negative.

Lymphomas with Secondary Lung Involvement

The lung and pleura are commonly involved by a number of systemic lymphoproliferative disorders, and a detailed description of all possible entities would include a litany of most known diseases in this category. Instead, we will focus on those entities in which pulmonary involvement is a common or distinctive feature. Many of the features of secondary lung involvement by malignant lymphomas such as Hodgkin's lymphoma have been discussed comparatively with their primary pulmonary counterpart above.

Mature B-Cell Lymphoproliferative Disorders

Histologically, secondary pulmonary lymphomas in the lung cannot be distinguished from those presenting in the lung.[53,66] The knowledge of prior lymphoma is therefore critical in making the proper diagnosis. This is particularly important when confronted with a low-grade B-cell lineage malignant lymphoma, as primary pulmonary MALT lymphoma bears histologic similarity to a number of systemic lymphomas that one may encounter on pulmonary biopsies, including B-cell small lymphocytic lymphoma, mantle cell lymphoma, and follicular lymphoma. Distinguishing primary pulmonary MALT lymphoma from these other diseases is important given the propensity of MALT lymphomas to involve other MALT sites. Also, some of these disorders, particularly mantle cell lymphoma, are typically more aggressive than MALT lymphoma.[184] As when evaluating any potential recurrence of a malignant neoplasm, comparison with the cytologic features of the initial lesion is of great utility. In malignant lymphomas this bears the additional importance of assessing for potential transformation of a low-grade neoplasm to a higher-grade process.

B-cell Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia

B-cell small lymphocytic lymphoma (Fig. 32.36) is histologically characterized by a tumefactive mass of small lymphocytes with scattered proliferation centers containing large prolymphocytes and paraimmunoblasts. Immunophenotypically B-cell small lymphocytic lymphoma is typified by aberrant coexpression of CD5 and CD23 by the neoplastic cells.[185] When proliferation centers are lacking, B-cell small lymphocytic lymphoma may resemble a MALT lymphoma. In these cases one may be forced to rely on the specific immunophenotype of B-cell small lymphocytic lymphoma, which may be detected in paraffin-embedded tissues, to establish the diagnosis.[68]

Mantle Cell Lymphoma

Mantle cell lymphoma has some similarities to B-cell small lymphocytic lymphoma in that it is typically a lymphoma composed of small B lymphocytes that aberrantly express CD5. In contrast to B-cell small lympho-