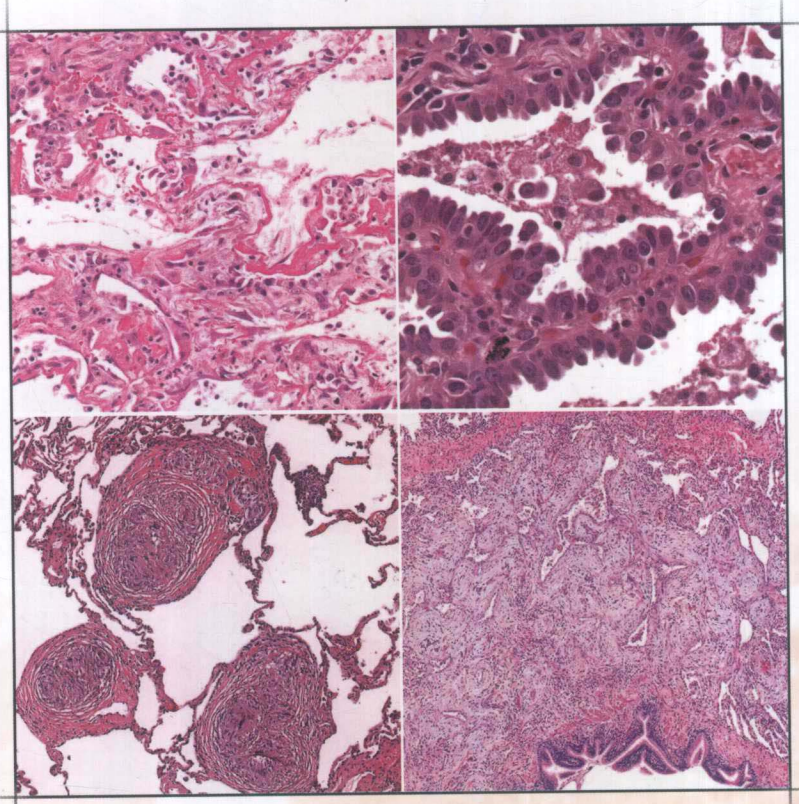
DIFFERENTIAL DIAGNOSES IN SURGICAL PATHOLOGY

Pulmonary Pathology

Rosane Duarte Achcar,
Steve D. Groshong, Carlyne D. Cool



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Differential Diagnoses in Surgical Pathology:
Pulmonary Pathology

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DEDICATION

This book is dedicated to my mother Eurydice, in loving memory, and to my father Nival, with heartfelt gratitude and deepest love for all their unconditional love, guidance, sacrifice, and support. I would also like to dedicate this work to my significant other Wesley, to my brothers Marcos and Marcelo, and to all close family members and wonderful friends in the United States and Brazil, whose love, support, encouragement, and infinite optimism over the years carried me through this and many other projects.

Rosane Duarte Achcar

This work is dedicated to the memory of my parents, Dale and Audrey.

Steve D. Groshong

To my husband, J. Scott Stewart, for his support and encouragement, to my children, Ian and Jacob, for their understanding, and to my coauthors for their friendship.

Carlyne D. Cool

PREFACE

Lung pathology is a highly specialized area of surgical pathology, which encompasses many unique diseases and is more than ever an essential part of clinical decision-making and patient management. Despite many advances, interpretation of lung pathology remains a significant source of diagnostic difficulty encountered by surgical pathologists every day. "Is this UIP or NSIP?" and "Is this malignant mesothelioma or reactive mesothelial hyperplasia?" are common dilemmas and questions faced on a daily basis. This book is intended to offer practicing pathologists, pathologists-in-training, residents and medical students a succinct and comprehensible reference with key clinical and microscopic findings of the most common to selected less frequently seen challenging disorders in neoplastic and non-neoplastic lung pathology. Our objective is to provide, through an appealing format of side by side tables and histopathology color images, a quick and user-friendly summary of information, which will assist in distinguishing challenging entities that have overlapping morphologic features in pulmonary pathology. The book is oriented primarily towards adult pulmonary pathology and a small array of references are supplied so that the reader can obtain more in depth material if desired. Writing a textbook is an immense undertaking and we sincerely hope that you will find this volume of *Differential Diagnosis In Surgical Pathology* enjoyable to read and a valuable consultative tool in the evaluation of pulmonary pathology specimens for study and for practice.

Rosane Duarte Achcar
Steve D. Groshong
Carlyne D. Cool

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I would like to express my deep gratitude to Dr. Jeff Kern for his friendship, mentorship, good advice, and constant good humor. I would like to extend my sincerest thanks and appreciation to Dr. Phillip Cagle for his generous review and constructive comments. Gratitude and appreciation is also extended to Dr. Yale Rosen and UPMC department of pathology for their illustrative material contribution from personal files and archival cases. Finally, I also would like to heartily thank my colleagues Dr. Carlyne D. Cool and Dr. Steve D. Groshong for their friendship, for sharing their expertise in pulmonary pathology on a daily basis in our practice, and for their hard work during the preparation of this book.

Rosane Duarte Achcar

Differential Diagnoses in Surgical Pathology:
Pulmonary Pathology

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1 ASTHMA VS. CELLULAR (CHRONIC) BRONCHIOLITIS

	Asthma	Cellular (Chronic) Bronchiolitis
Age	Any age. Extrinsic asthma (allergy to exogenous substances is recognized), usually begins in childhood. Intrinsic asthma (no exogenous factors can be identified) more often has its onset in adult life.	Any age. Age predilection depends on etiologic factors.
Location	Large and small airways.	Small airways including small bronchi, less than 2–3 mm in diameter, and membranous bronchioles (terminal and respiratory bronchioles). Terminal bronchioles are less than 1 mm in diameter and are just proximal to the respiratory bronchioles, the first airways that have alveoli budding from their walls.
Symptoms	Recurrent episodes of wheezing, coughing, chest tightness, and shortness of breath.	It varies depending on the causative agent. Dyspnea and usually nonproductive cough are common.
Signs	Increase in respiratory rate, end-expiratory wheezing, and peripheral blood eosinophilia. Spirometry shows reduced FEV1/FVC ratio that improves with bronchodilators.	High-resolution computed tomography (HRCT) scans may show centrilobular nodularity or tree-in-bud pattern.
Etiology	Genetic and environmental factors play a role. Extrinsic (atopic) asthma, the most common type, involves stimulation of Th2 responses by inhaled antigens, leading to type I immunoglobulin E-mediated hypersensitivity reactions. Symptoms may be triggered by exposure to allergens, respiratory tract infections, exercise, medications, gastroesophageal reflux, air pollution, cold, stress, and occupational exposure. Asthma can be associated with other diseases including allergic bronchopulmonary fungal disease, eosinophilic pneumonia, and Churg–Strauss syndrome.	Infection (e.g., virus and *Mycoplasma* infection); connective tissue disorders, especially rheumatoid arthritis and Sjögren syndrome; inherited or acquired immunodeficiency syndromes, extraintestinal manifestation of inflammatory bowel disease, graft-vs.-host disease, transplant-associated cellular bronchiolitis, lymphoproliferative diseases, or idiopathic. It may also occur secondary to large airways disease, particularly in small airways distal to markedly dilated large airways (bronchiectasis).
Histology	Luminal mucous plugs admixed with eosinophils, epithelial cells, and Charcot–Leyden crystals *(Fig. 1.1).* Airway with submucosal eosinophil-rich inflammatory cell infiltrate, goblet cell hyperplasia, subbasal lamina thickening due to collagen deposition, and submucosal smooth muscle prominence *(Figs. 1.2–1.4).*	Infiltration of the walls of small airways by chronic inflammatory cell infiltrate *(Figs. 1.5–1.7).*
Special studies	Gomori methenamine silver (GMS) special stain is used to exclude bronchial colonization by fungal organisms.	Tissue cultures and appropriate molecular testing are used to exclude infectious etiology.

	Asthma	Cellular (Chronic) Bronchiolitis
Prognosis	Symptoms usually improve or disappear as children become adults. Most patients respond to treatment with anti-inflammatory agents, bronchodilators, and avoidance of potential trigger factors, although some individuals will have persistent asthma even though exposure to causative agent has stopped. Complications include pneumonia, pneumothorax, pneumomediastinum, and respiratory distress, requiring intubation and mechanical ventilation.	It varies depending on the causative agent. May progress to constrictive bronchiolitis.

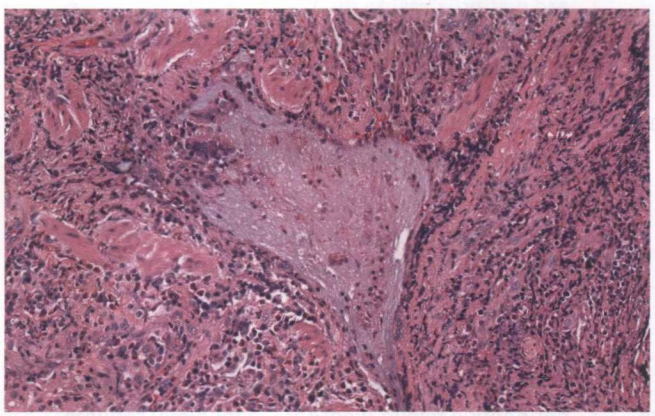


Figure 1.1 Asthma: Largely denuded bronchial wall showing luminal mucous plug admixed with eosinophils and Charcot–Leyden crystals. The airway is infiltrated by mixed eosinophil-rich inflammatory cell infiltrate.

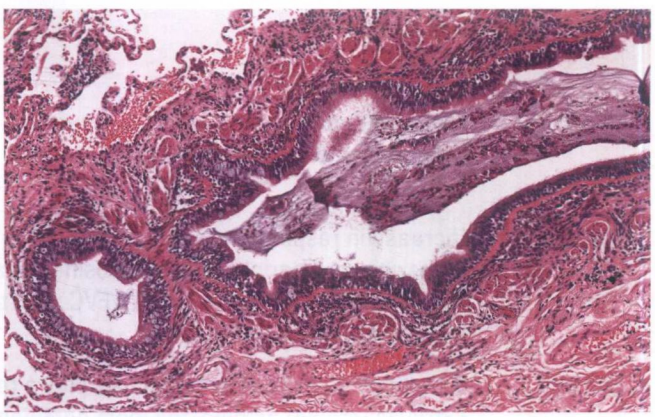
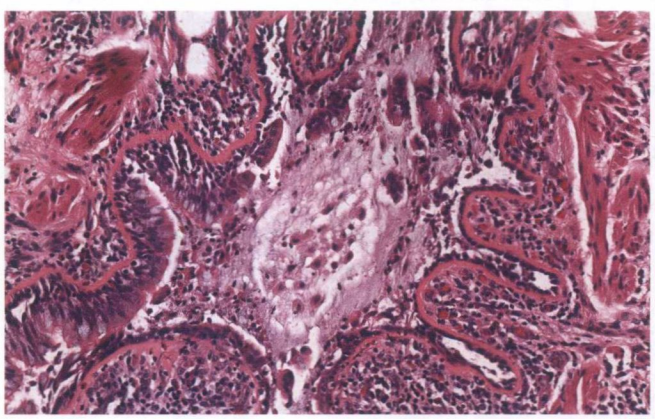


Figure 1.2 Asthma: The lumen is filled with eosinophil-rich mucous plug (*right*), the epithelium shows goblet cell hyperplasia, and the subbasal lamina is expanded.



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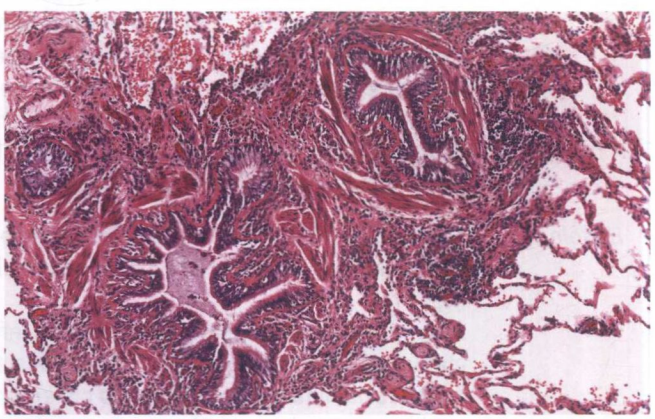

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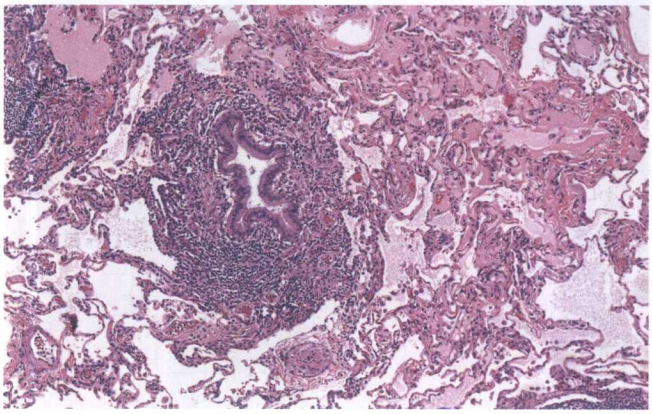


Figure 1.5 Cellular (chronic) bronchiolitis: Small airway wall with concentric infiltration by chronic inflammatory cell infiltrate.

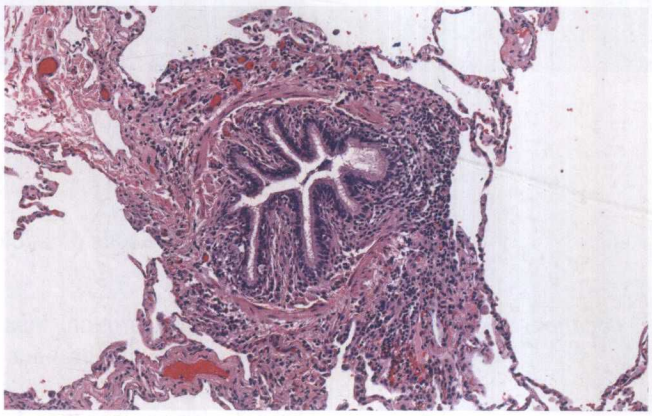
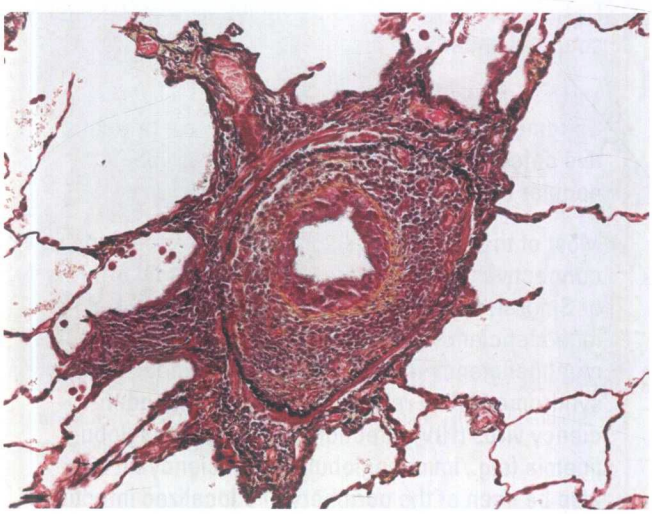


Figure 1.6 Cellular (chronic) bronchiolitis: Papillary epithelial hyperplasia and concentric bronchiolar wall infiltration by chronic inflammatory cell infiltrate.



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2 CELLULAR (CHRONIC) BRONCHIOLITIS VS. FOLLICULAR BRONCHIOLITIS

	Cellular (Chronic) Bronchiolitis	Follicular Bronchiolitis
Age	Any age. Age predilection depends on etiologic factors.	May occur in children and adults, but adults are affected most often (median age is 44 y).
Location	Small airways including small bronchi, less than 2–3 mm in diameter, and membranous bronchioles (terminal and respiratory bronchioles). Terminal bronchioles are less than 1 mm in diameter and are just proximal to the respiratory bronchioles, the first airways that have alveoli budding from their walls.	Small airways.
Symptoms	It varies depending on the causative agent. Dyspnea and usually nonproductive cough are common.	Dyspnea, cough, fever, and symptoms related to associated underlying diseases.
Signs	High-resolution computed tomography (HRCT) scans may show centrilobular nodularity or tree-in-bud pattern.	Spirometry may demonstrate obstructive or restrictive defects. HRCT shows bilateral centrilobular nodular or reticulonodular opacities.
Etiology	Infection (e.g., virus and *Mycoplasma* infection); connective tissue disorders, especially rheumatoid arthritis and Sjögren syndrome; inherited or acquired immunodeficiency syndromes, extraintestinal manifestation of inflammatory bowel disease, graft-vs.-host disease, transplant-associated cellular bronchiolitis, lymphoproliferative diseases, or idiopathic. It may also occur secondary to large airways disease, particularly in small airways distal to markedly dilated large airways (bronchiectasis).	Most of the cases are associated with an underlying connective tissue disease (e.g., rheumatoid arthritis or Sjögren syndrome); or congenital or acquired immunodeficiency states such as common variable immunodeficiency (CVID), acquired immunodeficiency syndrome (AIDS) related to human immunodeficiency virus (HIV) infection, or hypogammaglobulinemia (e.g., immunoglobulin A deficiency). It may also be seen at the periphery of a localized infectious process or be associated with some occupational exposure settings, such as in the case of nylon flock workers. Some cases are idiopathic.
Histology	Infiltration of the walls of small airways by chronic inflammatory cell infiltrate *(Fig. 2.1)*.	Numerous lymphoid follicles with well-formed germinal centers surrounding a bronchiolar wall *(Fig. 2.2)*. The hyperplastic lymphoid tissue may distort and narrow the bronchiolar lumen *(Fig. 2.3)*. The lymphoid infiltrate may extend into alveolar septa adjacent to the bronchiolar wall without significant extension into more distal lung parenchyma. The airspaces are uninvolved *(Figs. 2.4 and 2.5)*.
Special studies	Tissue cultures and appropriate molecular testing are used to exclude infectious etiology.	Special stains are usually not required. The lymphoid follicles should demonstrate a mixture of B (CD20 positive) and T (CD3 and CD5 positive) cell markers expression. The B cell–rich germinal center cells stain for CD20 and BCL6, while the interfollicular lymphoid cells stain for CD3 and CD5. The germinal center should be negative for BCL-2 and should be surrounded by immunoglobulin D and BCL2-positive mantle zones.
Prognosis	It varies depending on the causative agent. It may progress to constrictive bronchiolitis.	It varies depending on the underlying cause.

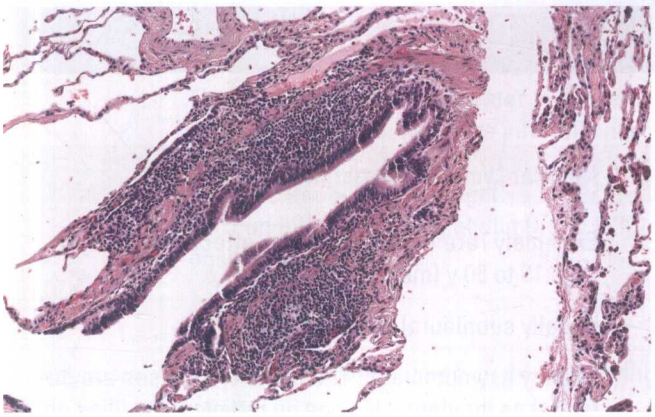


Figure 2.1 Cellular (chronic) bronchiolitis: Small airway wall showing concentric infiltration by chronic inflammatory cell infiltrate.

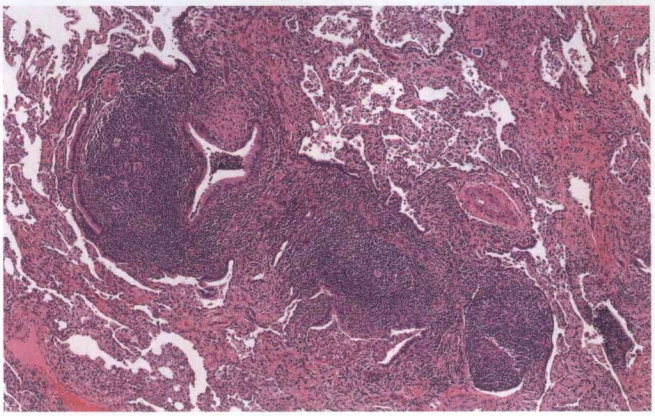


Figure 2.2 Follicular bronchiolitis: Lymphoid follicles with well-formed germinal centers surrounding and within a bronchiolar wall.

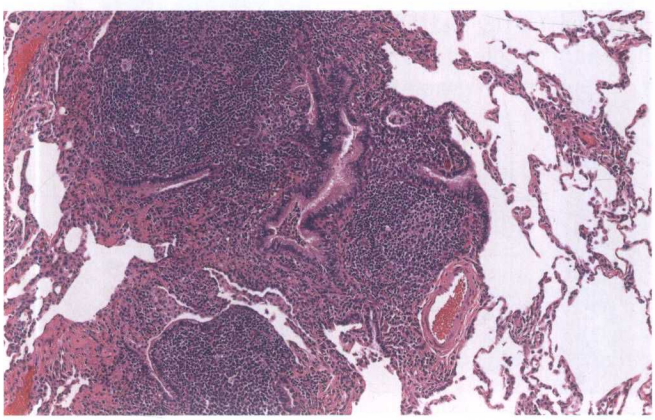


Figure 2.3 Follicular bronchiolitis: Hyperplastic lymphoid follicles compressing bronchiolar lumens.

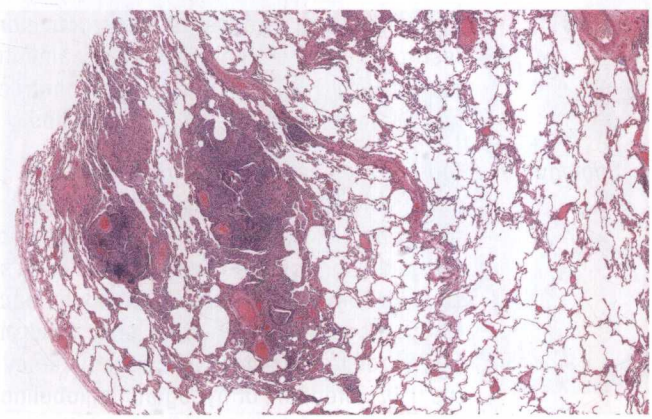


Figure 2.4 Follicular bronchiolitis: The lymphoid infiltrate (low power/2×) may extend into alveolar septa adjacent to the bronchiolar wall without significant extension into more distal lung parenchyma. The airspaces are uninvolved.

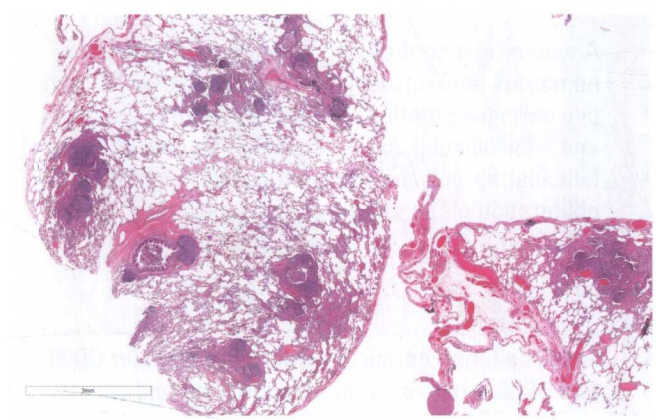
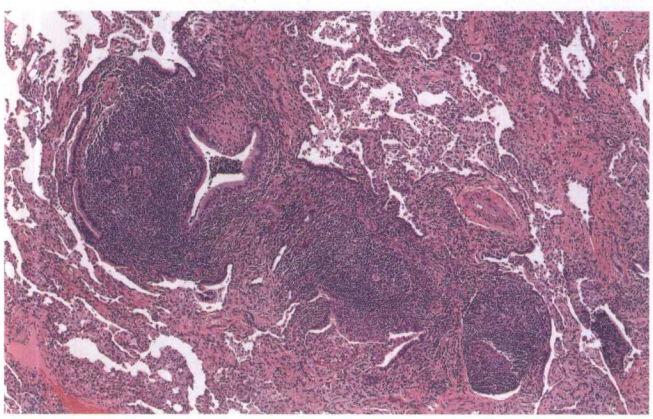


Figure 2.5 Follicular bronchiolitis: These peribronchial lymphoid infiltrates may be seen on HRCT as centrilobular nodules.

3 FOLLICULAR BRONCHIOLITIS VS. NODULAR LYMPHOID HYPERPLASIA

	Follicular Bronchiolitis	Nodular Lymphoid Hyperplasia
Age	May occur in children and adults, but adults are affected most often (median age is 44 y).	Extremely rare condition. It may affect people aged from 19 to 80 y (median, 65 y).
Location	Small airways.	Usually subpleural or peripheral.
Symptoms	Progressive dyspnea and cough occasionally associated with fever.	Usually asymptomatic. The majority of cases are detected as incidental lesions on radiologic studies obtained for other reasons. Symptoms, when present, may include shortness of breath, cough, and pleuritic chest pain.
Signs	Spirometry may demonstrate obstructive or restrictive defects. High-resolution computed tomography (HRCT) shows bilateral centrilobular nodular or reticular nodular opacities.	Chest x-ray and CT typically show a solitary pulmonary nodule or mass usually measuring between 0.5 and 6 cm in greatest dimension.
Etiology	Most of the cases are associated with an underlying connective tissue disease (e.g., rheumatoid arthritis or Sjögren syndrome) or congenital or acquired immunodeficiency state such as common variable immunodeficiency (CVID), acquired immunodeficiency syndrome (AIDS) related to human immunodeficiency virus (HIV) infection, or hypogammaglobulinemia (e.g., immunoglobulin A deficiency). It may also be seen at the periphery of a localized infectious process or be associated with some occupational exposure settings, such as in the case of nylon flock workers. Some cases are idiopathic.	Usually idiopathic.
Histology	Numerous lymphoid follicles with well-formed germinal centers surrounding a bronchiolar wall *(Fig. 3.1)*. The hyperplastic lymphoid tissue may distort and narrow the bronchiolar lumen *(Fig. 3.2)*. The lymphoid infiltrate may extend into alveolar septa adjacent to the bronchiolar wall without significant extension into more distal lung parenchyma. The airspaces are uninvolved *(Figs. 3.3 and 3.4)*.	A well-circumscribed nodule or mass composed of numerous back-to-back lymphoid follicles with reactive germinal center and preserved mantle zones and interfollicular zones. Variable amounts of interfollicular fibrosis may be present and may promote obliteration of the underlying lung parenchyma *(Figs. 3.5 and 3.6)*.
Special studies	Special stains are usually not required. The lymphoid follicles should demonstrate a mixture of B (CD20 positive) and T (CD3 and CD5 positive) cell markers expression.	The B cell–rich germinal center cells stain for CD20 and BCL6, while the interfollicular lymphoid cells stain for CD3, CD5, and CD43 (T-cell markers). The CD20-positive lymphocytes should not coexpress either CD5 or CD43. The germinal center should be negative for BCL2, and should be surrounded by immunoglobulin D and BCL2–positive mantle zones. CD21 should stain the network of follicular dendritic cells.

	Follicular Bronchiolitis	Nodular Lymphoid Hyperplasia
	The B cell–rich germinal center cells stain for CD20 and BCL6, while the interfollicular lymphoid cells stain for CD3 and CD5. The germinal center should be negative for BCL2, and surrounded by immunoglobulin D and BCL2-positive mantle zones.	A polyclonal pattern of kappa and lambda expression is present in the interfolicullar plasma cells, which should demonstrate bland cytologic features, not associated with Dutcher bodies. Pancytokeratin shows absence of destructive lymphoepithelial lesion. If immunohistochemical stains or flow cytometry studies are not conclusive, follow-up with molecular testing should be pursued to exclude B-cell clonality.
Prognosis	It is variable and depends on the underlying cause.	Benign lesion without risk of recurrence. Surgical excision is required for definite diagnosis.



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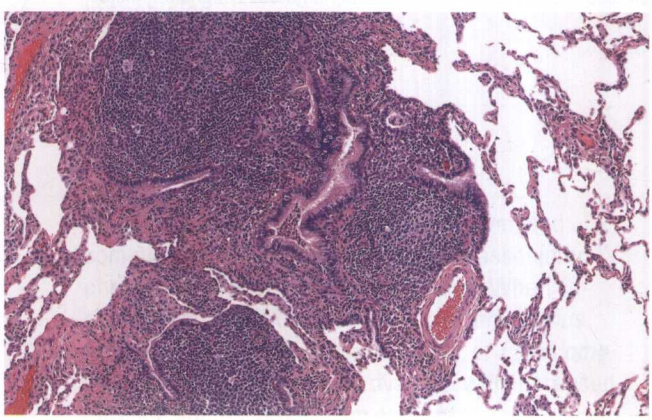

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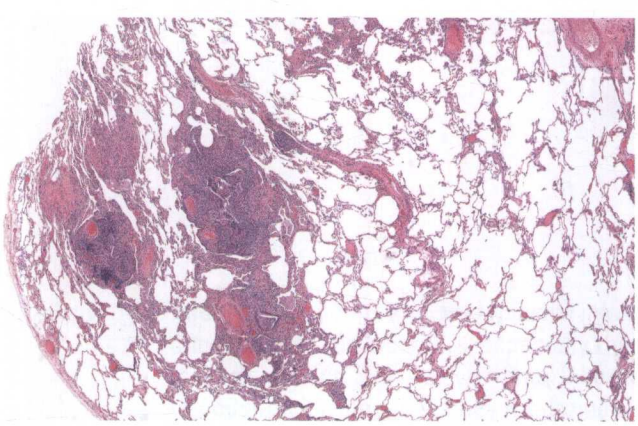

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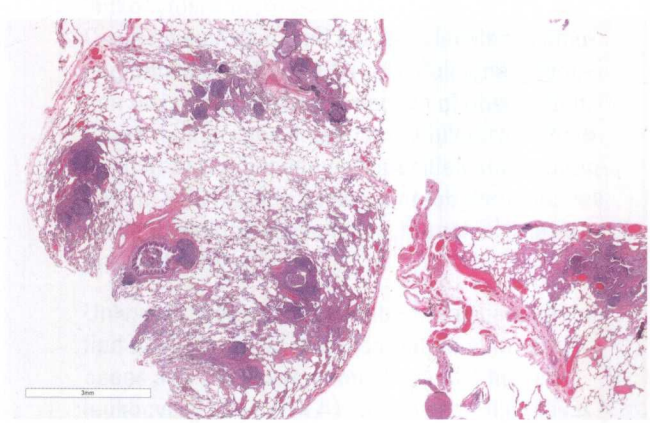

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