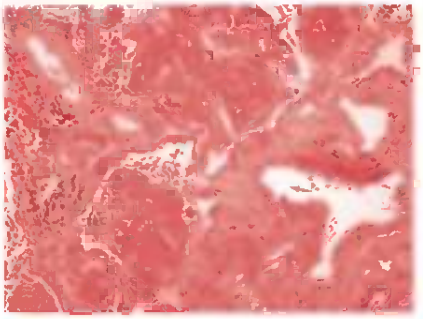
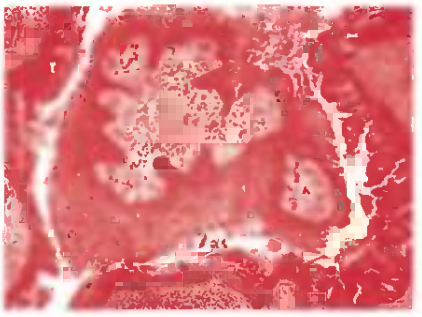
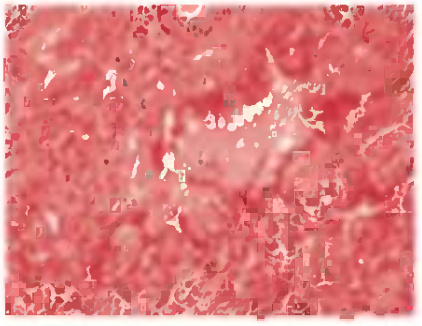
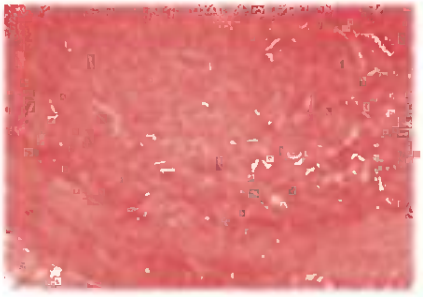
A Consultative Atlas









Lung Pathology

Current Clinical Pathology

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Lung Pathology

A Consultative Atlas

By

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PREFACE

Lung Pathology: A Consultative Atlas and its companion CD complement each other as a novel and substantive approach to teaching the complex elements of pulmonary pathology. They exhibit challenging yet exemplary cases of lung pathology to help the reader understand diagnostic elements of morphology and to work his or her way through tables of differential diagnoses. These cases have been drawn from a 20-yr file of more than 7000 referrals to Dr. Eugene Mark from pathologists throughout the world.

This volume introduces the reader to an updated approach developed by Dr. Mark in the interpretation of pulmonary pathology. Principles of this diagnostic approach are illustrated by many challenging cases of human lung pathology, each of which is illustrated in color on the companion CD.

The CD is a presentation of images and descriptive text in the presentation of 263 complicated referral cases of human lung pathology, including both medical and surgical lung disease. The histology of each case is illustrated by three to nine (usually five) color images captured to a personal computer by a state-of-the-art digital camera (Advanced SPOT, Diagnostic Instruments, Inc.), mounted on a Zeiss Axiophot microscope. These images are representative of the histology seen on the microscopic slides that were sent to Dr. Mark in consultation. The pathology captured by the images is described by the text from Dr. Mark's letters to the referring pathologists. The text includes the primary and/or differential diagnosis and pertinent histological features of each case, as well as clinical history, when available, and pertinent references to the literature, when relevant. Key words or phrases in the text are highlighted and digitally hyperlinked to associated images or regions of interest within those images to assist the readers in their correlation. The hypertext format is computer friendly and readily accessible to the reader.

The CD allows readers to differentiate subtle differences in histology when separating one disease entity from another. Examples of medical lung disease at different phases of progression will broaden the reader's understanding of the natural history of the disease. Furthermore, one's pattern recognition will be reinforced by histological similarities of various examples of lung disease. The HTML format of the CD facilitates the reader's ability to compare and contrast diagnostic features of pulmonary pathology as they relate to the compendium of cases incorporated within the CD.

It is anticipated that this format will appeal to general pathologists who are interested in lung pathology. The appeal of the consultative atlas will extend to academic institutions with staff pathologists who wish to broaden their expertise. Residents in anatomic pathology during routine training and during preparation for board examinations, as well as fellows in anatomic pathology who wish to gain expertise in difficult cases of lung pathology, will find this reference useful. The consultative atlas will also serve as a substantive reference to clinicians who treat patients with lung disease, such as pulmonologists and general thoracic surgeons.

The authors recognize that, as in many disciplines, changes in descriptive terminology and conceptual interpretation of pathologic entities and processes are an ongoing

dynamic. Because of the historic nature of the consultation letters, some of the current and recent changes in the way pathologists describe and interpret certain histopathologic patterns, such as BOOP, may seem to have been ignored. Some evolutionary changes in terminology have been addressed in the didactic text and index of the volume. In order to preserve the integrity, as well as the consistently rich descriptive thoroughness of the consultation letters, allusions to semantic changes in terminology were not interjected.

The authors gratefully acknowledge Ellen Melchionno and Rebecca L. Rockel for their technical assistance in the drafting of this manuscript.

Stuart Houser, *MD*
Ulysses J. Balis, *MD*
Eugene J. Mark, *MD*

Contents

GUIDE FOR USING THE *LUNG PATHOLOGY ATLAS ON CD-ROM*

I. Insert the *Lung Pathology Atlas on CD-ROM* into the CD drive. The Home Title should open automatically.

II. From the Home Title, one can click on one of four options:
   A. Table of Contents, from where one can click on
      1. (Text), to gain access to the Word format Table of Contents of the book, from where one can gain access to each chapter of text.
      2. Each chapter, gaining access to respective lists of cases, each of which, when clicked, is illustrated by images and consultative letters.
      3. On Section I: Introduction in Word format and then advance to the Table of Contents of the book in Word format.
      4. On Section II: Introduction and then advance to Chapters 9 and/or 10.
   B. Prologue, for orientation.
   C. Text, the first page of which is the title page, from which one can:
      1. Scroll through the entire manuscript of 10 chapters.
      2. Click on Table of Contents to selectively gain access to specific chapters of written text.
      3. Click on Prologue for orientation.
   D. Bibliography, which lists references of all chapters of the book.

III. Within each chapter, case numbers are highlighted, linking images to the manuscript, illustrating points of pathology in the text.

IV. At the end of each chapter (before the references), one can click on (Cases), gaining access to images of cases relating to the respective chapter, integrating didactic text with hyperlinked digital images.

V. After viewing an image, use your browser's "back" button to return to the current case page.

I Non-Neoplastic Lung Disease

INTRODUCTION

Non-neoplastic (medical) lung disease can be considered in two disparate arenas:

1. Acute lung disease, in which a frozen section may be requested and a diagnosis is expected by the clinician on the next day; and
2. Chronic lung disease, in which the final diagnosis can be contemplated and researched. This section will not reiterate the literature on the statistical frequencies of various types of medical lung disease; rather, it will provide a practical approach for the pathologist who sees fewer than one medical lung biopsy per day.

The following tables point out some basic tenets of terminology and then craft an outline of the big picture for medical lung disease.

A Specific Lung Disease

- Usual interstitial pneumonitis (UIP)
- Desquamative interstitial pneumonitis (DIP)
- Lymphocytic interstitial pneumonitis (LIP)
- Bronchiolitis obliterans (BO)
- Eosinophilic granuloma (EG)
- Diffuse alveolar damage (DAD)
- Pulmonary capillaritis

A Lung Disease or a Pattern

- Bronchiolitis with patchy organizing pneumonia (BPOP)
- Nonspecific interstitial pneumonitis (NSIP)
- Cellular interstitial pneumonitis
- Chronic eosinophilic pneumonia (CEP)
- Hemorrhage

A Lung Pattern

- DIP-like
- Lymphocytic interstitial infiltrate
- Granulomatous pneumonitis
- Diffuse interstitial fibrosis

A Clinical Evaluation, Not a Pathological Diagnosis

- Acute lung injury
- Rheumatoid lung disease
- Drug-induced lung disease
- Churg-Strauss syndrome

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
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A Common Observation

- Atypical pneumocytes
- Pigmented histiocytes
- Focal fibrosis

Medical Lung Disease: The Big Picture

- Acute
  - Floridly fibrotic (DAD, prognosis poor)
  - Fluid and cells (infection, hemorrhage, edema, fibrin, prognosis good)
- Chronic
  - Linear (interstitial, UIP, prognosis poor)
  - Nodular (bronchiolar and alveolar, BPOP, prognosis good)

General Guidelines in Diagnosis of Diffuse Lung Disease

- Have an idea of how ill the patient is
- Have an idea of the pace of the disease
- Appreciate problems in sampling (diffuse vs localized on X-ray)
- Use all tissue
- Do not overdiagnose (do no harm)

Pathological Findings in Open Lung Biopsy of Acute Respiratory Distress Syndrome

- DAD (90%)
- Hemorrhage (capillaritis)
- Infectious pneumonia
- Acute fibrinous pneumonia
- Acute eosinophilic pneumonia
- Edema (interstitial or alveolar)
- Emboli (blood clot, fat, talc, tumor)
- Bronchioloalveolar carcinoma
- Intra-alveolar fibrosis
- Acute transplant rejection

Lung Biopsy for Acute Disease or in the Immunosuppressed Patient: Technical Considerations

- Culture and smears
- Frozen section (DAD vs infection)
- Stains for organisms ordered at onset
- Direct immunofluorescence for unexplained hemorrhage
- Electron microscopy rarely crucial

Lung Biopsy for Chronic Disease: Technical Considerations

- Frozen tissue for immunopathology (collagen vascular disease, lymphoid proliferation)
- Fix quickly in one piece before lung deflates, then section
- Stains for elastic tissue and collagen ordered at outset
- Polarization microscopy
- Electron microscopy never crucial

Final Clinical and Pathological Correlation

- Acute or chronic
- Diffuse or localized
- Mild or life threatening

BIOPSY TYPES AND ARTIFACTS

The first step in evaluating a lung biopsy for medical lung disease is to determine the adequacy of the specimen. One way to accomplish this is to record the number of alveoli on a transbronchial biopsy or the number of lobules on an open biopsy. A bronchoscopic biopsy should have a minimum of 20 alveoli and optimally 100 alveoli. The interstitium is that space lying between epithelial basement membrane and vascular basement membrane. There is a continuity of the interstitium around bronchovascular bundles, alveolar walls, interlobular septa, and pleura. Interstitial pneumonitides generally have the least specific histological findings of the various categories of lung disease, and consequently they are the most difficult to diagnose on a transbronchial biopsy. A needle or bronchoscopic biopsy may be followed by open biopsy if a specific diagnosis is necessary. However, a specific diagnosis is not always necessary. It may be sufficient, for instance, to exclude sarcoidosis on a transbronchial biopsy and assume the diagnosis of usual interstitial pneumonitis with a nonspecific diagnosis of interstitial fibrosis histologically.

An open biopsy should have a minimum of three lobules, which means at least 2 cm in length and 1 cm in depth. A long but superficial biopsy, which samples only a few millimeters of subpleural lung, is unsatisfactory. Video-assisted thoracoscopy now supplants thoracotomy in most patients who require open lung biopsies. Thoracoscopic biopsies are intermediate in size between those obtained by a transbronchial technique and by an open thoracotomy. They are usually multiple (commonly three specimens), the larger number compensating for the smaller size of these specimens. About one half of each thoracoscopic biopsy will be compressed. Furthermore, these biopsies sample only the immediate subpleural zone and emphasize processes that can be seen rather than felt.

Artifacts lead to the overdiagnosis of a disease state and never contribute to a diagnosis of normal, which is psychologically the most difficult diagnosis to make. Most artifacts are produced either by irregular sampling or by the handling and squeezing of tissue during the surgical procedure. Each biopsy technique has artifacts peculiar to it. Diagnosis of interstitial lung disease is most prone to artifact, alveolar filling disease less so, and infectious disease and neoplasia least so.

Artifacts of Open Lung Biopsy

- Sampling of hard nodule
- Tip of lobe
- Left to deflate
- Crushed by clamp
- Operative hemorrhage
- Too small specimen

Diagnostic Considerations of Seemingly Normal Lung Biopsy

- Sampling problem—90%
- Respiratory bronchiolitis
- Constrictive bronchiolitis
- Cellular interstitial pneumonitis
- Interstitial edema
- Diffuse alveolar septal amyloid
- Pulmonary hypertension
- Fat emboli
- Veno-occlusive disease
- Cystic lymphangiectasis
- Capillary hemangiomatosis

1 Airway Disease

CONTENTS

INTRODUCTION

Inflammatory disease of small airways can present multiple histopathological patterns based on varying etiologies and clinical factors. Some of these entities are listed in the following table.

Bronchiolitis: Various Clinicopathological Entities

- Constrictive bronchiolitis
- Microgranulomatous bronchiolitis
- Respiratory bronchiolitis (RB)
- Bronchiolitis obliterans (BO)
- Follicular bronchiolitis
- Diffuse panbronchiolitis
- Bronchiolitis with patchy organizing pneumonia (BPOP)
- Bronchiolitis with interstitial pneumonitis (BIP)

CONSTRICTIVE BRONCHIOLITIS

Constrictive bronchiolitis **(6765)** consists of dense, chronic mucosal inflammation and a collar of collagen around respiratory bronchioles, resulting in a reduction of lumen size. A minute amount of scar may be seen, and areas of lung distal to this process may become hyperlucent or cystic. The etiology of constrictive bronchiolitis may be a postviral reaction, graft vs host disease, or unknown.

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MICROGRANULOMATOUS BRONCHIOLITIS

Microgranulomatous bronchiolitis **(6796)** may be comprised of focal bronchiolar and alveolar inflammation, consisting of lymphohistiocytic aggregates with few or no sarcoidal granulomas. Little scarring is present. This process is characteristic of an organic dust reaction.

RESPIRATORY BRONCHIOLITIS

In RB **(6566)**, pigmented histiocytes are seen filling bronchioles with little, if any, associated interstitial fibrosis. This disease is one of cigarette smokers. It might be considered to represent a mild form of desquamative interstitial pneumonitis (DIP).

BRONCHIOLITIS OBLITERANS

BO **(6764)** refers to pure intrabronchiolar inflammation and fibrosis without involvement of contiguous alveoli. There is mucosal necrosis with neutrophils and fibrin. Pure forms of BO are generally infectious and occur in children. These cases are rarely biopsied because the infectious nature is suspected clinically.

Bronchiectasis results in peribronchiolar scarring which destroys the exiting smaller bronchi and bronchioles. Linear scars resulting from this airway obliteration may produce a coarse form of interstitial fibrosis limited to some regions of a lobe or lobes. The clinical diagnosis of bronchiectasis is easy to overlook, and the disease has become rare in the United States; so the pathologist cannot rely upon the clinician to mention it in his differential diagnosis.

FOLLICULAR BRONCHIOLITIS

Follicular bronchiolitis **(6816)** indicates principally hyperplasia of the bronchus-associated lymphoid system, typified by lymphoid follicles around bronchioles.

The lymphoid hyperplasia may spill out into alveolar walls, resulting in lymphocytic interstitial pneumonitis. Scarring and luminal ectasia may or may not be present. Peribronchiolar lymphoid hyperplasia without scarring should raise the possibility of infection with Epstein-Barr virus or human immunodeficiency virus. It can present as a sequel to childhood pneumonia with scarring. It can also occur in rheumatoid lung disease.

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis **(7008)** is a Japanese disease with bad prognosis. Respiratory bronchioles contain intramural inflammation with vacuolated histiocytes.

Luminal stenosis results with distal hyperinflation. A chest X-ray may be normal in an individual with this disease.

BRONCHIOLITIS WITH PATCHY ORGANIZING PNEUMONIA

This entity is discussed Chapter 2.

BRONCHIOLITIS WITH INTERSTITIAL PNEUMONITIS

This entity is discussed Chapter 3.

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LETTERS

Case 6765

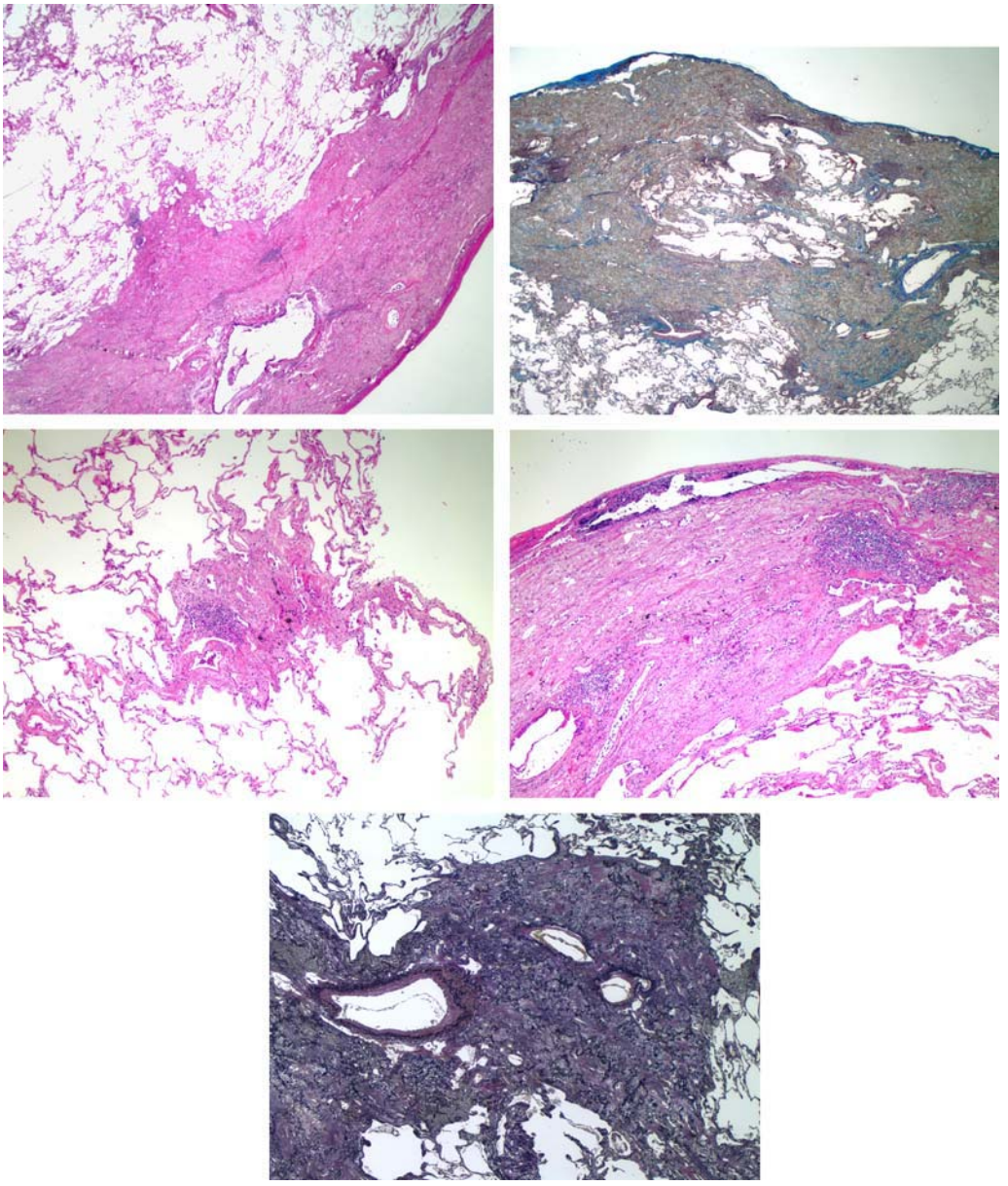
Diagnosis: Lung, open biopsy: Linear and focal scarring, cause undetermined, ? constrictive bronchiolitis, ? other.

This case is difficult because we are forced to deal only with late-stage scarring without inflammation. The scarring is not that of end-stage subpleural honeycomb fibrosis, and honeycomb change is not present on the X-ray. The pathology is not that of interstitial pneumonitis, including that of usual interstitial pneumonitis (UIP).

Constrictive bronchiolitis can produce enigmatic scars, and most of these scars have no bronchioles on either routine stain or elastic tissue stain. The relatively large size of the scars (trichrome stain) and subpleural plate-like scarring is not typical for constrictive bronchiolitis. However, the radiographs are consistent with that interpretation, in that there is overinflation associated with linear and focal scarring in all lobes without overall loss in lung volume. I favor this interpretation. If constrictive bronchiolitis caused these scars, I do not know what caused the constrictive bronchiolitis. Lymphoid hyperplasia that may be seen associated with Sjogren's syndrome is not present. There is no active bronchiolitis. Follicular bronchiolitis occurs in Sjogren's syndrome, and possibly the follicular bronchiolitis led to constrictive bronchiolitis. Another possibility is central bronchiectasis, whereby exiting bronchioles become obliterated and result in linear or plate-like atelectasis which reaches out to the pleural surface. The X-ray is not typical for bronchiectasis, and the bronchi do not have demonstrably thickened walls. Since a few of the scars have a stellate shape, I considered old eosinophilic granuloma, but the absence of even a lymphohistiocytic infiltrate much less Langerhans' cells is against this interpretation. I searched for old thromboemboli as the cause of infarct scars and find none. I considered pulmonary veno-occlusive disease, but there is an absence of hemosiderin and pulmonary hypertension. I do not believe the scars represent old organizing pneumonia (OP).

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. This is an elaboration of my earlier telephone message.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6765 (Chapter 1 – Airway Disease)

Case 6796

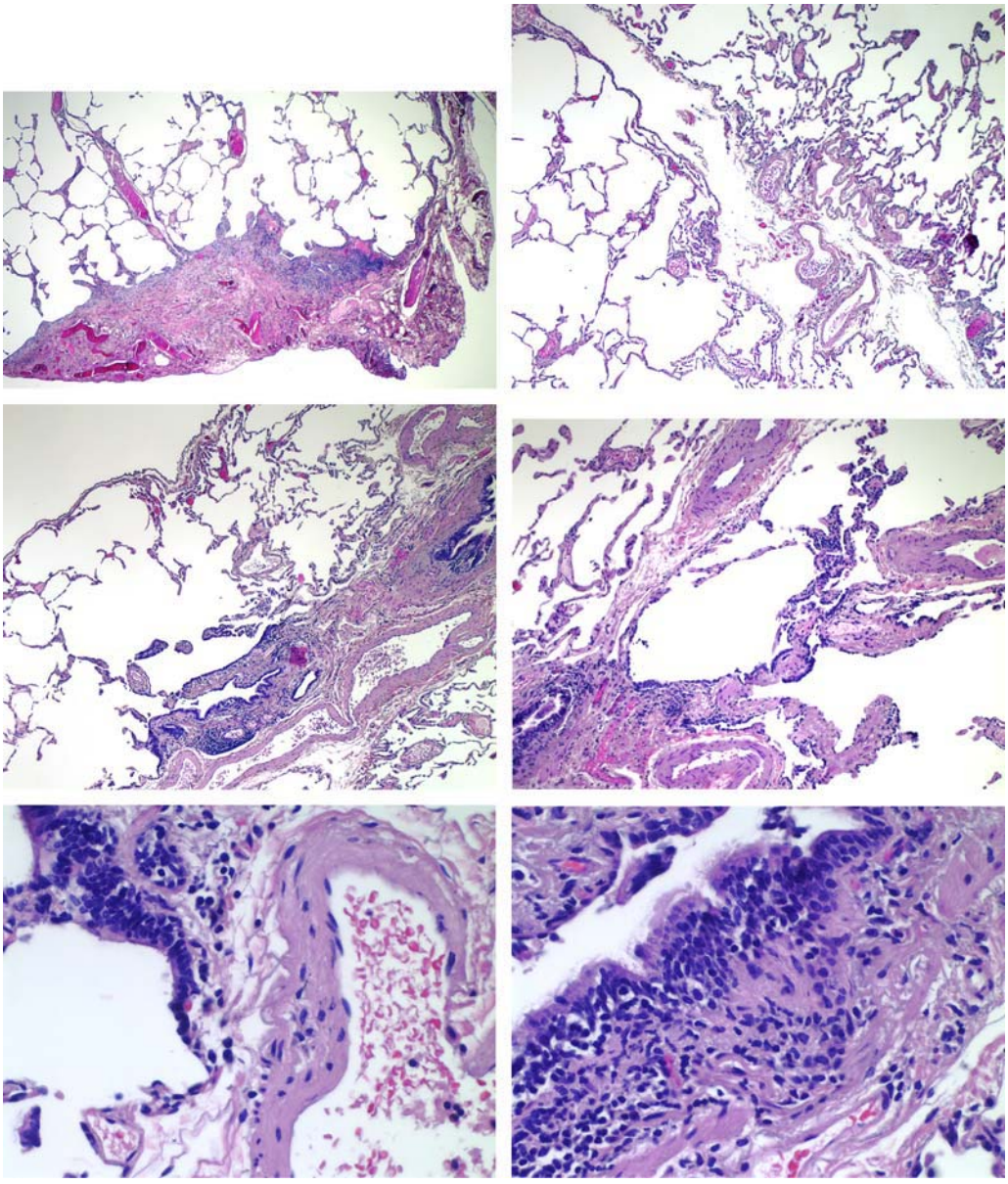
Diagnosis: Lung, open biopsy:

1. **Granulomatous bronchiolitis and Lamberthosis, with focal microscopic scars.**
2. **Emphysema.**
3. **Pleural fibrosis and pleural adhesions.**
4. **Edema of pleura and interlobular septa.**

Histiocytes, including multinucleated histiocytes in adventitia and mucosa of bronchioles, constitute a poorly described condition of granulomatous bronchiolitis, which may occur as a manifestation of rheumatoid lung disease. The Lamberthosis (peripheral extension of respiratory epithelium) is another marker of small airways disease. In this case, with extensive histological emphysema (many free-floating fragments of alveolar walls), cigarette smoke might be another cause of small airways disease. The pleural adhesions could represent old pleuritis and therefore be accounted for by rheumatoid lung disease. I do not know what has caused the interstitial edema. It is possible that the lung was clamped for some time before the biopsy specimen was removed. I cannot specifically apportion this patient's morphologically relatively mild disease between rheumatoid disease and cigarette smoking. I suspect that there is a contribution of both.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6796 (Chapter 1 – Airway Disease)

Case 6566

Diagnosis: Lung, open biopsy:

1. **RB with patchy interstitial fibrosis.**
2. **Peribronchiolar fibrosis and mucus plugging.**

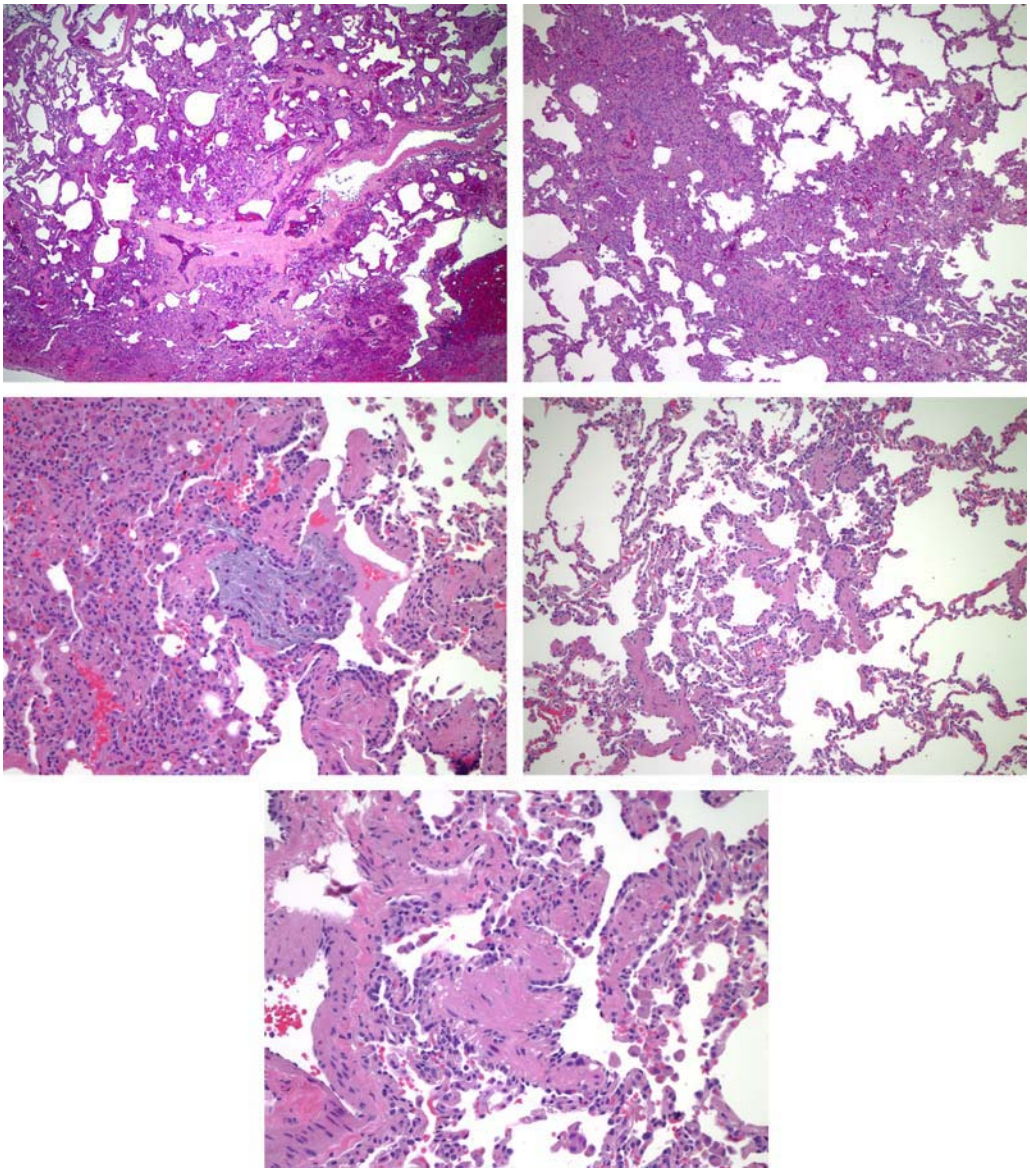
The principal pathology is the filling of bronchioles and alveoli by pigmented histiocytes. This constitutes RB, which in this case is associated with mild interstitial fibrosis. RB is caused by the smoking of cigarettes. The mucus plugs and peribronchiolar fibrosis (small airways disease) in this case also are part of cigarette smoking. I suspect that the RB and the fibrosis are responsible for the radiographic findings. There is focal atelectasis, attested to by circular spaces in compacted lung, and this atelectasis could either be related to bronchiolitis or to collapse of the lung after biopsy if the specimen remained in an unfixed state for several minutes. The blood in the lung is in pleura and intersititum as well as in some alveoli and does not expand the alveoli in which it lies, so I suspect that this blood is operative and not disease.

Thank you for referring this case in consultation. Please keep me informed of any follow-up.

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989;64:1373–1380.



Case 6566 (Chapter 1 – Airway Disease)

Case 6997

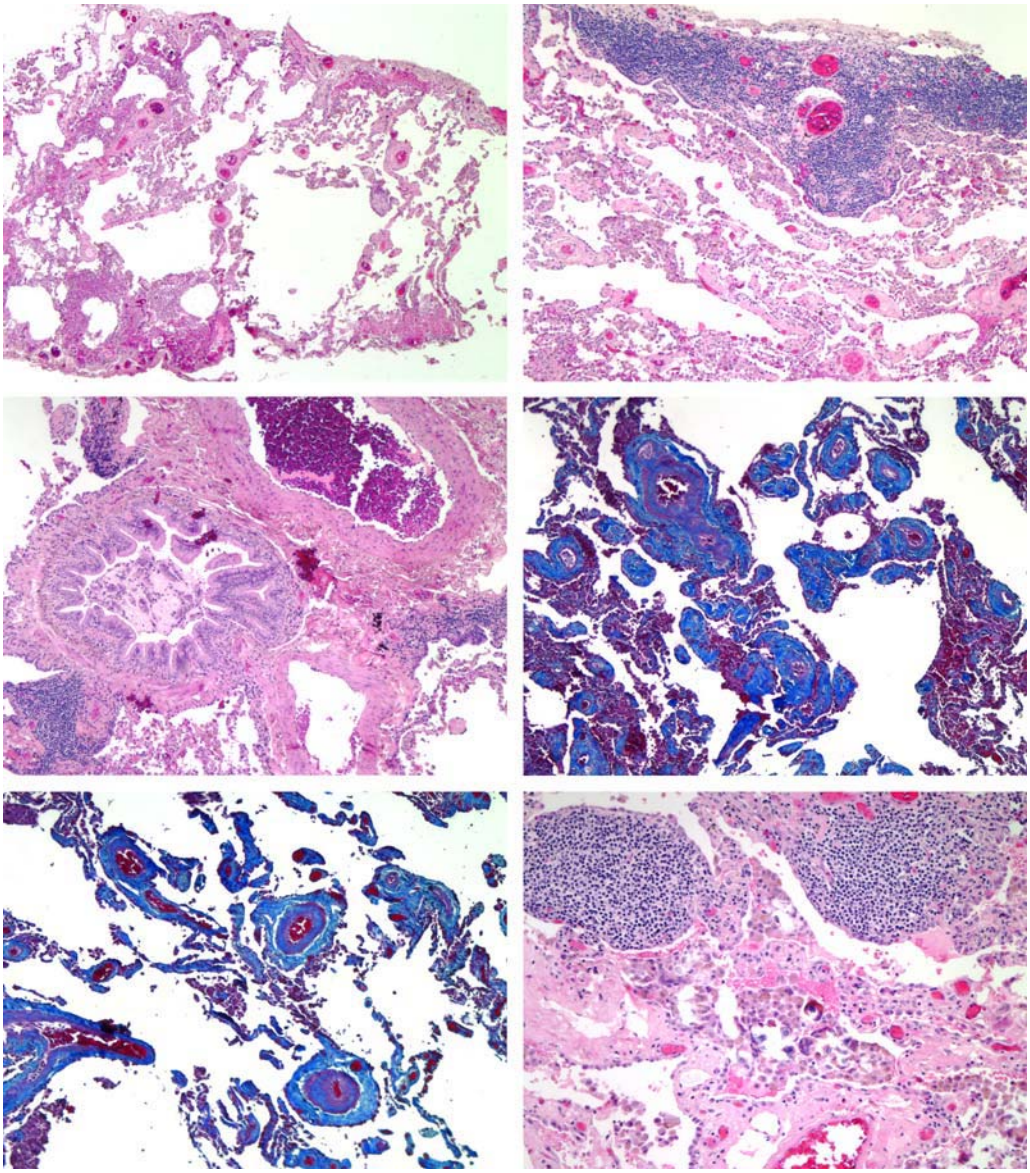
Diagnosis: Lung, open biopsy:

1. **RB with interstitial lung disease, slight.**
2. **Emphysema.**
3. **Hyperplasia of bronchus-associated lymphoid tissue, slight.**

The lung shows three different processes, although none of them is particularly marked. The aggregated histiocytes laden with pigment in respiratory bronchioles and alveolar ducts and subpleural alveoli indicate a mild form RB. The temporal and spatial diversity of UIP is not apparent, nor is there subpleural honeycomb fibrosis or active fibrosis. There is some associated interstitial fibrosis (trichrome stain), and this may be related to the RB. There is also emphysema, attested to by fragments of free-floating alveolar walls. A small amount of mucus plugging in terminal bronchioles may also be related to the smoking of cigarettes. Finally, there is a modest hyperplasia of lymphoid tissue around bronchovascular bundles. The first two processes are presumably related to the smoking of cigarettes. I do not know the cause of the lymphoid hyperplasia, although it is possible that it is related to hepatitis C infection. There is slight medial hyperplasia of some arteries, but I do not believe the changes merit a diagnosis of pulmonary hypertension. It is unclear which of these changes accounts for the patient's clinical and radiographic disease, but the RB may be doing so in combination with emphysema.

Thank you for referring this case in consultation. Please keep me informed of any follow-up, and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6997 – (Chapter 1 – Airway Disease)

Case 7124

Diagnosis: Lung, open biopsies: Bronchiolitis and peribronchiolitis with focal organizing pneumonia, ? respiratory bronchiolitis with interstitial lung disease (RB-ILD),? Chronic bronchitis, ? both, ? other.

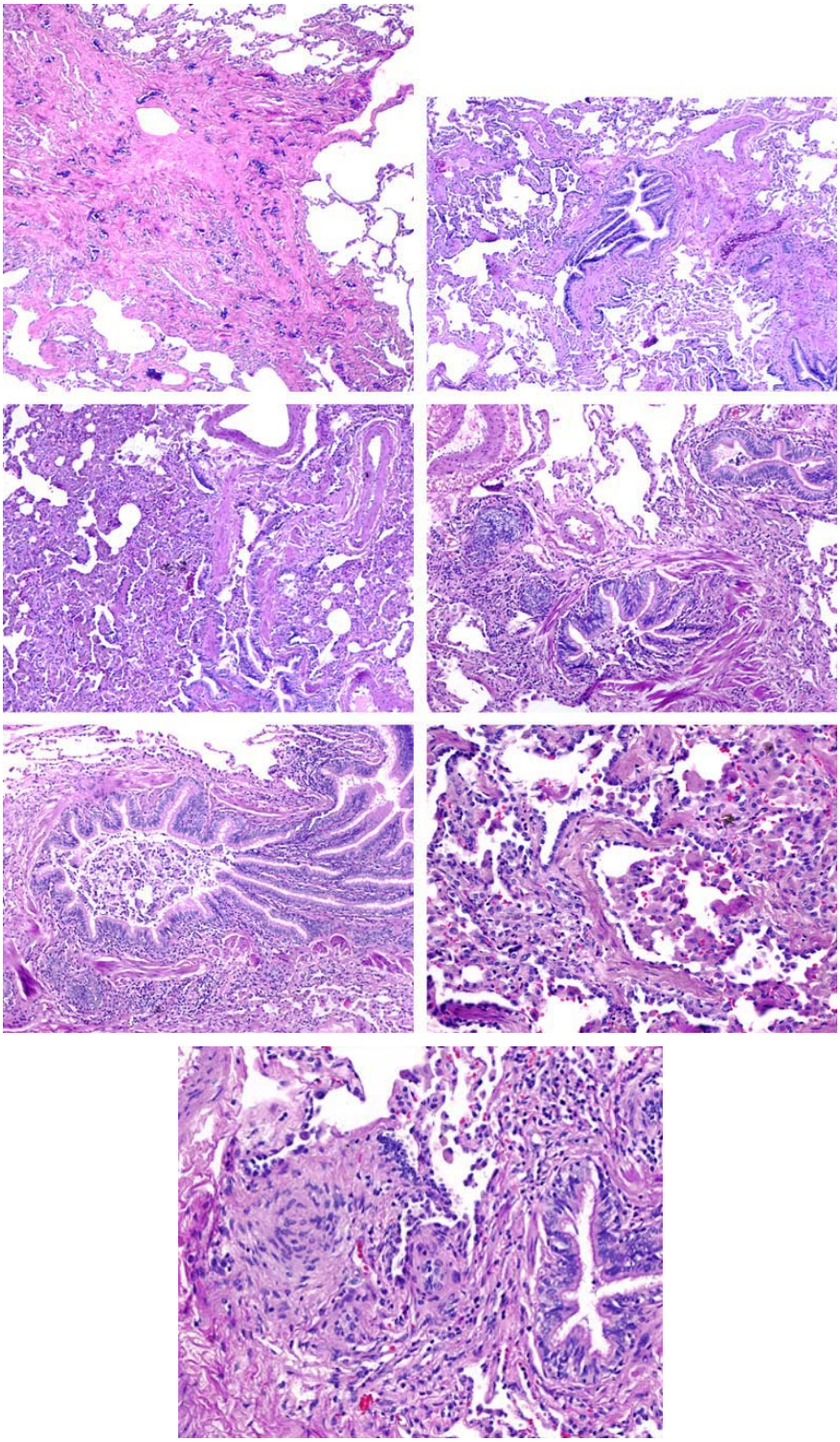
The principal pathology is centered on the bronchioles and particularly on the peribronchiolar interstitium, which is thickened due to old fibrosis and inflammation as well as active myxoid fibrosis in a few regions. This latter is not commonly observed in peribronchiolitis and indicates active disease. There is also filling of bronchioles and alveoli with pigment-laden histiocytes and interstitial fibrosis. These changes suggest RB-ILD, which I favor as the principal diagnosis. The cause of RB-ILD is the smoking of cigarettes. The disease is partially reversible with cessation of smoking of cigarettes.

There is also mucus plugging of a few bronchioles and wedge-shaped scars larger than usually seen with RB-ILD. Therefore, I suspect that there is an element of chronic bronchitis with mucus plugging leading to focal scarring, as contrasted to the more diffuse scarring which I attribute to RB-ILD. The chronic bronchitis would also be caused by cigarette smoking.

I cannot exclude other causes of bronchiolitis and peribronchiolitis, including hypersensitivity reaction. However, the OP generally seen with hypersensitivity pneumonitis is very modest in this case. Hypersensitivity reaction usually does not give this degree of peribronchiolar fibrosis. No eosinophils are present to support a diagnosis of hypersensitivity reaction. Another possibility is an idiopathic constrictive peribronchiolitis, but in my opinion in this case small airways disease would not be idiopathic if there is a history of heavy cigarette smoking.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7124 (Chapter 1 – Airway Disease)

Case 7193

Diagnosis: Lung, open biopsy:

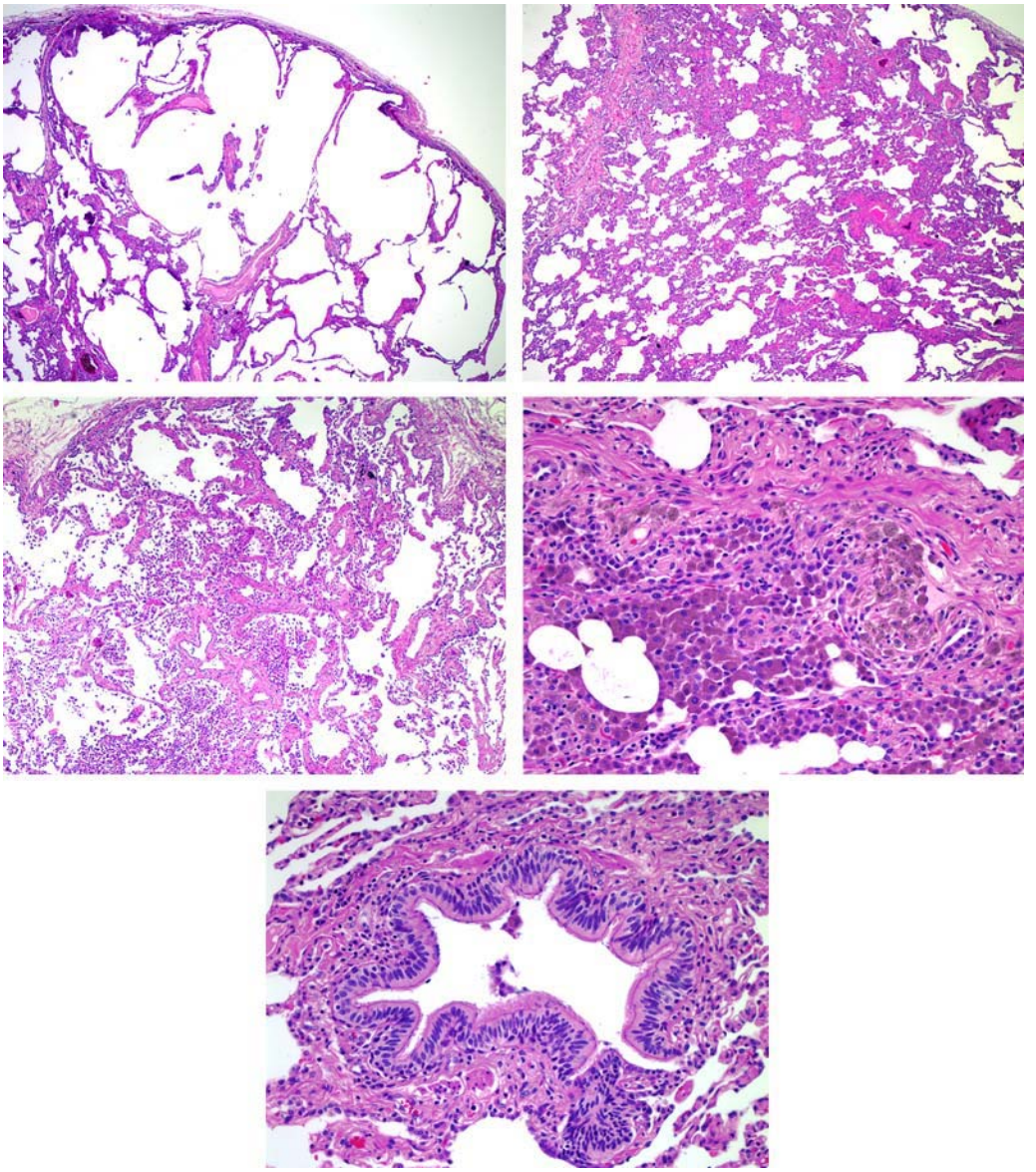
1. **RB-ILD.**
2. **Emphysema.**

Dilatation of airspaces with free-floating fragments of alveolar walls particularly beneath the pleura indicates that this patient has emphysema. Some lobules contain numerous pigment-laden histiocytes in respiratory bronchioles, alveolar ducts, and alveoli. I believe the pigment is principally so-called tobacco pigment. There is also rather extensive old, but delicate, interstitial fibrosis. Although there is more than one way to put this case together, the most logical in my opinion is that this represents RB-ILD in a patient who smokes cigarettes and has developed emphysema, both of which are contributing to the patient's symptoms. Cessation of cigarette smoking would be the first step in treatment in patients with RB-ILD, but it is unclear how much of the interstitial fibrosis is reversible, and it is even unclear how much of the interstitial fibrosis is related to the RB or possibly coexistent chronic bronchitis (which is not sampled in this specimen).

In the differential diagnosis we considered collagen-vascular disease causing interstitial fibrosis and UIP. The absence of coexistent pleuritis, bronchiolitis, and vascular disease are against collagen-vascular disease. The absence of honeycomb fibrosis and foci of active fibrosis as well as the absence of temporal heterogeneity are against UIP.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7193 (Chapter 1 – Airway Disease)

Case 6702

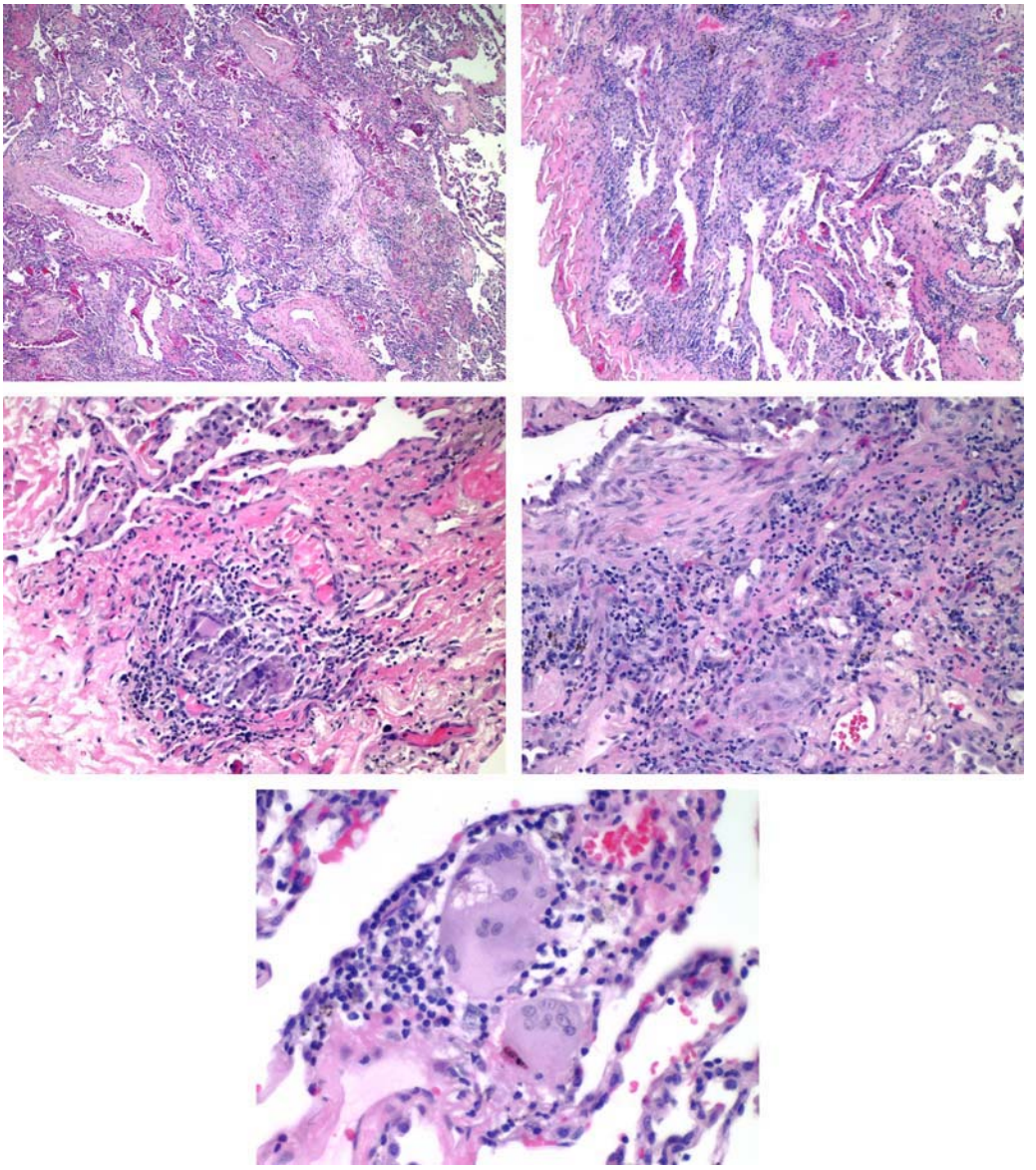
Diagnosis: Lung, open biopsy: BIP, eosinophils and granulomatous inflammation, ? hypersensitivity reaction.

The morphology includes BO, a small element of OP, a large element of diffuse interstitial inflammation and fibrosis, many eosinophils, many multinucleated histiocytes, and a few poorly formed granulomas. The case is unusual in that the bronchiolitis is associated with an interstitial pneumonitis, a phenomenon that we have been studying and categorize as bronchiolitis with interstitial pneumonitis. I am using that morphological diagnosis here. Our other cases have not had the numbers of eosinophils present here or the granulomatous inflammation. The best etiological diagnosis for this constellation of changes is hypersensitivity pneumonitis, which is essentially in keeping with your diagnosis. The clinical history is consistent with the morphology in that the changes appear 3 mo old at the greatest.

In the differential diagnosis, we considered UIP because of the diffuse character of the interstitial fibrosis, but other features of that diagnosis are not present. We also considered sarcoidosis, but I would anticipate more definite granulomas in sarcoidosis with disease as active as this.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6702 (Chapter 1 – Airway Disease)

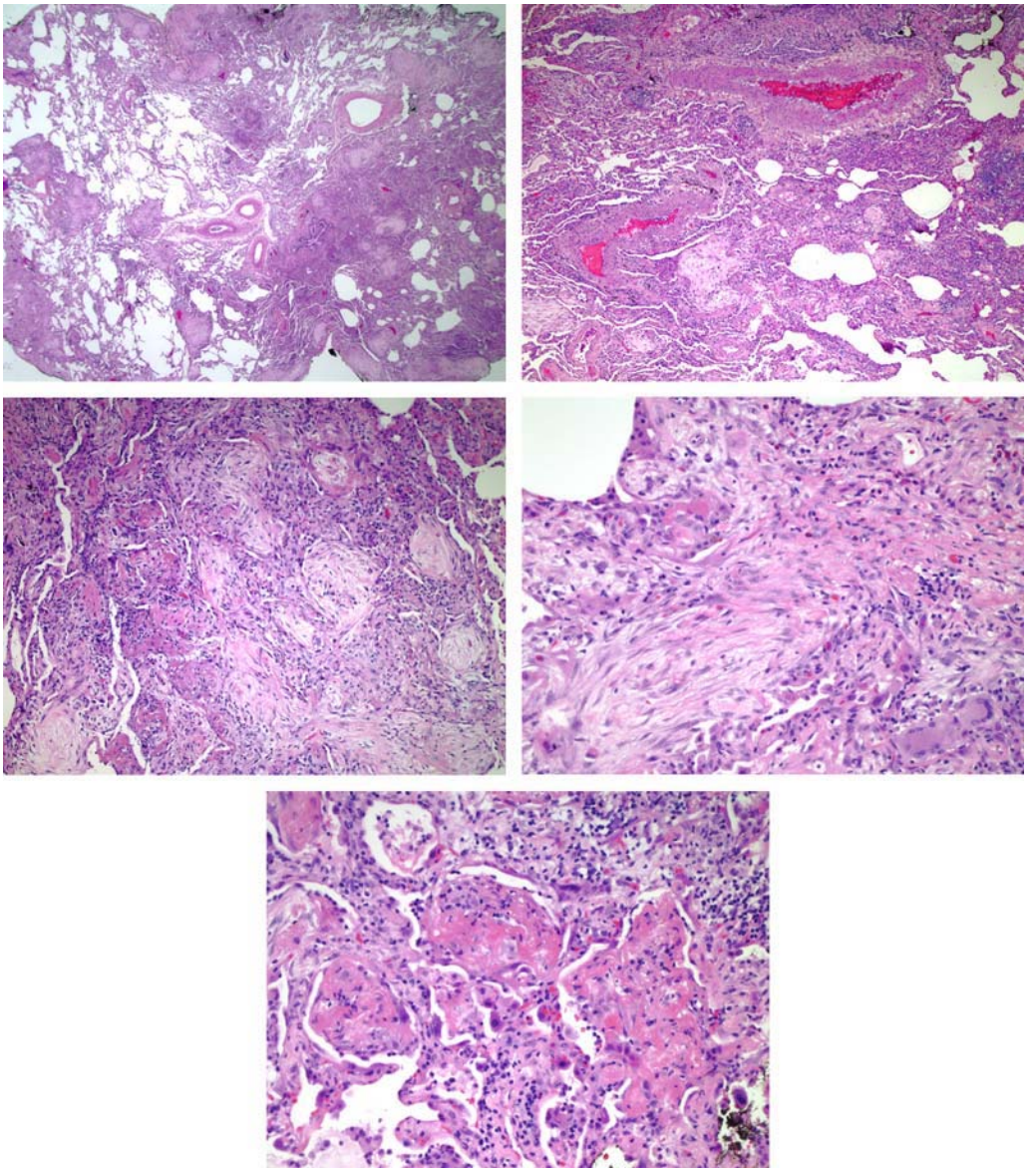
Case 6764

Diagnosis: Lung, open biopsy: BO, with small component of OP, ? infection, ? drug reaction, ? idiopathic.

This case presents a relatively pure example of BO. The disease is in an earlier stage than is usually examined, with active organizing fibrin as well as proliferative fibrosis, indicative of a disease of a few weeks duration and ongoing. A small component of organizing pneumonia in alveoli is also present, but the consolidated nodule typical of bronchiolitis obliterans organizing pneumonia (BOOP) is not well developed. Pure BO occurs particularly in infectious bronchiolitis. In this case, a drug reaction is also possible. A few eosinophils and multinucleated histiocytes are present. Drugs that have been implicated in BO include sulfasalazine, bleomycin, cyclophosphamide, and methotrexate. Thus, I agree with you that this BO is likely either infectious or a drug reaction, and I cannot distinguish between the two. Of course, the disease could also be idiopathic. No malignant lymphoma is present. Your stains for organisms are negative.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6764 (Chapter 1 – Airway Disease)

Case 6750

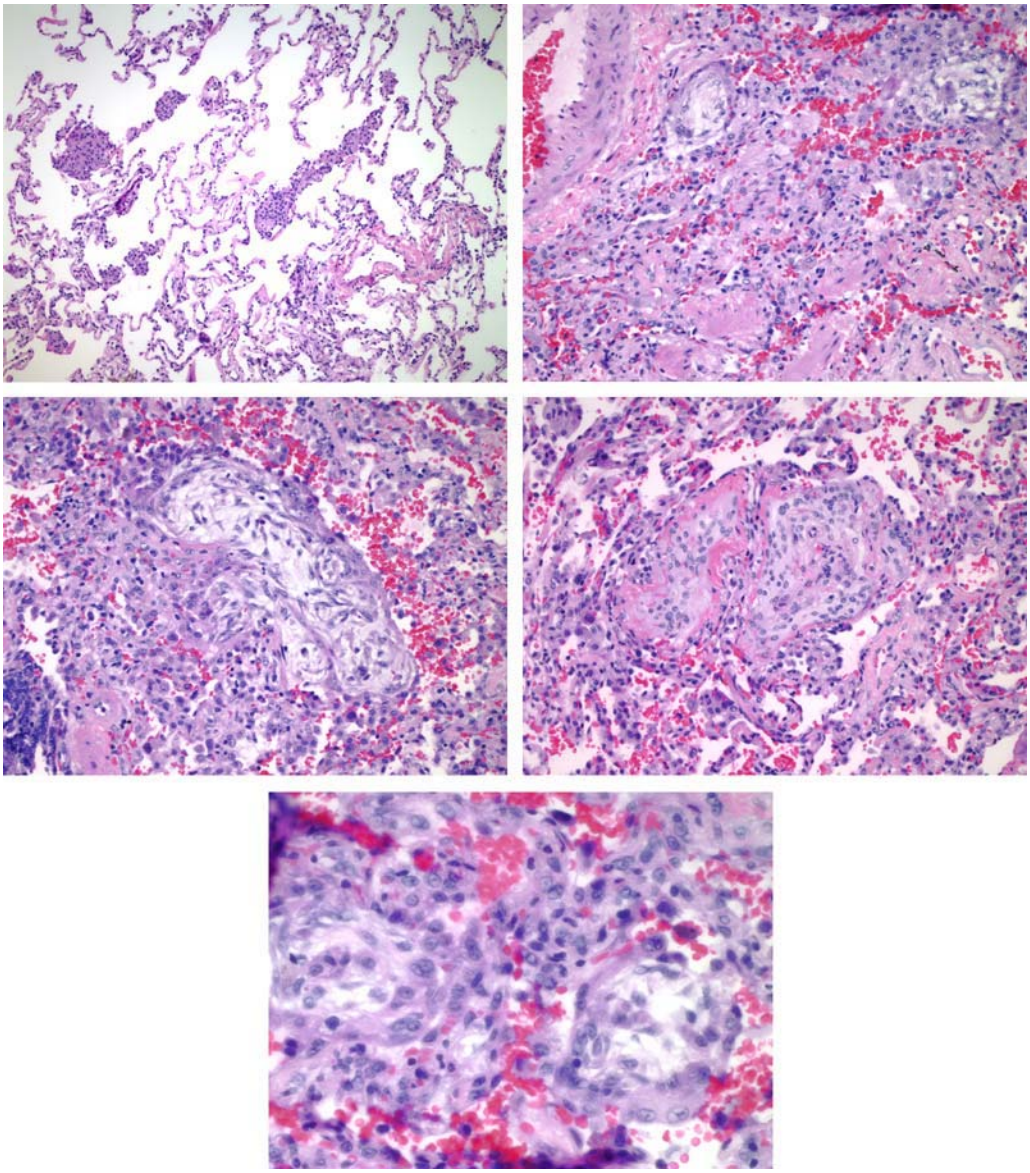
Diagnosis: Lung, open biopsy: BO, slight.

Changes are subtle and spotty. The most definite lesion is BO, whereby a few respiratory bronchioles are filled by myxoid connective tissue, which is in turn covered by reactive epithelial cells. I find one pigmented particle in one tuft of BO and one eosinophil in another tuft. OP, as usually observed in BOOP, is not apparent, although there are a few foci of organizing fibrin. A few tumorlets of chemodectoma type are present. The tumorlets are small even for tumorlets. Persons who live at very high altitudes, such as the Indians of Peru, can have increased numbers of chemoreceptor cells. I suspect the chemodectoma-like cells in this patient are within the range of normal.

I do not know the cause of the BO. Viral infection and toxic inhalant are possible. A hypersensitivity reaction cannot be excluded. No birefringent material is visible with polarized light microscopy. The patient's disease, after return to sea level, is the reverse of high altitude pulmonary edema. I do not appreciate pulmonary edema.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6750 (Chapter 1 – Airway Disease)

Case 6471

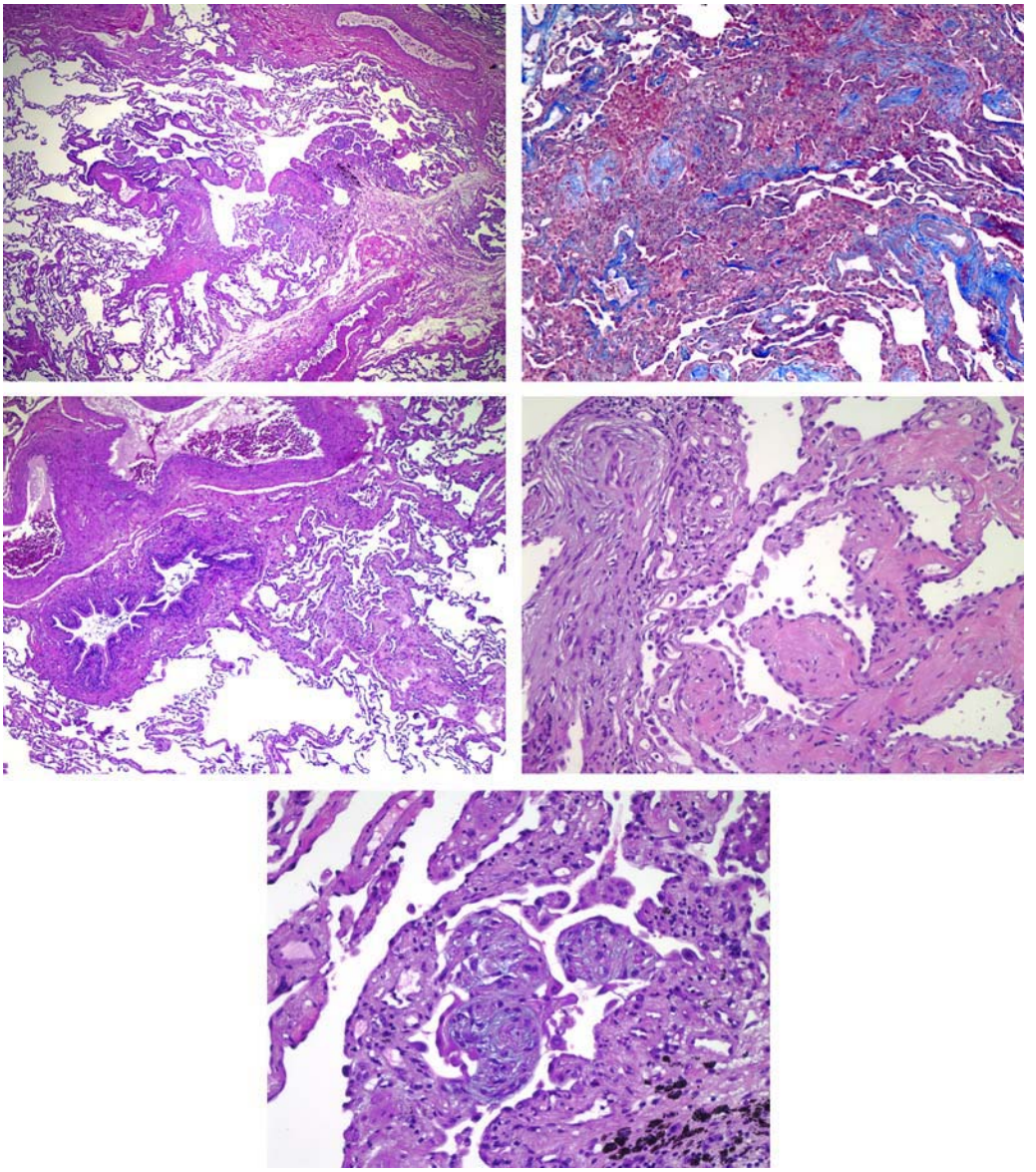
Diagnosis: Lung, open biopsy: BO, late phase.

The micronodular character of the disease seems to be the pre-eminent pathology, with fibrosis centered on bronchioles and a small amount of organizing fibrosis present in alveoli (trichrome stain) as well. I believe this is best described as a BO which has been sampled at a later stage than usual. The fibrosis could be several weeks or a few months in age. I considered diffuse alveolar damage in the differential diagnosis because of the atypia of the fibroblasts and pneumocytes, but the process is too nodular for that interpretation. I do not favor a diffuse interstitial fibrosis. I do not see the lymphocytic inflammation of UIP or the interstitial infiltrate we have observed in BIP.

The advanced degree of fibrosis may correlate with the reportedly poor response of the patient's disease to administration of corticosteroids.

Thank you for the opportunity to review this case. Two other pathologists have also studied this case and essentially concur with the above. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6471 (Chapter 1 – Airway Disease)

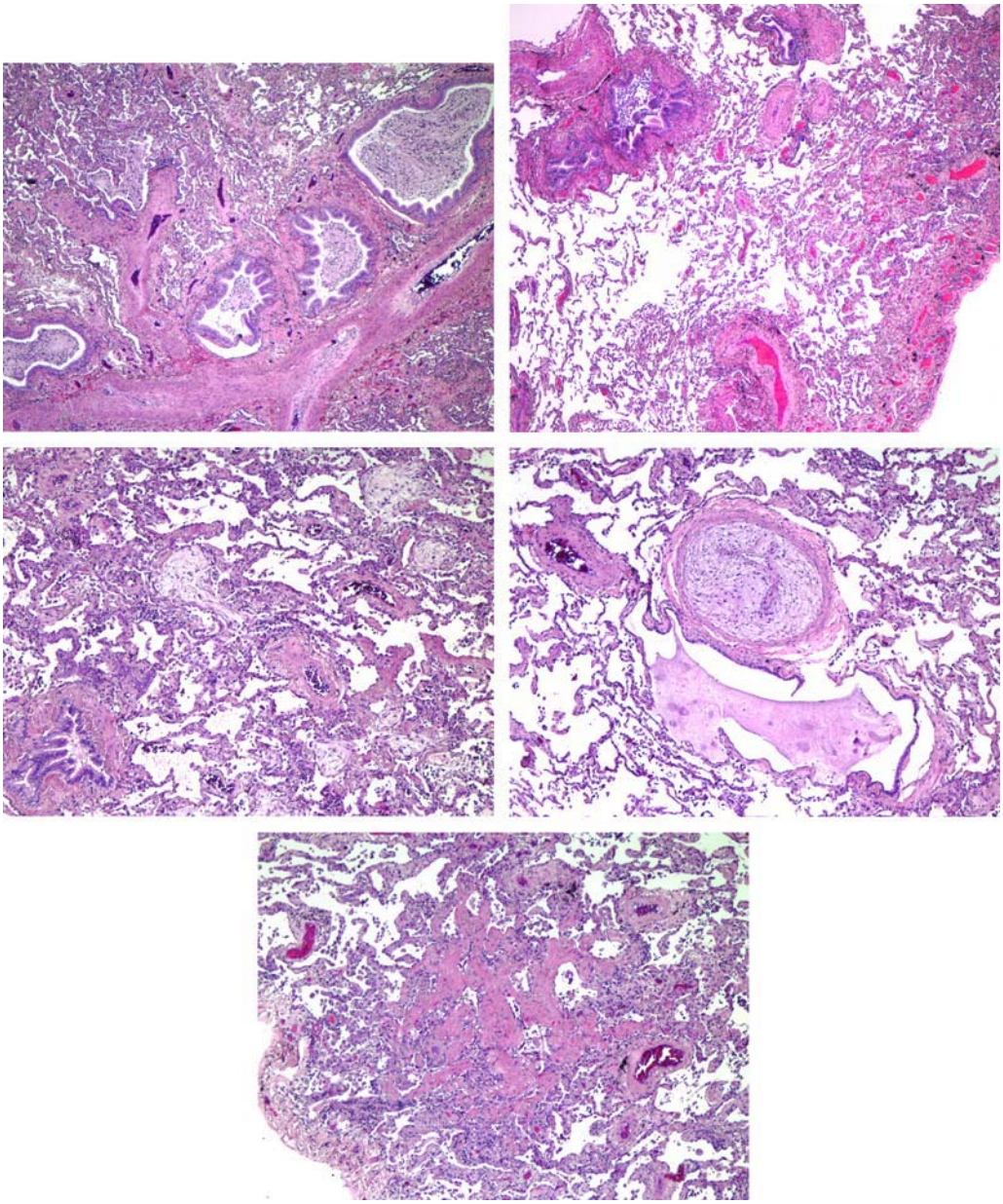
Case 6723

Diagnosis: Lung, open biopsy: BO, bronchiectasis with mucus plugs, interstitial fibrosis, arterial hypertensive change, and pleuritis with pleural adhesions, ? etiology, ? collagen-vascular disease.

This case does not fit into a precise morphological category. There is a variety of changes. To the degree that different anatomic compartments are involved (alveolar, bronchiolar, interstitial, vascular, pleural), one can consider a collagen-vascular disease, and there are some clinical signs and symptoms that are consistent with that interpretation. I suspect this is the case here, and this is in agreement with your interpretation. If the serological tests do not disclose a definite collagen-vascular disease, I might consider those conditions which are harder to confirm by serology, that is, dermatomyositis, mixed connective tissue disease, and scleroderma. The prominent myxoid change to the intimal hyperplasia in a few pulmonary arteries is dramatic, but most of the blood vessels are normal, and I am not at all sure that the arterial hypertensive change here means that the patient has physiological pulmonary hypertension. The classic diffuse interstitial lung disease associated with a collagen-vascular disease is usual interstitial pneumonitis. The pathology here is not characteristic of UIP. However, the interstitial fibrosis is extensive, and it may be that the interstitial fibrosis becomes the patient's most significant pulmonary problem.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6723 (Chapter 1 – Airway Disease)

Case 4431

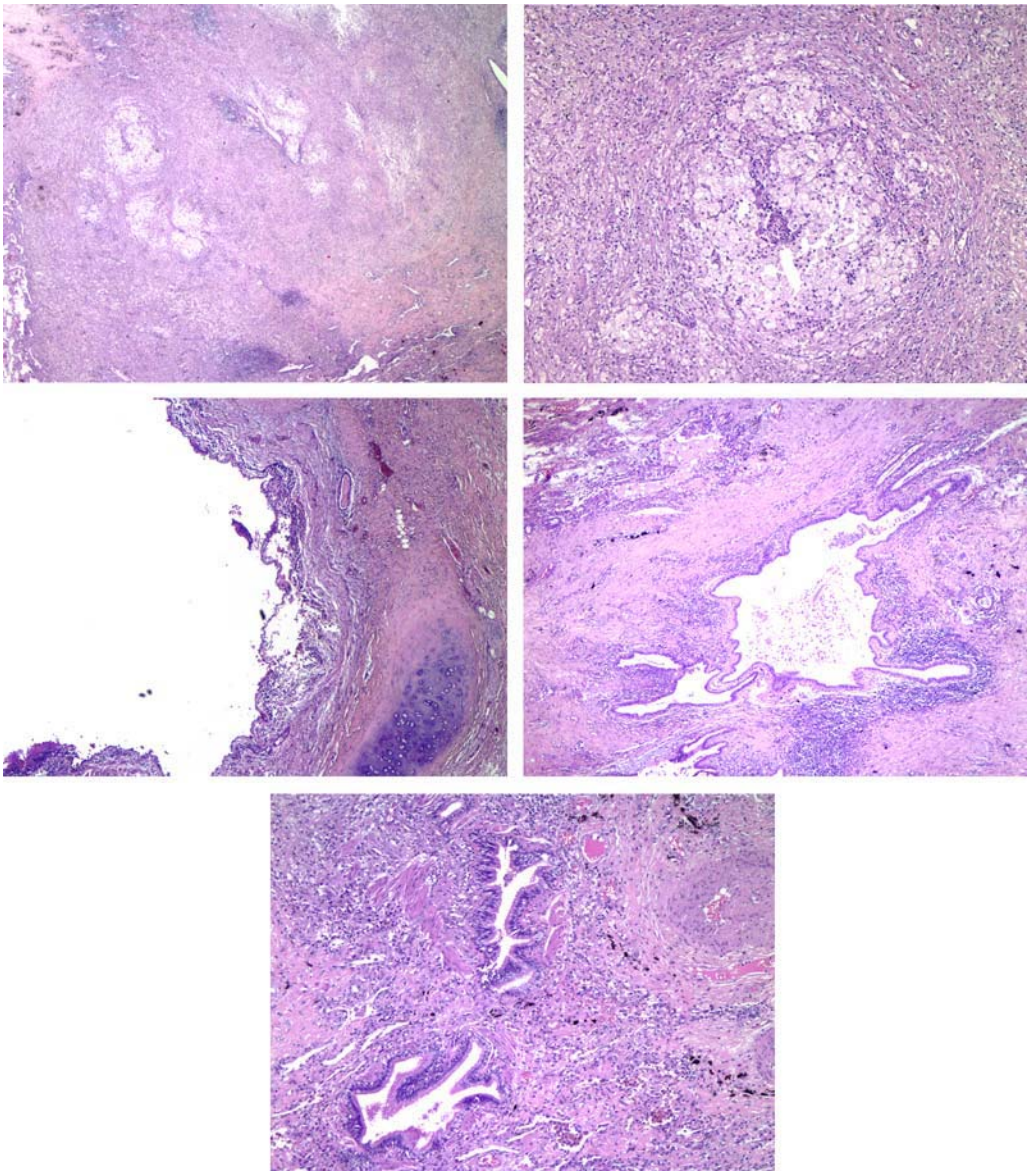
Patient: 50-yr-old female
Diagnosis: Lung, lobectomy:

1. **Bronchiectasis and bronchiolectasis.**
2. **Inflammatory pseudotumor.**

This case is complicated in regard to which is the primary and which is the secondary process. Ectatic bronchi and bronchioles encircled by collars of dense fibrous tissue signify widespread bronchiectasis and bronchiolectasis in this lobe and could account for progressive dyspnea. Dust macules with anthracosilicotic pigment are associated with the bronchiolectasis. There is also a mass of histiocytic inflammation which is undergoing central degeneration. I would call this an inflammatory pseudotumor. It is adjacent to bronchiectasis. The two processes may be independent. However, I suspect that one bronchiectatic segment became plugged and elicited a localized inflammatory mass. The case is instructive to me because it provides another cause of inflammatory pseudotumor, that is, bronchiectasis. No malignancy is present. This is essentially in agreement with your interpretation.

Thank you for sharing this case with us. It has been added to our permanent teaching collection in pulmonary pathology. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 4431 (Chapter 1 – Airway Disease)

Case 7132

Diagnosis: Lung, open biopsy:

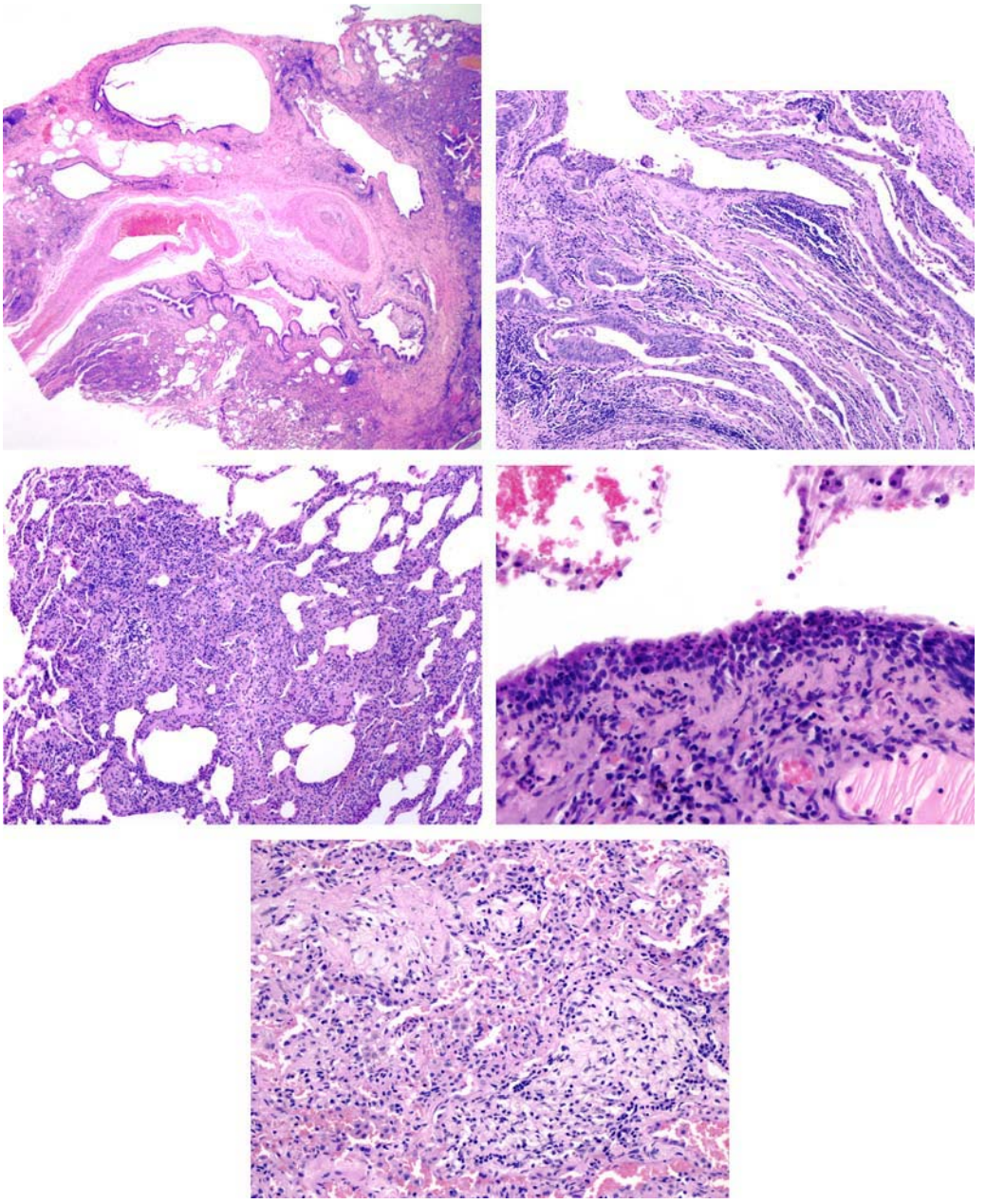
1. **Bronchiectasis, with subpleural cyst formation.**
2. **Chronic organizing pneumonia.**

There is bronchiectasis of conducting airways away from the pleura, whereby the lumens are abnormally large and abnormally contoured and the walls inflamed, although mucosal necrosis is not present. The character of the cysts beneath the pleura is quiescent with smooth muscle hyperplasia and intact respiratory epithelium. These cysts are not typical for honeycomb fibrosis because of their structure and relative lack of dense fibrous walls. The specimen also contains foci of chronic organizing pneumonia and interstitial fibrosis. The OP includes lymphohistiocytic infiltration in alveoli and interstitium.

I am not exactly sure how the bronchiectatic changes and the chronic organizing pneumonia relate. I favor bronchiectasis as a primary diagnosis, with or without chronic bronchitis as a potential cause for the bronchiectasis. I cannot exclude UIP, and the reported clinical findings of diffuse interstitial lung disease favors this interpretation, but I do not favor this interpretation morphologically and cannot make a diagnosis of UIP on this specimen. There is temporal variation in the disease in that there are old cysts and more recent inflammation, but there is not a continuum of activity of disease and no active fibrosis. On the other hand, if the patient's interstitial disease progresses clinically and radiographically to that degree, UIP becomes more probable.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7132 (Chapter 1 – Airway Disease)

Case 6904

Diagnosis: Lung, open biopsy:

1. **Peribronchiolitis with Lamberthosis, peribronchiolar fibrosis and smooth muscle hyperplasia, epithelial hyperplasia and mucus plugging.**
2. **RB, slight.**

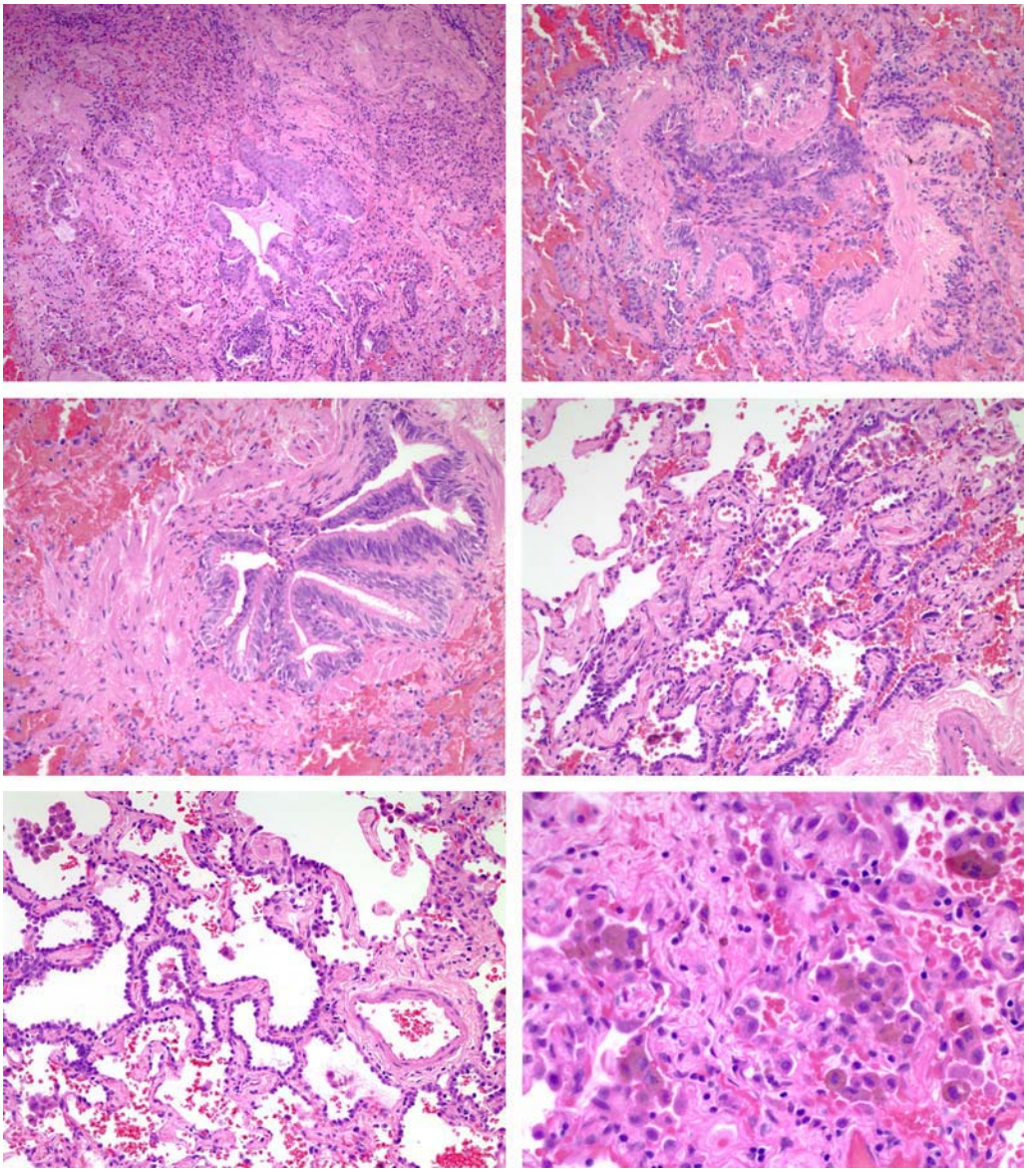
Two bronchiolar diseases are present, and I suspect that they are different. The more prevalent is the peribronchiolar fibrosis and smooth muscle hyperplasia of the type that is seen in patients with asthma and also in patients who are cigarette smokers. Mucus plugging suggests one or both of these conditions. The epithelial hyperplasia is of the type seen in asthma, but mucinous metaplasia that is seen in asthma is not present. Lamberthosis (distal extension of respiratory epithelium into alveoli) and squamous metaplasia in bronchioles are reparative processes. Peribronchiolitis is sometimes termed small airways disease, but the peribronchiolar thickening here is more marked than that randomly encountered in lungs resected for other reasons.

Separate is accumulation of pigment-laden histiocytes, to some degree in alveoli in the manner of a desquamative interstitial-like reaction and to a slight degree in respiratory bronchioles. These changes are generally attributed to cigarette smoke and are associated in this case with slight interstitial fibrosis.

I suspect that the peribronchiolitis is the more important disease from a clinical point of view. Peribronchiolitis apart from asthma and pertussis infection is not a well established entity but can cause clinical and radiographic abnormalities. Peribronchiolitis and RB are both distinct from BO, which is not present here.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6904 (Chapter 1 – Airway Disease)

Case 6907

Diagnosis: Lung, open biopsy: Peribronchiolitis, bronchiolectasis, and mucopurulent plugging, cause undetermined.

The pathology is that of a scarring bronchial and bronchiolar disease. The scarring involves small subsegmental bronchi with degeneration of cartilage, terminal bronchioles, and respiratory bronchioles. In fact, the most prominent scarring is in very small bronchioles, where the adventitia is thicker than the lumen. The pathology could be explained by asthma, although the involvement of the very small bronchioles would be somewhat unusual. In terms of a treatable condition, I searched for aspergillus, because allergic bronchopulmonary aspergillosis would be a possible clinicopathological condition, but I find none. Cystic fibrosis is another condition that can cause bronchiolar disease and rarely has been diagnosed for the first time in persons in their sixth decade. Finally, there is the enigmatic condition of peribronchiolitis, an entity with but few unifying features other than the sort observed here. Peribronchiolitis and constrictive bronchiolitis are related. The larger bronchioles in this specimen have peribronchiolitis, and the smaller bronchioles show constrictive bronchiolitis.

Peribronchiolar fibrosis can develop in cigarette smokers, as a sequel to pertussis infection, or in patients with inflammatory bowel disease or collagen-vascular disease. In many instances we do not know what is responsible for the condition, but it can cause radiographic interstitial disease and clinical symptoms.

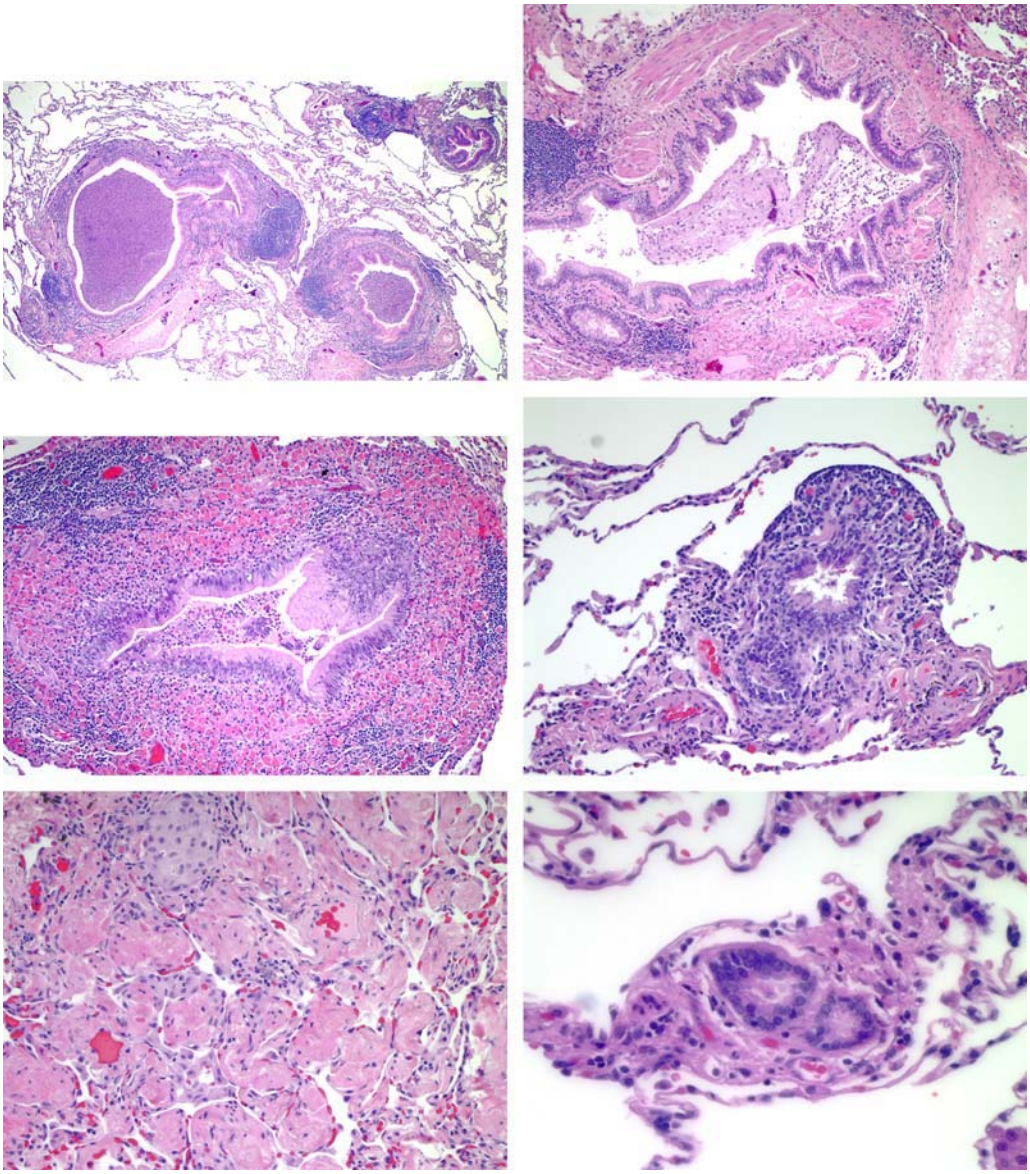
The pathology is not that of BO or BOOP. Only one bronchiole has an intraluminal fibrous plug of the type seen in BO. I do not believe this specimen shows UIP because the pathology is centered on bronchioles, and diffuse interstitial pneumonitis is not apparent.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Schlesinger C, Meyer CA, Veeraraghavan S, Koss MN. Constrictive (obliterative) bronchiolitis: Diagnosis, etiology, and a critical care review of the literature. Ann Diagn Pathol 1998; 2:321–334.



Case 6907 (Chapter 1 – Airway Disease)

Case 6669

Diagnosis: Lung, open biopsy:

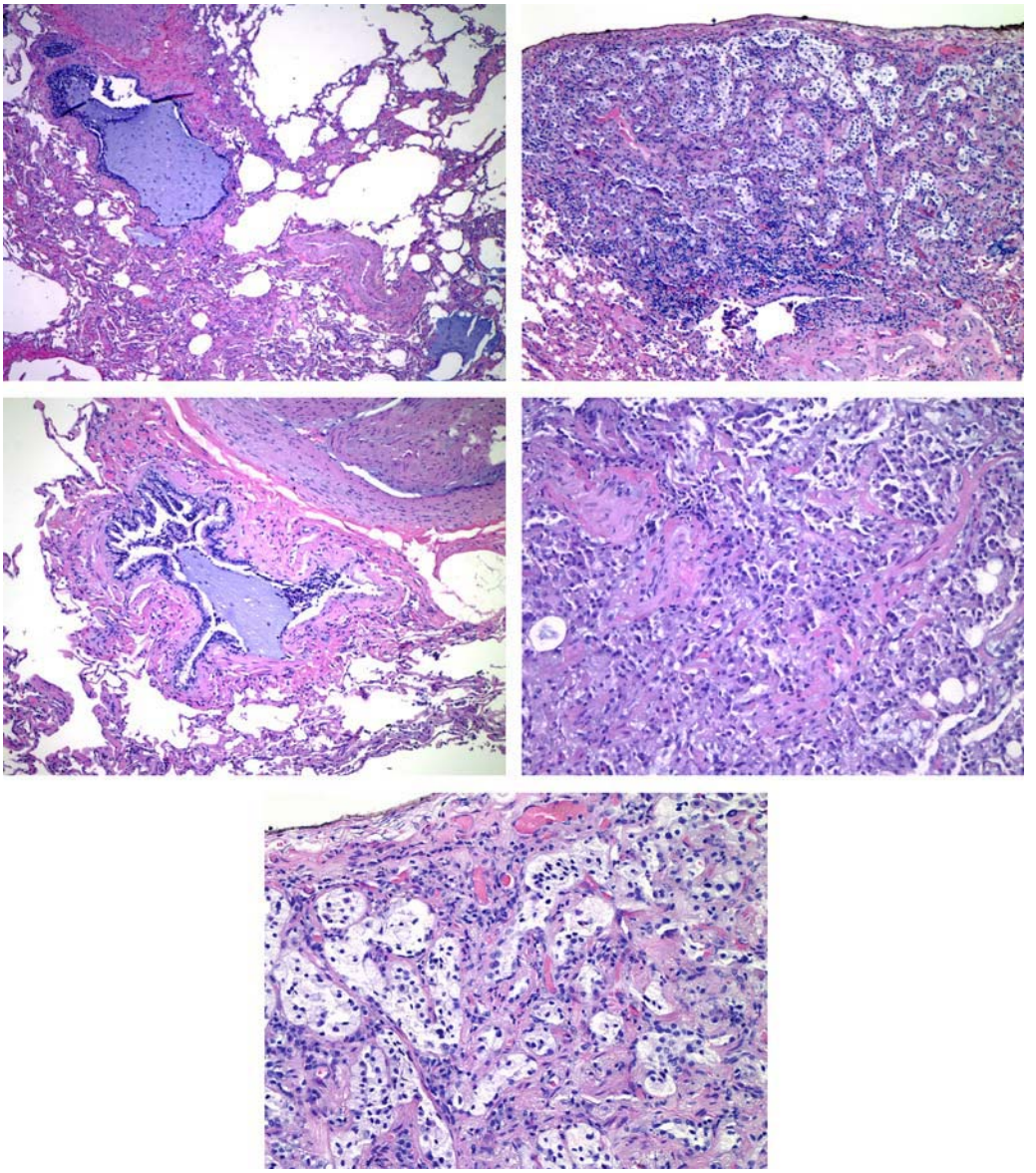
1. **Marked mucus plugging with bronchiolectasis and peribronchiolar inflammation and fibrosis.**
2. **Focal pneumocytic proliferation, nature uncertain, probably reactive.**

Most of the lung parenchyma away from bronchioles is normal. The bronchioles are markedly distended by mucus, and the walls of the bronchioles are thickened by a mild lymphocytic infiltrate and fibrosis. These changes could generically be described as small airways disease with mucus impaction and might be seen in a smoker with chronic bronchitis. There is no BPOP, UIP, DIP, or other form of diffuse inflammatory or fibrotic lung disease. There is no evidence of infection.

One small subpleural nodule has a proliferation of large cuboidal epithelial cells with clear cytoplasm. The process is unusual, and I do not know exactly what it represents, but I do not believe it is malignant. In the differential diagnosis I considered alveolar adenoma, pneumocytoma as described in patients with tuberous sclerosis, carcinoid tumor with clear cell change, and clear cell (sugar) tumor. However, I suspect that this is an unusual reactive nodule and not neoplastic.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6669 (Chapter 1 – Airway Disease)

Case 6698

Diagnosis: Lung, open biopsy: Diffuse neuroendocrine cell hyperplasia.

The salient pathology is a proliferation of Kultchitzky cells and epithelium herniating into lamina propria. The neuroendocrine cell hyperplasia is associated with a slight increase in lymphocytes and fibrosis surrounding bronchioles. The pathology of diffuse neuroendocrine cell hyperplasia can be associated with either restrictive or obstructive lung disease and either with tumorlets of carcinoid type or multiple carcinoid tumors, as well as diffuse interstitial fibrosis. I suspect that this process has caused the patient's symptoms. Some of the arteries have prominent media, but I would not prognosticate as to physiological pulmonary arterial hypertension from this biopsy alone (elastic stain).

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

Aguayo SM, Miller YE, Waldron JA, et al. Idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease. N Engl J Med 1992;327:1285–1288.

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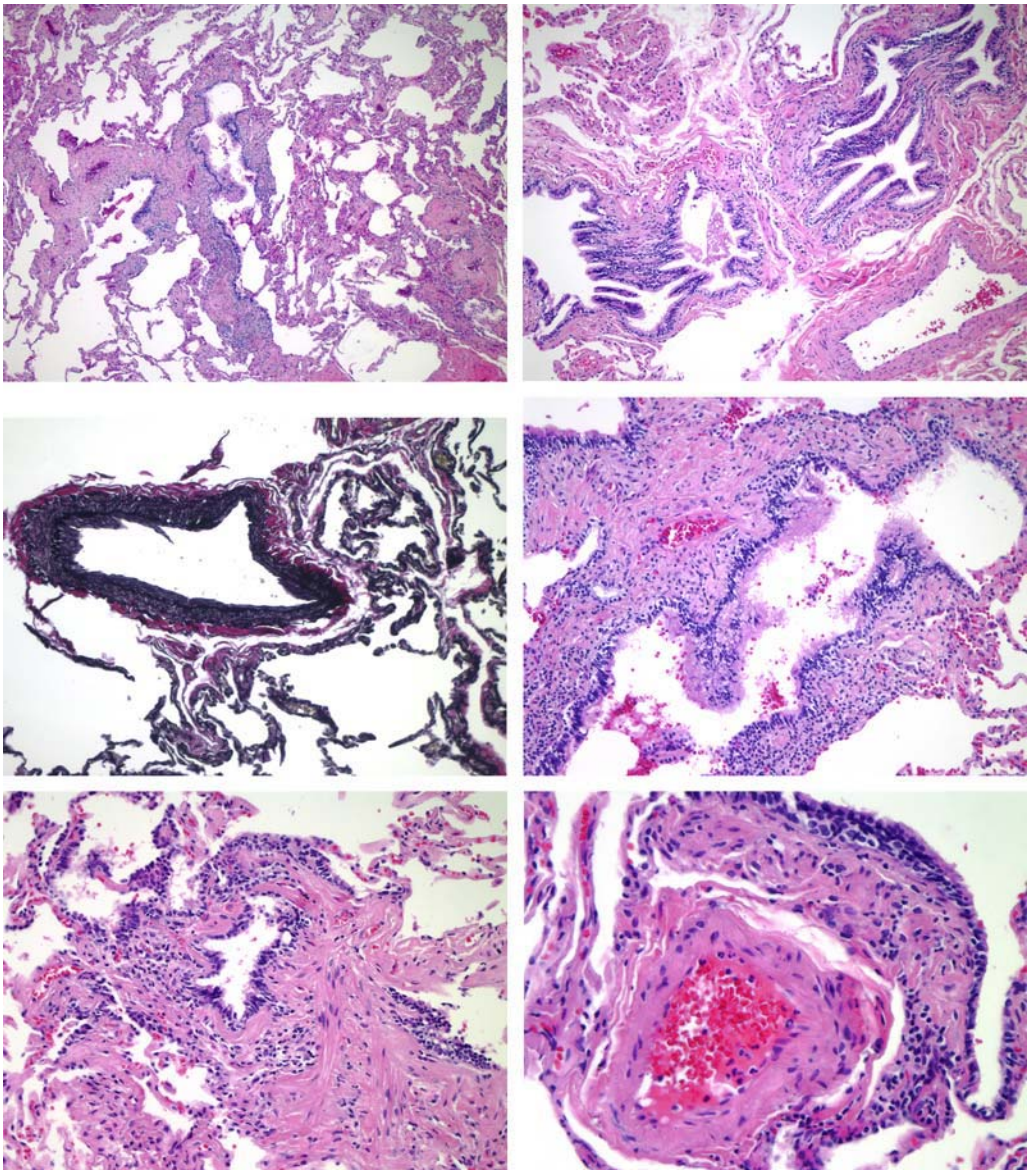

Case 6698 (Chapter 1 – Airway Disease)

2 Alveolar Disease

CONTENTS

DIFFUSE ALVEOLAR DAMAGE

Diffuse alveolar damage (DAD) is the histopathological substrate for most patients diagnosed clinically with the acute respiratory distress syndrome. The two terms are not synonymous, however, as some patients presenting with acute unexplained respiratory failure will be found to have a more specific disease. The benchmark for DAD is the hyaline membrane. Some authors have used the term acute interstitial pneumonitis for cases where the etiology of the DAD is unknown, and restricted the term DAD to cases where the etiology is known. The disease, when usually sampled, is subacute (weeks), principally alveolar rather than interstitial (alveoli filled by myxoid fibrosis), and not a pneumonitis (principally fibrosis rather than inflammation).

Overview

- Subacute (few weeks) when biopsied.
- Alveolar filling by fibrosis and hyaline membranes.
- Endothelial and epithelial necrosis; systemic, not inflammatory or confined to lungs.
- Clinicopathologic diagnosis (consensus classification) now "Acute interstitial pneumonitis."

Natural History

- Acute Phase (wk 1) **(4427)**
  - Edema
  - Hyperplastic pneumocytes
  - Hyaline membranes in alveolar ducts
  - Fibrinous pleuritis
- Organizing Phase (wk 2–3) **(6455)**
  - Hyaline membranes in alveoli
  - Myxoid alveolar fibrosis, sparing paraseptal alveoli
  - Hypertrophic fibroblasts

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

  - Organizing thrombi
- Fibrosing Phase (wk 4–8) **(7079)**
  - Compact alveolar fibrosis
  - Interstitial inflammation and fibrosis
  - Centriacinar overexpansion
  - Honeycomb change

An open biopsy for DAD generally takes place 2–3 wk after the patient first notices shortness of breath. Hyaline membranes at this time are just about gone. There is controversy among physicians regarding whether or not an open lung biopsy is indicated in adult respiratory distress syndrome, because the biopsy usually does not disclose a specific etiology and thus does not change treatment. There is controversy among pathologists regarding whether or not a lung biopsy showing DAD can be used to assess prognosis.

Cause Established Morphologically

- Unknown—90%
- Vasculitis or hemorrhage
- Virus (nuclear inclusions)
- Associated bacteria or pneumocystis
- Thromboemboli or infarction
- Contribution of oxygen
- Clinical history of hypotension or aspiration

BRONCHIOLITIS WITH PATCHY ORGANIZING PNEUMONIA

Bronchiolitis with organizing pneumonia (BPOP) **(6456)** produces nodules of organizing pneumonia 1–2 cm in diameter. The edge of the nodule is convoluted rather than serrated because the process is intra-alveolar rather than interstitial. The center of the nodule may contain immature, intra-alveolar fibrosis obliterating alveolar architecture, but alveoli between nodules are devoid of interstitial fibrosis. Bronchiolitis with percolation of neutrophils through bronchial mucosa and denudation of bronchial mucosa are characteristic of usual interstitial pneumonitis (UIP). Distinction of bronchiolitis with organizing pneumonia **(6981)** from UIP **(6460)** is particularly important because BPOP is responsive to steroids and has a good prognosis.

Clinical and Pathological Features

- Flu with persistent lung disease for several weeks
- Radiograph: patchy airspace consolidation
- Low power: rounded nodules of inflammation separated by normal lung
- High power: bronchiolitis with large amounts of alveolar filling by organizing inflammation and fibrous tissue several weeks in age
- Good response to steroids
- Clinicopathological diagnosis (consensus classification), now "Cryptogenic organizing pneumonia"

Bronchiolitis Obliterans With Organizing Pneumonia: Etiologies

- Organic dusts: thermophilic actinomyces, *Aspergillus*, bird dander. Inorganic dusts: acute silicosis, hard metal disease, asbestos

- Collagen-vascular disease, Wegener's granulomatosis (WG)
- Virus: adenovirus, respiratory syncytial virus, parainfluenza, measles
- Mycoplasma
- Bacteria: *Hemophilus influenzae*, *Hemophilus pertussis*
- Mycobacterium tuberculosis
- Metabolic: uremia, rheumatic fever
- Toxins and drugs: phosgene, nitrous oxides, penicillamine
- Graft-vs-host disease
- Lung transplant rejection

Acute Eosinophilic Pneumonitis

- Acute febrile illness
- Hypoxia
- Not infection nor asthma
- Eosinophils on lavage
- Pathology: like chronic eosinophilic pneumonia, but also with interstitial edema
- Interstitial eosinophils, fibrin and hyaline membranes

Chronic eosinophilic pneumonia (CEP) obscures the alveolar inflammation, but alveoli at the perimeter contain massed histiocytes and eosinophils **(7011)**. Pleural fibrosis is common, but diffuse interstitial fibrosis is not. Eosinophils infiltrate walls of blood vessels **(7038)**.

SUGGESTED READINGS

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Bronchiolitis Obliterans Organizing Pneumonia: Recently Described Clinicopathological Features

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LETTERS

Case 4427

Diagnosis: Lung, open biopsy: Acute and organizing DAD with hemorrhage, microfocal necrosis, and neutrophilic interstitial infiltrate.

The salient histopathology is DAD with hyaline membranes and organizing alveolar and interstitial fibrosis. The process ranges in age from active disease a few days in duration to older disease several weeks in duration. Because hemorrhage of this degree may occasionally be part of DAD, one could explain the hemorrhage without invoking some other disease. This is essentially in agreement with your interpretation.

The microfocal necrosis and interstitial neutrophilic infiltrate can be seen in WG with or without capillaritis and are not part of either DAD or Goodpasture's syndrome. Because Goodpasture's syndrome and WG overlap in approx 20% of cases, an overlap syndrome should be considered in the differential diagnosis. Goodpasture's syndrome may be recurrent in its own right. DAD is not a manifestation of Goodpasture's syndrome.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.

References:

Dahlberg PJ, Kurtz SB, Donadio JV Jr, et al. Recurrent Goodpasture's syndrome. Mayo Clin Proc 1978;53:533–537.

O'Donoghue DJ, Short CD, Brenchley PC, Lawler W, Ballardie FW. Sequential development of systemic vasculitis with anti-neutrophil cytoplasmic antibodies complicating anti-glomerular basement membrane disease. Clin Nephrol 1989;32:251–255.

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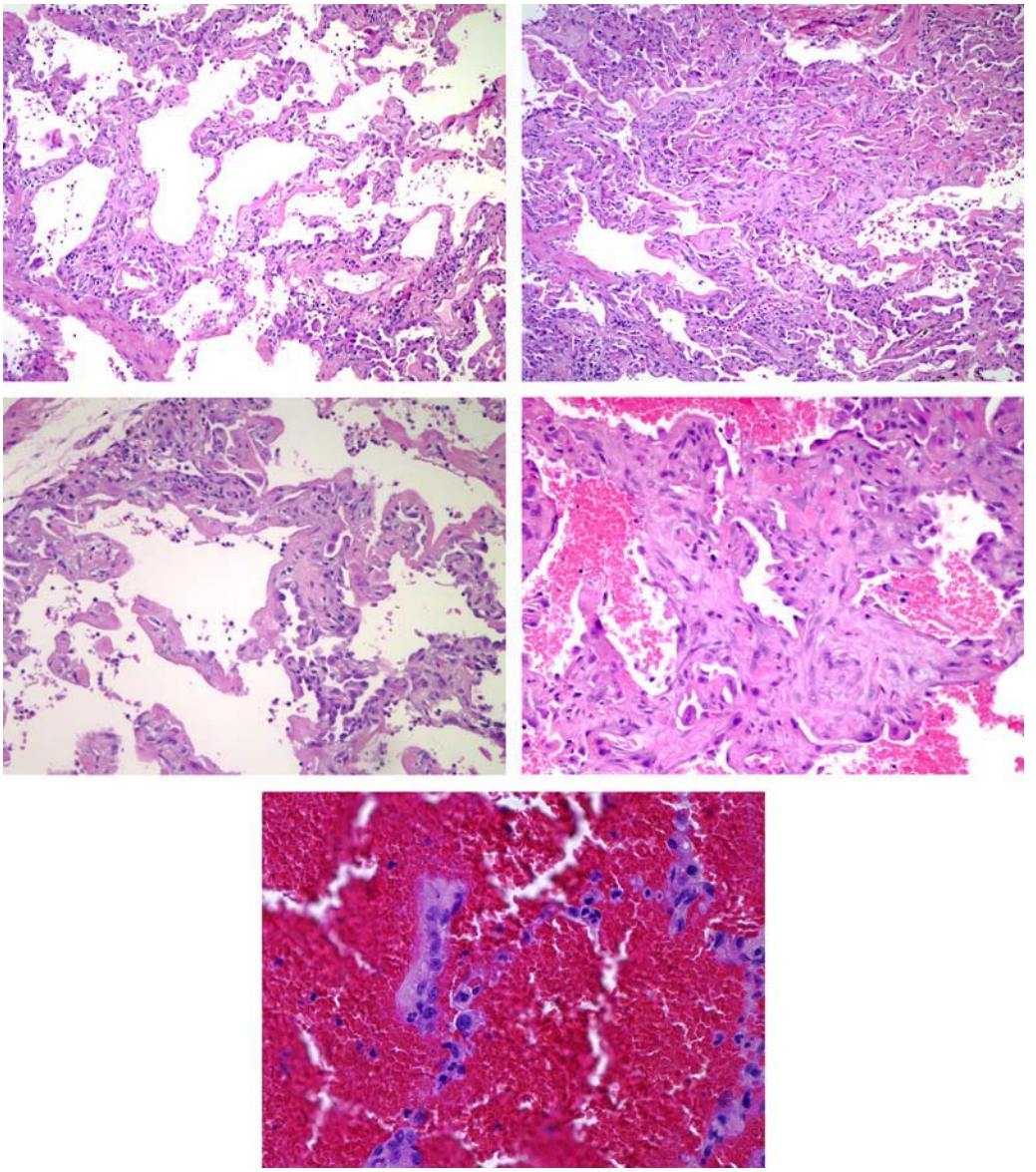


Case 4427 (Chapter 2 – Alveolar Disease)

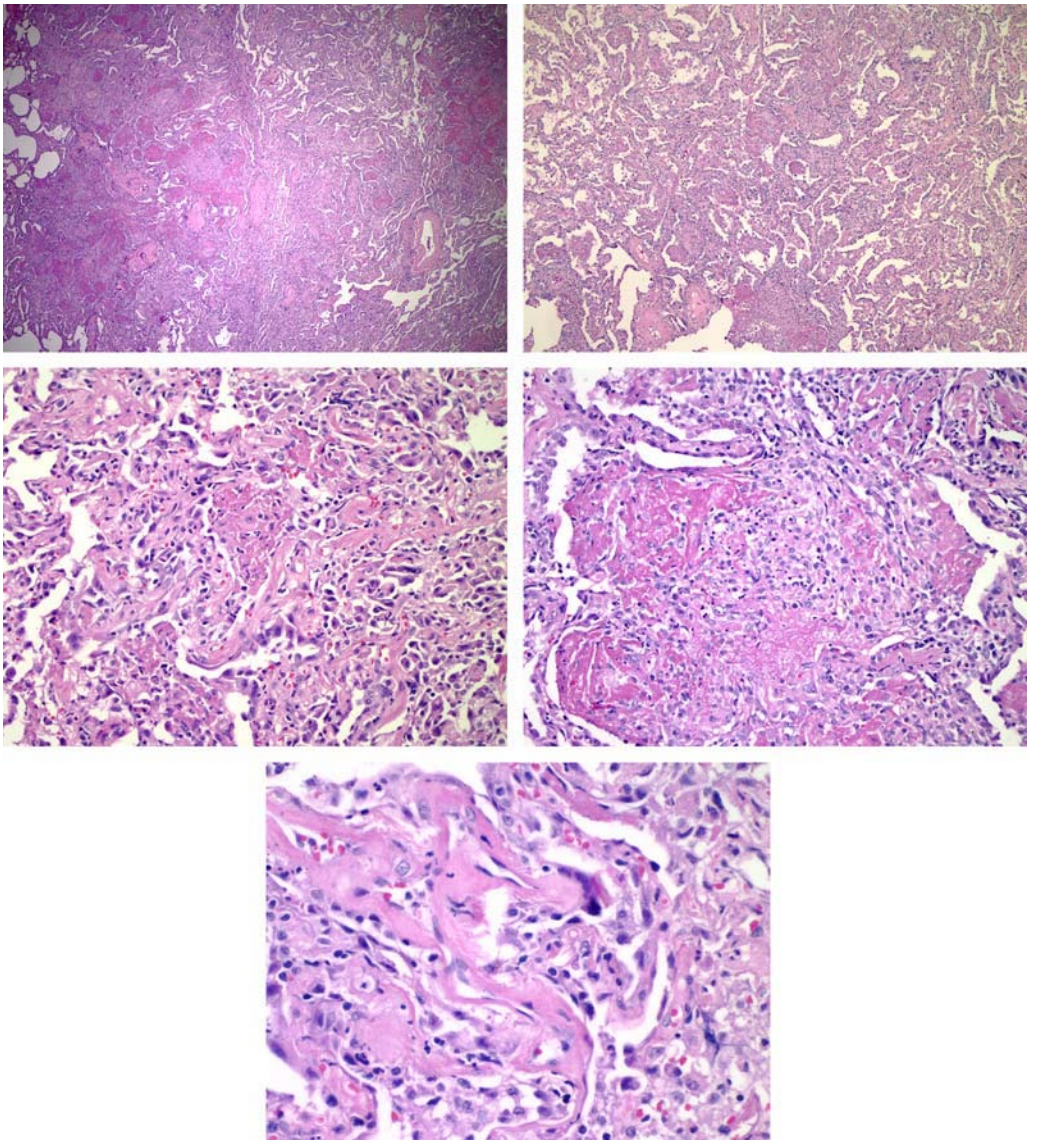
Case 4439

Diagnosis: Lung, open biopsy: DAD and microfocal fibrinous-purulent pneumonia.

The principal disease process is DAD with organizing hyaline membranes, hypertrophy of pneumocytes, and early fibrosis of several days duration. Also present are foci of acute fibrinous pneumonia with neutrophils, which probably represent an infectious component which either precipitated the DAD or has become superimposed upon it. I understand that the patient has been leukopenic due to chemotherapy; gram negative sepsis could precipitate DAD. Because of the fibrinous pneumonia and the occasional multinucleated epithelial giant cells, I considered respiratory syncytial virus in the differential diagnosis and am performing immunopathological investigation for intracellular viral antigens.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone calls.

Sincerely yours,
Eugene J. Mark, M.D.



Case 4439 (Chapter 2 – Alveolar Disease)

Case 6455

Diagnosis: Lung, open biopsy:

1. **Interstitial fibrosis with subpleural honeycomb change.**
2. **DAD, acute.**

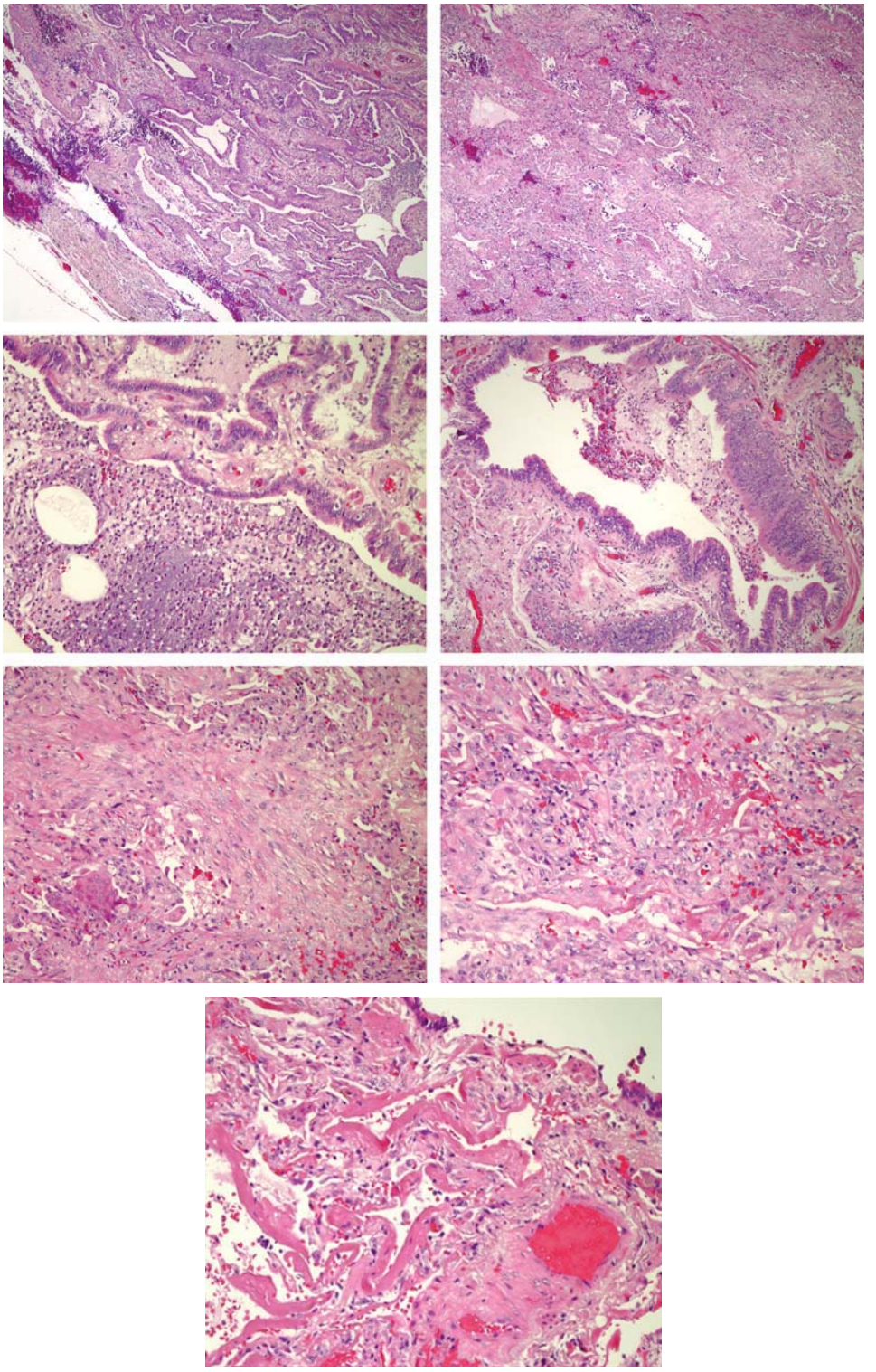
The interstitial fibrosis has smooth muscle hyperplasia and extensive squamous metaplasia. This process is months and probably years in duration. The changes are not specific as to etiology. UIP would enter the differential diagnosis, but bronchiectasis is one condition which is always very difficult to exclude in a patient whose subpleural honeycomb fibrosis is confined to one region of one lung. If we believe that bronchiectasis is present, I would attribute the interstitial fibrosis to that condition.

DAD includes hyaline membranes and organizing alveolar fibrosis. This process appears a few weeks in age with ongoing active disease. The DAD can be independent from the old interstitial fibrosis. Extensive squamous metaplasia probably represents the older disease, but in this case it is difficult to determine whether some epithelial regeneration may be due to the DAD as well. The mucus plugs with neutrophils are part of the honeycomb fibrosis and do not necessarily reflect bacterial pneumonia.

A unifying diagnosis is UIP in an accelerated phase. Since I do not know whether or not an interstitial pneumonitis has been present previously, I would not make a diagnosis of accelerated UIP in this case. On the other hand, if the chest radiographs show bilateral basilar interstitial infiltrates with bilateral honeycomb fibrosis, then I would favor accelerated UIP as a single diagnosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6455 (Chapter 2 – Alveolar Disese)

Case 7105

Diagnosis: Lung, open biopsy: DAD, with regions of eosinophilic pneumonia, cause undetermined.

This case is unusual in that there is a mixture of seemingly disparate elements, that is, (1) an eosinophilic pneumonia and (2) organizing alveolar fibrosis and occasional hyaline membranes characteristic of DAD. The combination of an eosinophilic pneumonia and DAD raises the possibility of acute eosinophilic pneumonia or a drug reaction. Among the many forms of methotrexate-induced drug reaction is DAD, although these cases are rare. Acute eosinophilic pneumonia also could represent an element of hypersensitivity or be idiopathic. Infection, including viruses, cannot be excluded as a cause of the DAD, but viral pneumonia typically does not have the foci of eosinophils seen here. Parvovirus usually causes an interstitial pneumonitis. Usually hantavirus causes edema and fibrin with relatively little inflammation.

We performed stains for organisms (acid-fast, silver, periodic acid-Schiff) on the blocks which you kindly provided, and these stains are negative. No viral inclusions are present.

Thank you for referring this case in consultation. I understand that the patient responded favorably to an initial course of corticosteroids. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 2000;15:373–381.

Buchheit J, Eid N, Rodgers G Jr, Feger T, Yabcoub O. Acute eosinophilic pneumonia with respiratory failure: a new syndrome? Am Rev Respir Dis 1992;145:716–718.

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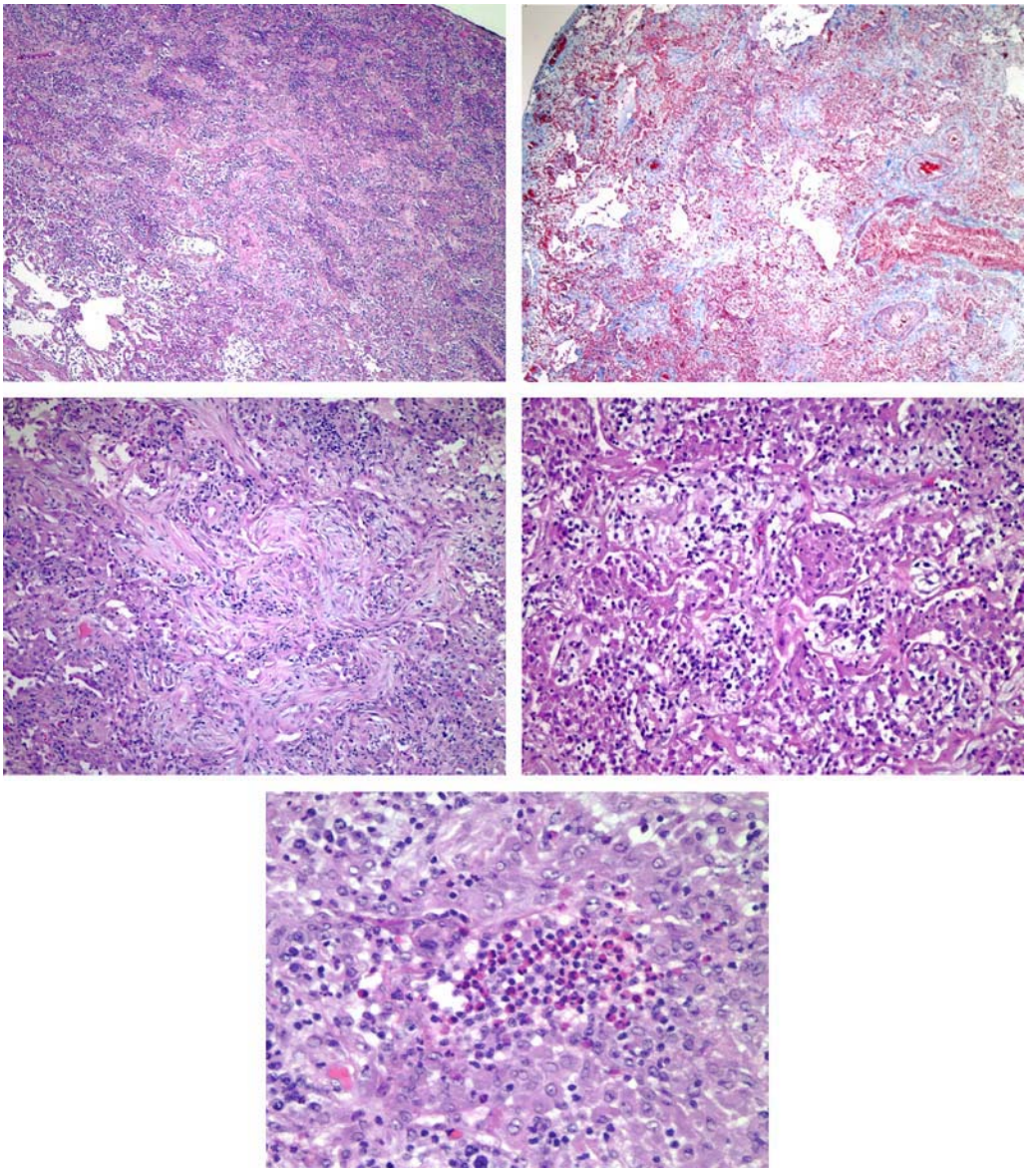


Case 7105 (Chapter 2 – Alveolar Disease)

Case 6925

Diagnosis: Lung, open biopsy:

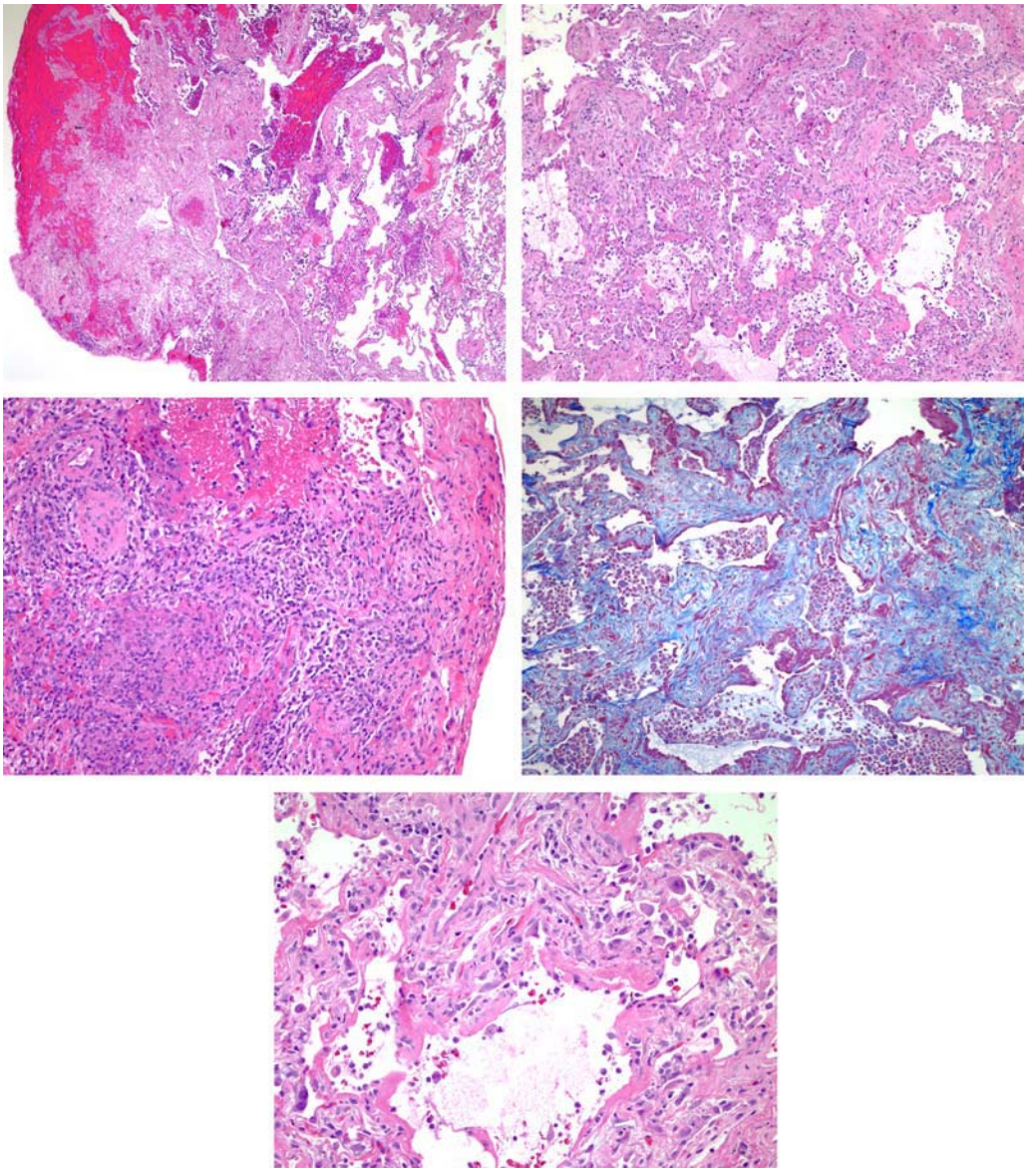
1. **DAD, acute and organizing phase.**
2. **Interstitial fibrosis, old, regional, with hyperplasia of smooth muscle, cause and significance uncertain.**

This case has both active and old disease. I am more confident of the significance of the acute disease than the old disease. Hyaline membranes, interstitial edema, and proliferation of fibroblasts in interstitium and in alveoli indicate DAD (acute interstitial pneumonitis) of a few weeks duration and correlate with the clinical history of recent shortness of breath. The cause of the DAD is not apparent. Possibilities include drug reaction, radiation reaction, viral or mycoplasmal infection, or other. This specimen also shows fibrinous pleuritis as well as one focus of granulomatous inflammation in alveoli beneath the pleura. Methotrexate is one cause of granulomatous reaction of this sort. Most cases of DAD acquired in hospital without a hypoxic episode are enigmatic and idiopathic.

The nature and significance of the old interstitial fibrosis (trichrome stain) is also not easy to determine. Underlying UIP is possible, but there is no diffuse pneumonitis, and it is also possible that the fibrosis is related to the specimen coming from the tip of the lobe and nothing more significant. In any case, the active disease overwhelms the old disease and is therefore the clinically significant one in my opinion.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6925 (Chapter 2 – Alveolar Disease)

Case 6876

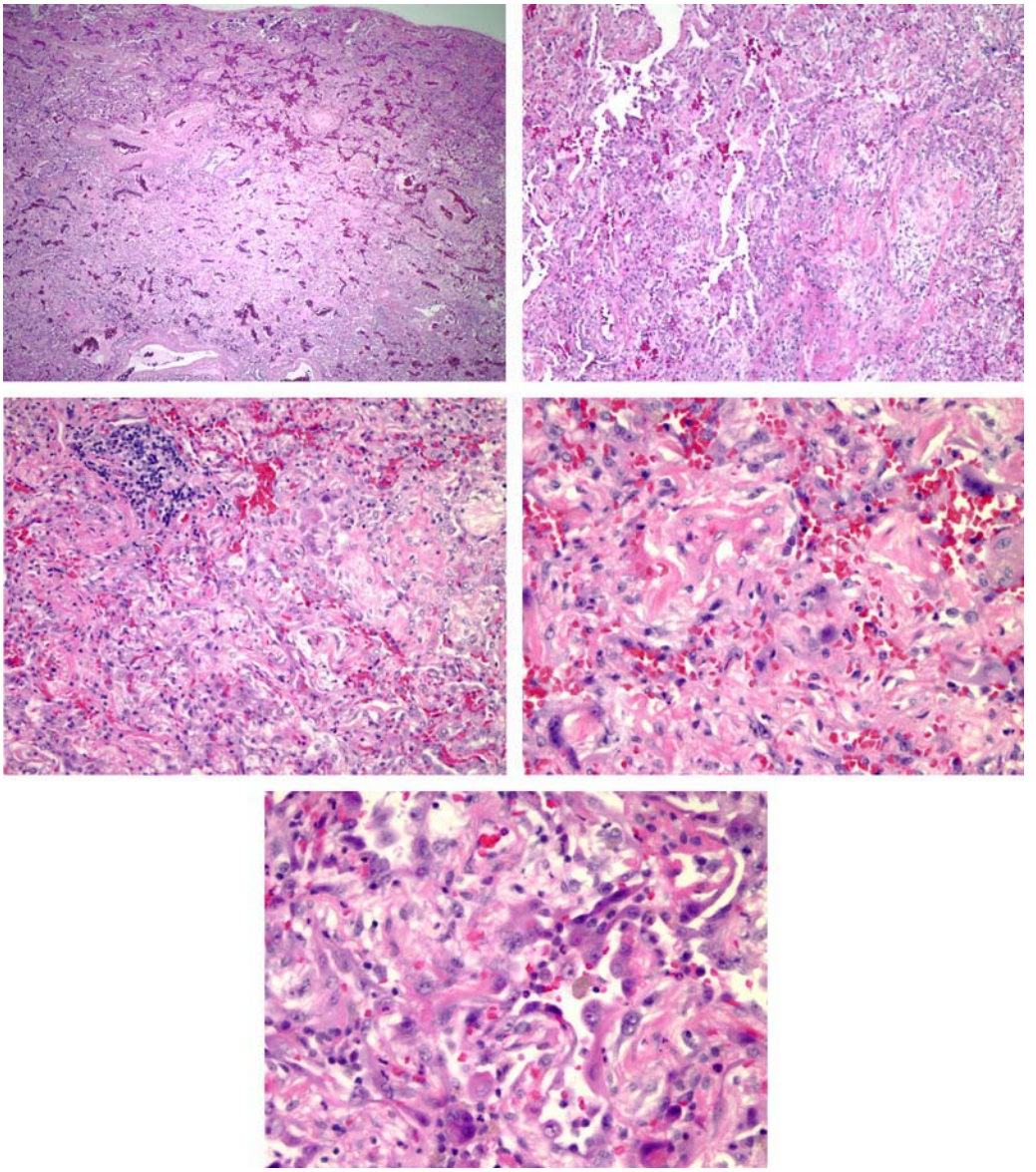
Diagnosis: Lung, open biopsy: DAD, late organizing phase.

This biopsy shows florid alveolar fibrosis with early incorporation into the interstitium, associated with hyaline membranes and atypical pneumocytes. The disease is subacute and appears histologically approx 6 wk of age, which is slightly more advanced than that stage at which DAD is usually biopsied. For this reason, there is a greater component of myxoid interstitial fibrosis and a lesser component of hyaline membranes. This histology has been termed acute interstitial pneumonitis by some authors. Patients with a subacute course of several weeks with this histology fit into the clinicopathological rubric of Hamman-Rich syndrome.

The old subpleural honeycomb fibrosis of UIP and the fibroblastic proliferation in alveoli in the accelerated phase of that condition are not apparent. No diffuse interstitial lymphocytic infiltrate is present.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6876 (Chapter 2 – Alveolar Disease)

Case 6851

Patient: 46-yr-old female

Diagnosis: Lung, open biopsy: Eosinophilic pneumonia, type uncertain, ? acute eosinophilic pneumonia.

The predominance of the eosinophils and their association with histiocytes make me believe that this disease is principally an eosinophilic pneumonia. Having said that, there are two possibilities: (1) acute eosinophilic pneumonia; (2) CEP/bronchiolitis obliterans organizing pneumonia (BOOP) overlap syndrome. Acute eosinophilic pneumonia of the sort that can cause adult respiratory distress syndrome can be an unpredictable disease, and its cause is generally unknown. One can see hyaline membranes and alveolar fibrosis of the sort seen in diffuse alveolar damage, and I suspect that is the situation here. The other possibility is CEP/BOOP overlap syndrome. The pathology is consistent with that interpretation, but against it is the activity of the fibrosis and the atypia of the proliferating epithelial cells, as you indicate. I favor acute eosinophilic pneumonia, possibly in a resolving phase.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

Tazelaar HD, Linz LJ, Colby TV, Myers JL, Limper AH. Acute eosinophilic pneumonia: histopathologic findings in nine patients. Am J Respir Crit Care Med 1997;155:296–302.

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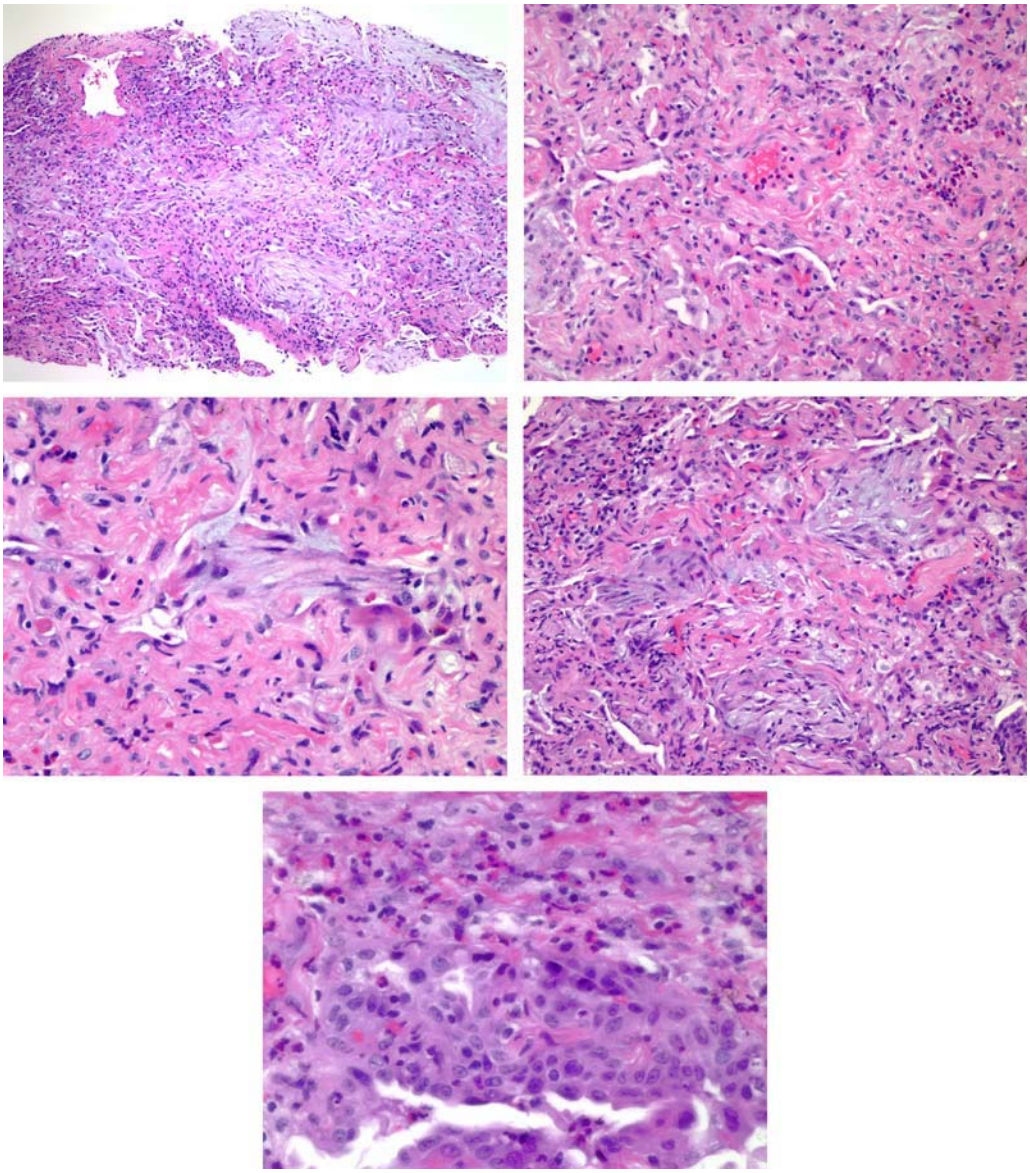


Case 6851 (Chapter 2 – Alveolar Disease)

Case 6546

Diagnosis: Lung, open biopsy:

1. **DAD, organizing, with prominent fibrinous exudate and neutrophils.**
2. **Arterial thrombosis or thromboembolism or both.**
3. **Multiple neuroendocrine cell hyperplasia.**

The principal pathology is a marked exudate of organizing intra-alveolar fibrin with atypia of pneumocytes and fibroblasts. This can best be described as DAD but is unusual, in that the process is focal (one lobule involved and an adjacent lobule uninvolved), more neutrophils than usual for DAD, and arterial clots with neutrophils away from the DAD. I do not believe the DAD is infectious but cannot exclude that possibility. The arterial clots are probably thromboses due to the DAD. I cannot exclude thromboembolic disease, including septic thromboemboli as a trigger for the DAD. The blood vessels have rare subendothelial mononuclear cells, which could represent either blasts or activated lymphocytes. Overall, the pathology is not that of a leukemic infiltration of the lung. DAD is relatively common at autopsy in patients dying with leukemia, and its etiology in these patients is unclear. Multifocal neuroendocrine cell hyperplasia might cause obstructive or restrictive lung disease in another patient, but in this patient this disease is not of significance at this time. There is extensive organizing fibrinous pleuritis and mesothelial hyperplasia suggesting a chronic effusion. Lobules of alveolar fibrin and the pleuritis could represent ischemia and early infarction, additional evidence raising the possibility of thromboembolism.

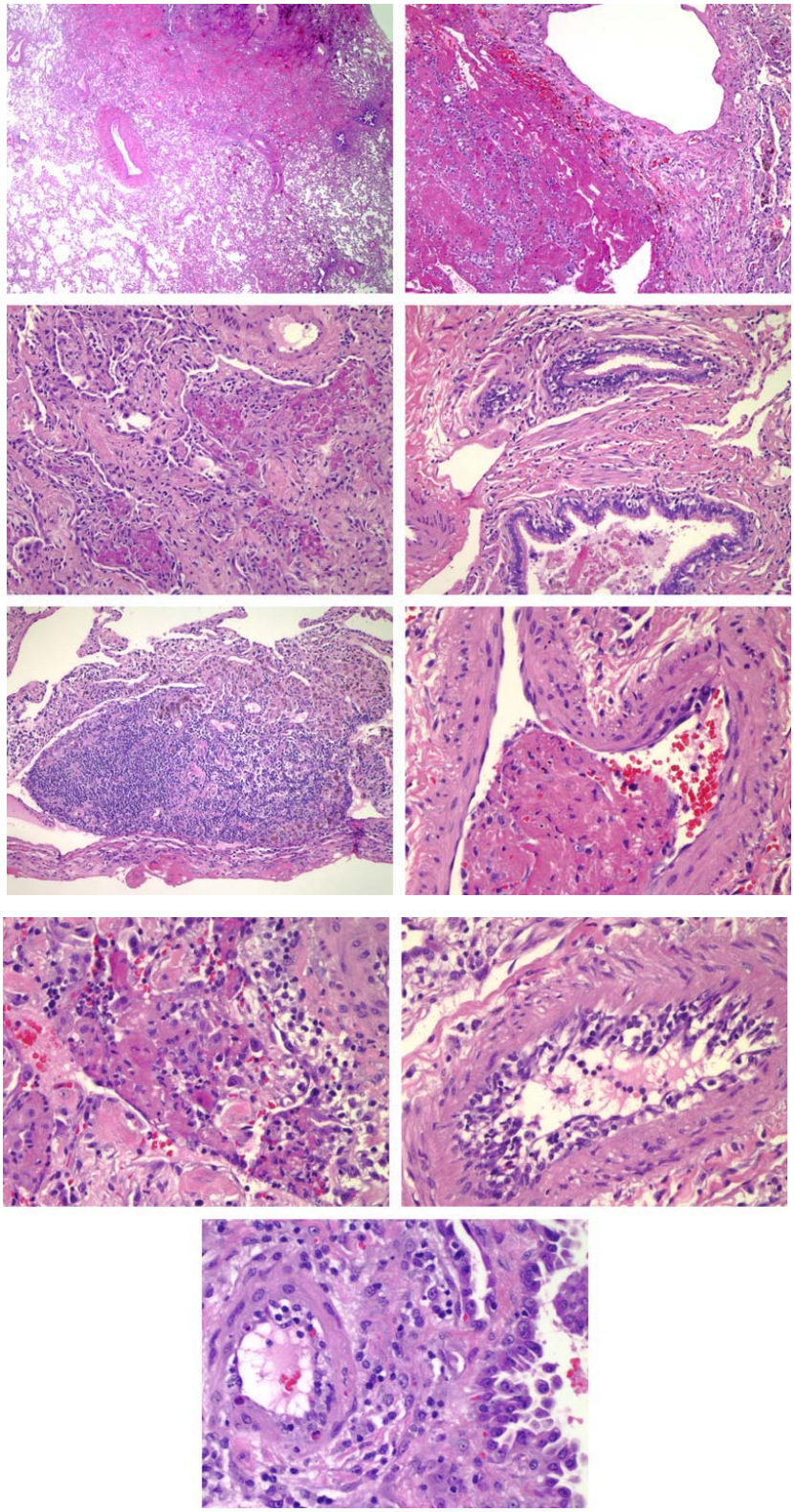
Thank you for referring this case in consultation. This is essentially in agreement with your interpretation. Please keep me informed of any follow-up. Your special studies are hereby returned. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

Doran HM, Sheppard MN, Collins PW, et al. Pathology of the lung in leukaemia and lymphoma: a study of 87 autopsies. Histopathology 1991;18:211–219.

Tryka AF, Godleski JJ, Fanta CH. Leukemic cell lysis pneumonopathy. Cancer 1982;50:2763–2770.



Case 6546 (Chapter 2 – Alveolar Disease)

Case 7022

Diagnosis: Lung, autopsy:

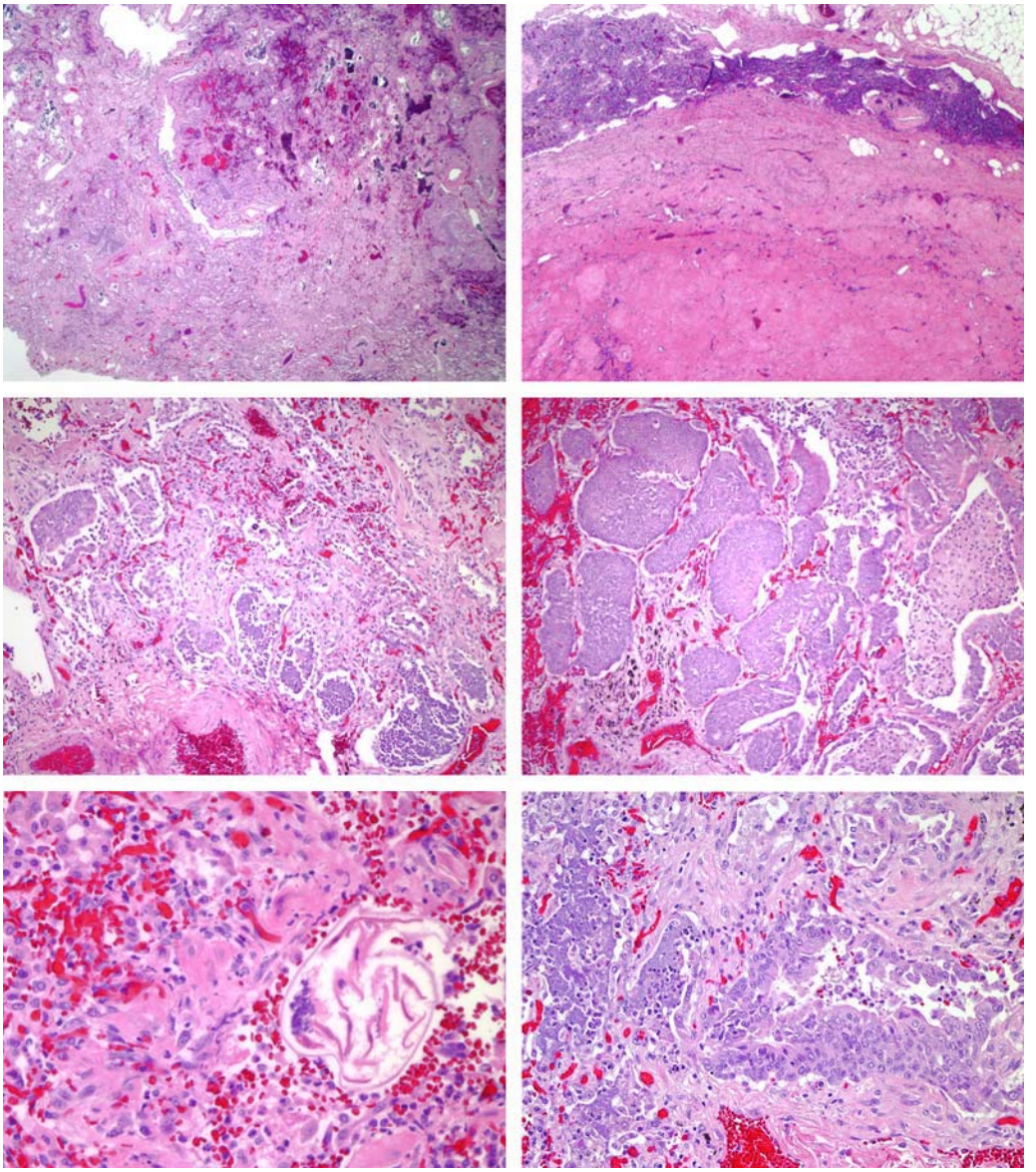
1. **DAD, late organizing phase.**
2. **Acute purulent bronchitis and microfocal bronchopneumonia.**

Lymph node (hilar): Hyalinized scars.

The lung has extensive organizing DAD with proliferating fibroblasts in alveoli and interstitium and distortion of architecture. The process appears several weeks old and possibly older. The cause of this DAD is not apparent. Possibilities include sequel to viral infection, hypoxic episodes, aspiration or idiopathic. Foci of squamous metaplasia in terminal airways produce tumorlets of squamous type. These reflect healing bronchiolar injury as might be seen with infection. Radiotherapy effect and chemotherapy effect cannot be excluded, but there are no specific markers in this tissue to suggest any specific drug, and the intimal hyperplasia of arteries as seen with radiotherapy is not present. The acute purulent bronchitis is a terminal event and appears only a few days old. No malignancy is present. The hyalinized scars in the lymph nodes could represent prior sites of Hodgkin's disease.

Thank you for referring this case in consultation. This is an elaboration of our earlier telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7022 (Chapter 2 –Alveolar Disease)

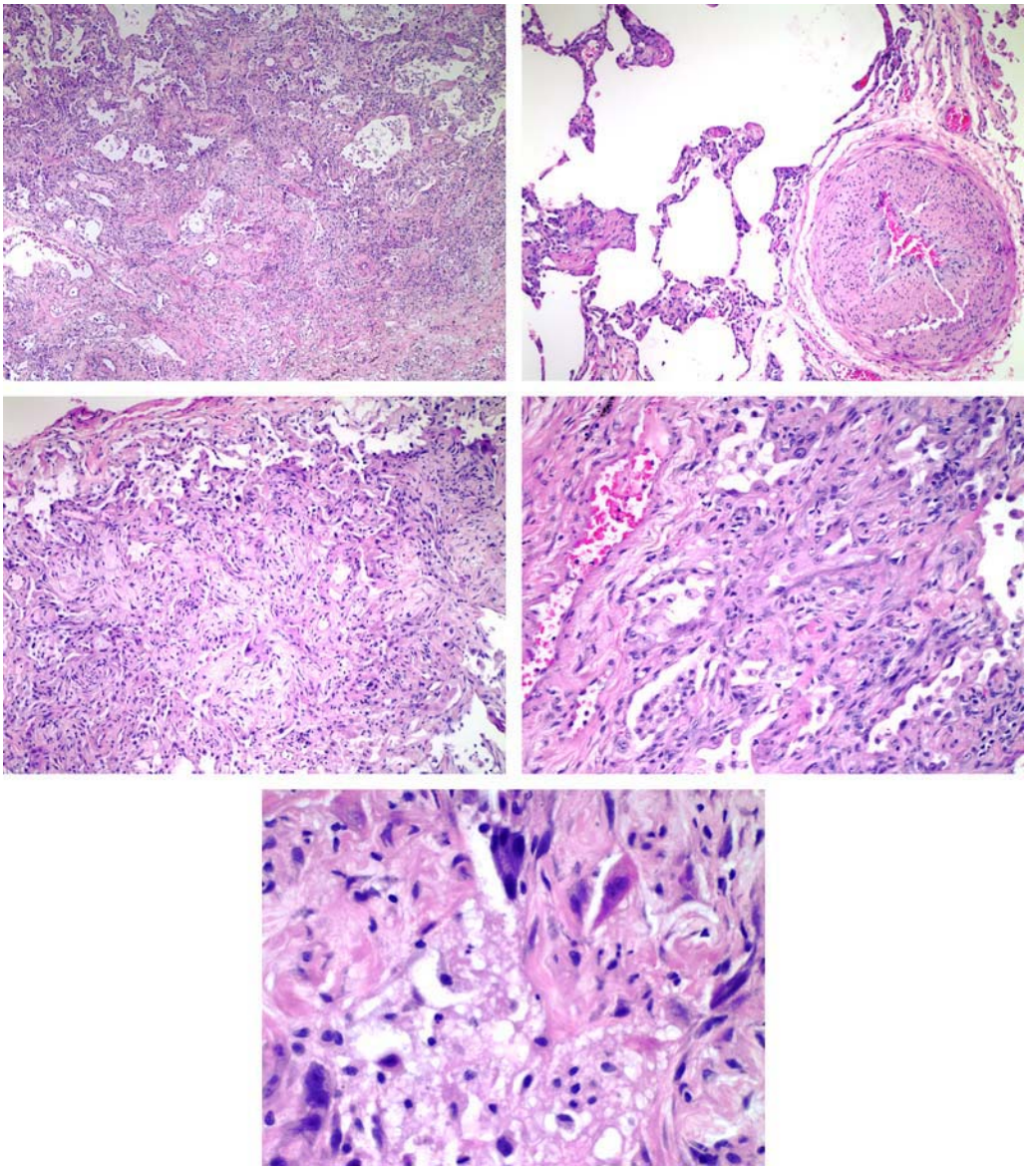
Case 7079

Diagnosis: Lung, open biopsy: DAD, late organizing and fibrosing phase.

Intra-alveolar myxoid fibrosis undergoes extensive incorporation into the interstitium. The process involves the entire specimen. The character of this fibrosis indicates a process several weeks in duration and ongoing. There is moderate atypia of pneumocytes and fibroblasts. The above constellation of findings is best explained as a late organizing phase of DAD (also known as acute interstitial pneumonitis). Hyaline membranes, which are the usual marker for DAD, are not apparent, but they disappear in DAD that has continued for more than a few weeks. A small amount of fibrin in alveoli is consistent with DAD. The principal differential diagnosis is UIP in an accelerated phase. Although there is some older fibrosis of months duration and old vascular sclerosis, the older disease is not sufficient for a diagnosis of UIP, and I do not favor this interpretation. No malignancy is present. No granulomas are present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7079 (Chapter 2 – Alveolar Disease)

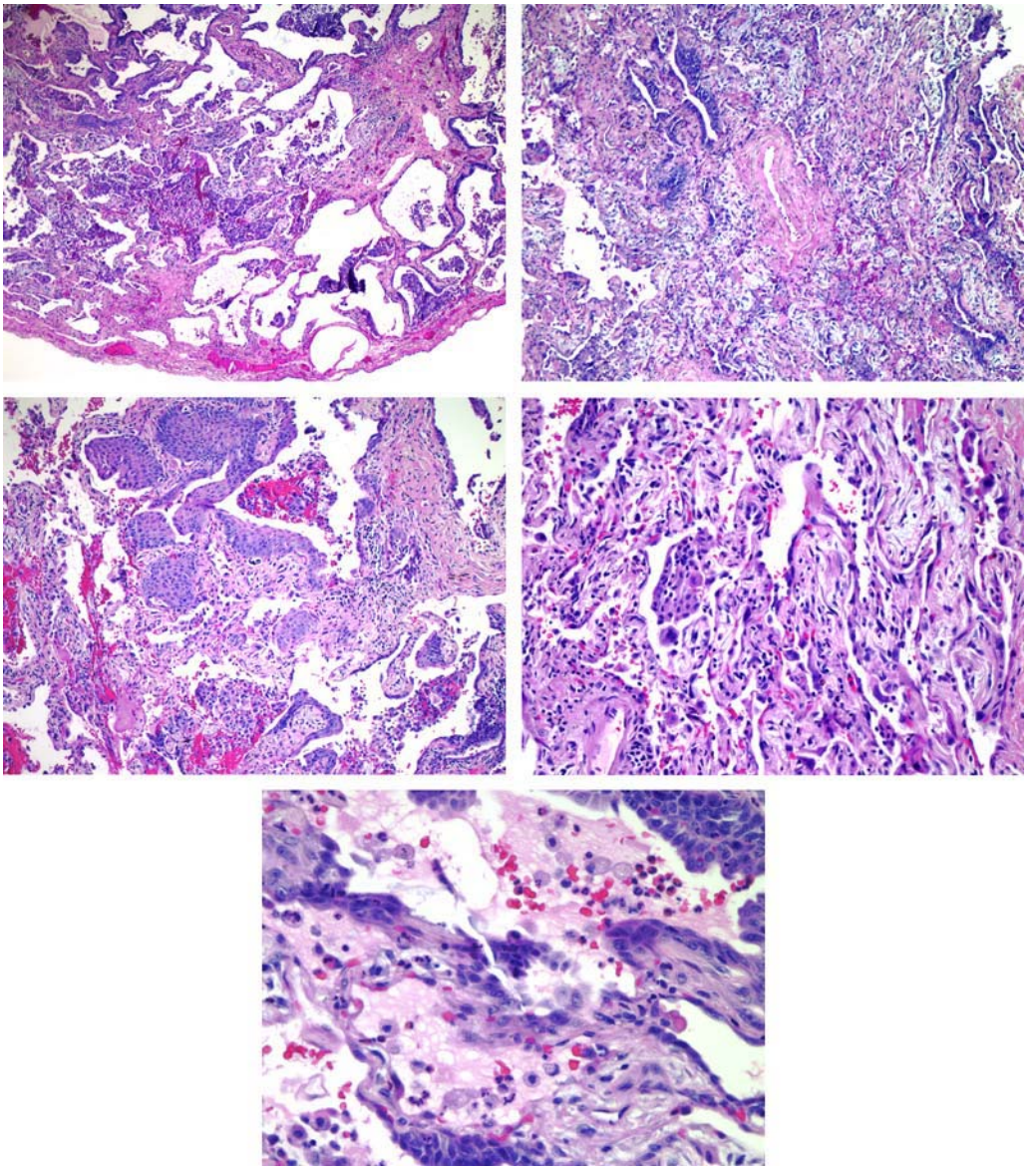
Case 7146

Diagnosis: Lung, open biopsy: Organizing interstitial fibrosis and focal alveolar inflammation and fibrosis, ? resolving phase of DAD, cause unknown.

This case is difficult, because there is a very diffuse but pronounced interstitial fibrosis associated with focal bronchiolar fibrosis as well as alveolar inflammation and fibrosis. The character of the organizing fibrosis in the interstitium, which is approximately 4 wk old, is most easily explained as a late resolving phase of DAD at a stage which is not usually sampled. Some authors would term this acute interstitial pneumonitis. The disease is older than the reported clinical symptomatology of 5 d of respiratory distress. Squamous metaplasia is extensive, and bronchioles contain neutrophils and histiocytes. These changes suggest a bronchiolar component to the condition, and we considered BOOP in the differential diagnosis. However, the diffuseness of the interstitial fibrosis is more in keeping with DAD, although an occasional case of BOOP is associated with diffuse interstitial fibrosis and has been termed bronchiolitis with interstitial pneumonia (BIP). A unifying diagnosis would be a viral bronchiolitis and pneumonia that progressed to DAD, and this is the interpretation I prefer but cannot prove. No active infection is apparent. No viral inclusions are present. No hyaline membranes are present. I do not believe this represents UIP because the disease is for the most part of uniform age, although there are a few areas of older scarring beneath the pleura. My morphological interpretations are essentially in agreement with your interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7146 (Chapter 2 – Alveolar Disease)

Case 7024

Diagnosis: Lung, open biopsy: Focal organizing pneumonia and fibrosis with scarred bronchioles and follicular lymphoid hyperplasia, nondiagnostic, consistent with resolved and ongoing BPOP with lymphoid hyperplasia.

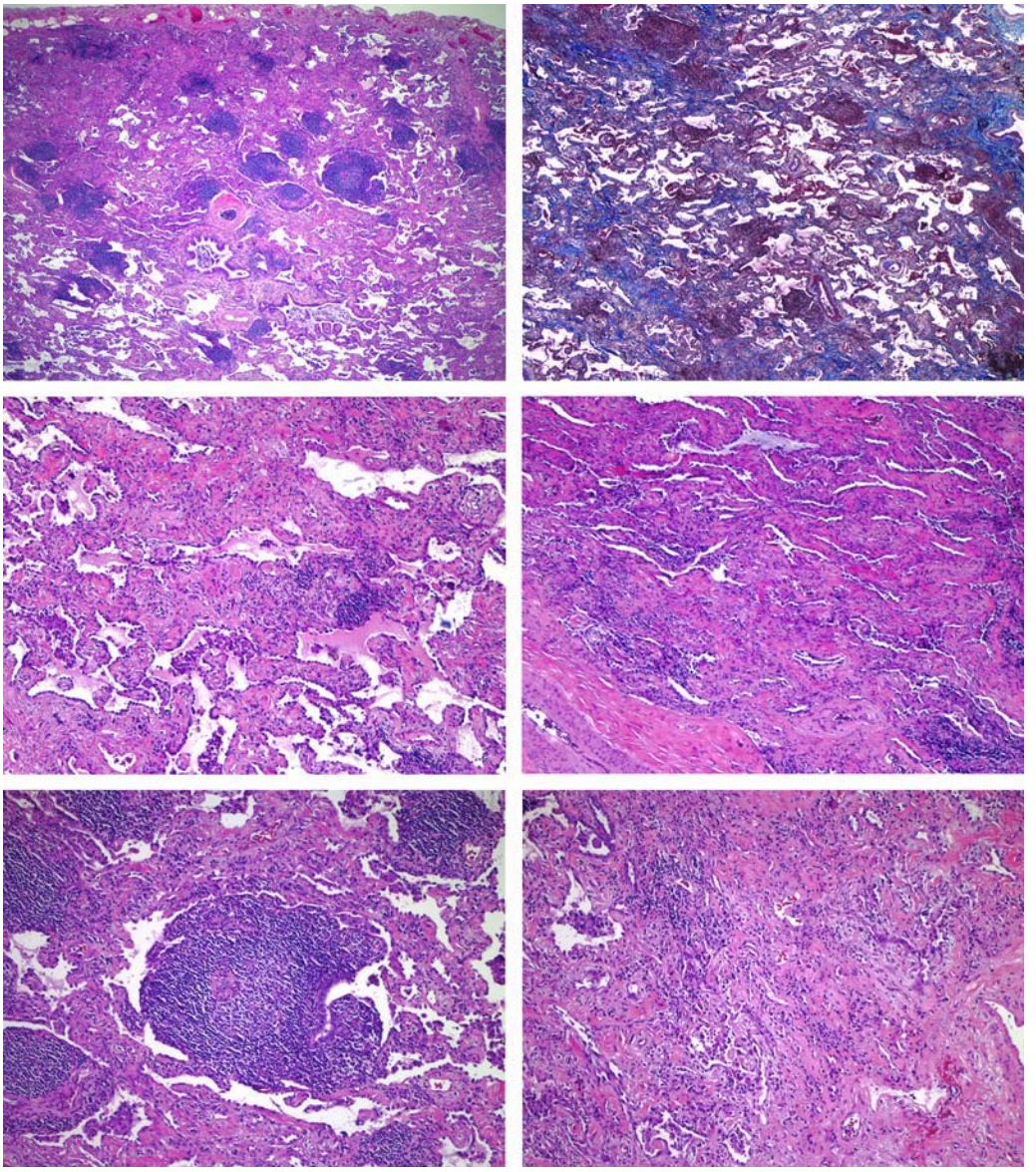
This biopsy is unusual because of the diffuseness of the interstitial fibrosis and the prominent hyperplasia of the bronchus-associated lymphoid tissue. A few lymphoid follicles with germinal centers are present. Focal old scarring is present. Some of the scars with obliterated bronchioles in their centers make me consider BOOP in a late phase, although the classic branching tufts of fibrous tissue in conducting airways as seen in subacute BOOP are not prominent. There is also an active pneumonia by virtue of edema and hyperplastic pneumocytes. The reported clinical and radiographic findings would be consistent with BOOP. Some regions of the lung with more global scarring could be described as chronic organizing pneumonia (COP) rather than BOOP. The British tend to use the term COP for cases that do not have a prominent bronchiolar component.

The differential diagnosis includes so-called nonspecific interstitial pneumonitis. I cannot exclude this possibility, but I do not like to make this diagnosis when a more specific diagnosis is possible, and I believe that the latter situation is present here.

The presence of the extensive fibrosis and the edema (trichrome stain) is not that of lymphocytic interstitial pneumonitis (LIP). The lymphoid hyperplasia makes one consider a hypersensitivity reaction, collagen-vascular disease, immunological disease and Sjogren's syndrome as possible etiologies for the fibrotic and inflammatory changes. Follicular bronchiolitis enters into the differential diagnosis, but usually follicular bronchiolitis does not give the degree of diffuse interstitial fibrosis as is present here. I do not favor a diagnosis of lymphocytic lymphoma. Demonstration of light chain restriction is not reliable on tissue fixed in formalin. If a clinical suspicion of malignant lymphoma arises in the future, tissue might be saved frozen for immunopathological study.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7024 (Chapter 2 – Alveolar Disease)

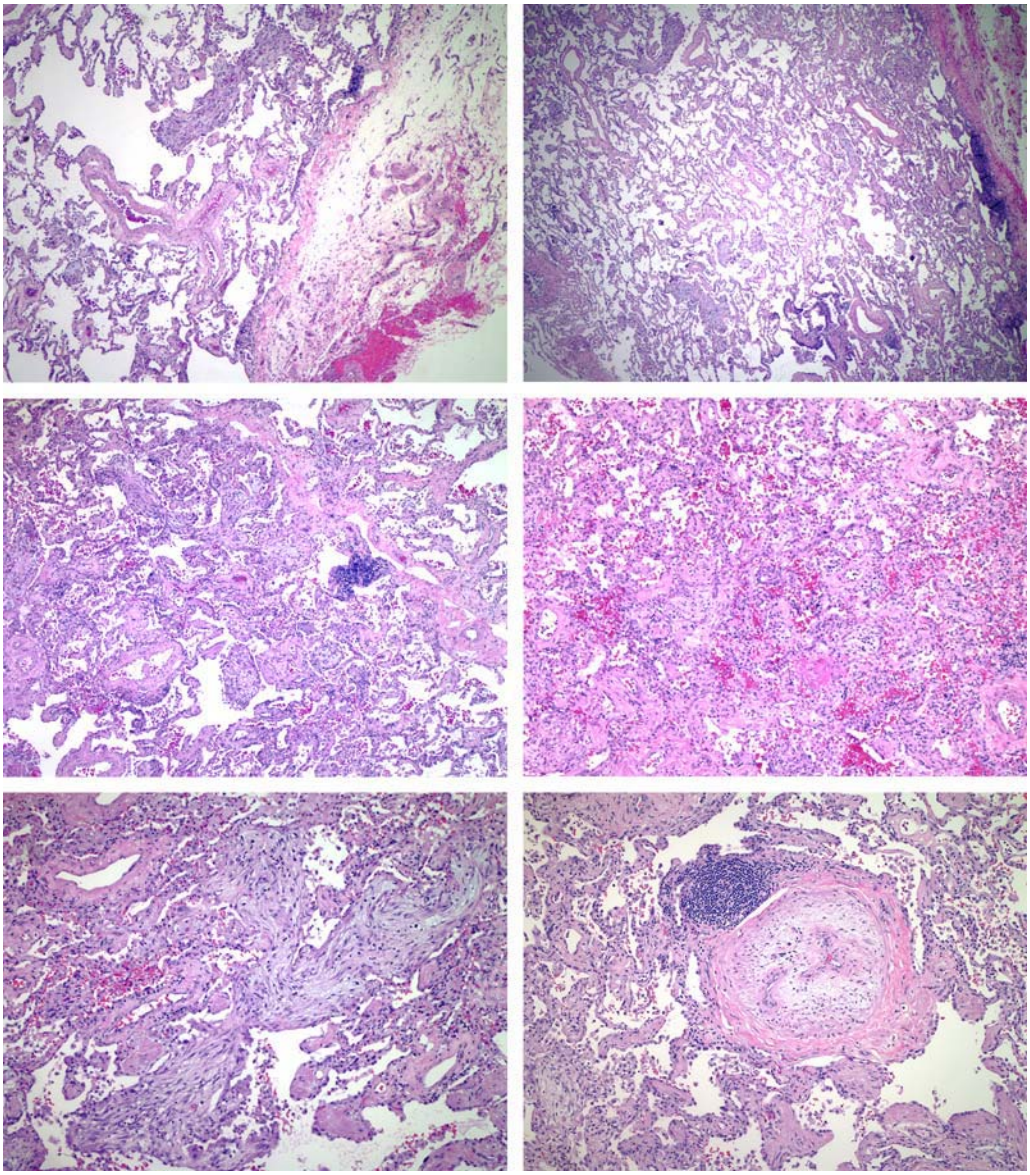
Case 6456

Diagnosis: Lung, open biopsy: BPOP, mid organizing phase.

The branching tufts of myxoid fibrous tissue in respiratory bronchioles and alveolar ducts characterize bronchiolitis obliterans (BO). A moderate amount of organizing alveolar inflammation and fibrosis is also present and constitutes the patchy organizing pneumonia. Edematous pleural adhesion is present as well. I detect no pulmonary emboli in these sections. Although organizing fibrosis can be part of thromboembolic hemorrhage or infarction, I appreciate no infarction and only minimal hemorrhage. I do not believe the BO could be attributed to an embolus. Therefore, I believe BPOP is the best clinicopathological diagnosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6456 (Chapter 2 – Alveolar Disease)

Case 6514

Diagnosis: Lung, open biopsy:

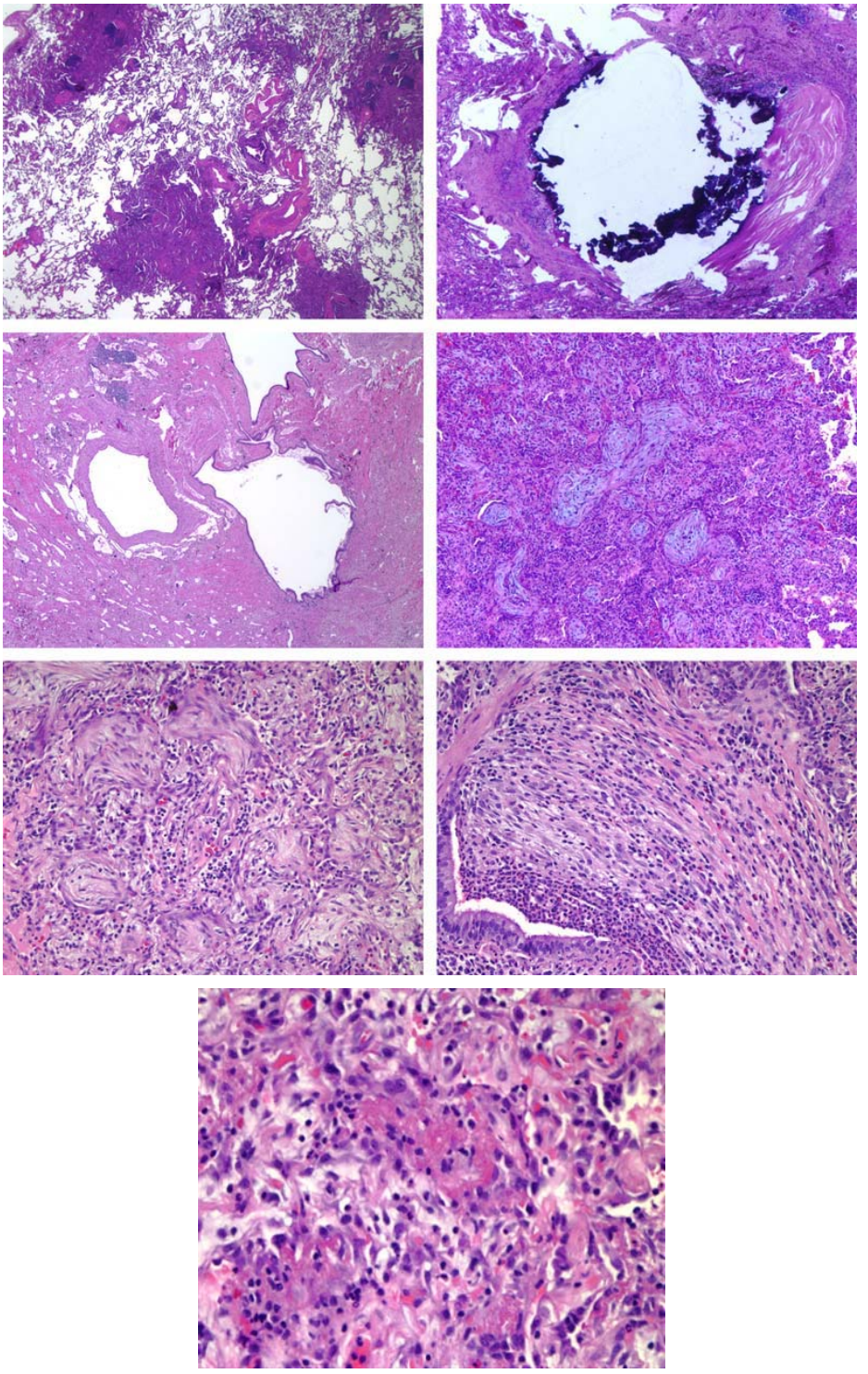
1. **BPOP, with neutrophils and eosinophils and granulomatous inflammation.**
2. **Scar with bronchiectasis.**

An acute purulent bronchiolitis with eosinophils is associated with organizing fibrinous pneumonia in alveoli of a few weeks duration. The process appears multifocal on the slides and constitutes BPOP. Also present in several slides are fibrous scars of months or years duration associated with bronchiectasis, the latter of which may be of traction type secondary to the scar or alternatively causing the scar. I believe the scarring is a process separate from the BPOP because it is so much older. A calcified nodule is present in one scar. No malignancy is present. Blood vessels appear normal.

I do not know the cause of the BPOP. The purulence suggests infection, but the granulomatous features suggest either aspiration or hypersensitivity reaction.

Thank you for referring this case in consultation. This is essentially in agreement with your interpretation and with that of another pathologist, who contacted you during my absence. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6514 (Chapter 2 – Alveolar Disease)

Case 6513

Diagnosis: Lung, open biopsy:

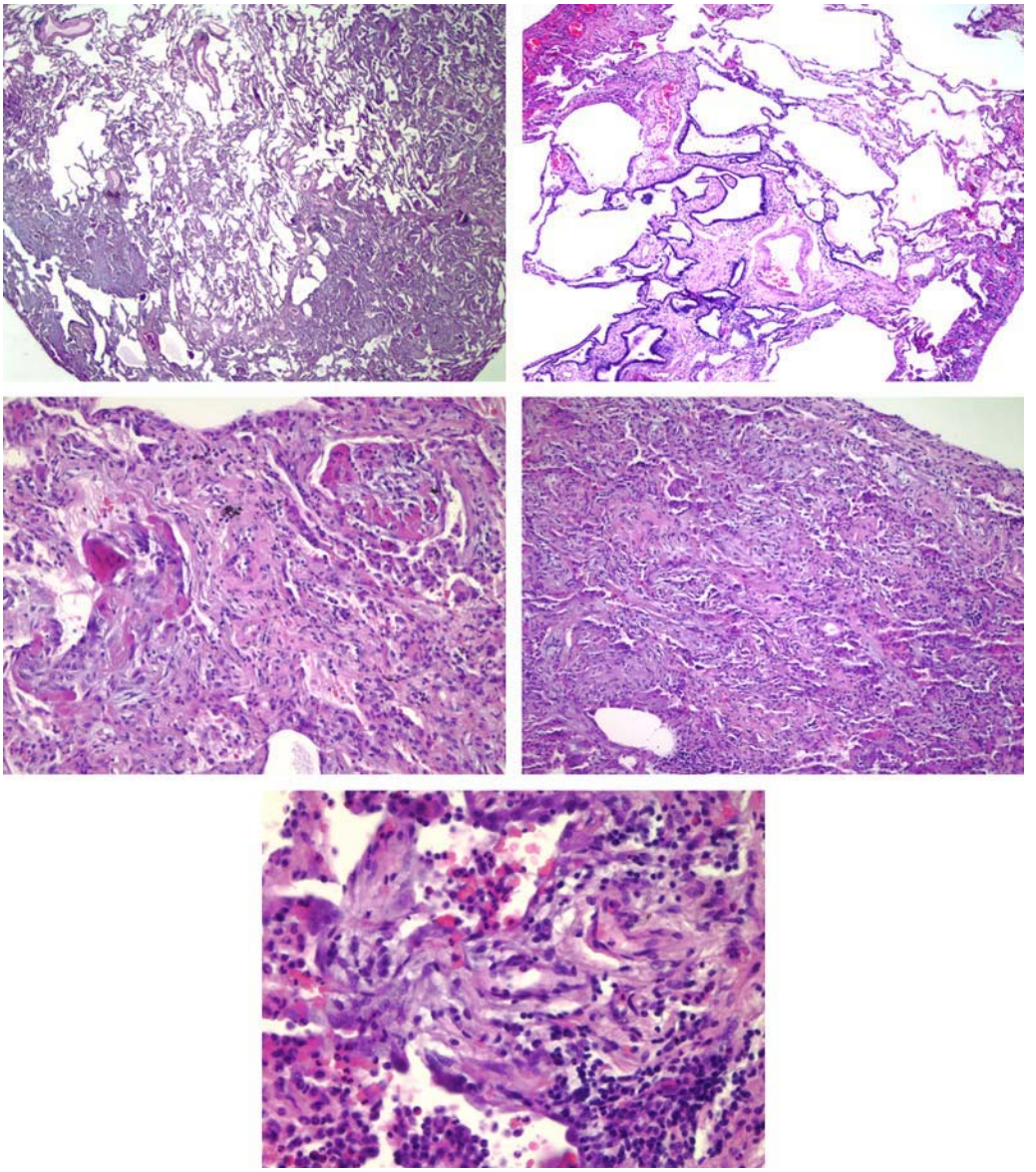
1. **Focal organizing fibrinous and purulent pneumonia, ? BPOP.**
2. **Interstitial fibrosis with Lamberthosis.**

The principal pathology is multifocal organizing pneumonia. The organization involves fibrin in some areas and neutrophils in other areas. Organizing intra-alveolar fibrosis is a few weeks in duration. Although the process is not particularly bronchiolocentric or associated with BO, the multifocality of the process is consistent with BPOP. Separate is old interstitial fibrosis which is months or years in age. This is associated with extension of respiratory epithelium to line peribronchiolar alveoli. This process, techinically termed Lamberthosis, could represent prior bronchiolar disease and thus a prior episode of BPOP.

The pathology does not suggest UIP, desquamative interstitial pneumonitis (DIP), or organizing DAD. The cause of the BPOP is uncertain. Infection and hypersensitivity reaction and collagen-vascular disease are generally the leading possibilities. Blood vessels are normal. There is no evidence of malignancy. There are no granulomas.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6513 (Chapter 2 – Alveolar Disease)

Case 6795

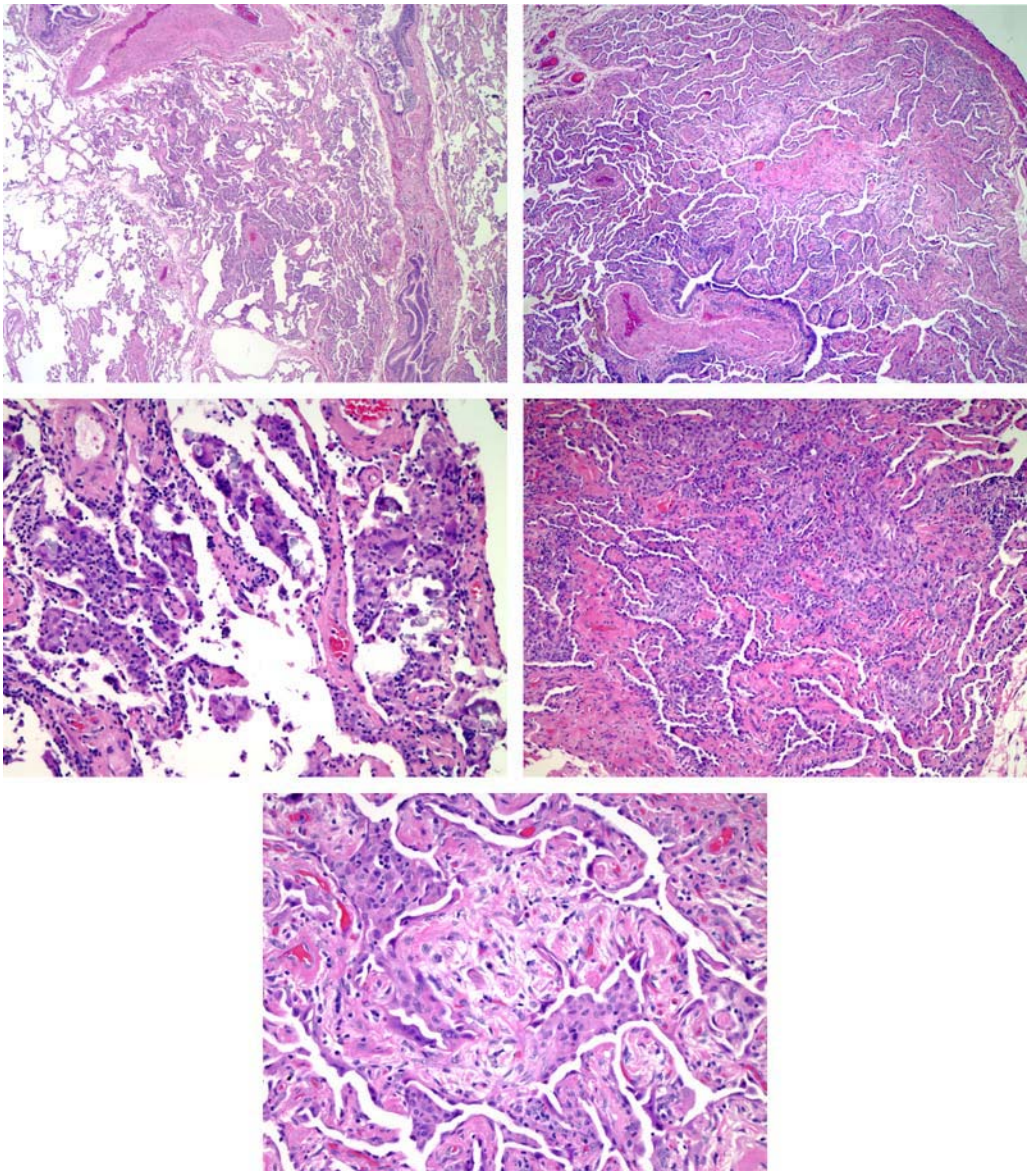
Diagnosis: Lung, open biopsy: BPOP, with focal DIP-like change, granulomatous inflammation, and focal scarring.

The poorly defined nodules of alveolar fibrosis with branching tufts of fibrosis in bronchioles indicate that the primary process is BPOP. The case is complicated because there is more advanced fibrosis than is usually encountered in that condition. However, I do not believe spatial or temporal variation characteristic of UIP is present, and the active fibrosis of UIP is not apparent. Features are present and raise the possibility of hypersensitivity as a cause for the disease. Many blue bodies are present, as you indicate. These are associated with the histiocytic inflammation of the DIP-like reaction, which in this case is nonspecific.

Some pathologists might term this a nonspecific interstitial pneumonitis in a fibrosing phase. I believe the histology is best considered as BPOP with the various features listed above.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



6795 (Chapter 2 – Alveolar Disease)

Case 6679

Diagnosis: Lung, open biopsy: BPOP and collections of purulent inflammation, cause undetermined.

OP associated with intrabronchiolar fibrosis and forming nodular consolidation characterizes BPOP. The disease is active, with a large amount of fibrin. The purulent foci are somewhat unusual in BPOP and raise the possibility of an infectious etiology. BPOP can occur as the morphology of some drug reactions, but I am not aware of its appearance as part of amiodarone toxicity. I do not see the numerous vacuolated histiocytes in interstitium or diffuse pneumonitis or DAD, three processes that are generally described in amiodarone toxicity. However, I cannot absolutely exclude amiodarone as a cause of this process.

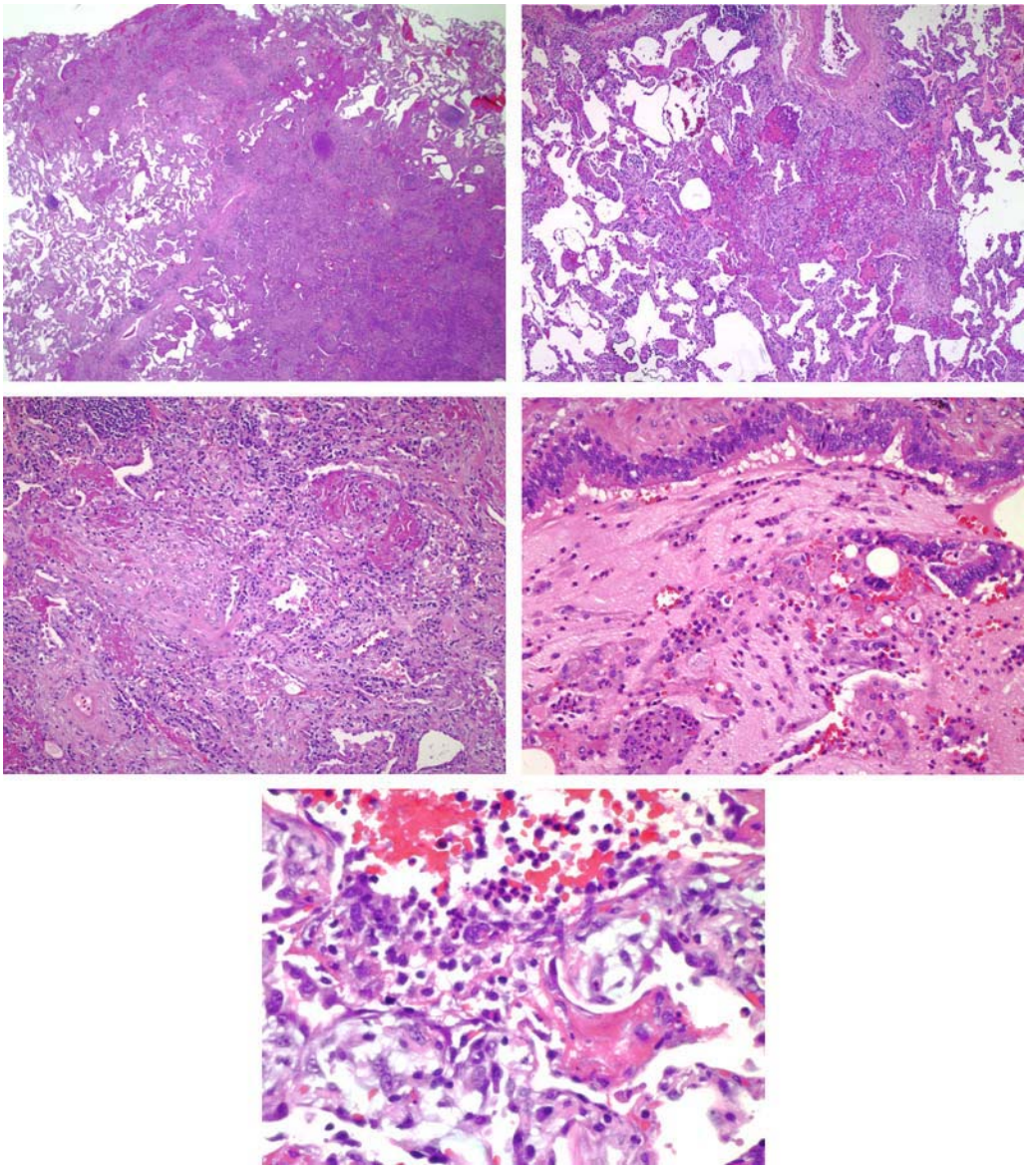
Thank you for referring this case in consultation. This is a confirmation of my telephone call. Results of the electron microscopic examination will be reported separately from our electron microscopy laboratory.

Sincerely yours,
Eugene J. Mark, M.D.

References:

Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part 1). Chest 1988;93:1067–1075.

Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part 2). Chest 1988;93:1242–1248.



Case 6679 (Chapter 2 – Alveolar Disease)

Case 6674

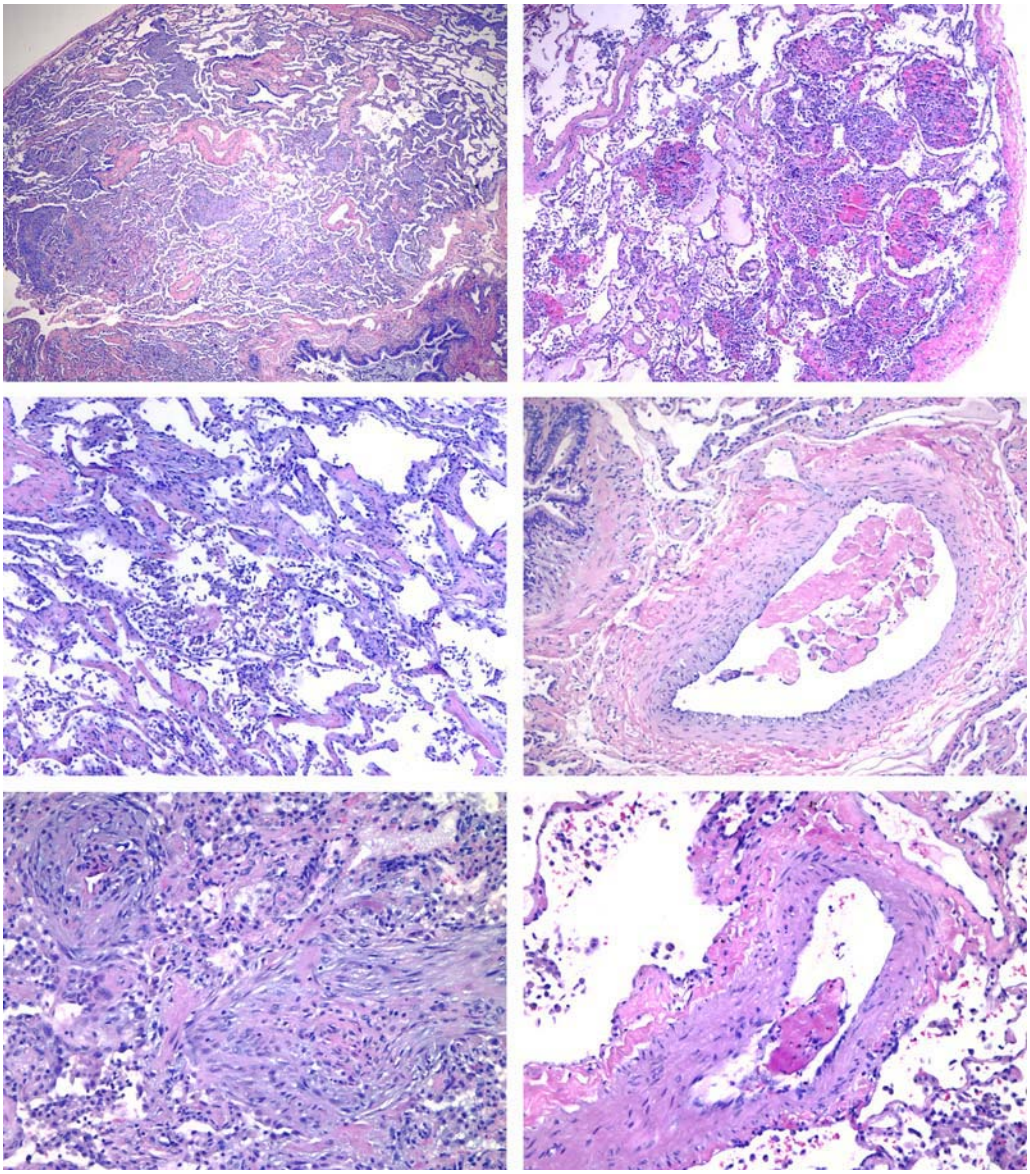
Diagnosis: Lung, open biopsies: BPOP.

This case illustrates the branching tufts of fibrous tissue characteristic of BO as well as the nodular consolidation due to alveolar filling by fibrin and histiocytes. The combination constitutes BPOP. In the differential diagnosis we considered late organizing DAD, because in one region there is a more diffuse interstitial process, but the pathology as well as the reported clinical and radiographic features better fit BPOP.

Organizing blood clots are present in a few small pulmonary arteries and veins. Those in the artery could represent thromboembolic disease, but I have seen such clots in other examples of BPOP and favor thrombotic disease rather than embolic disease. The presence of organizing clots in at least one vein is consistent with thrombosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6674 (Chapter 2 – Alveolar Disease)

Case 6550

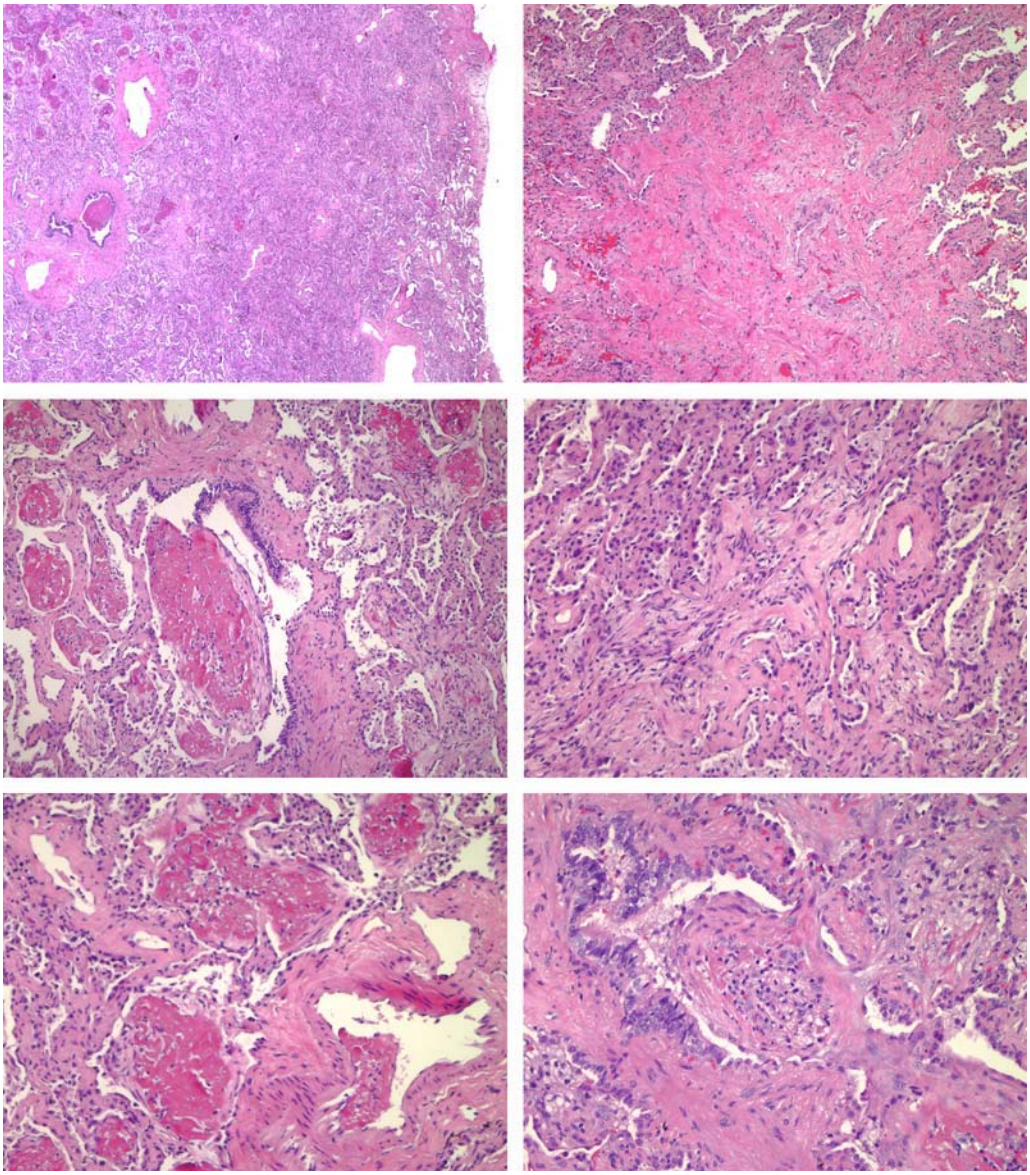
Diagnosis: Lung, open biopsy: Organizing fibrinous pneumonia, ? confluent BPOP.

All of the lung is involved with organizing fibrinous pneumonia which is ongoing. The older disease has mature collagen in alveoli with incorporation into interstitium of approx 1-mo duration. The ongoing disease is unorganized fibrin. The inflammation involves bronchioles but is not bronchiolocentric. The differential clinicopathological diagnosis in my analysis is an organizing infectious pneumonia, confluent BPOP (implying an etiology other than infection), or cryptogenic organizing pneumonia (a British term used for BPOP creating lobar consolidation). I favor a previous infectious etiology despite the failure to demonstrate an organism. I suspect that there is no longer an active infection. Since BPOP can also be infectious, one could also consider this as a case of confluent BPOP, and therefore all three above interpretations would be correct.

The principal clinical differential is organizing DAD, as you indicate. Although the process is diffuse, the absence of hyaline mebranes, absence of marked pneumocyte atypia, and the absence of tissue culture-like growth of fibroblasts are against that interpretation. Only a small amount of vascular thrombosis is present; I would expect more with organizing DAD. The clinical story also is more in keeping with organizing fibrinous pneumonia than with DAD.

Thank you for sending this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6550 (Chapter 2 – Alveolar Disease)

Case 6981

Diagnosis: Lung, open biopsy: BOOP.

Prominent branching tufts of myxoid fibrous tissue in respiratory bronchioles and alveolar ducts and a modest amount of organizing pneumonia (OP) with histiocytes in alveoli characterize BOOP. The nodular pattern of the disease can be appreciated on the glass slides without microscopic magnification, so this is a particularly good example of the nodular character of this disease. Somewhat unusual is the large terminal bronchiole similarly occluded by myxoid fibrous tissue. In this particular plug can be seen the highly vascular nature of BOOP in some instances. Some authors believe this vascularity accounts for the reversibility of the process.

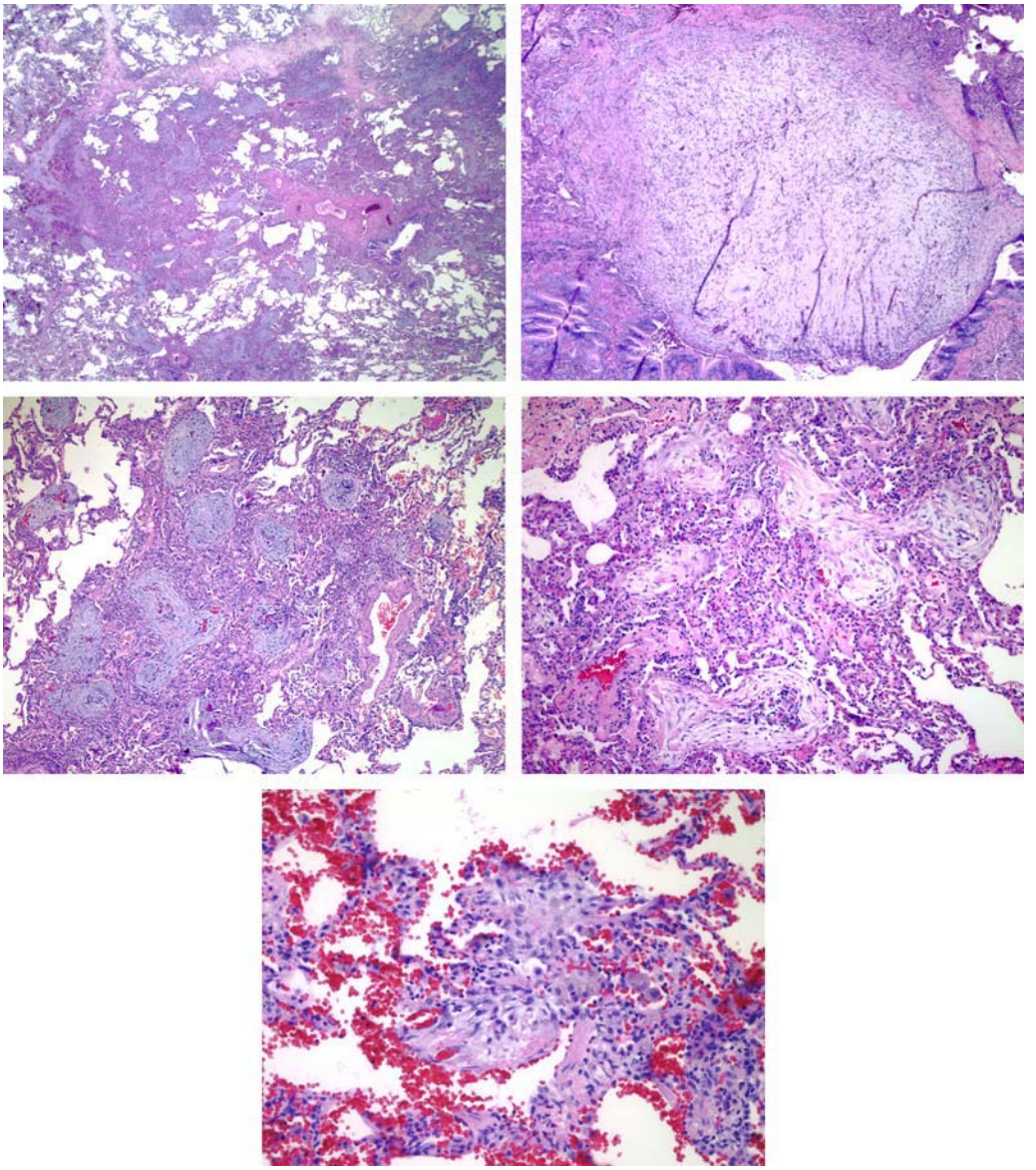
The above observations are essentially in agreement with your interpretation. The old interstitial fibrosis, temporal and spatial diversity, and honeycomb fibrosis characteristic of UIP are not present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Lappi-Blanco E, Kaarteenaho-Wiik R, Soini Y, Risteli J, Paakko P. Intraluminal fibromyxoid lesions in bronchiolitis obliterans organizing pneumonia are highly capillarized. Hum Pathol 1999;30:1192–1196.



Case 6981 (Chapter 2 – Alveolar Disease)

Case 6707

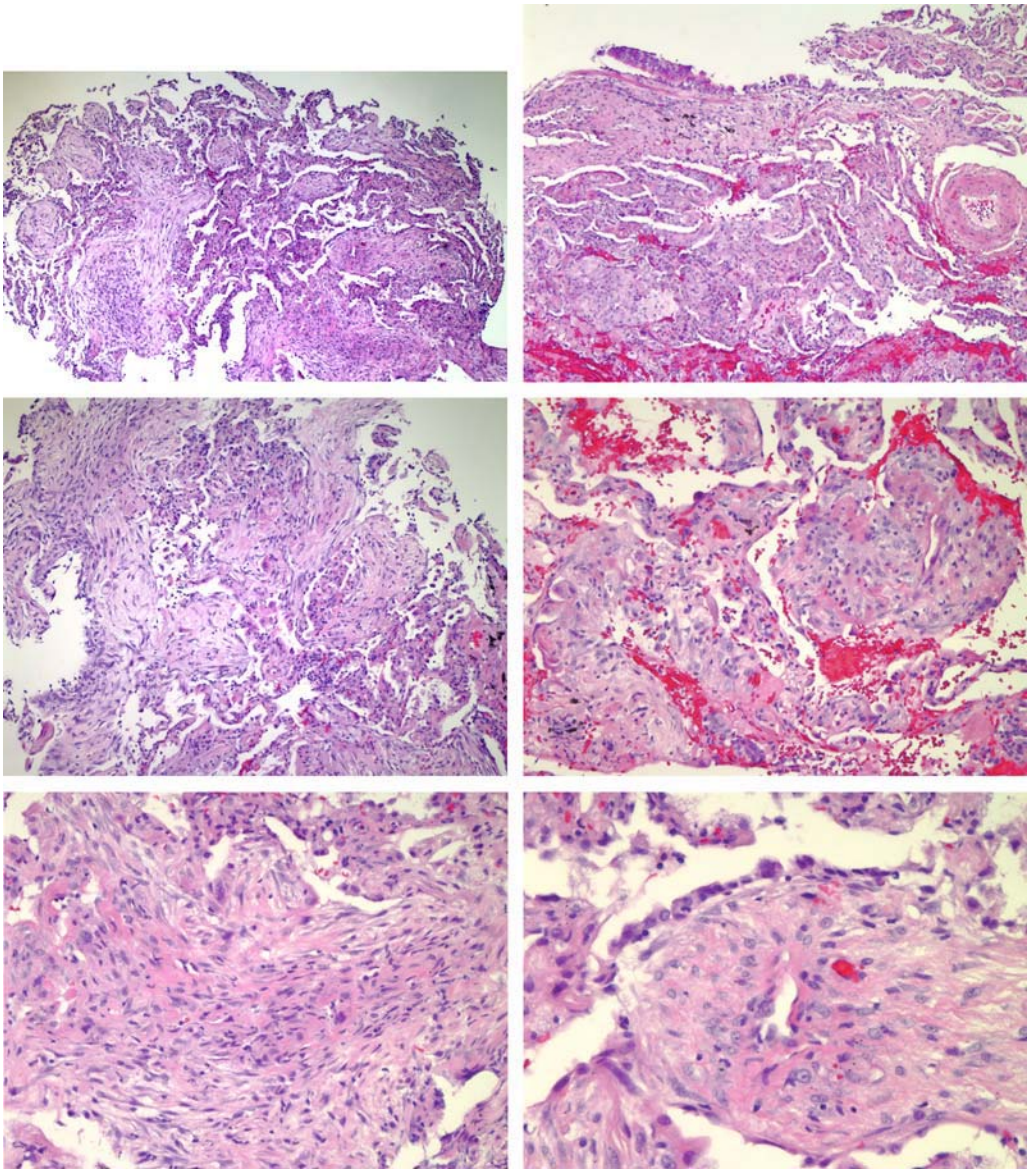
Diagnosis: Lung, transbronchial biopsy: BOOP.

The principal pathology are the branching tufts of myxoid connective tissue in alveolar ducts and respiratory bronchioles (RB). This constitutes BO. There is also a small component of OP with histiocytes and fibrin. Broad bundles of mature collagen in the cores of some of the BO are more advanced than usually seen in biopsy material of BOOP and suggest that the process is 4–6 wk in duration, while the myxoid fibrosis indicates an ongoing process as well. Eosinophils are not present. The causes of BOOP include resolving infection, hypersensitivity reaction, collagen-vascular disease, and others.

Regenerating epithelial cells have bizarre nuclei and raise the possibility of DAD in late organizing phase, but the focality of the process with some regions of normal lung and the bronchiolocentricity of the disease are against that interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6707 (Chapter 2 – Alveolar Disease)

Case 6846

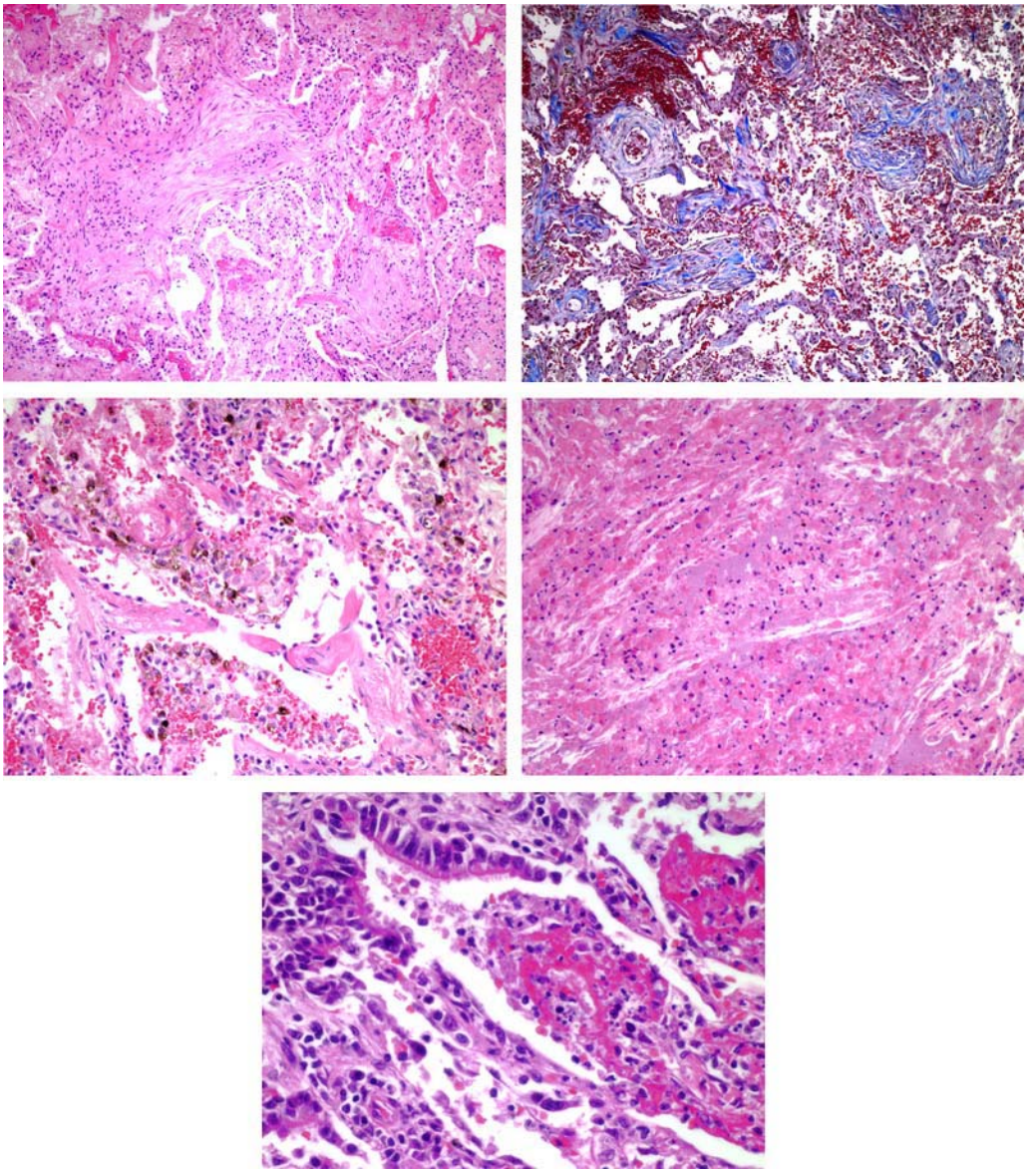
Diagnosis: Lung, open biopsy: Necrotizing bronchiolitis and pattern of BOOP, cause undetermined, ? infectious.

There are processes of two different ages. The more acute is necrotizing bronchiolitis with hemorrhage, nuclear dust, and reactive epithelial cells. The second and more chronic is a pattern of BOOP forming nodules with branching tufts of myxoid fibrous tissue and organizing fibrinous pneumonia. The histology of the BOOP (trichrome stain) alone might suffice for the clinicopathological diagnosis of BOOP, but in a patient who may be immunosuppressed, I am reluctant to make an outright diagnosis of BOOP as a clinicopathological diagnosis and would consider it a reactive pattern until proven otherwise. In this case, I suspect that the primary process is an acute infectious bronchiolitis and that the BOOP is a healing phase. Among the causes of such focal hemorrhagic bronchiolitis are viruses, including herpesvirus, cytomegalovirus, and adenovirus. Other viruses, mycoplasma, and bacteria are also possible.

To further evaluate the possibility of viral infection, we performed immunopathological studies. These studies do not show the presence of herpes simplex I, herpes simplex II, or cytomegalovirus. No nuclear inclusions or smudge cells are present. Thus, a viral etiology is not confirmed. Other special histochemical stains do not provide additional diagnostic information.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6846 (Chapter 2 – Alveolar Disease)

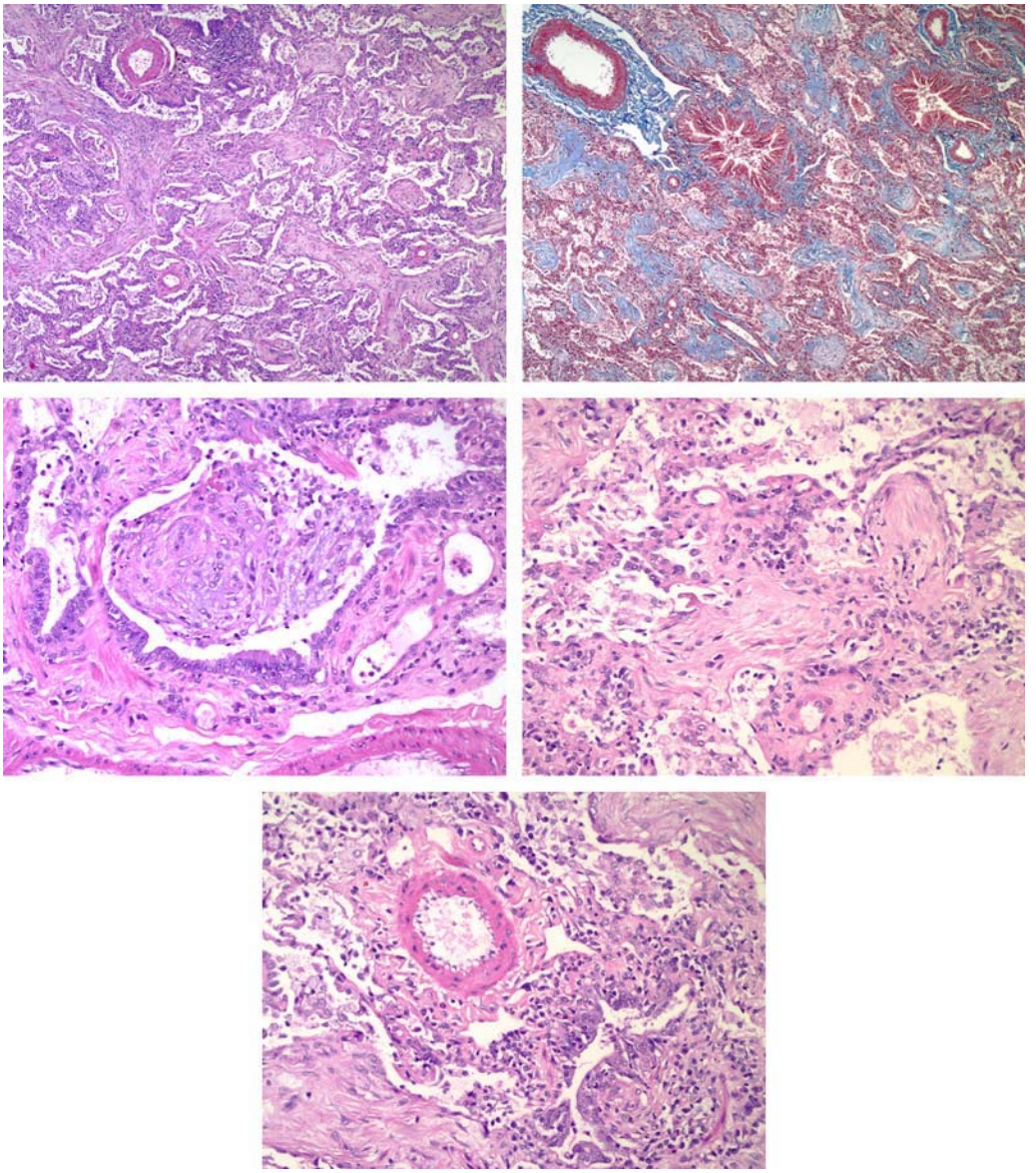
Case 6700

Diagnosis: Lung, open biopsy: BOOP.

The predominant feature is branching tufts of myxoid tissue bifurcating in respiratory bronchioles and alveolar ducts (trichrome stain). This is the defining feature of BOOP and is in agreement with your interpretation. The clinical history is also consistent with that diagnosis. The component of OP is relatively small. The pathology is not that of UIP, DIP, or other specific or nonspecific interstitial processes. The cause of BOOP is generally not established. We presume infection or hypersensitivity reaction is the cause of many cases. Collagen-vascular disease is another consideration.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6700 (Chapter 2 – Alveolar Disease)

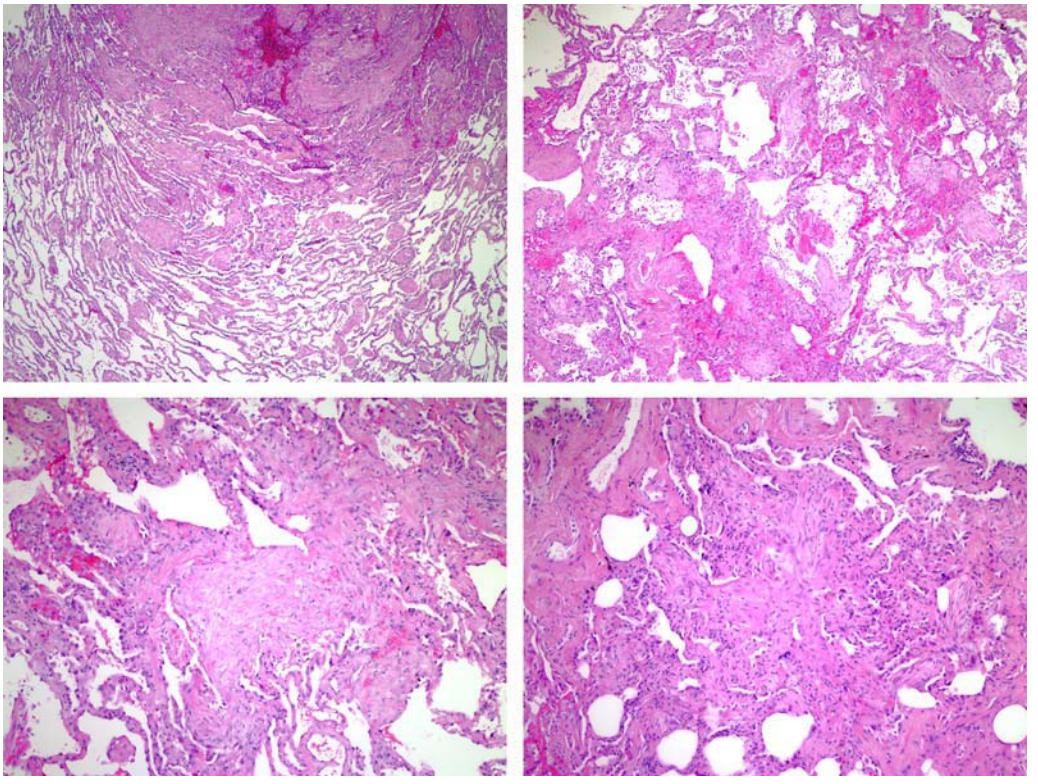
Case 7091

Diagnosis: Lung, open biopsy: BOOP.

Ill-defined nodules of actively proliferating fibrosis lie in bronchioles and alveolar ducts and alveoli. The fibrosis is of approximately the same age, that is, several weeks. The fibrosis is somewhat more advanced than the typical appearance in BOOP and has also undergone more incorporation into the interstitium than is usual in BOOP. Nevertheless, the process has sufficient uniformity to enable one to make this diagnosis and exclude UIP. The more advanced nature of the fibrosis may correlate with the reported lack of responsiveness to corticosteroids.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7091 (Chapter 2 – Alveolar Disease)

Case 6578

Diagnosis: Lung, open biopsy: BOOP.

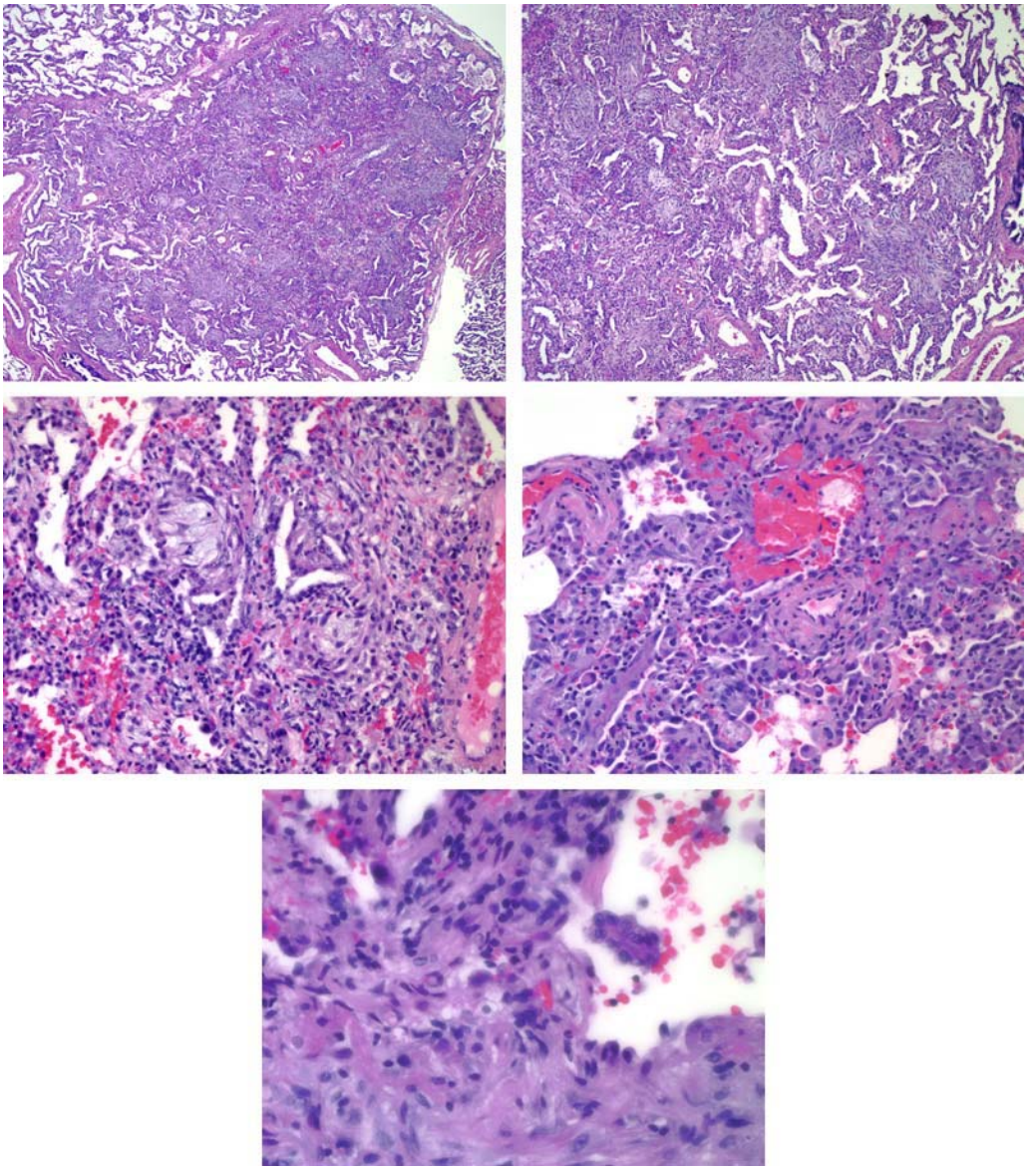
Nodular consolidation of the lung at low power with alveolar filling by organizing fibrosis coupled with branching fibrosis in alveolar ducts characterizes BOOP. DAD (acute interstitial pneumonitis) enters into the differential diagnosis because there is fibrin and focally prominent atypia of both mesenchymal and epithelial cells, but the focality of the process is against that interpretation. The absence of old disease including particularly subpleural honeycomb fibrosis and permanent scarring is against UIP. The disease in this case is quite active with occasional neutrophils as well as the fibrin. Although most patients with BOOP respond to corticosteroids, not all do. As with other cases, the etiology of BOOP includes principally hypersensitivity reaction, organization of prior infection, collagen-vascular disease, or idiopathic.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Watanabe K, Senju S, Wen F-Q, et al. Factors related to the relapse of bronchiolitis obliterans organizing pneumonia. Chest 1998;114:1599–1606.



Case 6578 (Chapter 2 – Alveolar Disease)

Case 6998

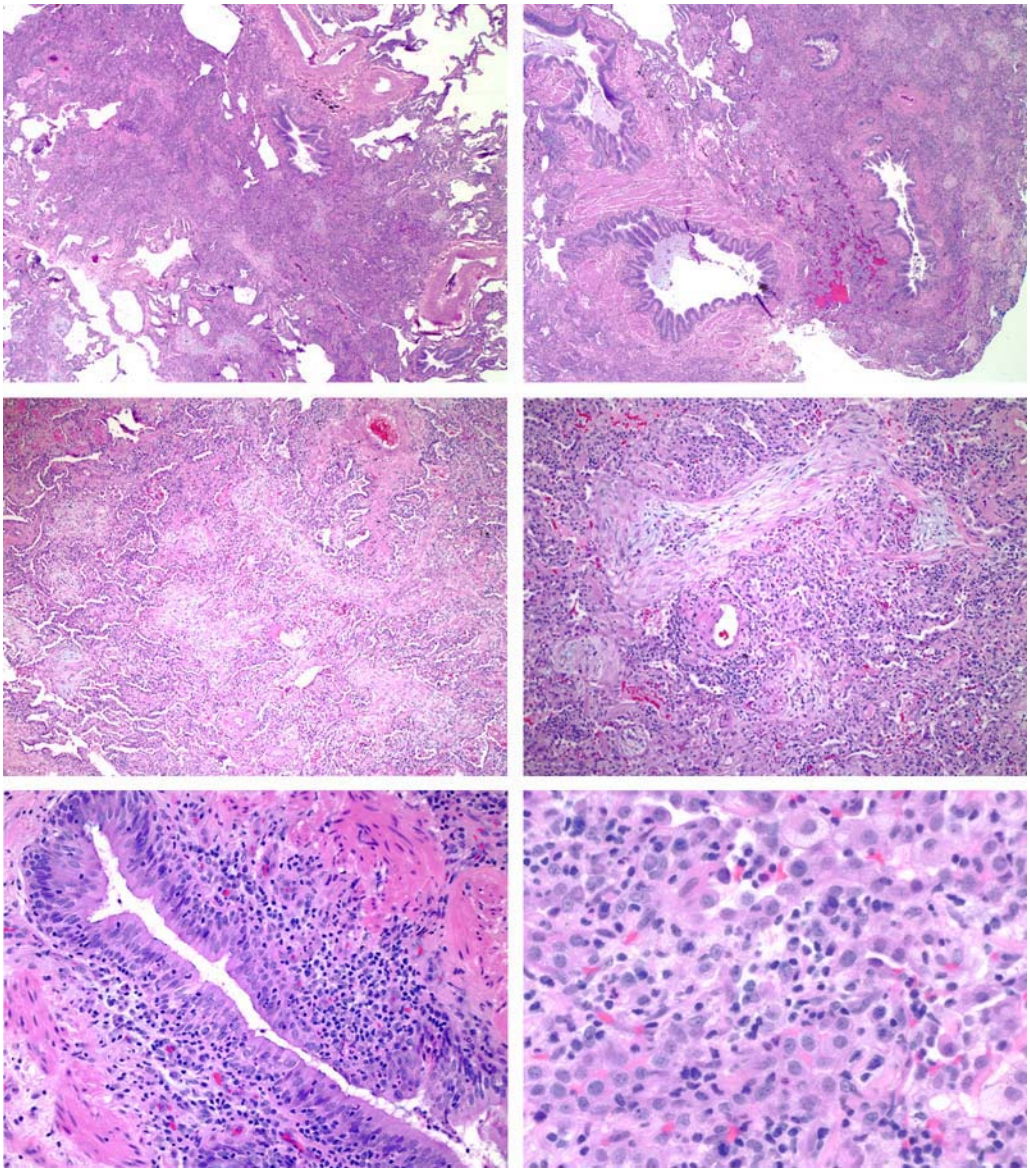
Diagnosis: Lung, open biopsies: BOOP, ? infectious, both specimens.

An inflammatory and fibrosing process is somewhat nodular and contains fibrous tufts in conducting airways with surrounding OP characteristic of BOOP. The presence of occasional neutrophils and eosinophils in some areas supports this diagnosis, and the eosinophils argue against the primary alternative diagnosis of UIP. Although honeycomb fibrosis is present in a few areas, most of the lung does not have advanced fibrosis. The process appears several weeks in age.

Neutrophils infiltrate bronchial mucosa in a few areas, and one bronchiole is markedly infiltrated by polymorphonuclear lymphocytes in both lamina propria and epithelium. This change suggests an active or resolving infectious etiology, although other causes of BOOP cannot be excluded. The other causes typically are collagen-vascular disease, aspiration, drug reactions, and idiopathic. Because of the prominent neutrophilic infiltrate, WG also enters the differential diagnosis, in that it rarely presents with a pattern of BOOP, and serum anti-neutrophilic cytoplasmic antibody (ANCA) test might be evaluated.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6998 (Chapter 2 – Alveolar Disease)

Case 6558

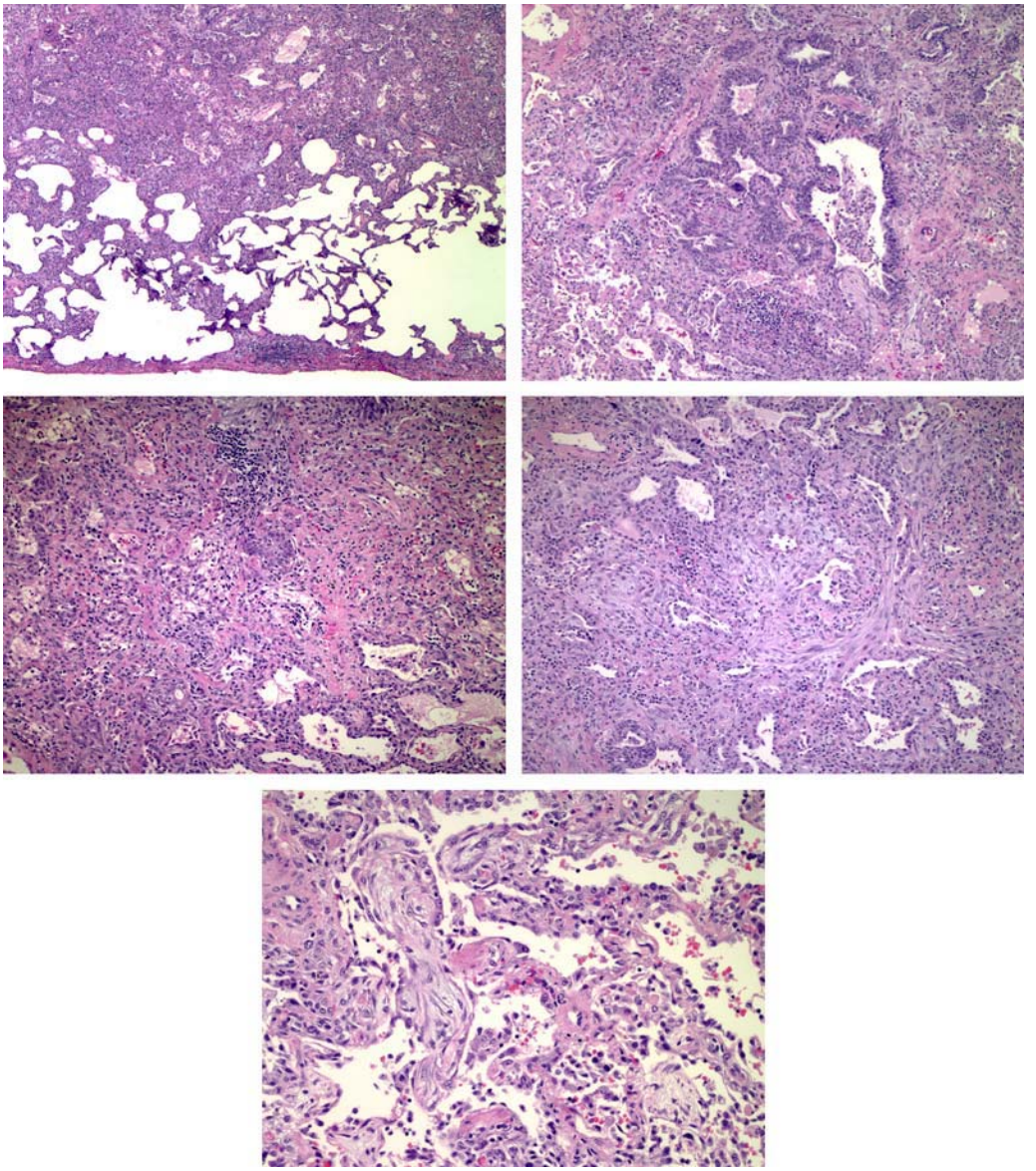
Diagnosis: Lung, open biopsy: BOOP, late phase, with regional hyperinflation.

Organizing fibrosis in bronchioles is several weeks in duration and associated with squamous metaplasia of bronchioles and alveolar ducts. The pathology is therefore later than one normally encounters in lung biopsies done for BOOP. Further proof of the bronchiolar nature of the disease is regional hyperinflation, which possibly could account for the cystic change on radiographic studies. Extensive alveolar fibrosis is in areas older than that. Incorporation of course fibrosis into interstitium suggests that the alveolar fibrosis is months old.

I do not know the cause of the BOOP. The usual considerations are post-infectious, collagen-vascular disease, hypersensitivity reaction, or idiopathic. If this were an infectious process initially, I do not believe there is active infection at this time. Because the fibrosis is more advanced than that in the majority of cases of BOOP at the time of biopsy, the prognosis in this case may be less sanguine than in other patients with the disease.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. I have retained one slide stained with hematoxylin and eosin for our teaching conference and hereby return the remainder. If you require that one slide, please let me know.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6558 (Chapter 2 – Alveolar Disease)

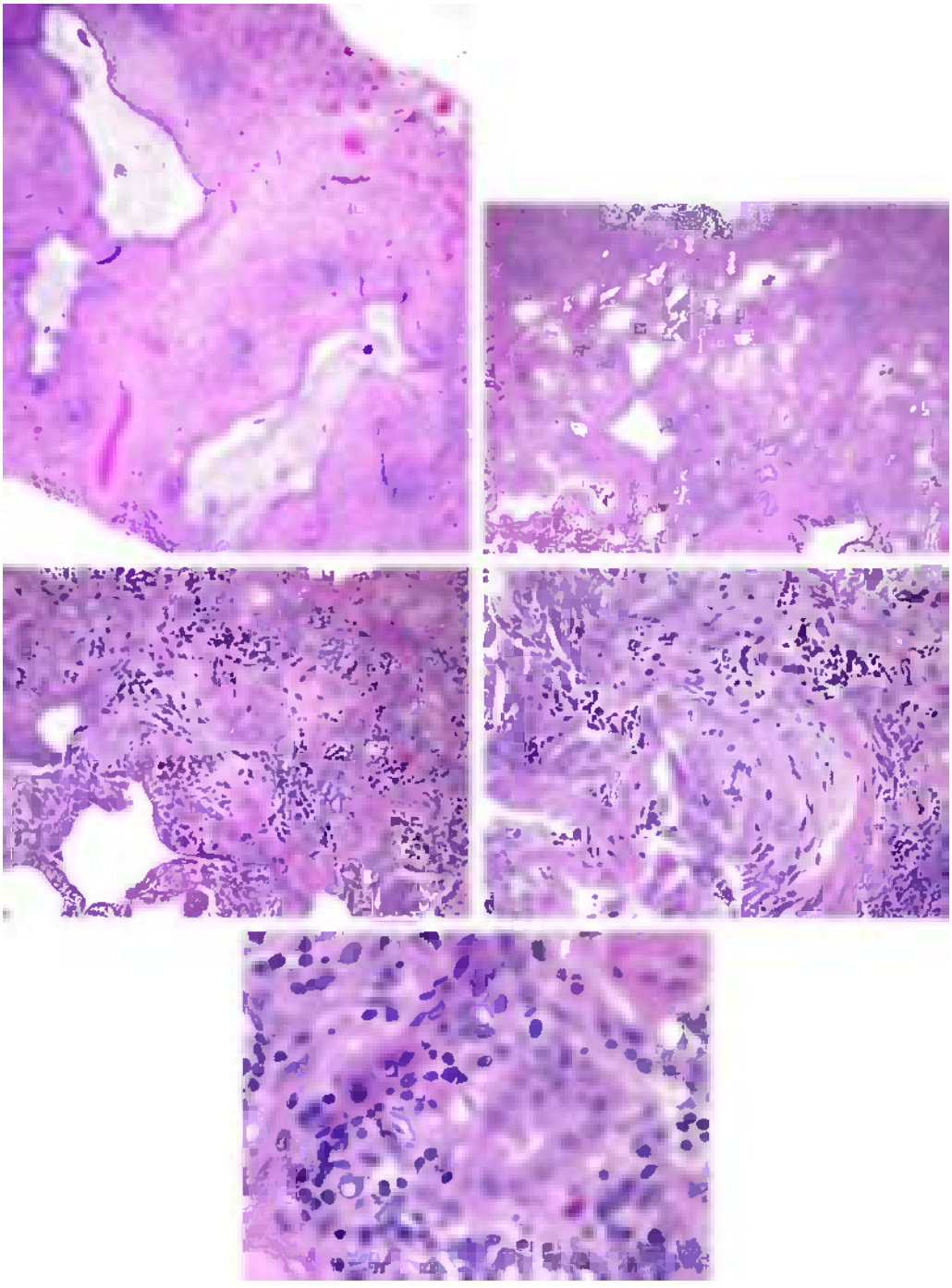
Case 7168

Diagnosis: Lung, open biopsy: Interstitial pneumonitis, bronchiolectasis with mucus plugging, lymphohistiocytic inflammation with giant cells, and eosinophilia, cause uncertain, ? accelerated phase of UIP, ? other.

This case is problematic in my opinion. Elements of interstitial pneumonitis with old fibrosis are associated with end-stage fibrotic disease including bronchiolectasis with mucus plugging. This could represent a relatively advanced stage of UIP with subpleural honeycomb fibrosis, and this is the diagnosis I prefer. However, not typical for UIP is an element of BO as well as scattered eosinophils. Because BO and eosinophilia often overlap, I cannot absolutely exclude an advanced stage of BOOP. A diagnosis of UIP suggests an idiopathic and untreatable nature, whereas BOOP leaves open the possibility of hypersensitivity reaction, resolving infection, aspiration and collagen-vascular disease. Because BOOP has potentially treatable aspects, I am reluctant to assign this case automatically to UIP, even though this is the disease generally encountered in patients with familial idiopathic pulmonary fibrosis. I do not generally make a diagnosis of nonspecific interstitial pneumonitis, because it leaves open questions such as adequacy of sample and spectrum of disease and I would not do so in this case.

Thank you for referring this case in consultation. I understand that clinical details are not available at this time. This is an elaboration of our telephone call. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7168 (Chapter 2 – Alveolar Disease)

Case 7025

Diagnosis: Lung, open biopsy:

1. **Focal subacute and chronic organizing pneumonitis and scattered eosinophils, consistent with resolving phase of BOOP/CEP overlap syndrome.**
2. **Organizing intravascular blood clots, ? organizing thrombi, ? organizing thromboemboli.**

The histology shows focal chronic organizing pneumonia of many months duration (trichrome stain) with coarse scarring as well as subacute active disease with edema and proliferating pneumocytes. The focality of the process and the absence of established subpleural honeycomb fibrosis exclude UIP. A few eosinophils are present. I cannot make a diagnosis of CEP from this specimen, but eosinophils may be scarce in the BOOP/CEP overlap syndrome and particularly scarce after chronic disease and after treatment with corticosteroids. Therefore, this histology could represent a scarring phase of the BOOP/CEP overlap syndrome. The scarring is more extensive than normally seen with that condition. There has been lung atrophy associated with the scarring and parasitized systemic arteries entering the lung associated with pleural adhesions

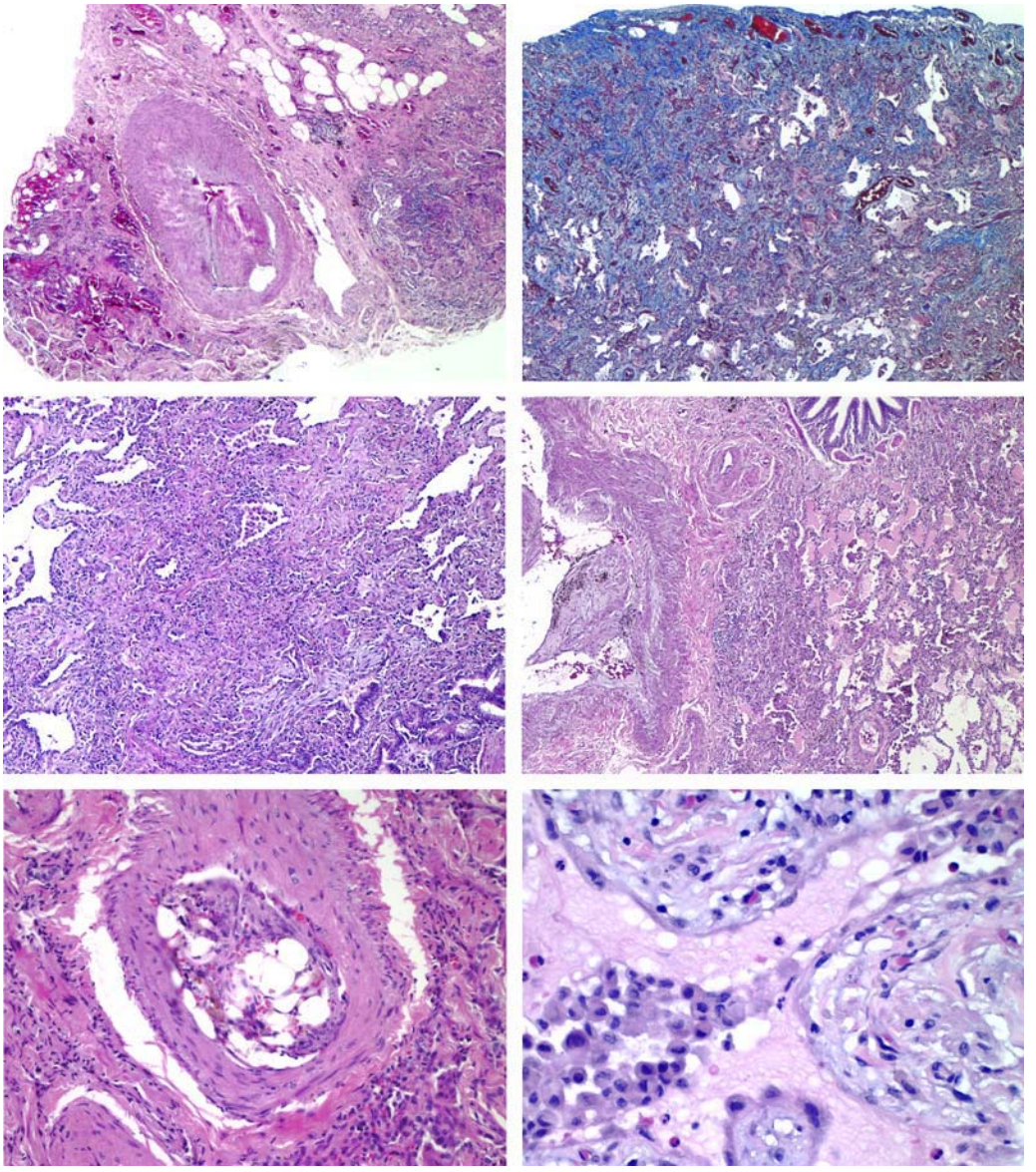
Several organizing thromboemboli or thrombi are present as well as one organizing bone marrow embolus. The significance of these is uncertain. The degree of inflammation could account for these clots as thrombi, but if they are thromboemboli, an extrapulmonary source might be sought. The organizing blood clots are numerous and sufficiently large as to possibly have physiological significance and contribute to respiratory difficulty.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Cooney T. Interrelationship of chronic eosinophilic pneumonia, bronchiolitis obliterans, and rheumatoid disease: a hypothesis. J Clin Pathol 1981;34:129.



Case 7025 (Chapter 2 – Alveolar Disease)

Case 7011

Diagnosis: Lung, open biopsy: BOOP/CEP overlap syndrome, with bronchiectasis and extensive interstitial fibrosis (rheumatoid lung disease variant).

This case is difficult and intriguing. The most specific finding is the alveolar filling by histiocytes and eosinophils. In isolation this qualifies as CEP. However, the scarring is much in excess of what one anticipates for that condition, and the clinical history is also against CEP. The second facet is centrilobular scarring (trichrome stain) including obliteration of small conducting airways and a resultant marked cholesterol pneumonia at the periphery of the lobules, the latter representing bronchiolar obstruction even when the luminal narrowing cannot be well defined. This, in conjunction with bronchiectasis in this case, makes me believe that this patient clinically falls into the spectrum of progressive airway obliteration in association with rheumatoid disease, a well recognized form of severe pulmonary disease in patients with rheumatoid arthritis. The florid organizing fibrinous pleuritis is in keeping with a collagen-vascular disease.

There is a significant overlap between BOOP and CEP in general, and I suspect that overlap applies here in this patient, who has rheumatoid arthritis. The BOOP/CEP overlap syndrome has been described before in rheumatoid disease (see references).

What remains is diffuse and extensive interstitial fibrosis. By itself in a patient with rheumatoid arthritis, this would be considered UIP until proven otherwise, but in this case with more specific attributes, I suspect that the fibrosis is more in keeping with the BOOP/CEP overlap syndrome rather than with UIP. The temporary response of the patient's pulmonary disease to methotrexate and prednisone favors BOOP/CEP overlap syndrome over UIP.

I note the high platelet count and anemia. I cannot exclude a coexistent myelodysplasia, which possibly could contribute to the eosinophilia in the blood and in the lung. Nevertheless, a morphological diagnosis of CEP applies. In my experience with this form of rheumatoid lung disease with bronchiectasis, the prognosis is not sanguine.

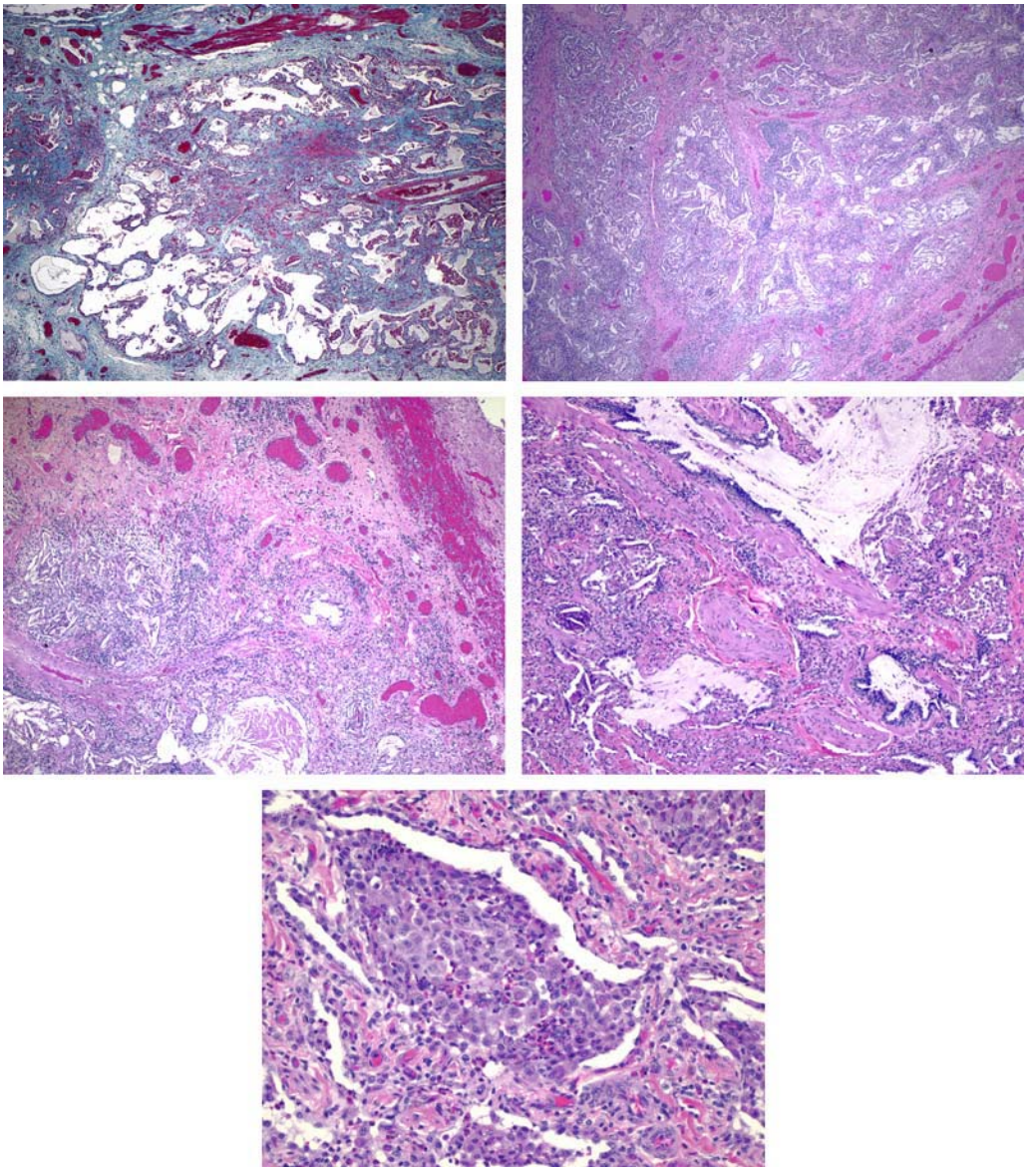
Thank you for sharing this very instructive case with us. Best wishes until we meet again.

Sincerely yours,
Eugene J. Mark, M.D.

References:

Cooney TP. Interrelationship of chronic eosinophilic pneumonia, bronchiolitis obliterans, and rheumatoid disease: a hypothesis. J Clin Pathol 1981;34:129–137.

Geddes DM, Corrin B, Brewerton DA, Davies RJ, Turner-Warmic M. Progressive airway obliteration in adults and in association with rheumatoid disease. Q J Med 1977;46:427–444.



Case 7011 (Chapter 2 – Alveolar Disease)

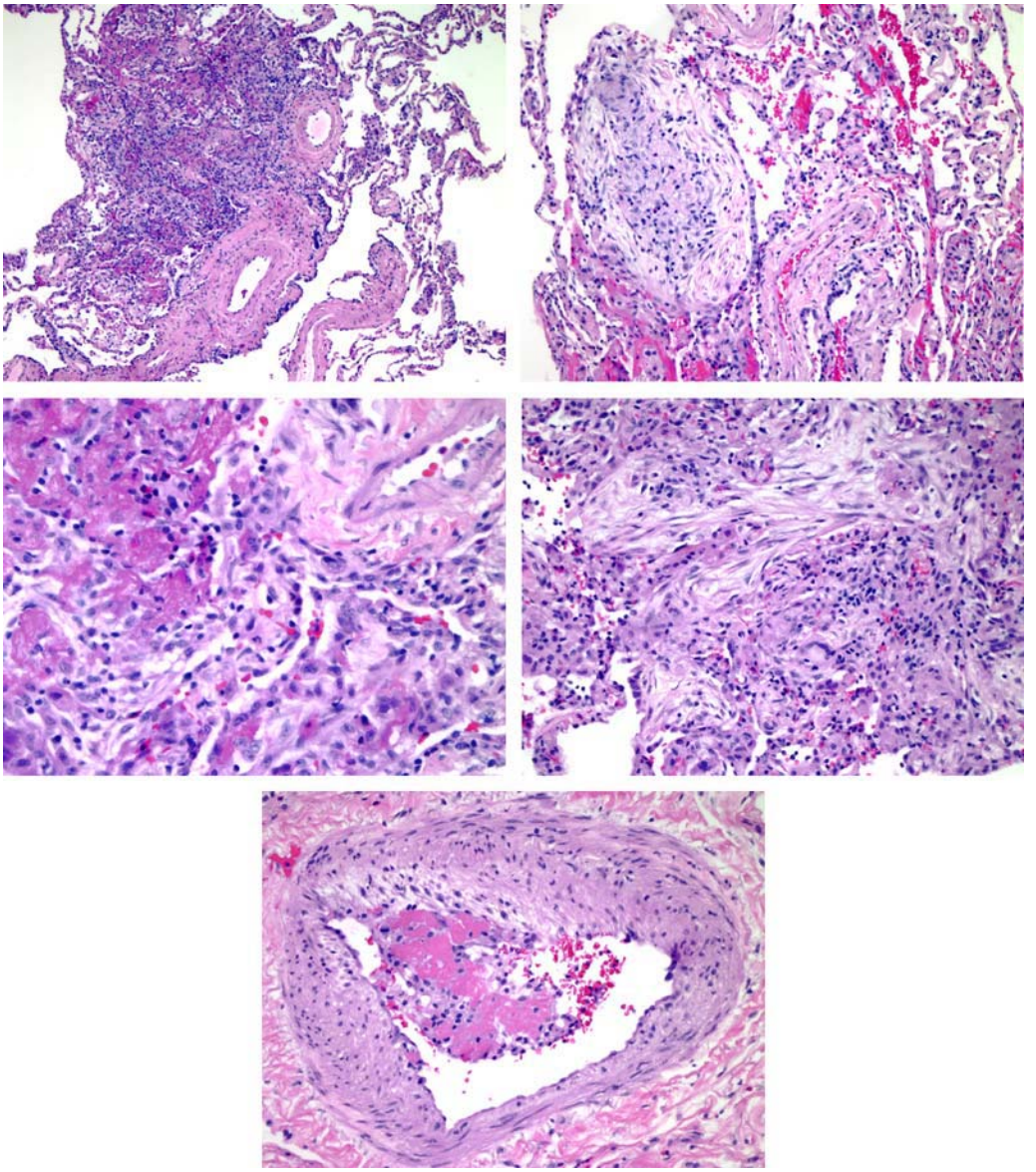
Case 7112

Diagnosis: Lung, open biopsy: BOOP with eosinophilia, cause unproven, ? hypersensitivity reaction.

There is an active bronchiolitis with fibrinous exudate and neutrophils and many eosinophils associated with obliterated bronchioles. The BO is of a relatively early stage without destructive scarring, but proof of the absence of bronchioles is the presence of arteries unattended by bronchioles of similar size. The cause of such BOOP is not apparent from this biopsy, but the numerous eosinophils raise the possibility of a hypersensitivity reaction. This could be due to inhaled particles or systemically administered drugs. I cannot absolutely exclude an infectious etiology, but I do not favor this. One microscopic recent organizing blood clot could be associated with the inflammatory process and does not necessarily indicate systemic thromboembolism, although I cannot exclude this possibility. I detect no fibrous bands or webs in pulmonary arteries to indicate chronic thromboembolism in this biopsy.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7112 (Chapter 2 – Alveolar Disease)

Case 6763

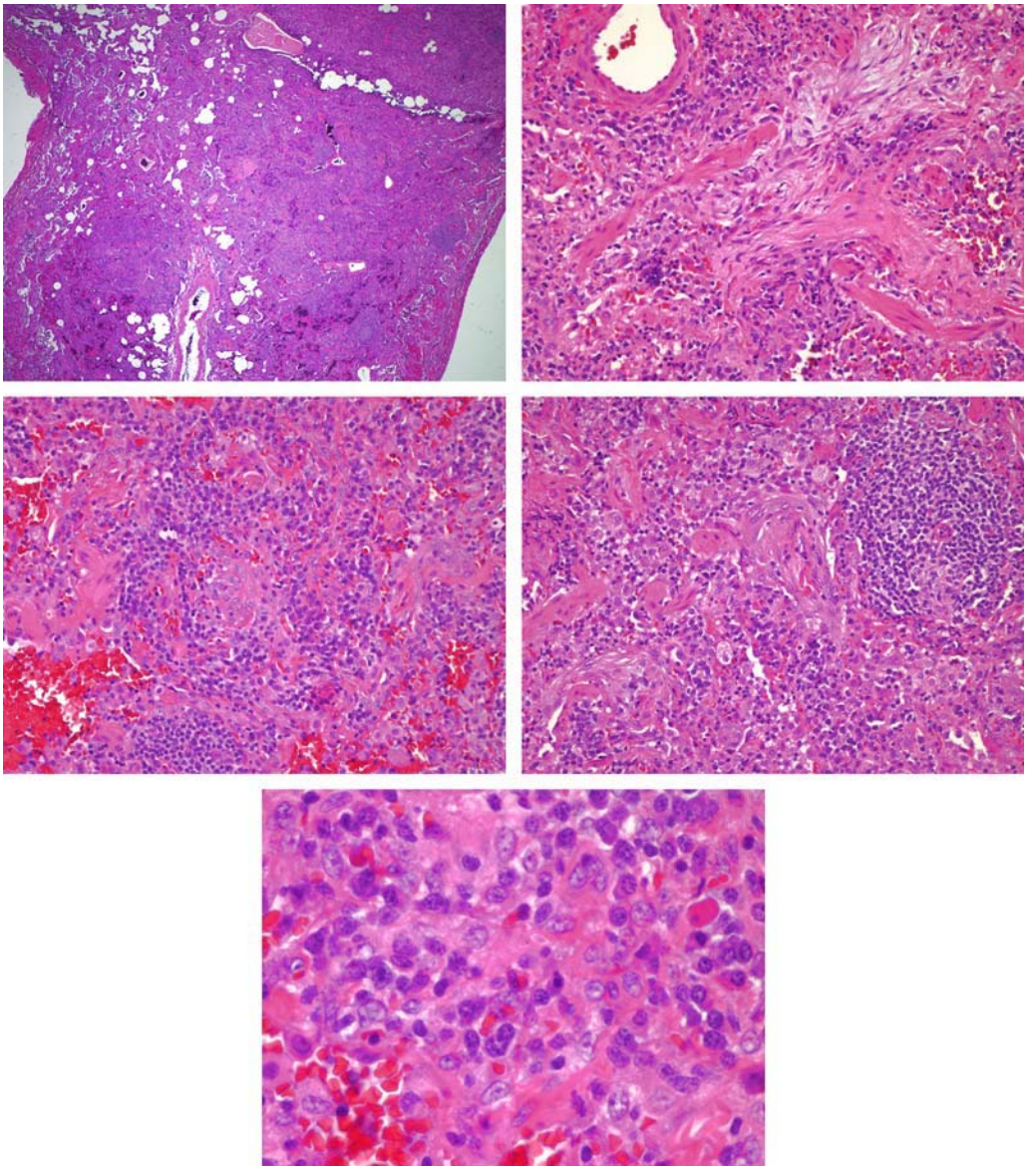
Diagnosis: Lung, open biopsy: Organizing fibrinous pneumonia with bronchiolitis and eosinophils, ? BOOP, ? other.

This lobular OP has an acute phase with fibrin and a more chronic phase with lymphohistiocytic inflammation and fibrosis filling alveoli. These changes can be described as an OP. There is an element of bronchiolitis, and both the clinical and pathological findings could represent BOOP. Occasional eosinophils are consistent with that interpretation, as some patients have an overlap syndrome of BOOP and CEP. I am reluctant to make an unequivocal diagnosis of BOOP in this case, because it is possible that this represents an unusual infection such as mycoplasma or chlamydia. Hypersensitivity reaction is also possible as a cause of BOOP. I do not believe this biopsy represents extrinsic allergic alveolitis, which I use principally as a clinical diagnosis, because of the extent of the OP. Many cases of BOOP represent resolving infections, in distinction to active infections, and other cases are associated with collagen-vascular disease or are idiopathic.

In the differential diagnosis we considered DIP but do not favor this interpretation. We do not believe the pathology is that of UIP, DIP, or LIP. The lymphoid tissue is hyperplastic but overshadowed by the OP.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6763 (Chapter 2 – Alveolar Disease)

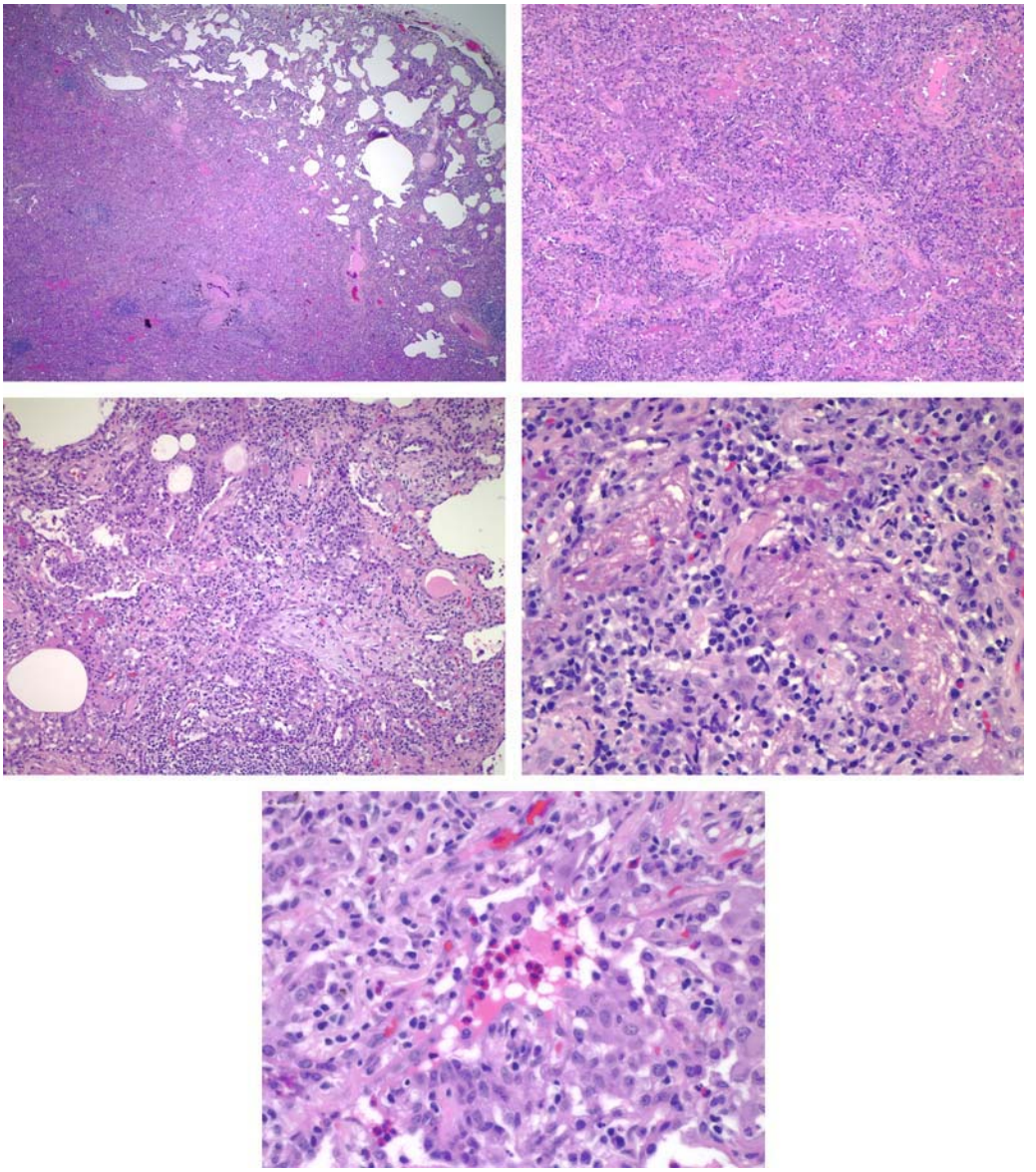
Case 6699

Diagnosis: Lung, open biopsy: OP, subacute, with edema and eosinophils, cause unknown, ? CEP,? infection, ? hypersensitivity pneumonitis, ? other.

This case can be classified principally as an OP with intra-alveolar histiocytes and loose alveolar collagen associated with a lesser degree of interstitial fibrosis. The predominance of alveolar over interstitial disease makes me consider this an OP rather than an interstitial pneumonitis. I do not believe this represents either UIP or DIP. The disease is active with edema and fibrin. The absence of hyaline membranes and myxoid fibrosis is against DAD (acute respiratory distress syndrome, acute interstitial pneumonitis), as is the clinical history. Eosinophils are numerous in some areas, and this histology could represent CEP in a late organizing phase. CEP is not infrequently associated with BOOP, and I suspect that this scenario is present here, but we have only the OP and not the BO. An infectious etiology is possible, but the eosinophils would make infection less likely. If this is infectious, I would consider an unusual organism such as mycoplasma or chlamydia. The clinical and pathological features are not typical for hypersensitivity pneumonitis, but occasionally a localized OP with eosinophils may be the morphological representation of a hypersensitivity reaction. In other regions are unexplained microabscesses with eosinophils, which raise WG into the differential diagnosis, and which might be further considered if the antineutrophil cytoplasmic antibody test were positive.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6699 (Chapter 2 – Alveolar Disease)

Case 7125

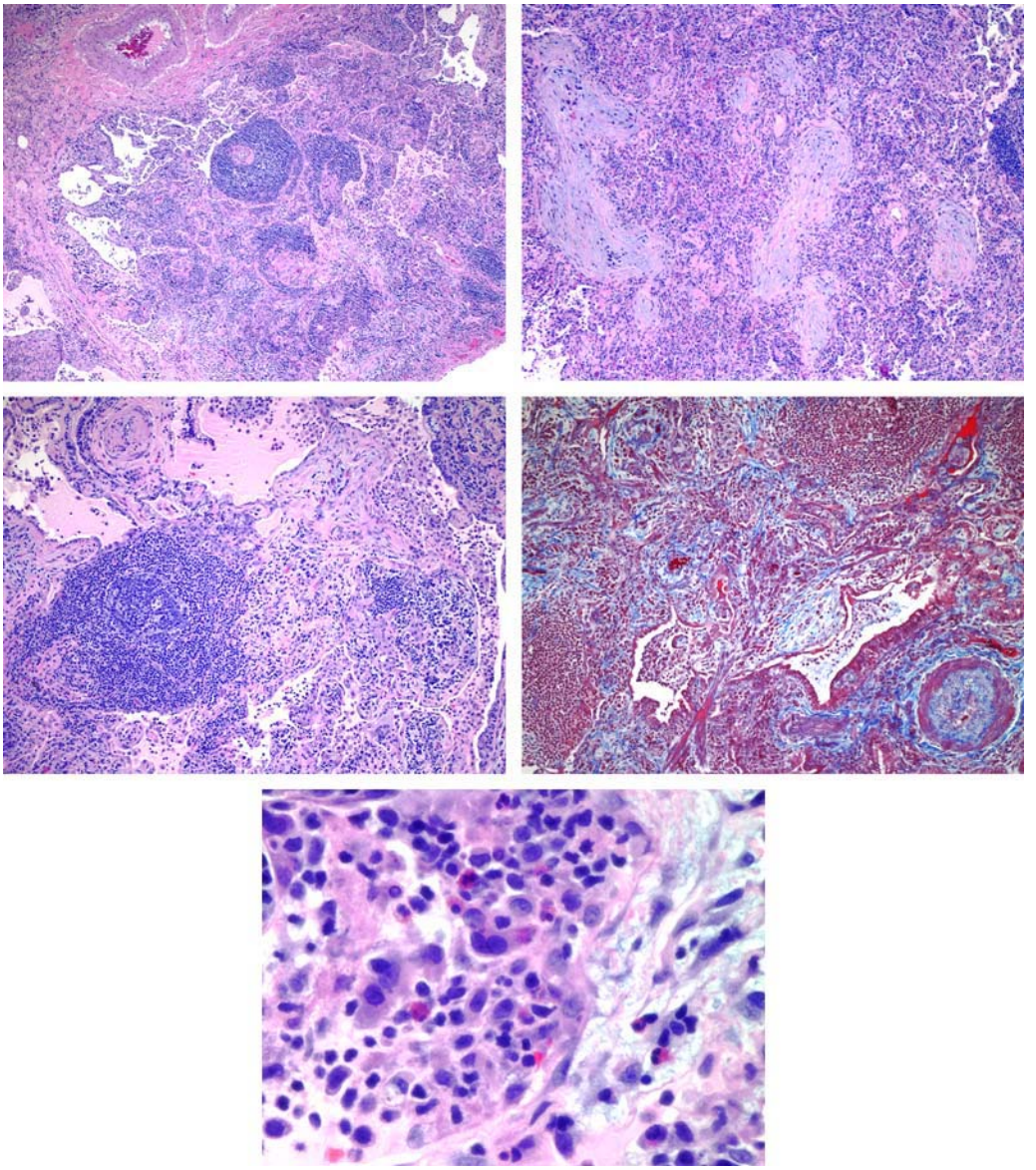
Diagnosis: Lung, open biopsy: BOOP, with follicular lymphoid hyperplasia and eosinophils and edema.

The predominant pathology is BOOP. The fibrous tufts with central vessels and inflammatory cells (trichrome stain) are particularly prominent in this case and associated with OP as well as with follicular lymphoid hyperplasia. The absence of bronchioles in some areas and the prominence of the lymphoid follicles make me wonder whether an element of follicular bronchiolitis has contributed to the BO.

We have seen follicular lymphoid hyperplasia of this degree in other cases of BOOP. Patients with BOOP due to collagen-vascular disease can have particularly prominent lymphoid hyperplasia. Eosinophils are present but not in sufficient numbers for me to consider this as an example of the overlap syndrome of BOOP with CEP even though the radiographic findings suggest the latter. The above observations are essentially in agreement with yours.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7125 (Chapter 2 – Alveolar Disease)

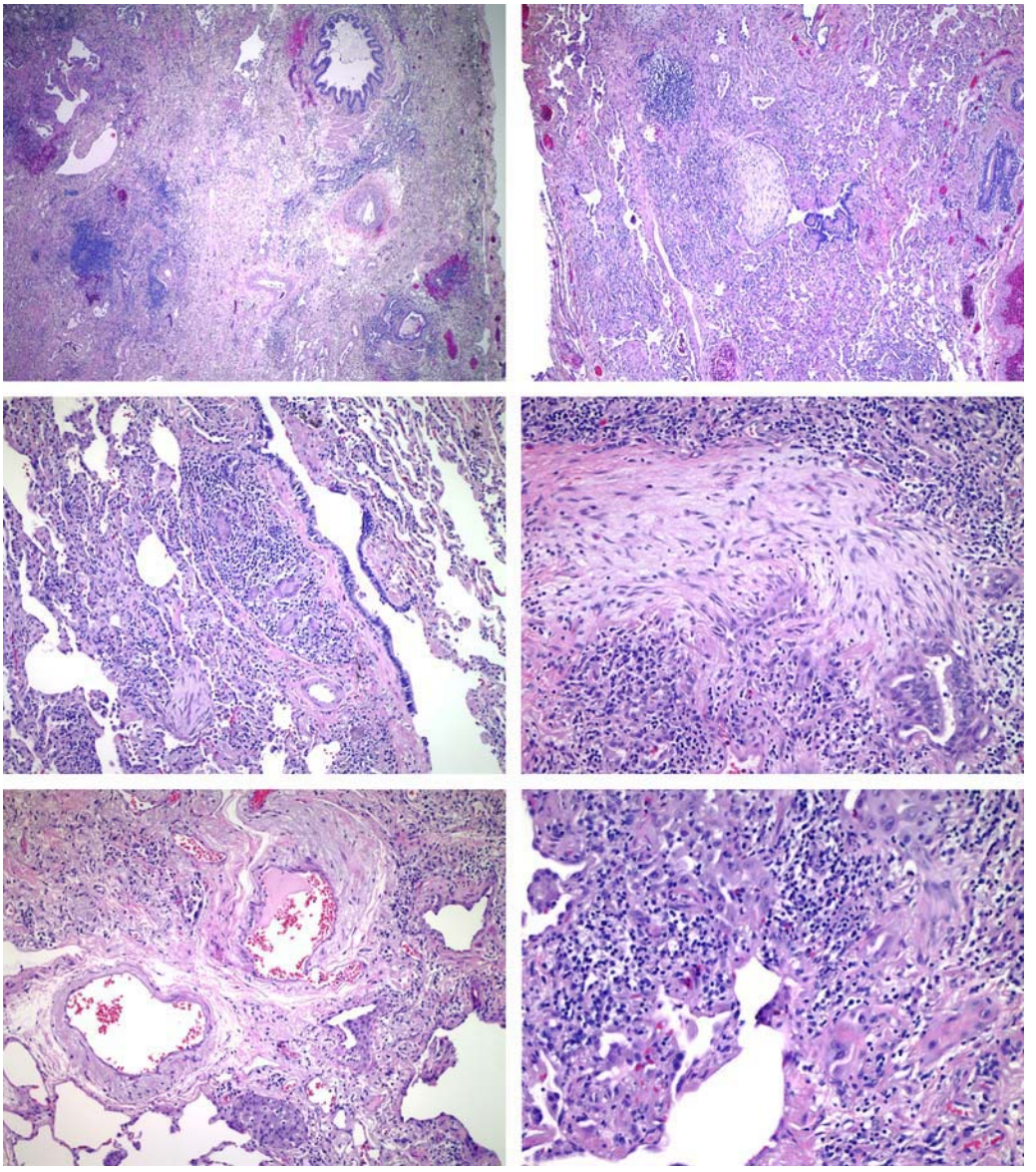
Case 6762

Diagnosis: Lung, open biopsy: Bronchiolitis, OP, eosinophils and occasional granuloma, nondiagnostic, ? BOOP, ? other.

This biopsy raises the differential diagnosis of BOOP and sarcoidosis as the principal considerations. I favor BOOP because of the distinct BO in a few areas, other areas of OP without granulomas, and foci with many eosinophils. Many cases of BOOP overlap with CEP, and I favor that interpretation. Granulomatous inflammation can be seen in BOOP, and the combination of bronchiolitis with eosinophils and granulomatous inflammation in this case raises the possibility of hypersensitivity reaction, which could further be investigated by clinical and serological tests. Usually hypersensitivity reactions have more diffuse granulomatous inflammation and not the relatively discrete granulomas which are present here. I cannot exclude sarcoidosis, but if this is sarcoidosis, there is a coexistent OP and not the "lymphocytic alveolitis" sometimes described in active sarcoid. There is subpleural scarring with bronchiolectasis, which is not common in hypersensitivity reaction but might correlate with the relatively protracted clinical course in this patient. Because of the scarring, I considered UIP but do not favor that diagnosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6762 (Chapter 2 – Alveolar Disease)

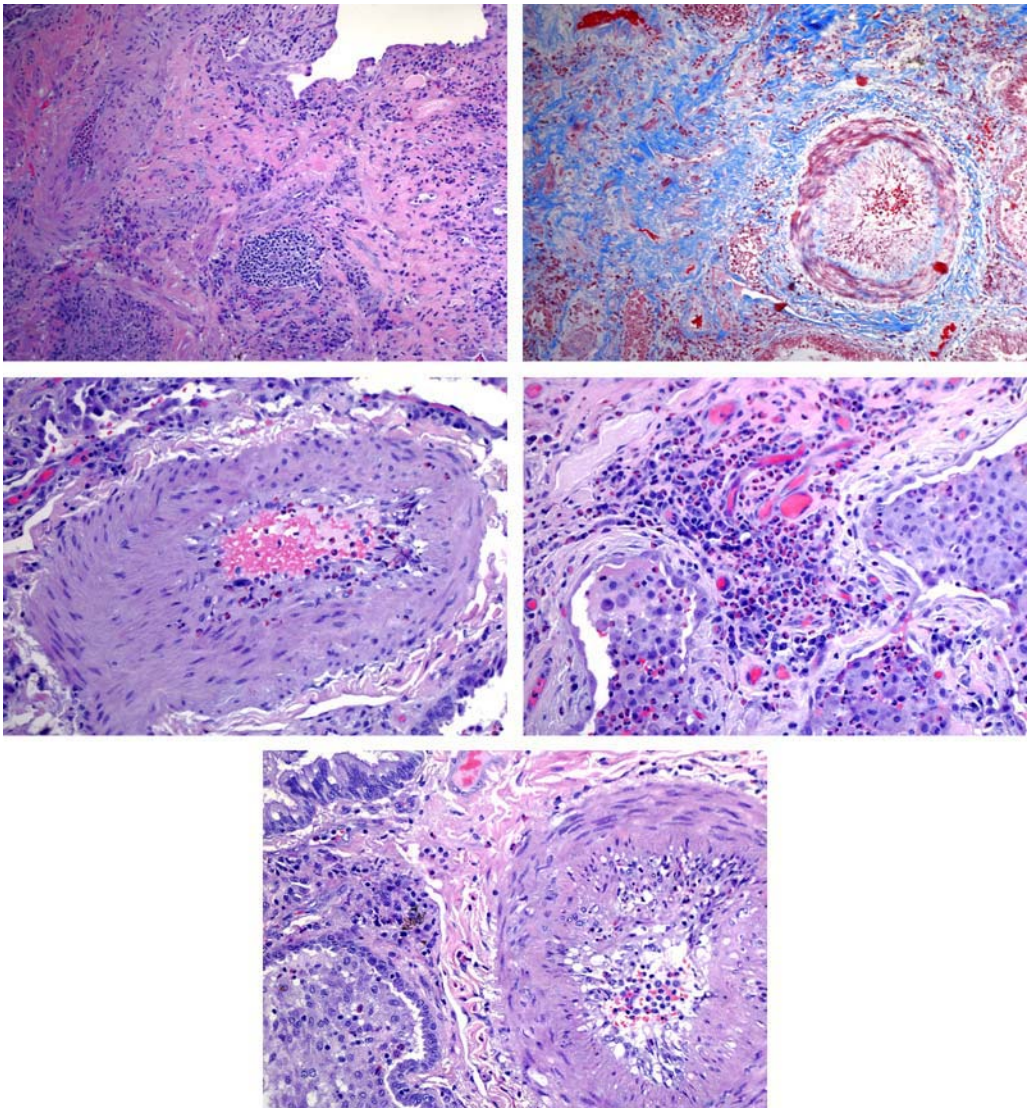
Case 7038

Diagnosis: Lung, open biopsy: Eosinophilic pneumonitis and pneumonia and vasculitis with extensive old interstitial fibrosis, ? Churg-Strauss syndrome (CSG), ? Wegener's granulomatosis, ? CEP superimposed on old scarring, ? other.

A marked eosinophilic infiltrate involves three anatomic compartments, that is, airspaces, interstitium, and walls of blood vessels. Although no necrotizing vasculitis is present, the extent of the eosinophilic infiltrate in large vessels would make me term this an eosinophilic vasculitis. In combination with the clinical and laboratory findings, I believe it reasonable to consider that this patient has a systemic vasculitis. The distribution of the eosinophils and their magnitude make me consider CSG. This is a condition which I consider to be a clinicopathological syndrome and one I would be reluctant to diagnose in a patient without a history of asthma. Reportedly there is allergic rhinitis. CSG has been seen recently in asthmatics on leukotriene antagonists and after withdrawal of corticosteroids. WG can produce this pathology. I do not see focal necrosis of the pathergic type. Serum studies for ANCA would be useful. CEP would raise the possibility of a drug reaction. I am not sure whether or not the eosinophilic pneumonitis is the cause of the underlying extensive interstitial fibrosis, which is old (trichrome stain) and has resulted in some honeycomb fibrosis. It is possible that the patient has an unrelated scarring disease, probably not of great importance considering his acute disease. Another possibility is that we have sampled the tip of a lobe and that the lung is not elsewhere so extensively scarred.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7038 (Chapter 2 – Alveolar Disease)

Case 6863

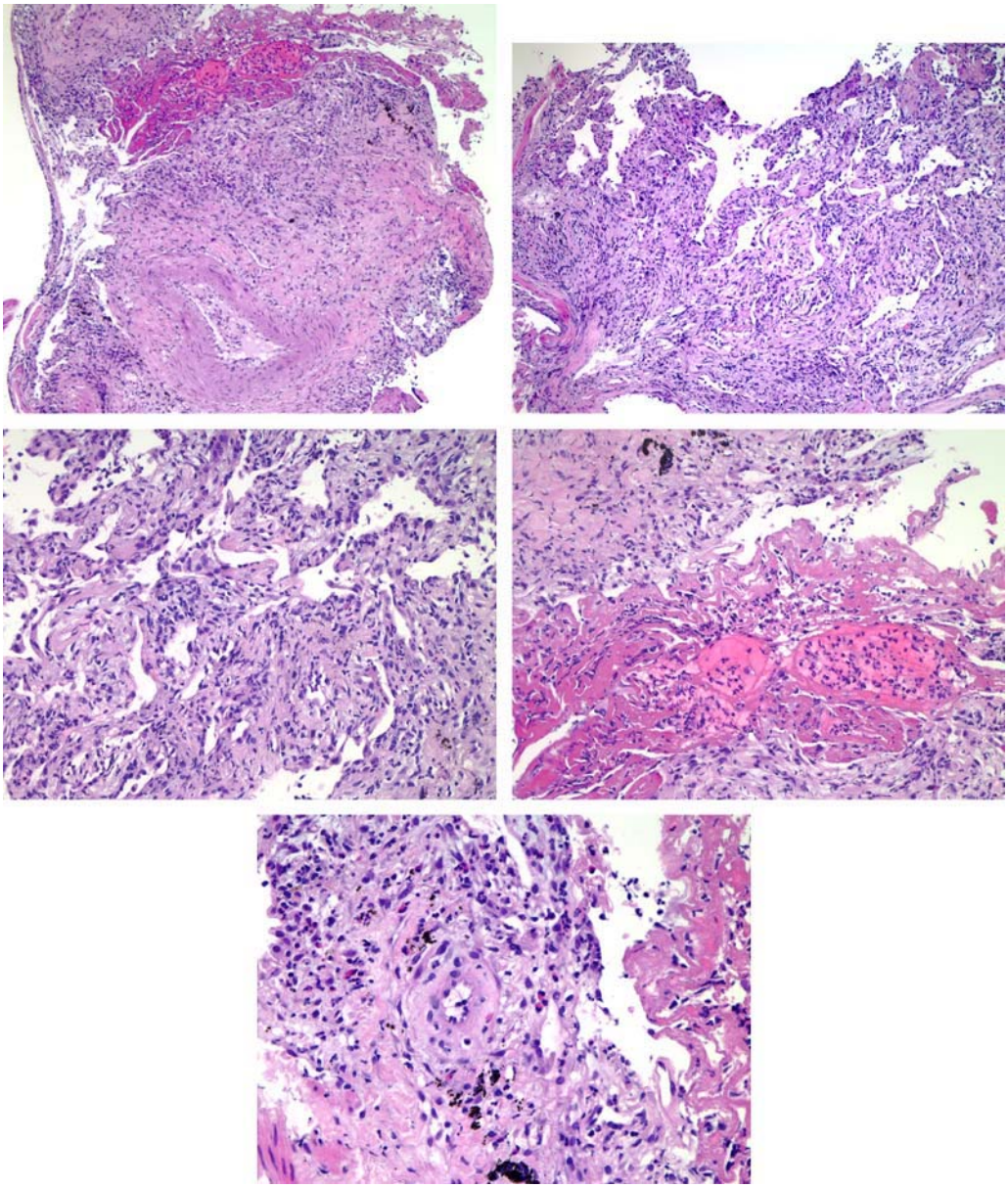
Diagnosis: Bronchus, bronchoscopic biopsies:

1. **OP.**
2. **Ulceration of respiratory epithelium with neutrophils and eosinophils.**

The majority of the specimen consists of intra-alveolar lymphohistiocytic inflammation and organizing fibrosis of a few weeks duration. Other regions of the specimens show ulceration of bronchial epithelium with a neutrophilic and eosinophilic infiltrate. The changes are nonspecific. The ulceration could represent bronchiectasis or be a mucosal erosion over a mass not sampled. The OP could be post-infectious, post-obstructive, associated with bronchiectasis, or a sample of BPOP. The combination of ulceration, OP, and eosinophils raises the possibility of WG, which can be further assessed clinically and serologically. There is no evidence of carcinoma, lymphoma, granulomas, or vasculitis. Your silver stains for organisms are negative. I cannot be sure that the biopsies have sampled a mass lesion.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6863 (Chapter 2 – Alveolar Disease)

Case 6729

Diagnosis: Lung, open biopsy: Organizing fibrinous pneumonia, subacute, cause undetermined, ? BOOP.

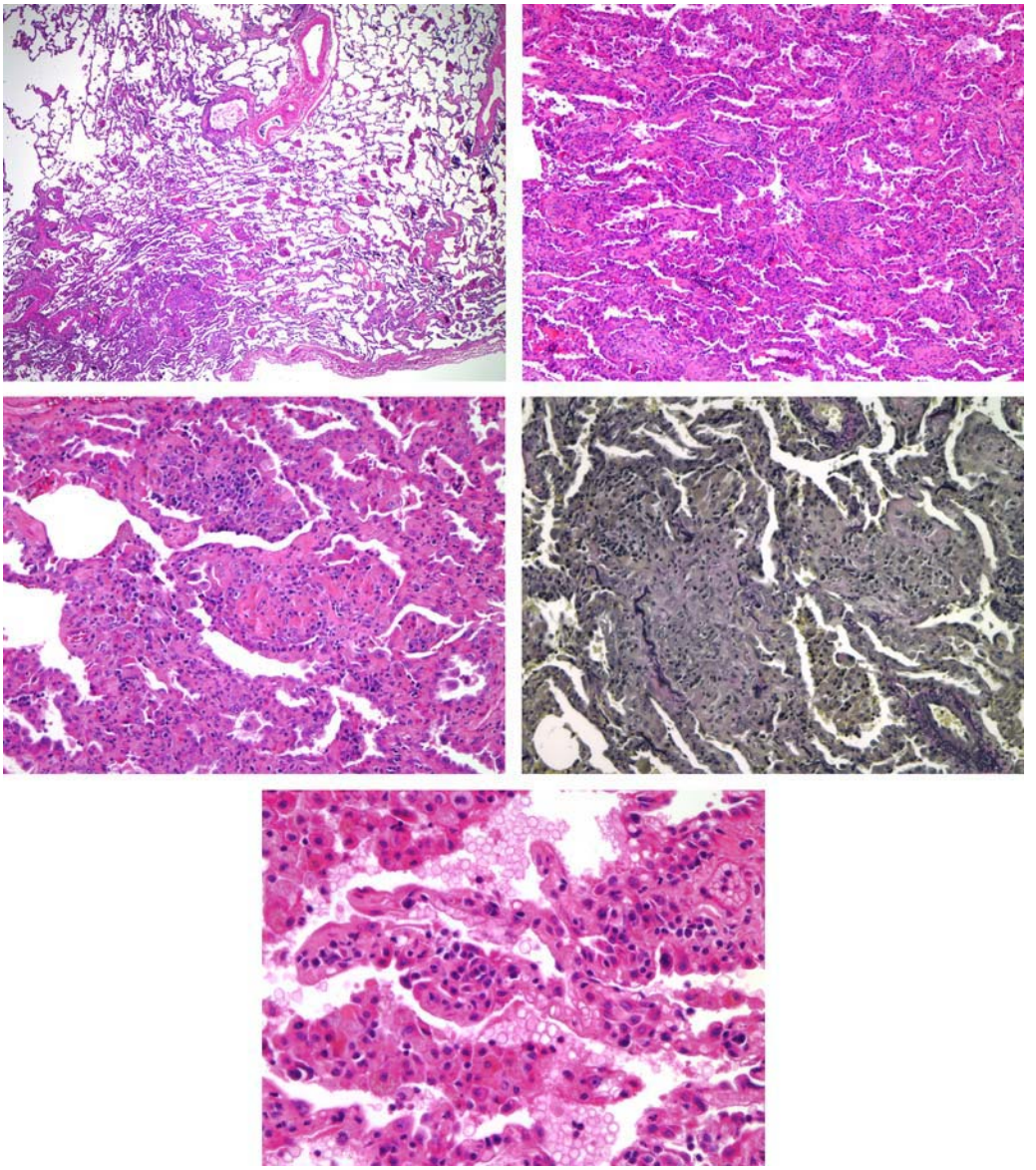
The clinical and pathological features are complex, and I cannot be dogmatic about cause. The predominant morphology is organizing fibrin in alveoli with histiocytes and fibrosis indicating an OP of several weeks in duration and ongoing. There is no prominent bronchiolitis obliterans, but many bronchioles have been destroyed on the elastic tissue stain (as you indicate), and I favor a diagnosis of BOOP with a predominance of OP. Having said that, I do not know the cause of the OP. Viral infection is possible. No viral inclusions are present, although some smudged nuclei are present. I cannot exclude drug reaction or graft-vs-host disease. The common changes in the lung in graft-vs-host disease are lymphocytic bronchiolitis, BO, constrictive bronchiolitis, and lymphocytic interstitial pneumonitis. We have seen a case of BOOP which we believe was graft-vs-host disease.

The differential diagnosis includes a late organizing phase of DAD (as you again indicate). I do not favor this interpretation because there is much fibrin but no hyaline membranes and because the process has a somewhat focal distribution with regions of normal lung remaining.

I would exclude cytomegalovirus and pneumocystis infection by immunostaining and silver staining, respectively.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6729 (Chapter 2 – Alveolar Disease)

Case 7019

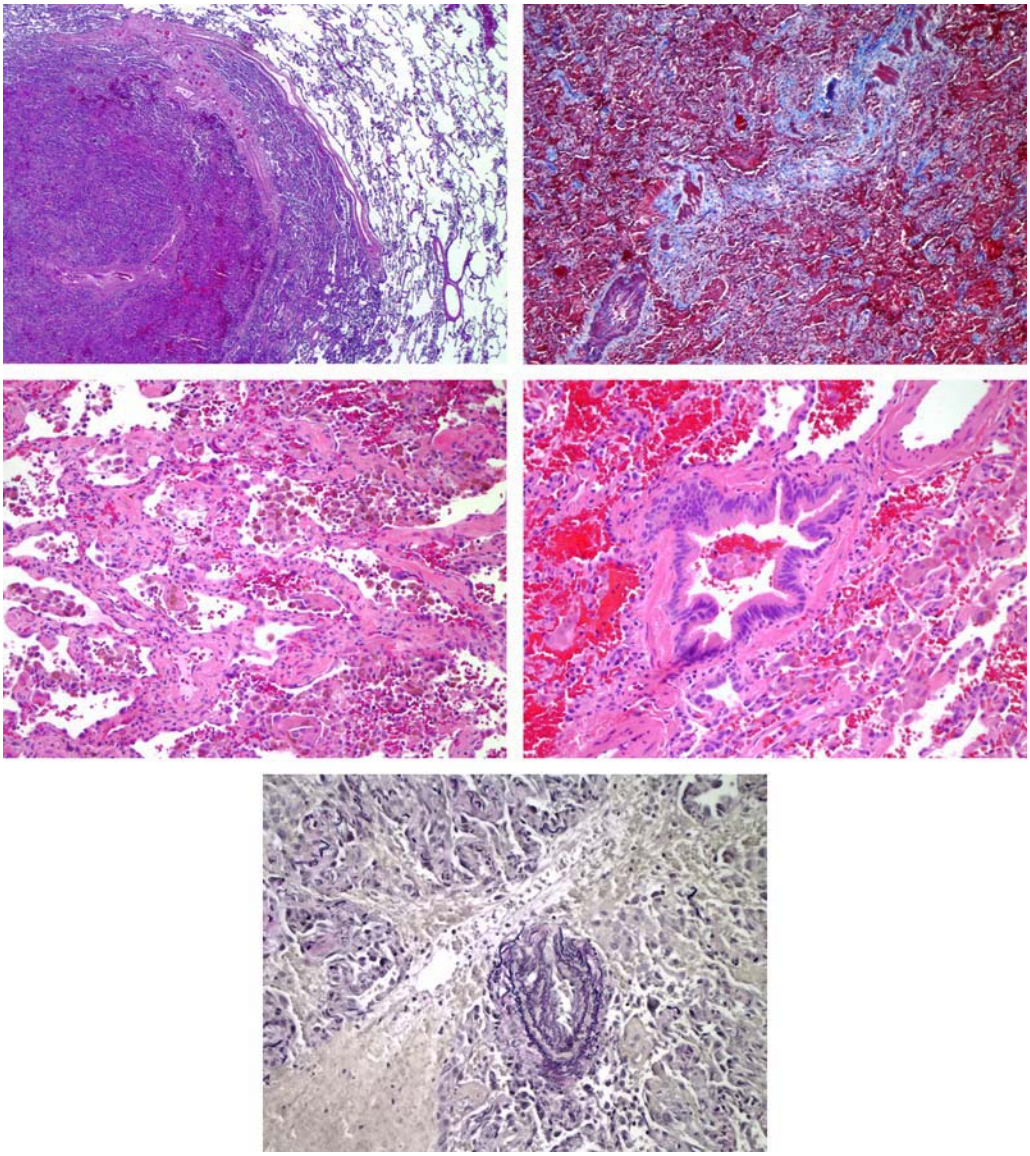
Diagnosis: Lung, open biopsy: Organizing fibrinous and histiocytic bronchiolitis and pneumonia, cause undetermined, ? resolving infection.

This case is enigmatic and does not have diagnostic features of any well described entity. The focal nature of the process suggests a disease centered on bronchioles, although distinct BO is not present. Nevertheless, I believe the fibrin and histiocytes involving alveolar ducts and alveoli can best be described as a fibrinous and histiocytic bronchiolitis and pneumonia. There is interstitial inflammation and fibrosis (trichrome stain) in these nodular areas indicative of disease at least a few weeks old. Based on the clinical and pathological features, I would favor an infectious etiology that is now resolving. I doubt the usual bacteria, because no neutrophils are present. No granulomas are present. Possibilities include a prior chlamydial or mycoplasmal or viral bronchiolitis. Legionella can produce unusual histology and pneumonias with prominence of histiocytes. I cannot exclude a hypersensitivity pneumonitis, but usually bronchiolitis is more apparent in hypersensitivity reactions, and more granulomatous features and lymphoid hyperplasia are also present.

In the differential diagnosis, we considered RB and eosinophilic granuloma (EG). Although there are pigmented histiocytes attesting to the patient's history of smoking, the clinical history is unusual for RB, and the pathology is not classic for that condition. The many histiocytes made us further investigate EG, but Langerhans' cells are few in number on our stains for S-100 and CD1a antigens, and we do not favor this interpretation. A disrupted artery is present in our elastic stain, and we believe this is a technical effect that accounts for the slight focal hemorrhage.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7019 (Chapter 2 – Alveolar Disease)

Case 7012

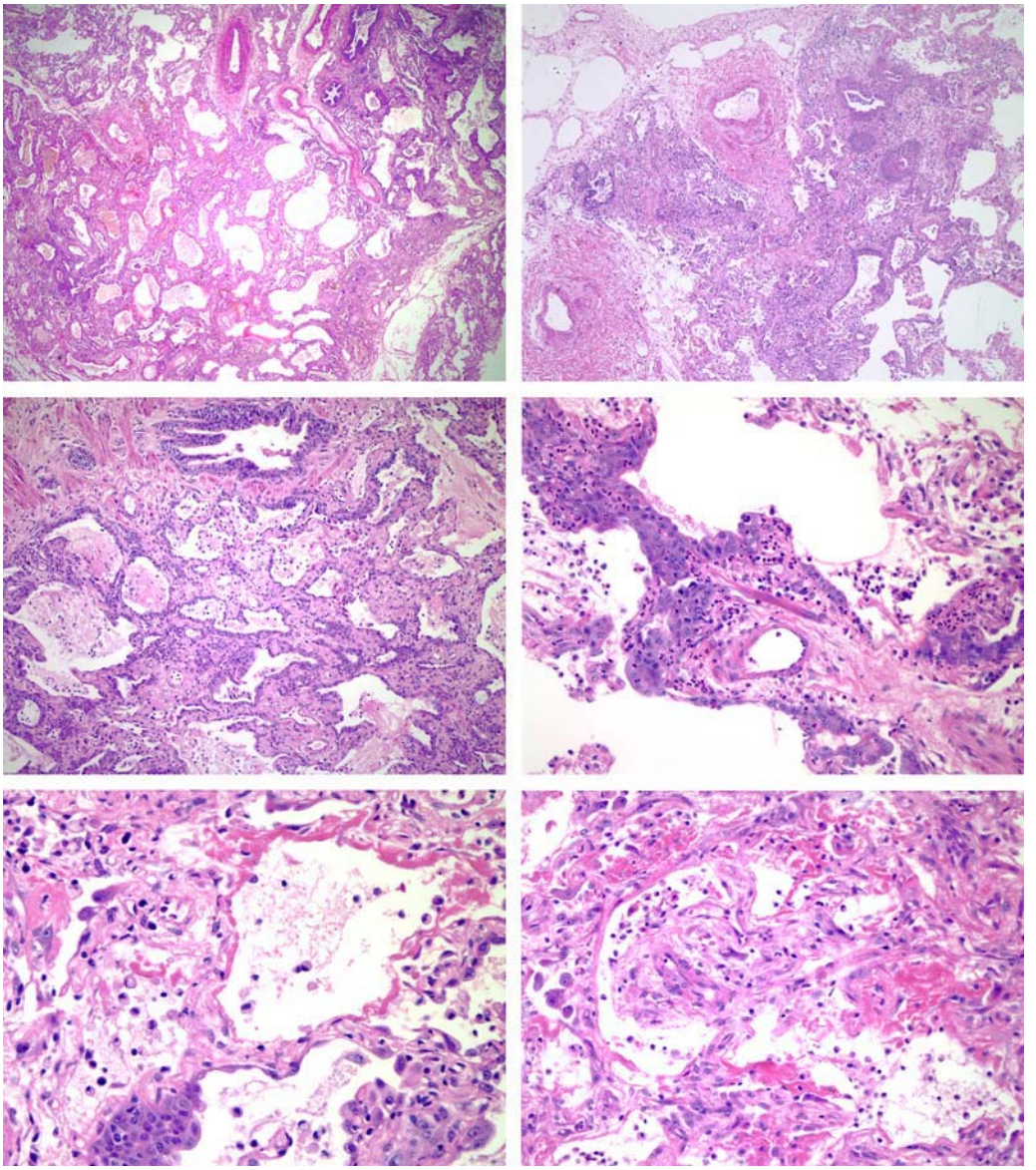
Diagnosis: Lung, open biopsy: OP with interstitial fibrosis, ? resolving BPOP, ? late resolving phase of DAD, ? other.

This case does not fit into any precise category, but the most salient feature is active and ongoing disease. Active disease is manifest by hyaline membranes and active proliferation of fibroblasts in alveoli. Healing disease is manifest by extensive squamous metaplasia and Lamberthosis (distal extension of respiratory epithelium), two markers of possible prior bronchiolitis, and for this reason I include resolving BPOP of a possibly infectious etiology in the differential diagnosis. Neutrophils in bronchioles and in bronchiolar epithelium suggest that interpretation. I do not believe this is UIP, because there is no definite established old fibrosis or subpleural honeycomb change.

If this case represents resolving BPOP, the prognosis is probably sanguine. If this case represents evolving DAD, the prognosis is more guarded, as the disease would fit into the general clinicopathological syndrome of Hamman-Rich. Clinical history might aid in distinguishing these two conditions.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is an elaboration of my telephone message. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7012 (Chapter 2 – Alveolar Disease)

Case 6995

Diagnosis: Lung, open biopsy:

1. **Chronic organizing pneumonia.**
2. **Hemosiderosis.**

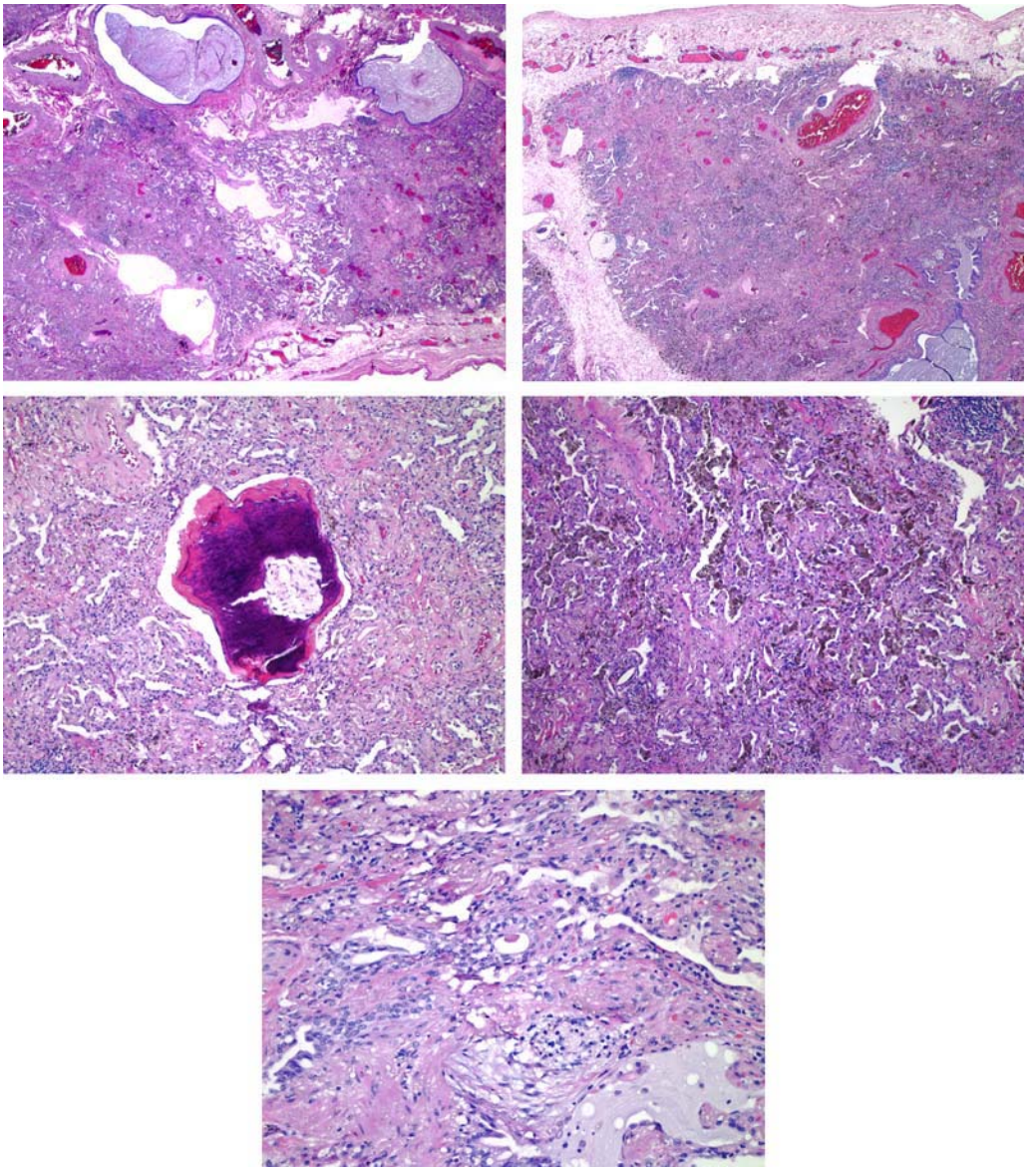
The lung is extensively damaged, and virtually no normal lung is present. The principal pathology is alveolar filling by lymphohistiocytic inflammation, hemosiderin and fibrosis. The fibrosis is all of approximately the same age, which is approximately several weeks in duration. The panlobular distribution and uniformity of age suggests an OP, and the most likely etiology would be resolving infection, although no active infection is apparent. Extensive hemosiderin is present, and in the context of fibrosis, a diagnosis of hemosiderosis is appropriate. However, the hemosiderosis might also be a residue of a prior infectious pneumonia including viral pneumonia. There is also bronchiolectasis with mucus plugging, which could represent either traction bronchiectasis or damage due to cigarette smoke. Occasional small nodules of metaplastic bone are present. I do not believe these have clinical significance.

Because of the extensive hemosiderin, we searched for a vasculitis, but we find none. Nevertheless, a serum ANCA test might be performed in the unlikely event that this is a resolved example of WG. The extensive lung atrophy with fatty replacement beneath the visceral pleura raised usual interstitial pneumonitis into the differential diagnosis, but the uniformity of the process and the absence of honeycomb fibrosis are against that interpretation.

I understand that the patient became ill after doing repair work around pipes and floorboards at home. I understand that he required intubation but is now improving. I understand that a Candida species and an unusual bacterium (Pichia species) have been recovered from bronchial fluids.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6995 (Chapter 2 – Alveolar Disease)

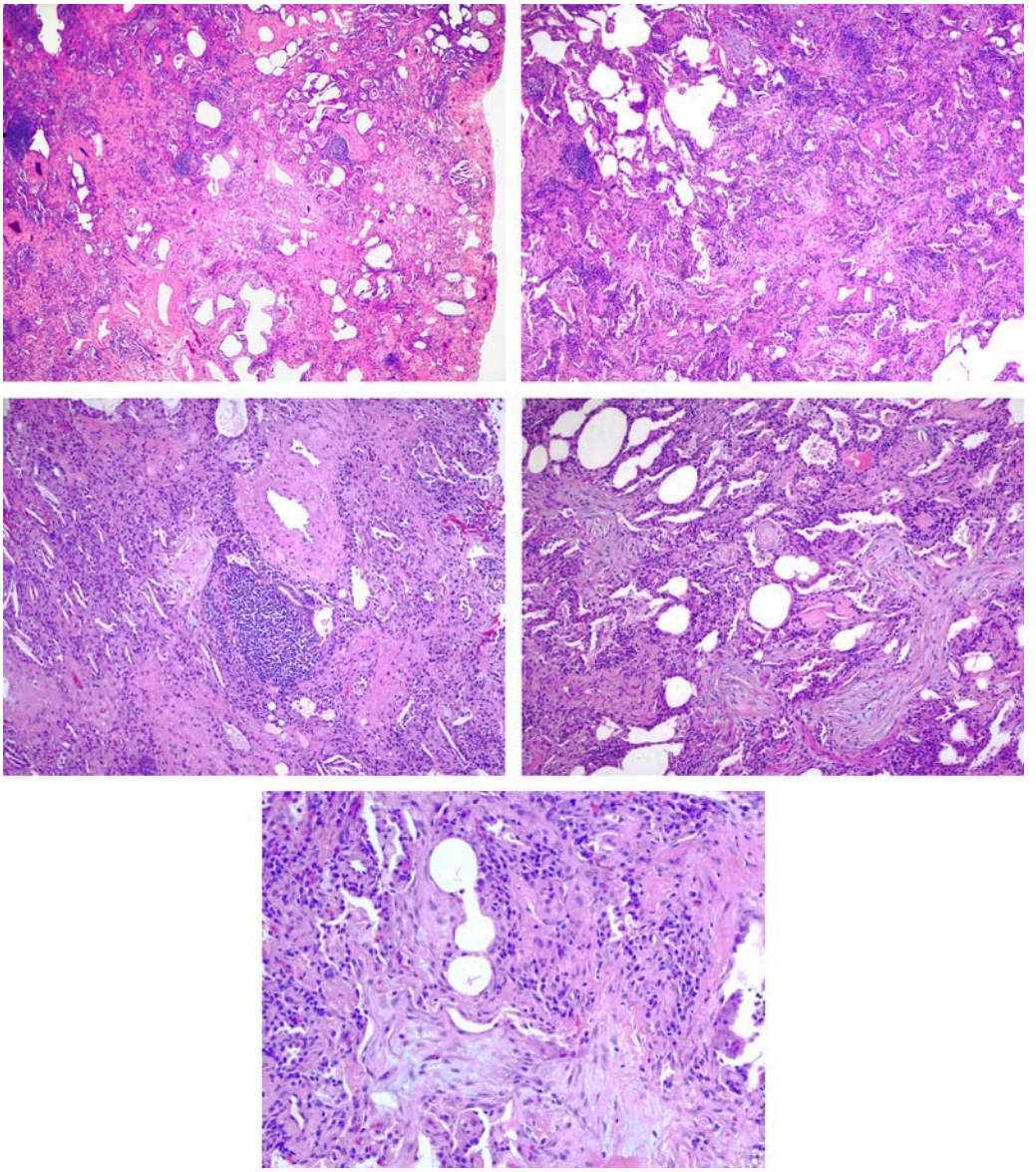
Case 6497

Diagnosis: Lung, open biopsy: Organizing alveolar fibrosis, consistent with chronic organizing pneumonia (COP).

Organizing intra-alveolar fibrosis involves the majority of the specimen. The fibrosis is several weeks in age histologically, and fibrosis is even older as it has undergone incorporation into the interstitium. The differential diagnosis is principally between COP and UIP. Because of the relative uniformity of the process temporally and spatially, I favor COP. Most persons, including me, consider COP of this sort as a variant of BPOP but without the bronchiolocentricity, which is not apparent here. The British have used the term cryptogenic organizing pneumonia to mean COP of this sort. I cannot absolutely exclude UIP, but the preponderance of alveolar disease here favors COP. UIP occasionally has an accelerated phase with prominent alveolar disease, but I do not favor this interpretation, even though the clinical story is consistent with UIP. Some of the alveoli contain cholesterol clefts. These presumably represent bronchiolar obstruction with distal accumulation of histiocytes disintegrating into lipid material.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6497 (Chapter 2 – Alveolar Disease)

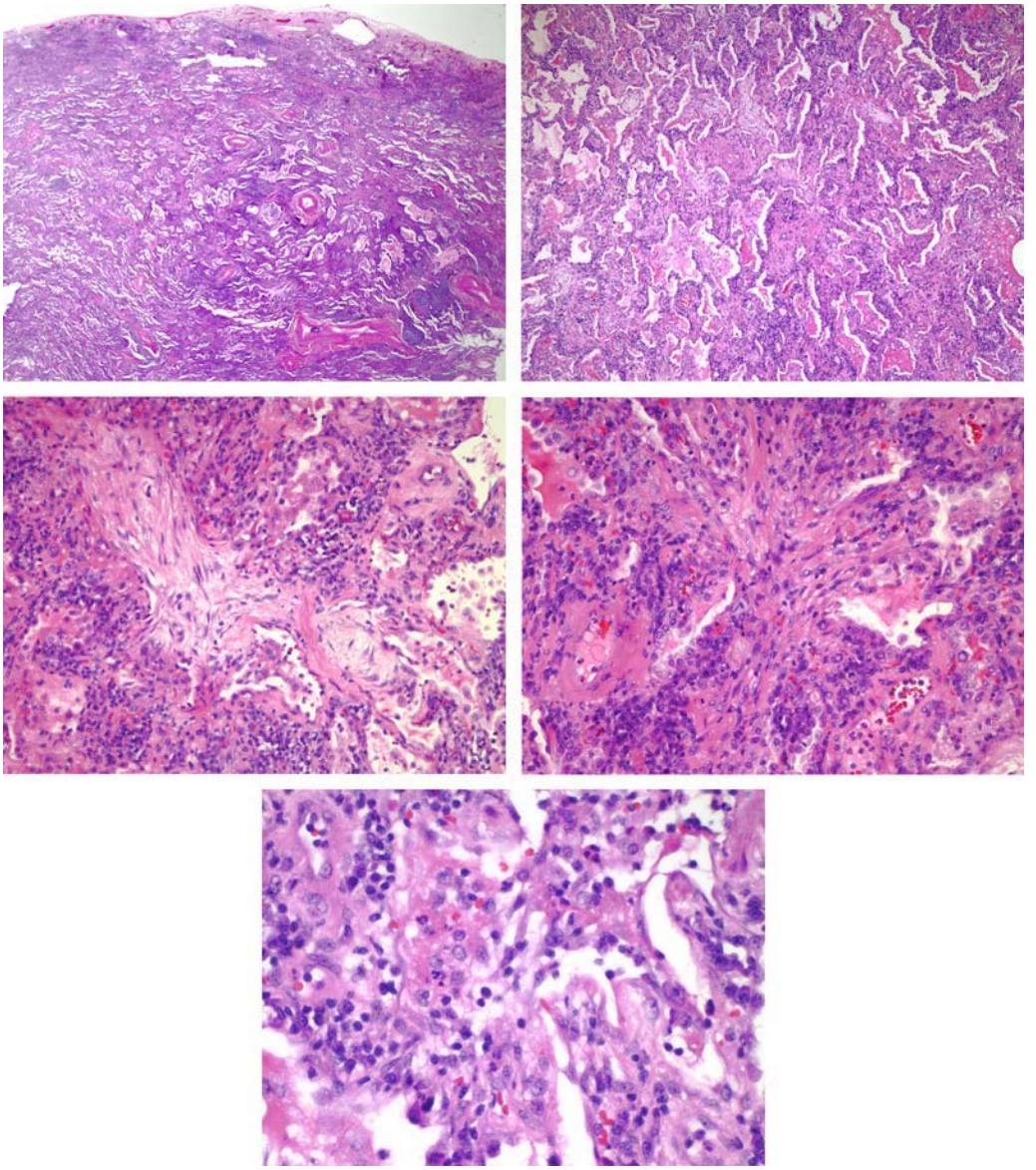
Case 6718

Diagnosis: Lung, open biopsy: Subacute and chronic organizing pneumonia with component of BO, cause and significance uncertain.

This case is difficult because the differential diagnosis includes BOOP, cryptogenic organizing pneumonia, an accelerated phase of UIP, and a late organizing phase of DAD. In such a case I must resort to the predominant pathology on a quantitative basis, and in this case the predominant pathology is organizing inflammation and fibrosis in alveoli. Thus, the morphology is best classified as a pneumonia. The edema and neutrophils indicate ongoing activity. If this were ongoing DAD, I would expect hyaline membranes. The lack of temporal and spatial heterogeneity means that this would be a very unusual picture for UIP, although the reported clinical and radiographic features might suggest that interpretation. I am left with the descriptive diagnosis of subacute and chronic organizing pneumonia with small component of bronchiolar disease. This could be a residue of infection, hypersensitivity reaction, or other causes. I think of the disease in this case as similar in its etiological possibilities to BOOP. I agree that a course of corticosteroids might be attempted if clinical circumstances allow it.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6718 (Chapter 2 – Alveolar Disease)

Case 6916

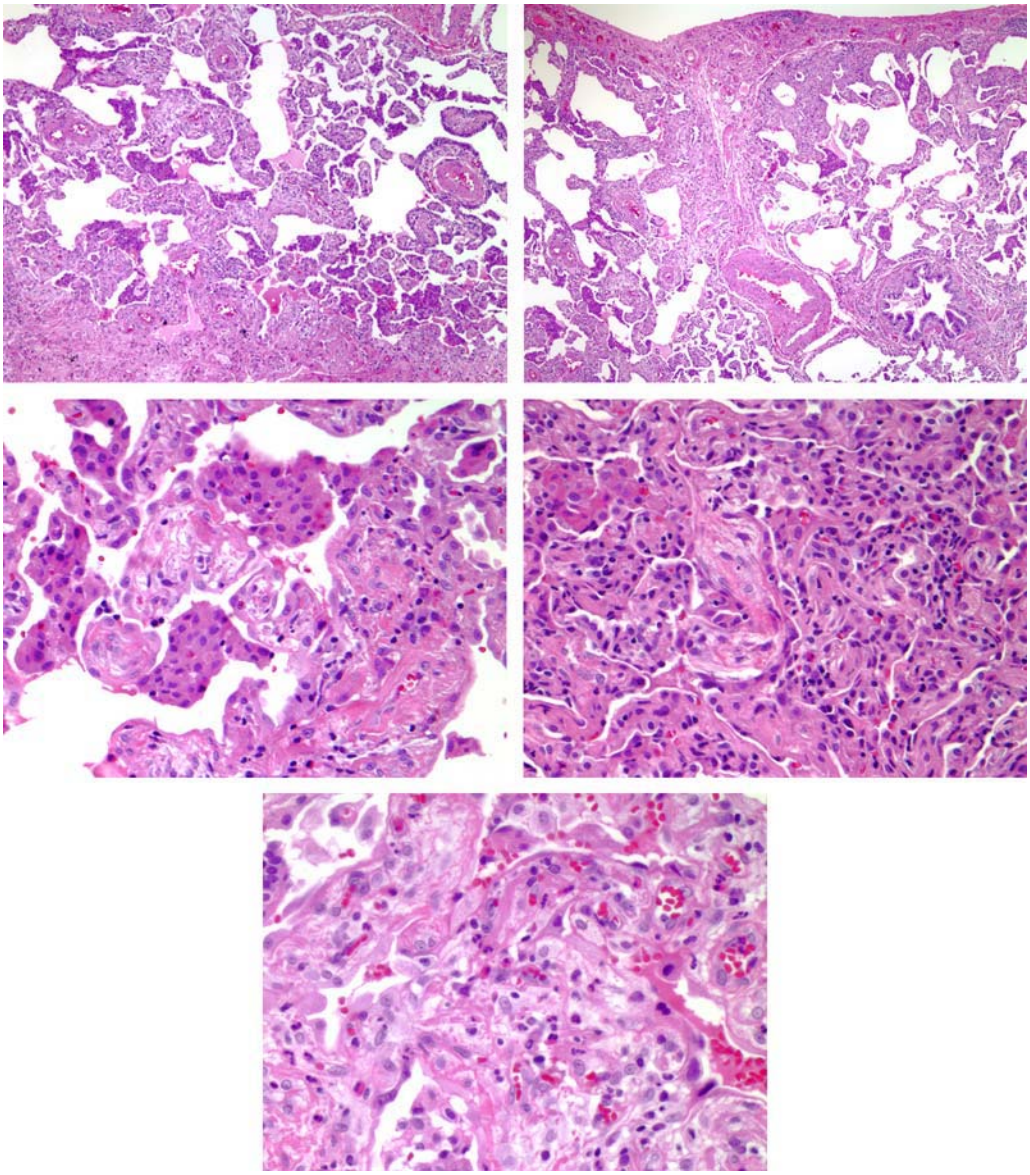
Diagnosis: Lung, open biopsy: Chronic interstitial and alveolar histiocytic inflammation with neutrophils and eosinophils, cause undetermined, consistent with subacute and chronic organizing pneumonia.

This case is difficult because the differential diagnosis is broad and includes UIP, DIP, CEP, hypersensitivity reaction, BPOP, or a subacute and chronic organizing pneumonia (COP). Diagnostic features of none of these conditions are present in this relatively small sample. The most clinically important of these diagnoses would be UIP, which I do not favor because the scarring has not resulted in subpleural honeycomb fibrosis, and the cellularity is more than one generally sees with that condition. There is a DIP-like filling process, and DIP is another possibility, but I do not favor this interpretation. CEP also enters into the differential diagnosis because of the DIP-like reaction and eosinophils, but I cannot make this diagnosis. This is more OP and fibrosis than usually encountered in CEP. Another consideration is hypersensitivity pneumonitis, because of the eosinophils and histiocytes.

The distinction of BPOP and COP is in part semantic, and these two terms have been used interchangeably by some authors. This biopsy could represent a chronic organizing pneumonia. The clinical history and the reported radiographic findings are consistent with that interpretation, and I favor that interpretation. Whether or not the COP was infectious or of other cause cannot be determined from the biopsy. There is no purulent component to the inflammation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is an elaboration of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6916 (Chapter 2 – Alveolar Disease)

Case 6923

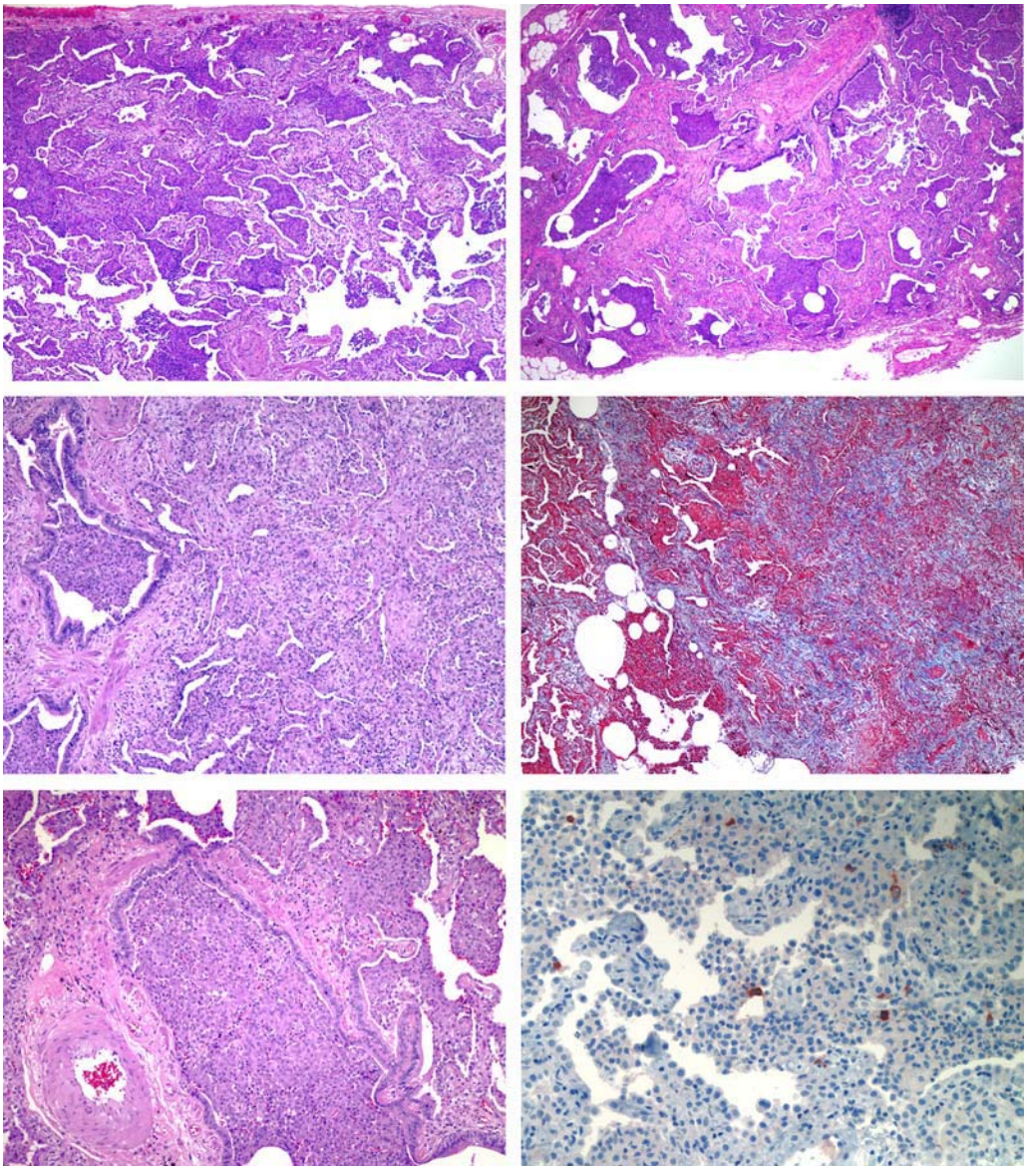
Diagnosis: Lung, open biopsy: Alveolar filling by histiocytes and interstitial fibrosis, nature and cause undetermined, ? unusual OP, ? other.

This case is difficult, and the histology does not fit into a well recognized category. The predominant finding is marked alveolar filling by histiocytes in a manner suggestive of DIP, but the histiocytic filling of bronchioles, the cohesive character of the histiocytic aggregates, and the absence of eosinophils are against DIP. One slide has subpleural honeycomb fibrosis, and so another possibility is UIP, which can be associated with a DIP-like reaction but generally not with such a massive histiocytic infiltrate. Neither DIP nor UIP correlate well with the reported clinical features in this patient. The irregular character of the scarring makes me favor a diagnosis of a generic OP such as might be seen in a resolving infection including unusual organisms such as virus, mycoplasma or Legionella. This is the interpretation I prefer. Another consideration is BOOP, which would be a possibly noninfectious cause of an OP, and I cannot exclude this possibility, but alveolar filling by histiocytes usually is not so pronounced in BOOP.

In the differential diagnosis we also considered EG, and we performed stains for Langerhans' cells (S100, CD1a), but Langerhans' cells are present in only small numbers and scattered individually amidst the histiocytes, so this is not EG. We performed an iron stain to further evaluate the nature of the histiocytes, and they do not contain hemosiderin. Elastic stain and trichrome stain show old irregular fibrosis and no distinct vascular or bronchiolar disease.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6923 (Chapter 2 – Alveolar Disease)

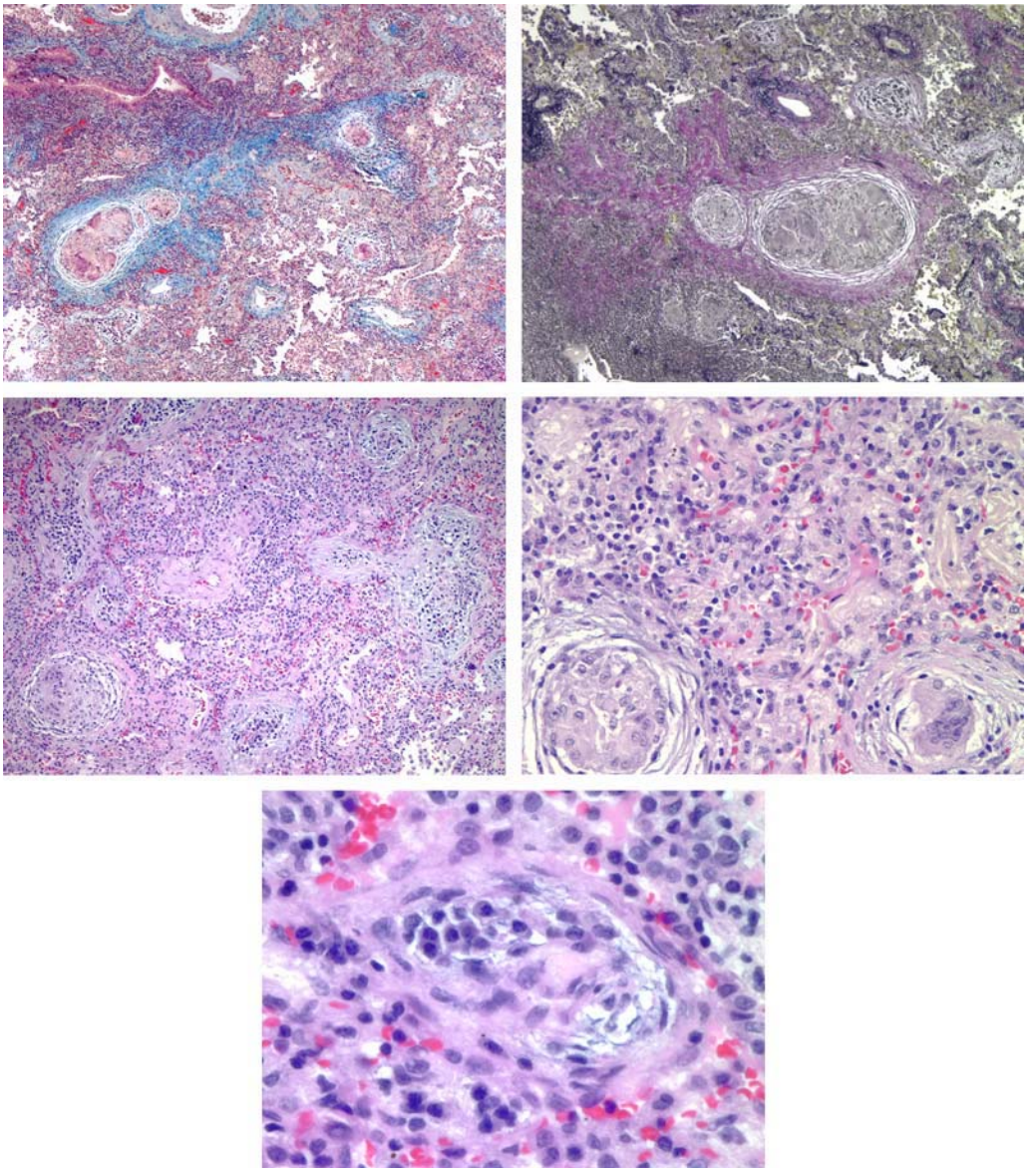
Case 6787

Diagnosis: Lung, open biopsy: OP and discrete compact granulomas with prominent Langhans' cells, cause undetermined, ? aspiration.

This case is unusual by virtue of the combination of an organizing lymphohistiocytic infiltrate with numerous plasma cells, representing an OP, upon which are superimposed numerous compact and discrete granulomas. Numerous multinucleated histiocytes are present. Some of the granulomas may be in vessels. The histology is not typical for sarcoidosis, although that diagnosis cannot be absolutely excluded. Other causes of this unusual histology would include embolic foreign material or aspiration of foreign material.

Thank you for referring this case in consultation. We have recut the blocks which you kindly sent us and stained them for elastic tissue, trichrome, periodic acid-Schiff, and silver. These stains provide no additional information.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6787 (Chapter 2 – Alveolar Disease)

Case 7192

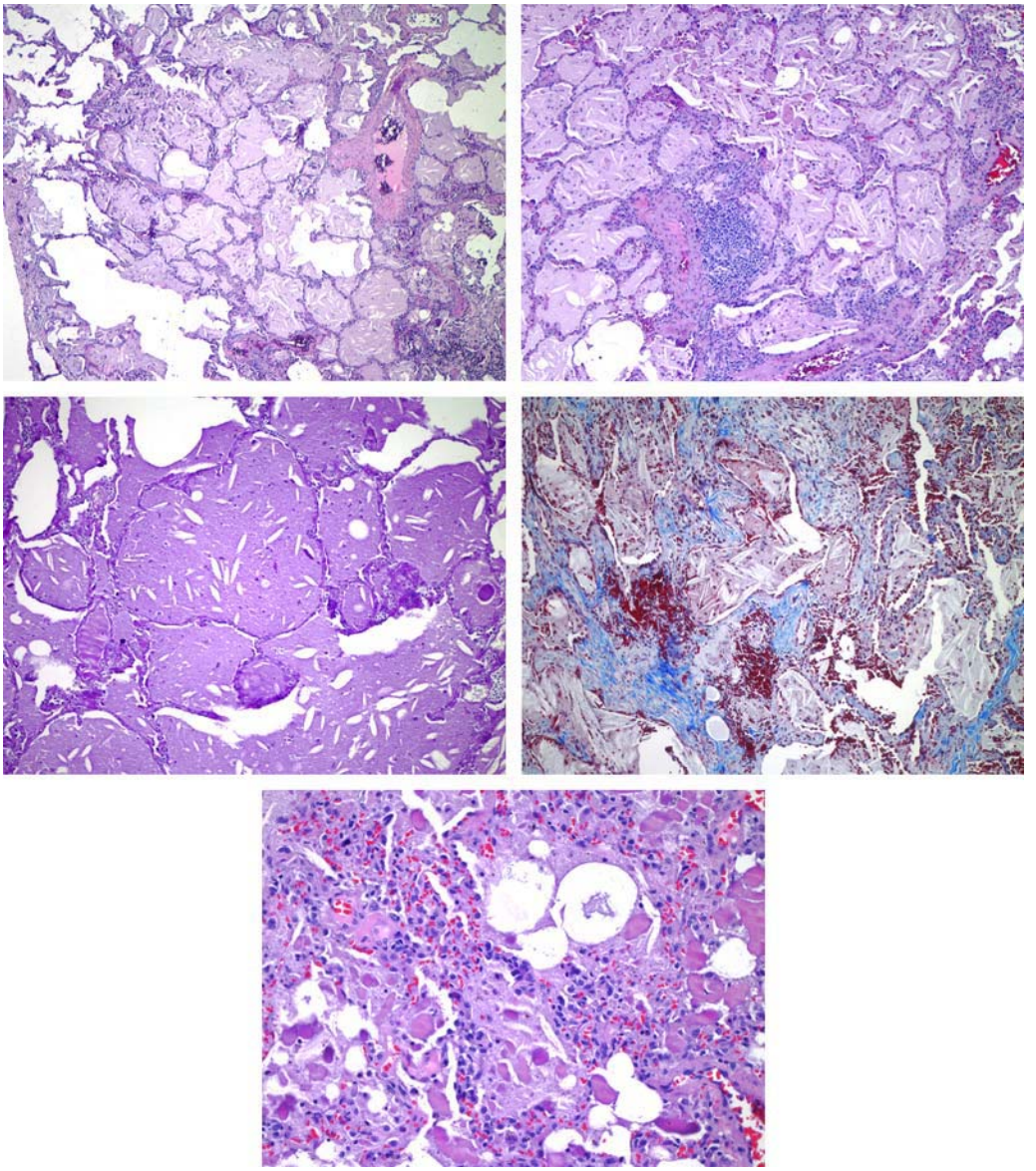
Diagnosis: Lung, open biopsy: Pulmonary proteinosis, with focal interstitial and alveolar fibrosis.

The distension of the alveoli by the relatively opaque albeit pale granular material with cholesterol clefts characterizes pulmonary alveolar proteinosis. Denser eosinophilic globules are present amidst the proteinaceous material. The focal inflammation and fibrosis in alveoli and alveolar walls (trichrome stain) are sometimes seen in pulmonary alveolar proteinosis and account for the reported interstitial pattern that is sometimes observed on chest radiographs.

The histogenesis of pulmonary alveolar proteinosis generally includes either production or a decreased clearance of surfactant. Exposure to silica can cause lipo-proteinosis. I am not aware of heavy metals causing the disease.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7192 (Chapter 2 – Alveolar Disease)

3 Interstitial Lung Disease

CONTENTS

INTRODUCTION

The two most common diseases encountered in an open biopsy for chronic lung disease are usual interstitial pneumonitis (UIP) and bronchiolitis with patchy organizing pneumonia (BPOP). The initial determination is to separate these two **(6733)**, and the distinction is important histologically and clinically. UIP is a disease with temporal and spatial heterogeneity and continuous progression. The patient is likely to get worse even with therapy. BPOP is a disease often representing a single event, so the disease tends to be all of about the same age, usually 4–6 wk in duration when biopsied. By definition, the disease is centered on bronchioles and therefore focal and classically micronodular.

Interstitial pneumonitides generally have the least specific histological findings of the various categories of lung disease and consequently are the most difficult to diagnose on a transbronchial biopsy. A histological diagnosis of fibrosis is often taken to mean diffuse interstitial fibrosis by the physician if the patient has diffuse interstitial disease on the chest radiograph. A sharp distinction should be made between fibrous tissue (normal or abnormal) and fibrosis (a disease process).

INTERSTITIAL FIBROSIS: WAYS TO OVERDIAGNOSE

- Squeeze effect
- Atelectasis
- Peribronchiolar fibrosis
- Interlobular septum

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

USUAL INTERSITITIAL PNEUMONITIS

Ground Rules

- Nomenclature varies
- Clinicopathologic diagnosis (consensus classification; Travis et al., 2002) now cryptogenic fibrosing alveolitis (CFA) /Idiopathic pulmonary fibrosis (IPF)
- Cause generally unknown
- Related to collagen-vascular disease
- Therapy ineffective
- Disease common

UIP is patchy, interstitial, lymphohistiocytic, and scarring. The inflammation and scarring will be more severe in some areas than in others. A few normal alveoli may be present. The disease is not centered on bronchioles, but bronchioles are often ectatic and filled with mucus and small numbers of neutrophils. The interstitial thickening may be delicate or coarse and associated with intra-alveolar as well as interstitial fibrosis. In cases with a marked lymphocytic reaction, germinal centers may be present. This is seen particularly in rheumatoid lung disease. Alveoli may be filled with pigment-laden histiocytes. Interstitial neutrophils and eosinophils, granulomas and pleuritis are rare and suggest alternate diagnoses. If the biopsy comes from the tip of a lobe or in a patient with late-stage disease, pathology may show end-stage coarse interstitial fibrosis and honeycomb change and minimal inflammation. A diagnosis of UIP is not possible on such a biopsy. Diagnostic features of UIP can be remembered using the mnemonic PILSNER:

- Patchy
- Interstitial
- Lymphohistiocytic
- Scarring
- Not on transbronchial
- Elimination
- Relentless

The two essential features of UIP are:

- Spatial diversity
- Temporal diversity, including old honeycomb fibrosis and active fibroblastic foci

Differential Diagnosis, Depending on Stage of Disease

- Diffuse alveolar damage (DAD)
- Desquamative interstitial pneumonitis (DIP)
- Bronchiolitis with interstitial pneumonitis (BIP)
- Bronchiectasis
- Hypersensitivity reactions
- Sarcoidosis, end stage
- Chronic eosinophilic pneumonia, late organizing stage
- Drug reaction
- Asbestosis
- Eosinophilic granuloma (EG), mid stage
- Pulmonary veno-occlusive disease

The differential diagnosis of UIP is given above. DAD in patients who survive more than 4 wk has many remnants of hyaline membranes incorporated into intra-alveolar

fibrosis. The immature fibrous tissue is myxoid with stellate fibroblasts. UIP has foci of similar myxoid fibrous tissue scattered through the biopsy, in alveoli as well as partially incorporated into the interstitium. These foci are now termed active fibroblastic foci. This is in contrast to the mature fibrosis with eosinophilic fibers of collagen and spindle-shaped fibroblasts commonly seen in UIP of long duration. One way to think about UIP is as microfocal DAD occurring sporadically over time. When the fibrosis becomes florid, one may then have the clinicopathological syndrome of accelerated UIP **(6535)**.

NONSPECIFIC INTERSTITIAL PNEUMONITIS

The principal reason for considering a diagnosis of nonspecific interstitial pneumonitis (NSIP) is so as not to overdiagnose UIP, which has a grim prognosis. As originally described and best utilized, the term NSIP **(6953)** is a reaction pattern and not a disease. Many etiologies are possible, but the name implies that one cannot be proven in the individual case. In general, NSIP is updated to cases with features suggestive of UIP but lacking active fibrosis or honeycomb fibrosis or both. It may or may not be a distinct condition and, importantly, it should not be overdiagnosed as a fatal pneumonitis (UIP).

Reasons Why a Biopsy May Be Nonspecific

- Too-small sample
- Technical artifact (crush, atelectasis)
- Sampling problem
- Very early or very late disease
- Not typical histology
- Not specific, not diagnostic, not encountered before, or no specific etiology

Some Situations in Which Histology May Seem Nonspecific

- Early UIP with little scarring
- Late UIP with little inflammation
- Mild or focal DIP
- Early or cellular EG
- Hypersensitivity reaction with little granulomatous inflammation
- BIP
- Cellular interstitial pneumonitis in children

EOSINOPHILIC GRANULOMA

Proliferation of Langerhans' cells to a degree sufficient to cause microscopic nodules defines pulmonary EG **(6681)**. The disease occurs for the most part in cigarette smokers. Langerhans' cells proliferate in the lung in several diffuse interstitial diseases and in reaction to neoplasms. The proliferation may be of such degree in bronchiolitis obliterans (BO) as to make distinction of EG from bronchiolitis a problem **(6705)**. EG in late phase has retention of the starfish configuration of the scarring or at least tentacles of the starfish. Intervening alveoli are normal. Admixed with lymphocytes and histiocytes in the scarred interstitium are aggregates of chocolate-brown histiocytes.

Histological Stages

- Early: nodules of Langerhans' cells and eosinophils
- Mid: starfish-shaped scars with pockets of Langerhans' cells and DIP-like reaction
- Late: scars and cysts with relics of Langerhans' cells, lymphocytes and brown pigment

- Clinical scenario: smoker with nodules (r/o sarcoid) or cysts (r/o lymphangioleiomyomatosis) on X-ray

DESQUAMATIVE INTERSTITIAL PNEUMONITIS

DIP has alveolar inflammation in excess of interstitial inflammation. Fibrosis is less extensive and less marked than in UIP. Eosinophils are more frequent in DIP than UIP. DIP is often patchy. The predominant pattern dictates the diagnosis **(6779)**, but occasionally there are equal portions of UIP and DIP and distinction is not possible. The prognosis is much better for patients with DIP than for those with UIP. DIP may be related to smoking, particularly when it overlaps with respiratory bronchiolitis (RB). Patients with UIP who smoke fare worse than nonsmokers.

OTHER CHRONIC DISEASES THAT MAY SHOW INTERSTITIAL DISEASE

Asbestosis in late stage is primarily fibrosis, but in early stage, an interstitial lymphocytic infiltrate may be marked. Asbestosis in early stage may be accentuated around respiratory bronchioles and beneath the pleura. This localization is not part of UIP. The presence of one or more asbestos bodies per slide excludes UIP **(6867)**.

Sarcoidosis and chronic berylliosis have granulomas which are arrayed in a lymphangitic pattern around bronchovascular bundles and in the interlobular septa and pleura **(6623)**. Granulomas may be present in hilar lymph nodes when they are absent in the lung. In early disease, a lymphocytic infiltrate may be prominent both in the airspaces and in the interstitium. In late stage, granulomas may be represented only by small circular hyaline scars, which are clearer in lymph nodes than in markedly fibrotic lung. Some cases of berylliosis lack granulomas, and distinction from UIP **(6611)** may be impossible on histologic grounds. Calcium oxalate/carbonate crystals are common in multinucleated histiocytes in sarcoidosis and may be misinterpreted as talc or other inspired particles.

SUGGESTED READINGS

Usual Interstitial Pneumonitis

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LETTERS

Case 4428

Diagnosis: Lung, open biopsy: BIP.

Organizing bronchiolitis and interstitial lymphocytic pneumonitis are combined here in an unusual manner. Bronchiolitis obliterans and usual interstitial pneumonitis are two very different diseases biologically and histologically. However, features of both diseases occasionally appear together and were included as the entity BIP in Dr. Averill Liebow's seminal classification of interstitial pneumonitides in 1968. This is essentially in agreement with your interpretation.

There is little published data on the natural history of bronchiolitis with interstitial pneumonitis. In my experience the disease has more in common with bronchiolitis with organizing pneumonia (BOP) than with UIP. Little established scarring in this case suggests that this patient has a good probability of responding to corticosteroids in the manner of BOP. I do not know what has caused the BIP.

Thank you for referring this case in consultation. Please keep me informed of any follow-up, and call if you have question

Sincerely yours,
Eugene J. Mark, M.D.

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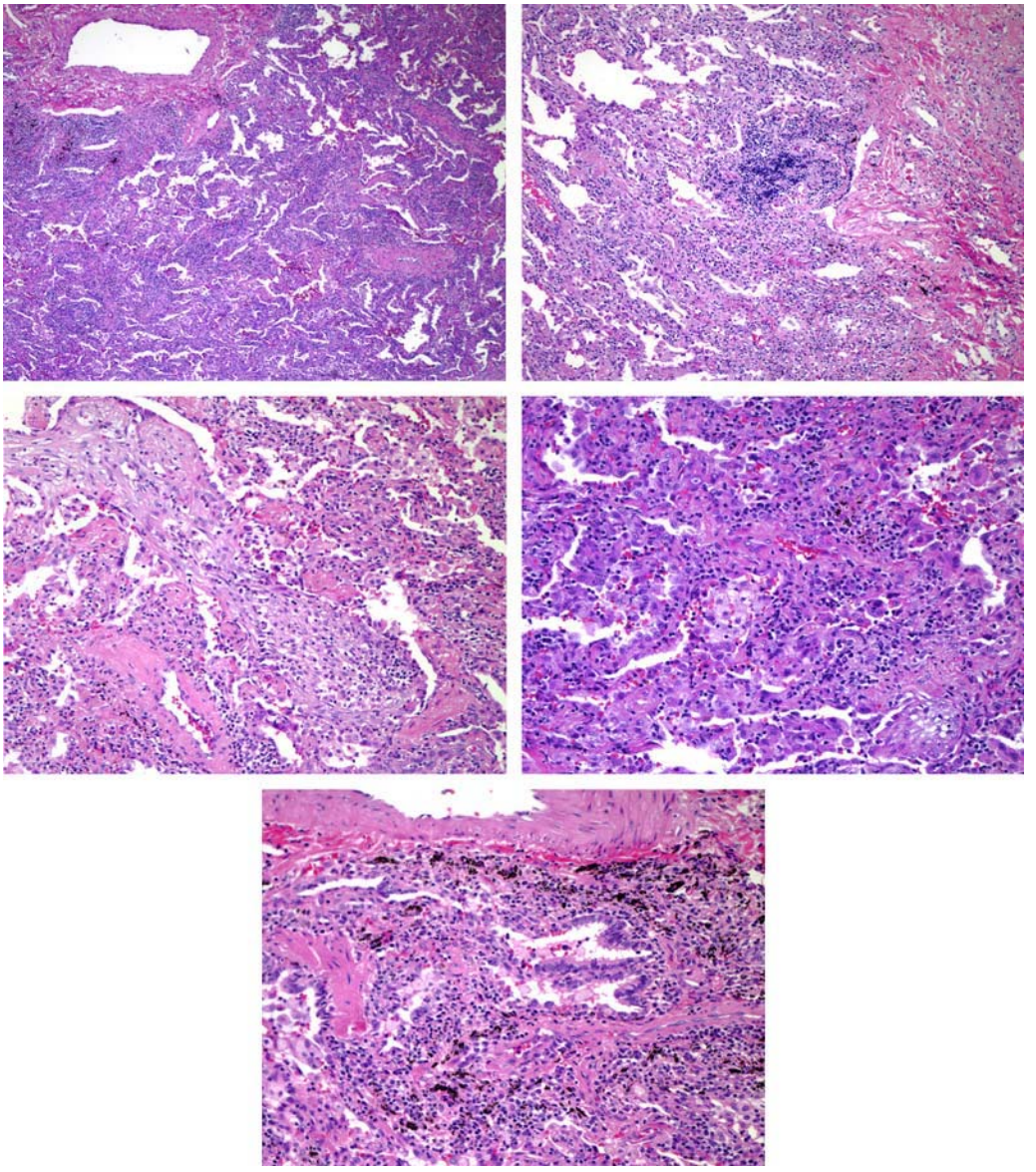


Case 4428 (Chapter 3 – Interstitial Lung Disease)

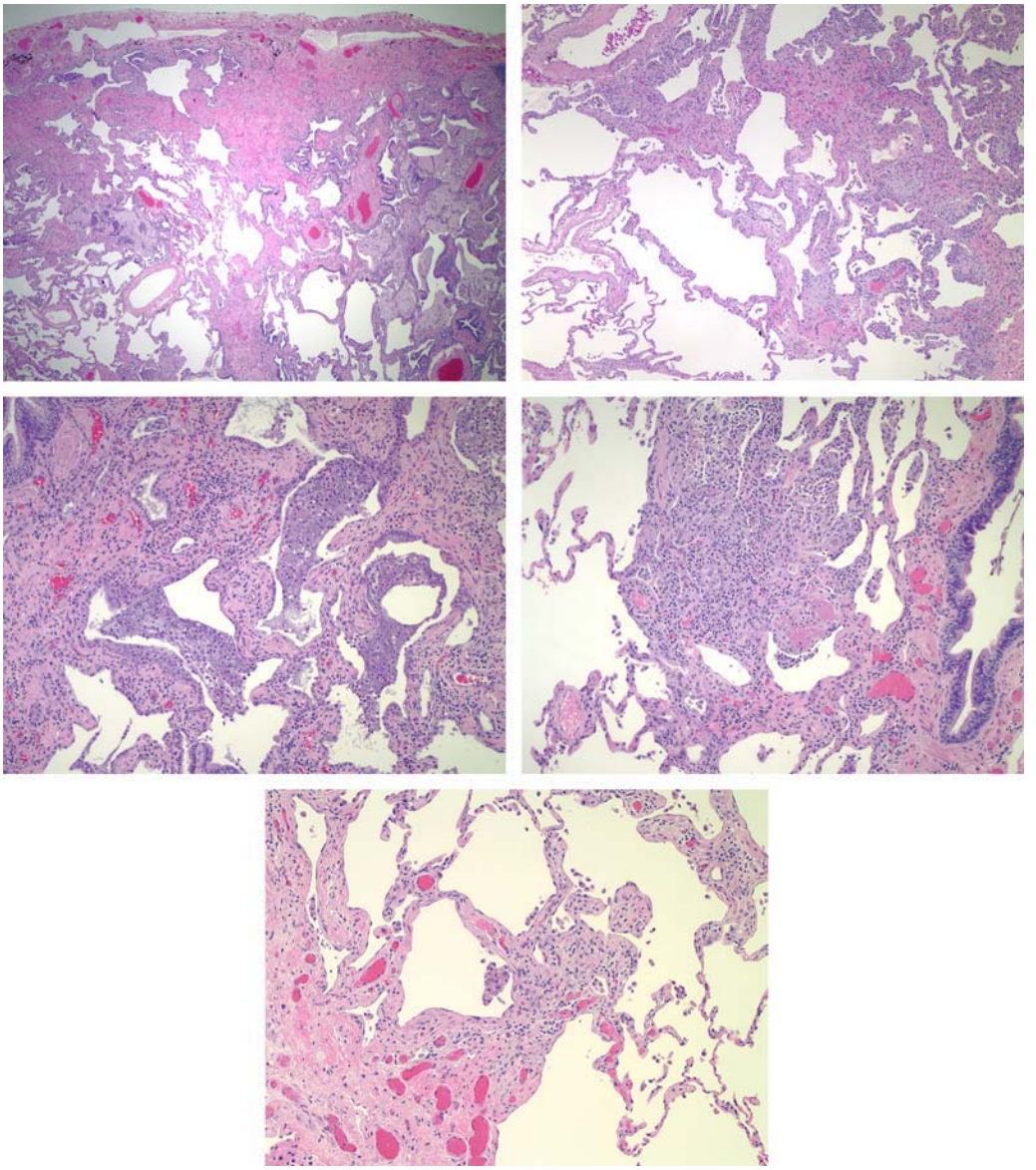
Case 6460

Diagnosis: Lung, open biopsy: UIP.

The temporal and spatial diversity of the disease is characteristic of UIP. The temporal changes cover an unusually broad spectrum, from early organizing fibrin to later organizing intra-alveolar fibrosis to interstitial fibrosis to end-stage honeycomb fibrosis. The spatial diversity ranges from normal lung to regions of superficially normal lung but with rounded contours indicating early interstitial thickening to regions of coarse fibrosis to regions of subpleural honeycomb change with mucopurulent plugs. An interstitial lymphocytic infiltrate is present in many areas. The primary differential diagnosis is BPOP, which arises because of a nodular character of the inflammation in a few areas. However, the other features are against BPOP. I also considered EG because of the stellate shape of a few nodules of histiocytes, but Langerhans' cells are not apparent and other features of EG are not present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6460 (Chapter 3 – Interstitial Lung Disease)

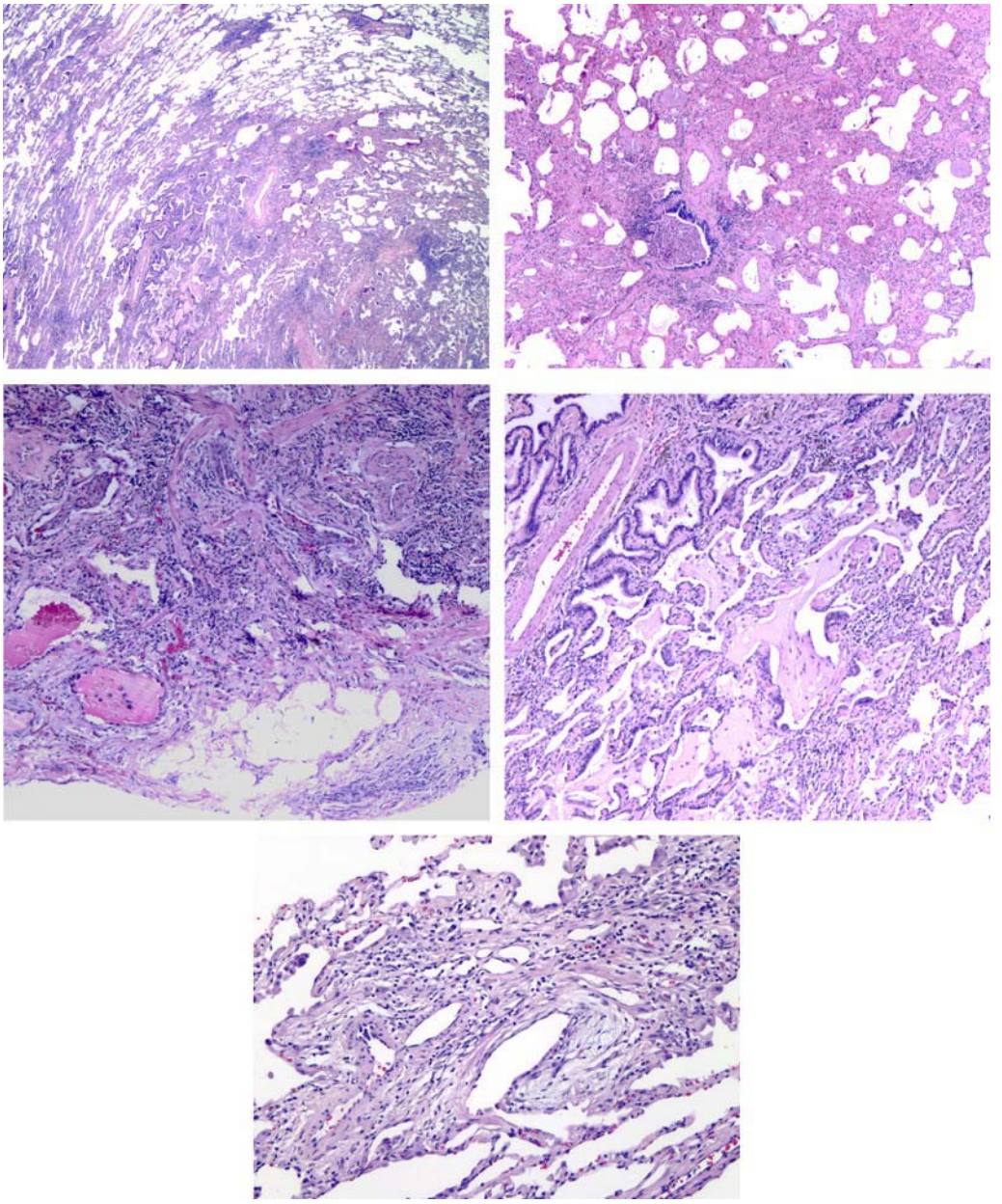
Case 6710

Diagnosis: Lung, open biopsy: UIP.

This case has an interstitial pneumonitis with early fibrosis, which is more marked in the peripheral lung zone than in the central lung zone. The differential diagnosis has two possibilities: 1) UIP, or 2) NSIP consistent with an early phase of UIP. These two diagnoses probably are essentially equivalent from the standpoint of clinical management. I believe that the degree of older interstitial fibrosis beneath the pleura with histological suggestion of early honeycomb fibrosis in conjunction with active organizing fibrosis with pneumocyte hyperplasia as well as the spatial diversity of disease are sufficient for a diagnosis of UIP. Acute and old disease are not present in this specimen. The histological changes appear several months in duration but not several years in duration. There is a prominent lymphocytic interstitial component, which might possibly respond to corticosteroid therapy.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6710 (Chapter 3 – Interstitial Lung Disease)

Case 6733

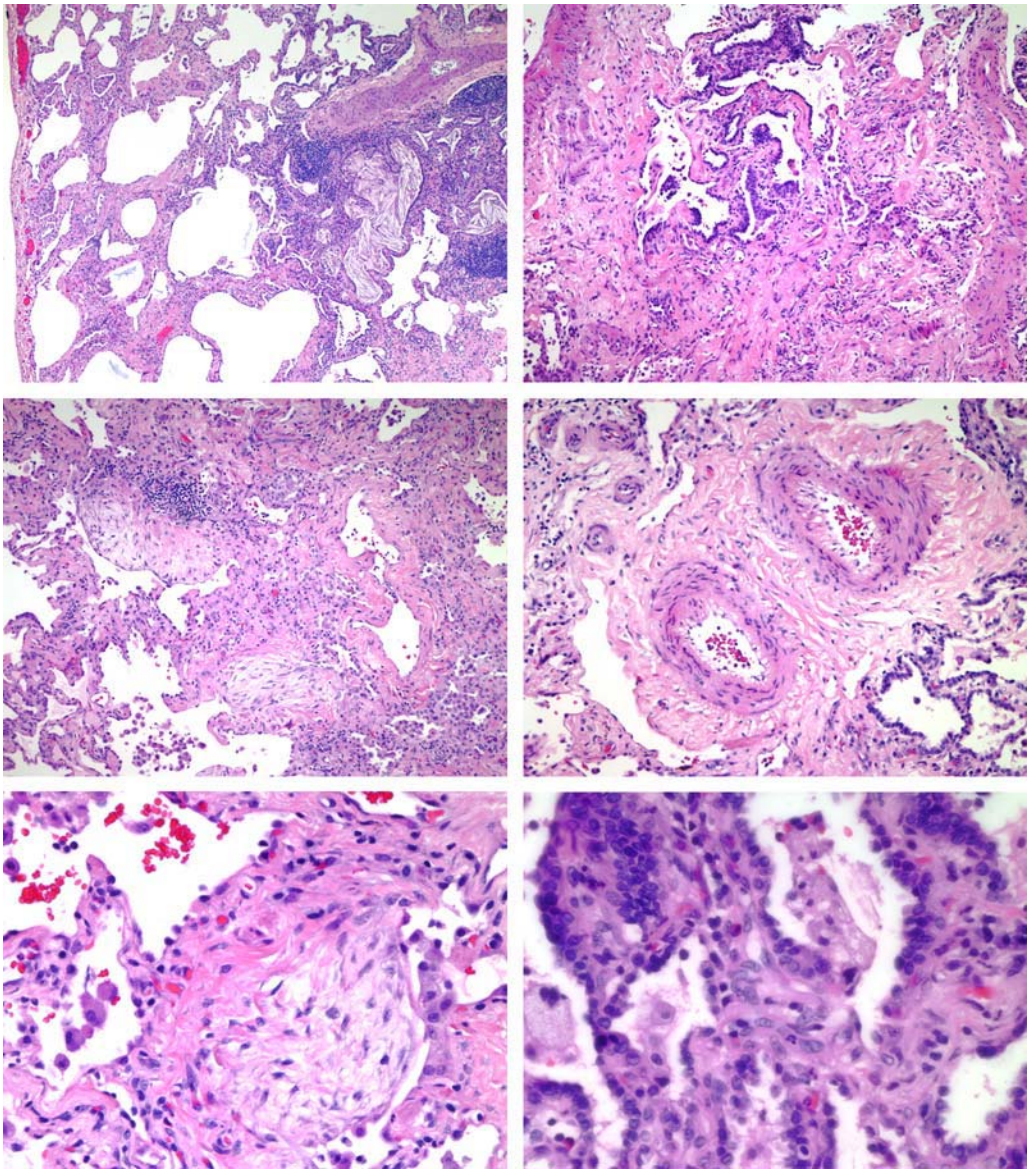
Diagnosis: Lung, open biopsy: UIP.

The predominant pattern is that of UIP whereby there is a variation in the pneumonitis from old (subpleural honeycomb fibrosis with coarse collagen) to subacute (myxoid expansions of fibrous tissue in alveolar ducts and alveoli) to ongoing, with a lymphocytic infiltrate as well as occasional neutrophils and eosinophils. There is also associated Lamberthosis (distal extension of respiratory epithelium into peribronchiolar alveoli). One nodule of organizing fibrosis would by itself suggest BPOP, but in this case I interpret it as a more extensive form of the alveolar fibrosis of UIP. No normal lung is present.

Collagen-vascular diseases of all forms have UIP as the most common parenchymal lung disease, and I believe that is the case here. BPOP can also be a manifestation of collagen-vascular disease, and the one focus of BPOP in this case is consistent with that interpretation. Overall, I believe the patient's clinical course will be that of UIP, the worse of the two possibilities. Though the moderate inflammatory infiltrate could possibly respond to therapy, I understand that therapy has not had any appreciable effect. Pulmonary arteries show moderate degrees of pulmonary hypertensive change. The pleura shows only vascular ectasia. Eosinophils raise the possibility of a drug reaction, and I cannot exclude that possibility as a component of the disease, but I do not favor that interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6733 (Chapter 3 – Interstitial Lung Disease)

Case 6800

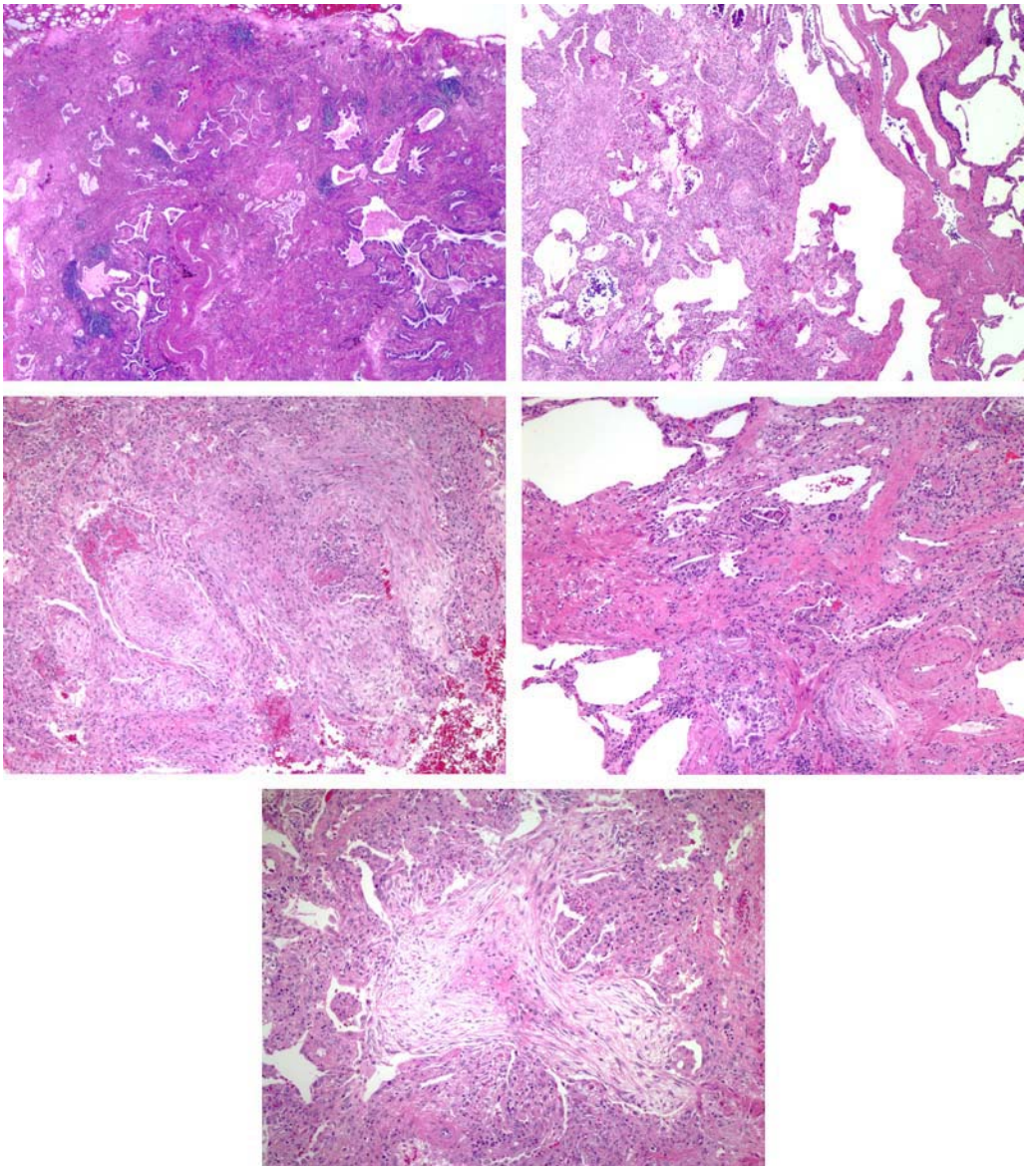
Diagnosis: Lung, open biopsy:

1. **UIP.**
2. **Bronchiolitis obliterans organizing pneumonia (BOOP), active.**

This case is distinctive. I agree that one must make a diagnosis of underlying UIP, because there is old diffuse interstitial fibrosis with subpleural honeycomb change and focal active fibrosis as well. I understand that in retrospect there may be old disease on chest X-ray. The differential diagnosis for the active fibrosis includes a second diagnosis or a unifying diagnosis of accelerated phase of UIP. Because there is a clinical history of recent surgery preceding the acute disease, I would consider BOOP in this case on the basis of circumstance. Pathologically, I am impressed with the branching and tufted character of the fibrosis and its focality, as well as the exudative quality with fibrin. I would make a diagnosis of BOOP if there were no underlying UIP, and in this case I make the diagnosis despite the underlying UIP. I am not following Occam's razor but feel compelled to make two diagnoses. An event at or around the time of surgery might have precipitated the BOOP. Aspiration and infection are usual suspects for abrupt onset of BOOP.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is an elaboration of our telephone conversation. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6800 (Chapter 3 – Interstitial Lung Disease)

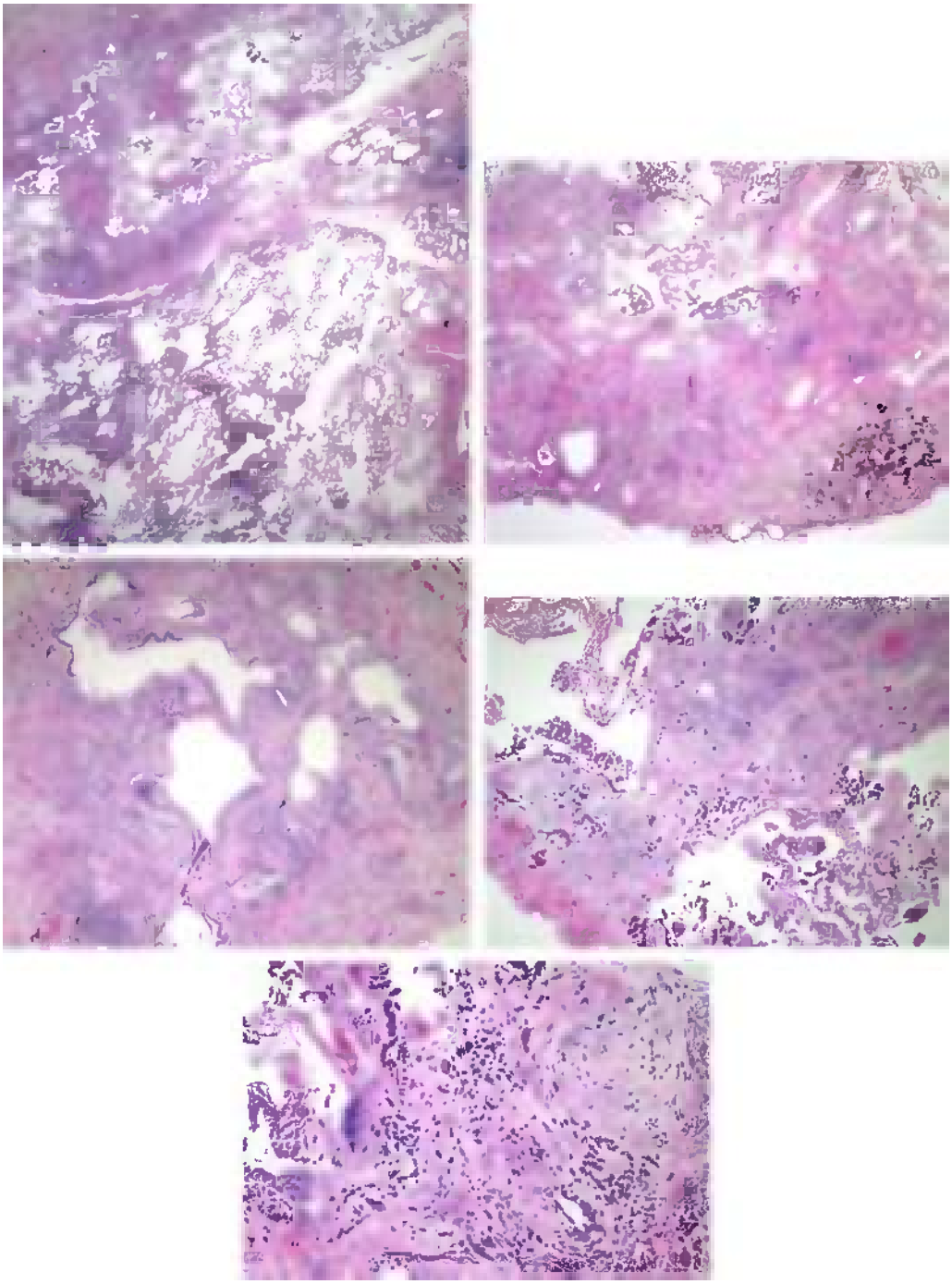
Case 6660

Diagnosis: Lung, open biopsies: Subpleural honeycomb fibrosis and focal active fibrosis, consistent with UIP.

I believe this patient's biopsy shows UIP because there is old advanced honeycomb fibrosis and small foci of active alveolar fibrosis with reactive changes in the pneumocytes. With these observations, the spatial and temporal diversity of UIP is satisfied. I am reluctant to make a diagnosis unequivocally, however, because the majority of the lung is normal. However, the clinical and laboratory findings also suggest UIP, and I believe the correct clinicopathological diagnosis (as contrasted to purely pathological diagnosis) is UIP. I believe this is essentially in agreement with your interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6660 (Chapter 3 – Interstitial Lung Disease)

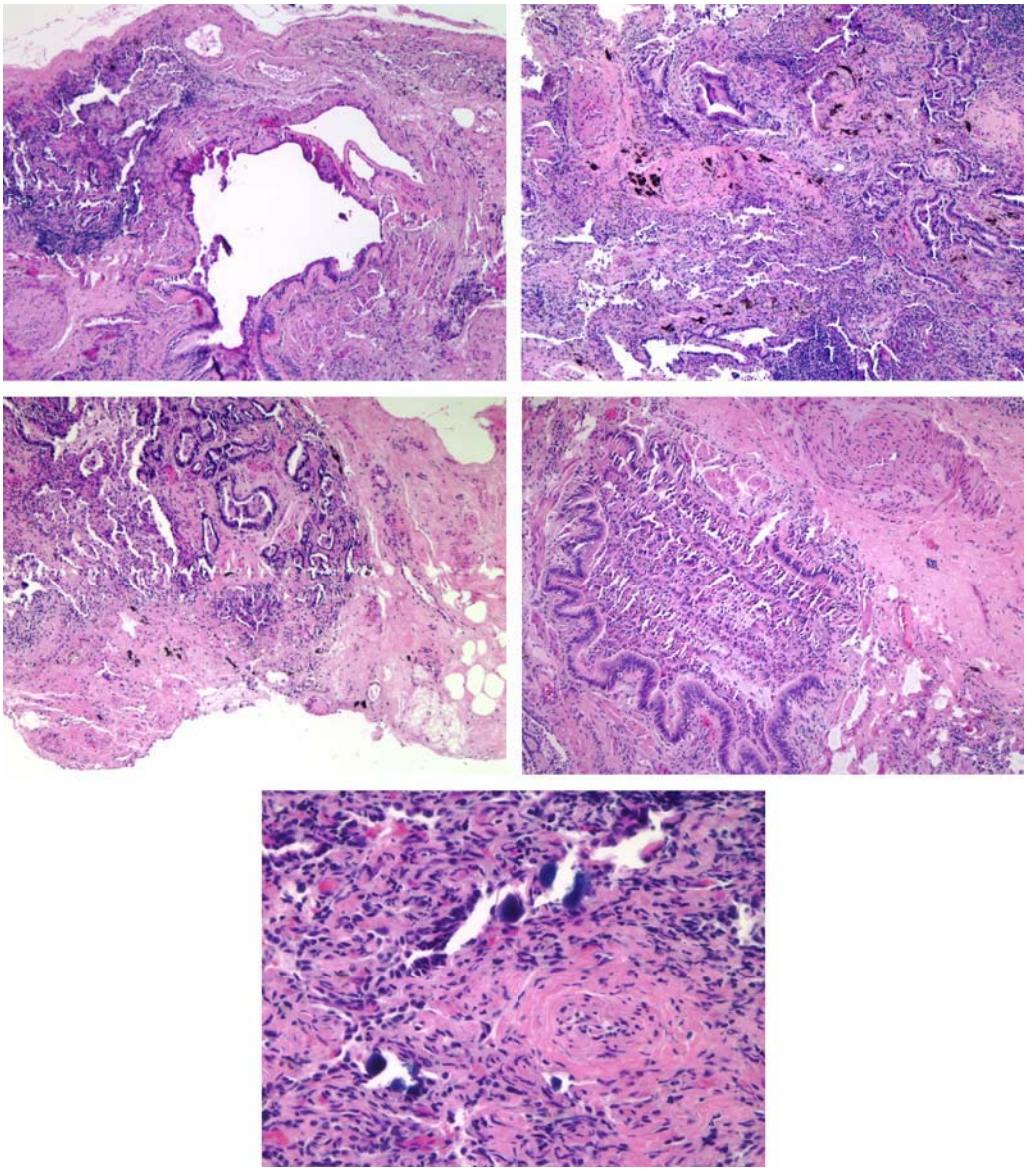
Case 6900

Diagnosis: Lung, open biopsy: Honeycomb fibrosis and interstitial lymphocytic inflammation and fibrosis, consistent with UIP.

The majority of the biopsy consists of end-stage honeycomb fibrosis, old scarring, hyperplasia of smooth muscle, and arterial hypertensive change in the region of scarring. Focal calcification of mucus is present. The region of honeycomb fibrosis is not by itself diagnostic of etiology, and I could not from this morphology alone exclude bronchiectasis as a primary disease. However, there is one relatively small portion of the lung that shows an interstitial infiltrate of lymphocytes and histiocytes, early interstitial fibrosis, and more active alveolar fibrosis. If this histology were more extensive in the sample, I would make a diagnosis of UIP. On morphological grounds alone, I favor this interpretation but cannot prove it. However, the clinical history is highly suggestive of UIP. In particular, the elevated anti-neutrophilic cytophilic antibody (ANCA) and ANA, the arthralgias and arthritis, and the progressive interstitial disease in the lower lung fields all suggest UIP associated with collagen-vascular disease. Approximately one-third of cases of UIP are associated with some form of collagen-vascular disease, most commonly rheumatoid disease but also any of the other forms. The precise nature of the collagen-vascular disease is not clear to me from the clinical history. Positive ANCA can be seen in patients with either lupus erythematosis or rheumatoid arthritis. The biopsy specimen shows no active Wegener's granulomatosis (WG), and I doubt that the scarring is due to old WG.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. I have retained one slide and hereby return the remainder. The chest radiographs have been returned under a separate cover.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6900 (Chapter 3 – Interstitial Lung Disease)

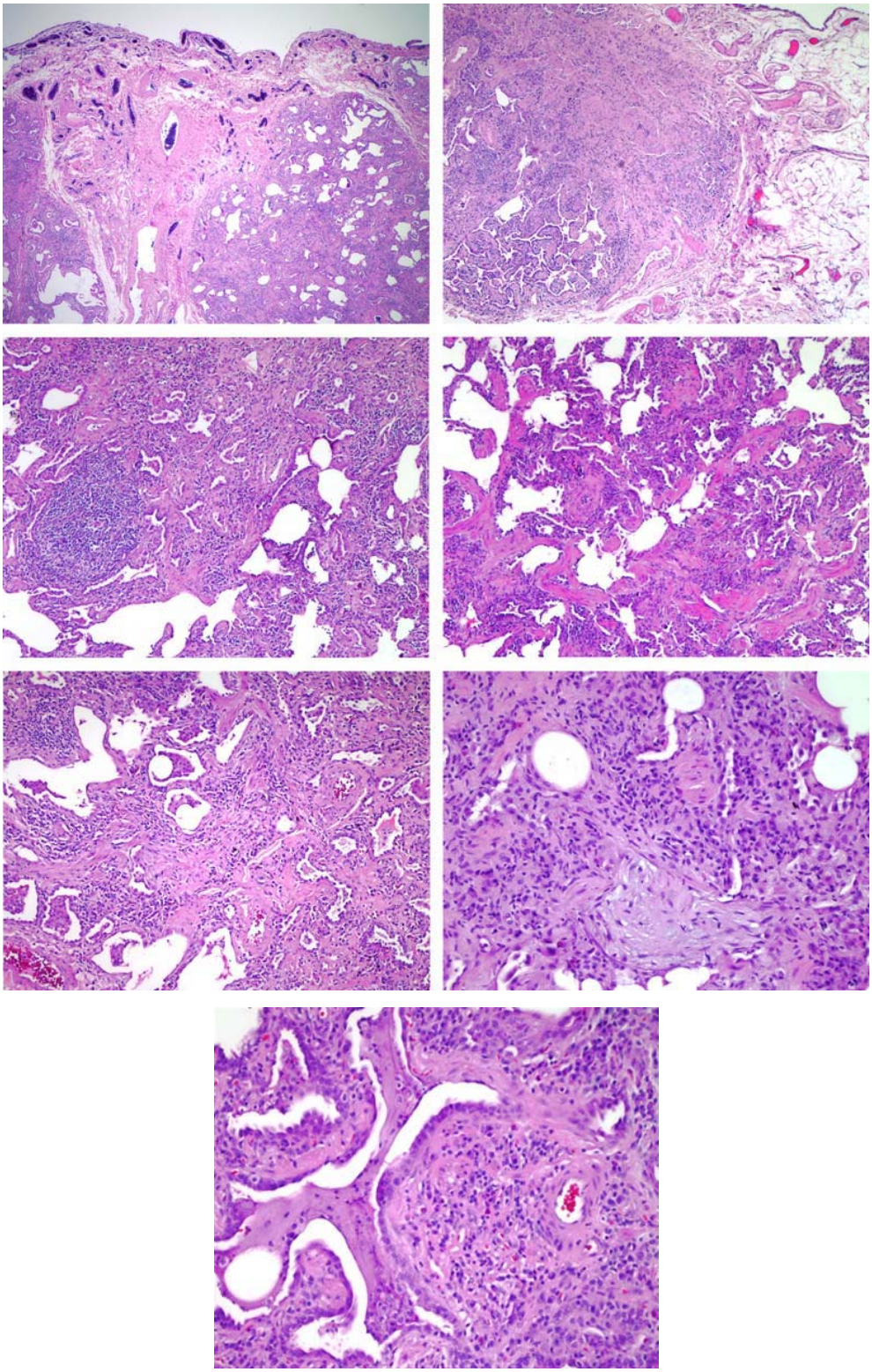
Case 6766

Diagnosis: Lung, open biopsy: Interstitial pneumonitis with extensive interstitial fibrosis, nondiagnostic, consistent with UIP.

The differential diagnosis in this case includes BPOP, UIP, or some other category such as so-called NSIP. To me, one value of the diagnosis of nonspecific interstitial pneumonitis is a description of a case which does not have all of the classic morphology, so that a diagnosis of this ominous disease is not made prematurely. This case falls into such a category. There are elements not typical of UIP, including focal BO, eosinophils in areas, and absence of established subpleural honeycomb fibrosis. On the other hand, there is atrophy of lung and a very diffuse fibrotic process which is well established at the alveolar level. I believe that this is UIP in a cellular phase and that the natural history probably will be that of UIP, but for the above reasons, I would not make that diagnosis with certainty at this time. Although most patients with UIP do not respond particularly well to medical therapy, there are elements in this case of both lymphocytic inflammation and bronchiolitis, each of which might be amenable to medical therapy. There is a prominent proliferation and ectasia of blood vessels in the pleura associated with a pleural adhesion.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6766 (Chapter 3 – Interstitial Lung Disease)

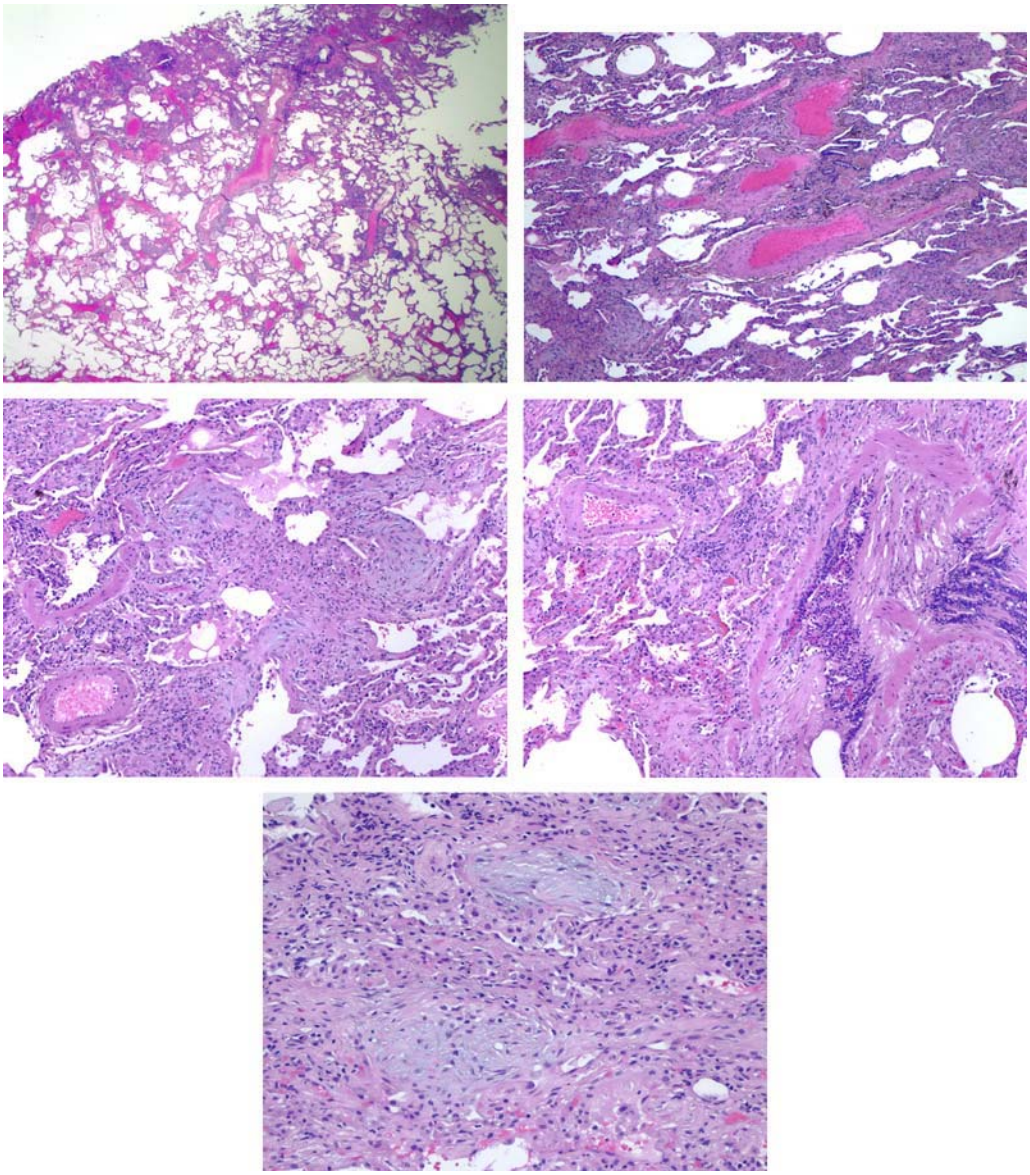
Case 6524

Diagnosis: Lung, open biopsy: UIP, accelerated phase.

One slide shows variegated interstitial inflammation and fibrosis indicative of usual interstitial pneumonitis. Although most of the lung in this slide is aerated, the circular shape of the alveoli indicate early interstitial thickening involving almost all alveolar walls. The other three slides show a different picture with florid intra-alveolar fibrosis causing airspace consolidation and hypertrophy of pneumocytes. This pathology could be seen in DAD, but in the context of a patient with UIP it is consistent with the accelerated phase of UIP, which was discussed in a Case Records of the Massachusetts General Hospital (NEJM 1991; 324: 1345–1357). This can be seen in a patient with the clinicopathological syndrome of Hamman and Rich. The above is essentially in agreement with your interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6524 (Chapter 3 – Interstitial Lung Disease)

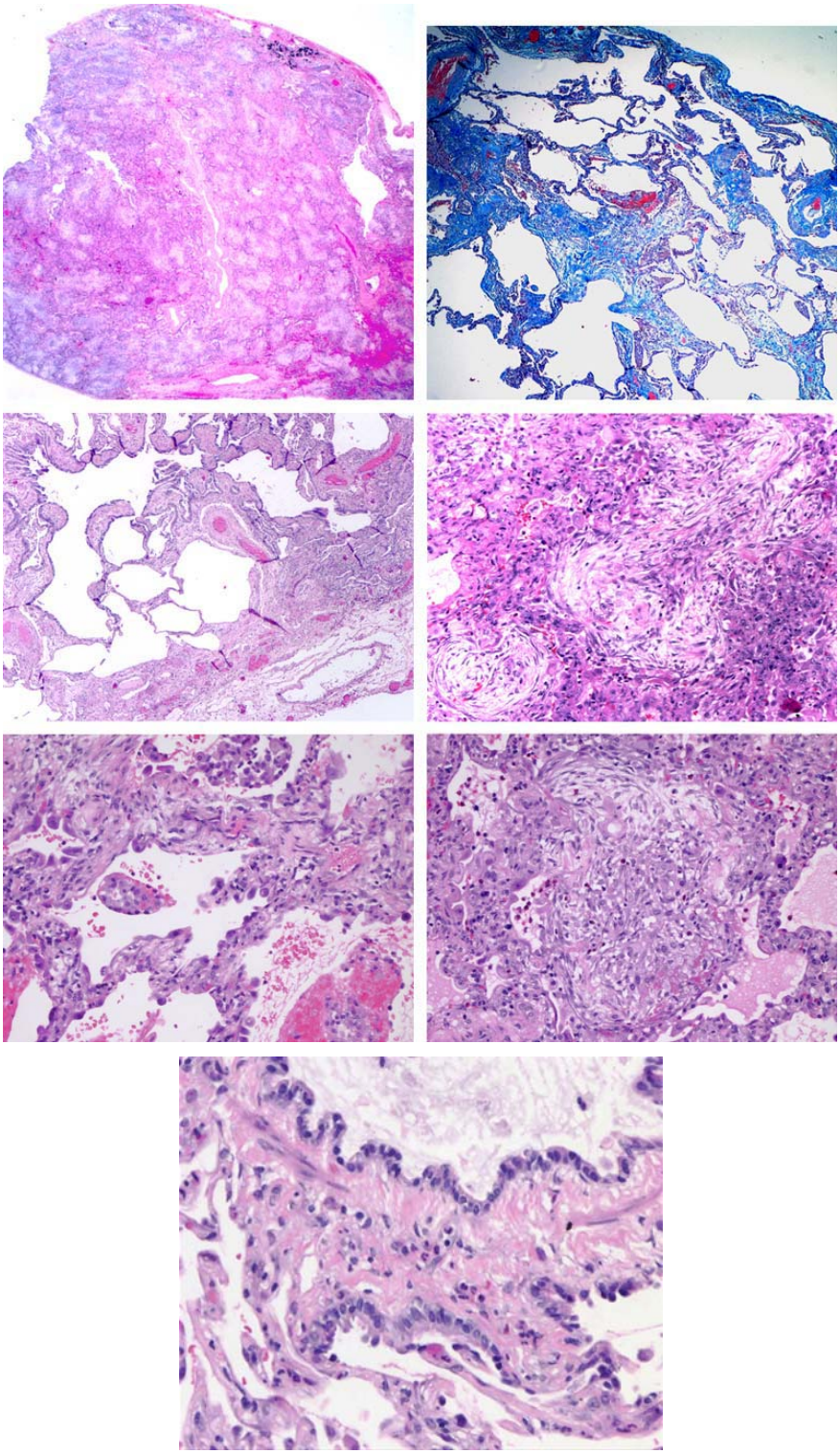
Case 6535

Diagnosis: Lung, open biopsy: UIP, in accelerated phase.

Old diffuse interstitial fibrosis has created ectatic and rounded alveoli (trichrome stain). Virtually no normal lung is present. End-stage subpleural honeycomb fibrosis is present. A lymphocytic infiltrate is associated with the interstitial fibrosis. The above changes characterize UIP. Other regions show florid tissue culture like proliferation of fibroblasts in alveolar airspaces associated with atypia of pneumocytes and fibroblasts. These regions appear similar to organizing DAD. Thus, there is an accelerated phase of the UIP histologically. This is in agreement with your interpretation. Some of the proliferative fibrosis has a vaguely nodular character, which raises BPOP into the differential diagnosis. But using Occam's razor, I would make the unifying diagnosis of UIP in accelerated phase. The neutrophils probably are due to mucus or aspirated material. Unusual are regions with numerous eosinophils. This made me consider acute eosinophilic pneumonia, but I do not favor that interpretation either clinically or pathologically.

Thank you for the opportunity to review this case. I will incorporate it into our study. Your special stains are returned. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6535 (Chapter 3 – Interstitial Lung Disease)

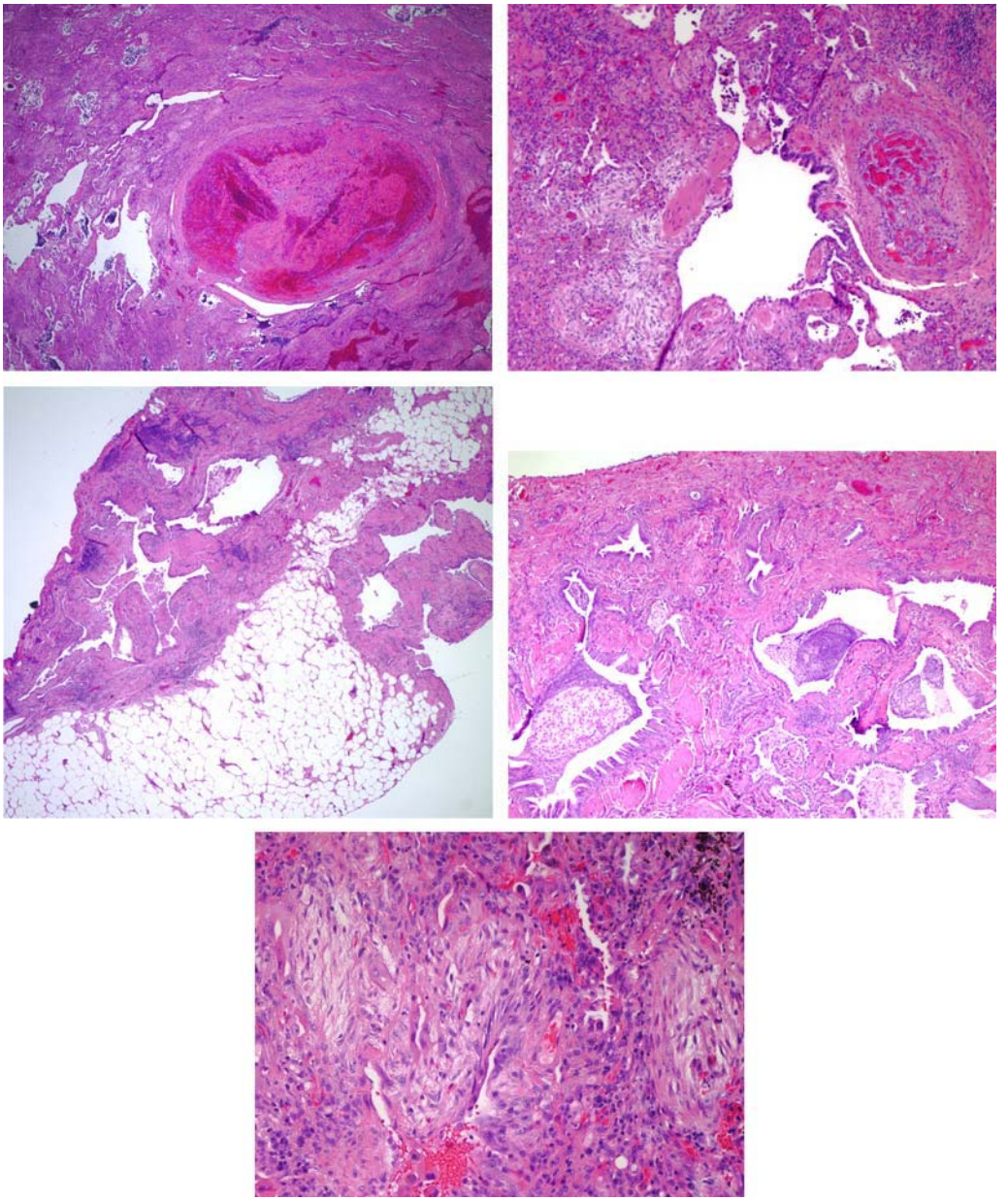
Case 6512

Diagnosis: Lung, open biopsy: Old and organizing fibrosis, consistent with UIP in accelerated phase.

Two temporally disparate processes are present. First is honeycomb fibrosis with old coarse collagen of months or years duration. Subpleural fat indicates lung atrophy and is consistent with UIP. Superimposed in all regions of the lung is organizing alveolar fibrosis with incorporation into the interstitium. This process is several weeks in duration. Such florid fibrosis suggests DAD, but in this specimen hyaline membranes of DAD are no longer present. However, the extensive thrombosis is part of organizing DAD. Although the old and new diseases might be different, using Occam's razor, I would attribute the patient's condition to UIP in accelerated phase as a unifying diagnosis. This constitutes one of the clinicopathological conditions in the syndrome of Hamman and Rich. UIP in accelerated form was discussed at a Case Records of the New England Journal of Medicine (NEJM 1991; 324: 1345–1357). The patient in the Case Records had a clinical history of polymyalgia rheumatica. I suspect the disease in your patient is related to his rheumatoid condition rather than to methotrexate toxicity.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6512 (Chapter 3 – Interstitial Lung Disease)

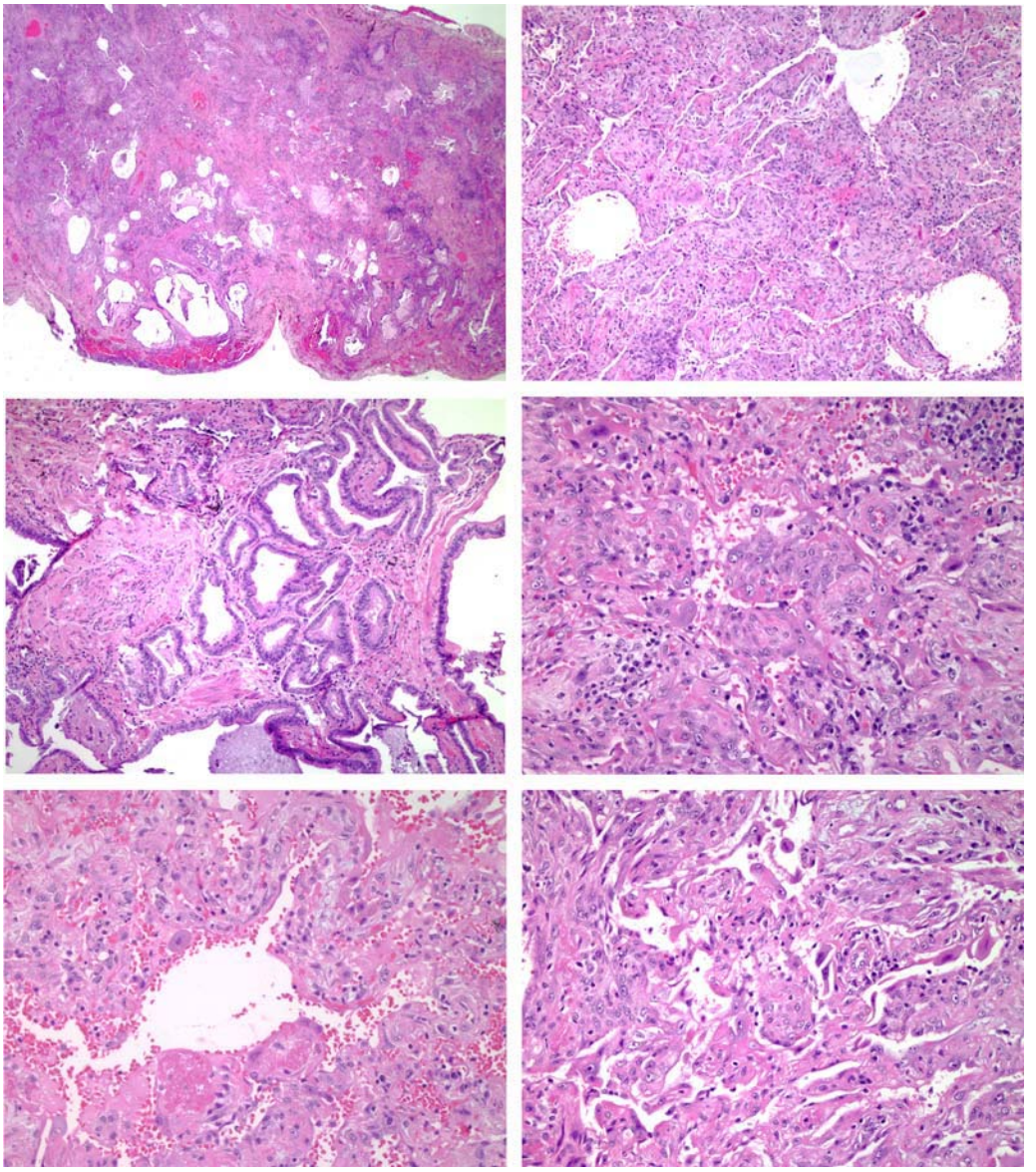
Case 6849

Diagnosis: Lung, open biopsy: UIP, in accelerated phase, with marked epithelial atypicality.

This complicated case shows old diffuse interstitial fibrosis with a lymphocytic infiltrate and early subpleural honeycomb fibrosis. In conjunction with the clinical history, the most appropriate diagnosis is UIP. The disease has entered into an accelerated phase with rapid progression of myxoid fibrosis in airspaces in a manner simulating a tissue culture and obliteration of lung architecture. A few hyaline membranes are present. This form of disease is sometimes clinically referred to as the Hamman-Rich syndrome. In the accelerated phase of UIP with elements of DAD (hyaline membranes), the epithelial cells can become markedly atypical. In this case there is atypia of pneumocytes entrapped within fibrosis as well as marked squamous metaplasia with atypia in bronchioles. The latter indicates healing injury in distal airways. There is also traction bronchiectasis and hyperplasia of columnar epithelium within the honeycomb fibrosis. I detect no carcinoma or other malignancy in this specimen.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6849 (Chapter 3 – Interstitial Lung Disease)

Case 6837

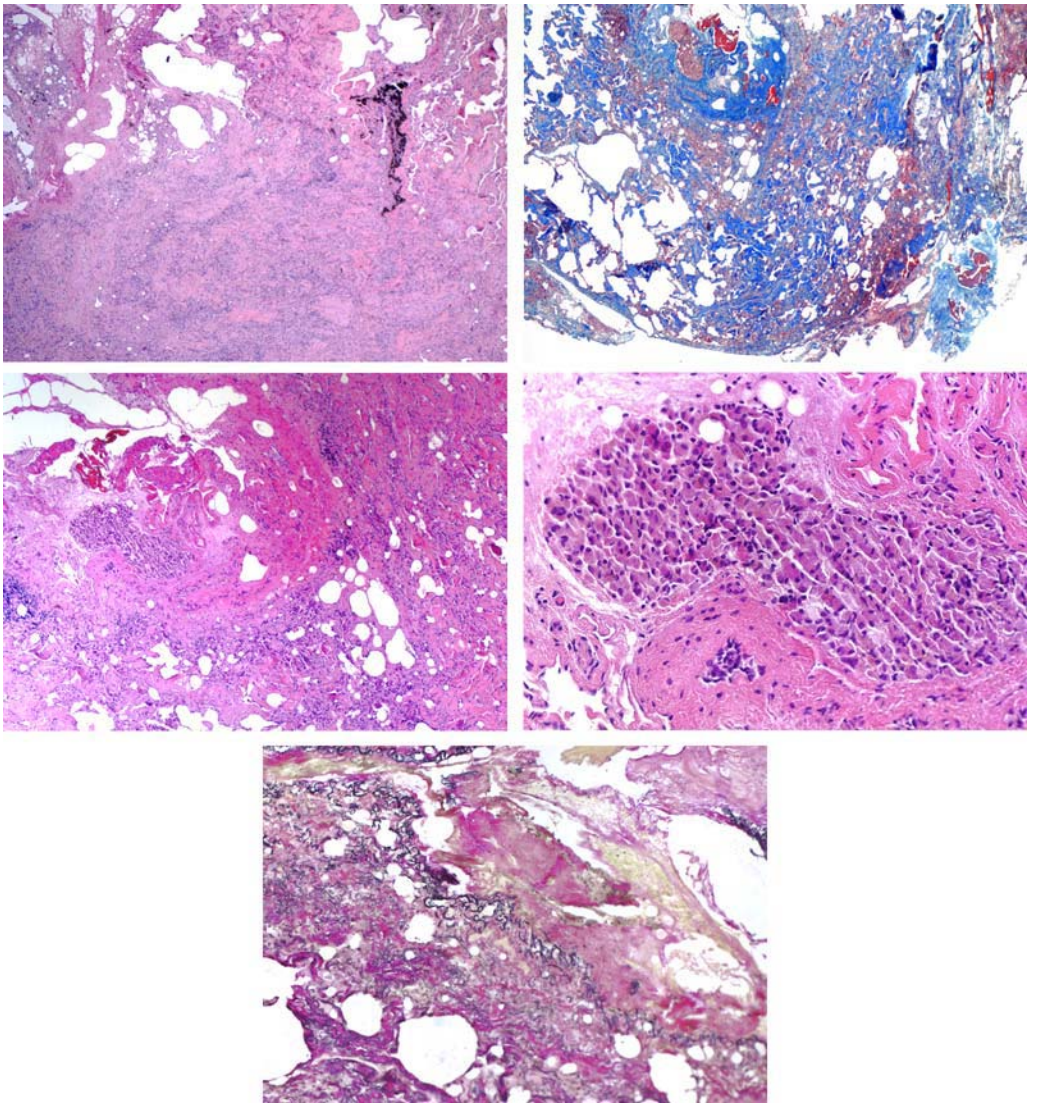
Diagnosis: Lung and pleura, open biopsy: Old fibrous scar, cause undetermined.

This relatively circumscribed scar has old collagen within it, as well as old interstitial fibrosis in the lung adjacent to the scar. Our elastic and trichrome stains show that part of the scar is within pleura and part within the lung. Entrapped epithelial cells are present within the pulmonary portion of the scar. I do not know the cause of this lesion. I considered an old infarct, but the elastic tissue stain does not support that interpretation. I considered a history of trauma or instrumentation in this region. I considered a lymphangioma with sclerosis because there are serpentine ectatic spaces in the pleura that could represent lymphatics, but I do not favor this interpretation. I considered that some of the circular spaces in the lung are the so-called "bubble effect" due to compression. I considered BO giving rise to the scar, but I cannot demonstrate any BO in this specimen, and the dense fibrous pleural adhesion would be unusual with that diagnosis.

No malignancy is present. No granulomas are present. No active infection is present.

Thank you for referring this case in consultation. Please keep informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6837 (Chapter 3 – Interstitial Lung Disease)

Case 6744

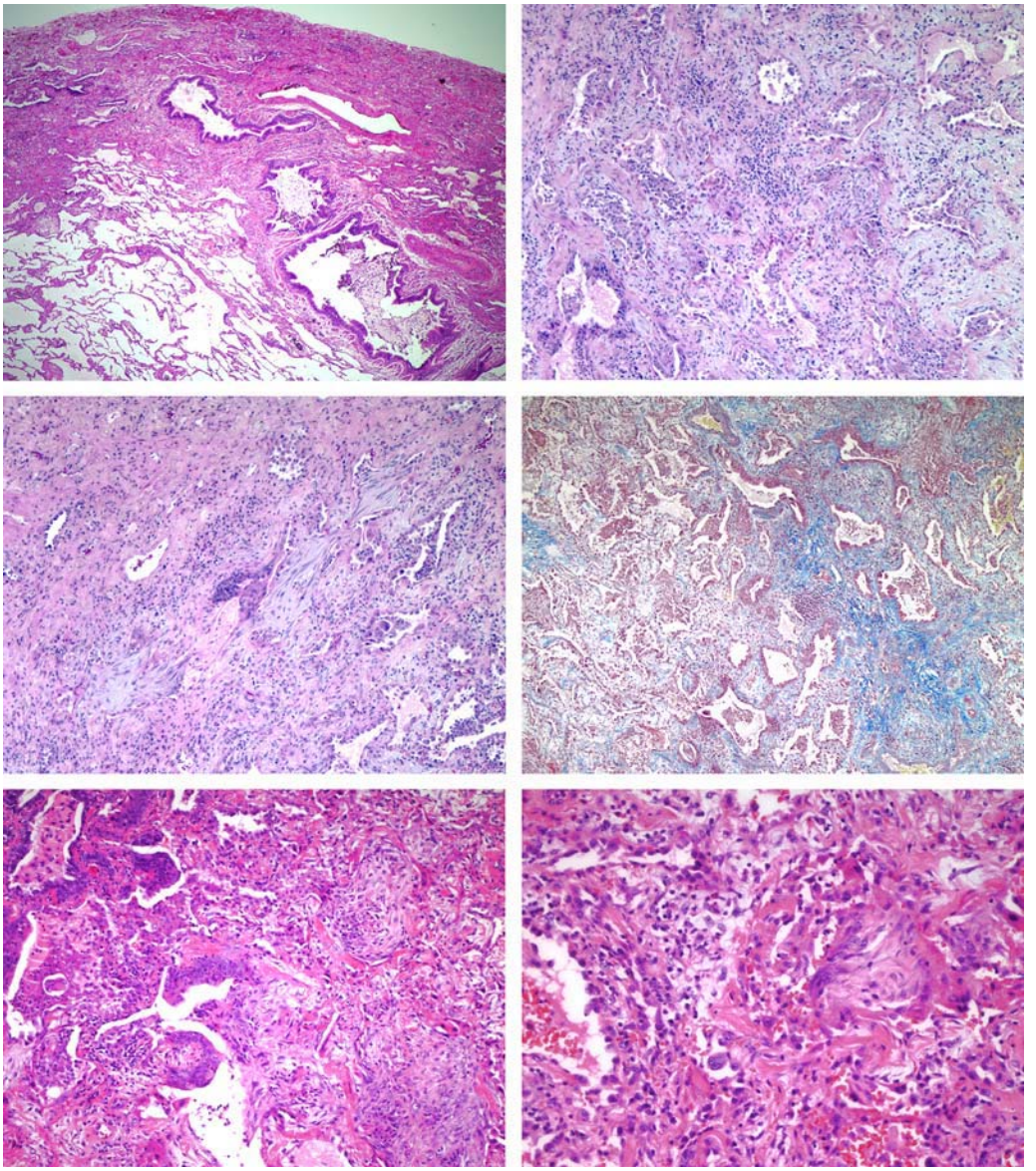
Diagnosis: Lung, open biopsy: Old interstitial fibrosis and active alveolar fibrosis, ? organizing pneumonia, ? accelerated phase of UIP, ? other.

This case is problematic in that there is both old and new disease. The old disease has established honeycomb fibrosis with mature collagen. Intermediate disease has proliferative fibrosis in interstitium of alveolar walls and an interstitial pneumonitis. Acute disease has active fibrosis filling alveoli. The alveolar fibrosis is extensive (trichrome stain) and exuberant. I favor organizing pneumonia (OP), including that which may be seen in BOOP, but no BO is present in the specimen. The OP could also be the result of prior infection, such as virus. No active infection is present. There are no hyaline membranes, no purulence, and no viral inclusions. The computerized tomograms show principally airspace disease in a lobular pattern with little honeycomb fibrosis and favor OP. The clinical history also favors OP over a chronic interstitial pneumonitis.

The histological honeycomb fibrosis may be localized, a result of sampling of the tip of lobe, and have little clinical significance. The older fibrosis also could represent UIP or some other disease that can cause honeycomb fibrosis, and in that case, the acute disease could either be an OP superimposed on the old scarring or represent the accelerated phase of UIP. Either of these latter two interpretations would be less sanguine for the patient than the diagnosis of OP as the principal diagnosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6744 (Chapter 3 – Interstitial Lung Disease)

Case 7164

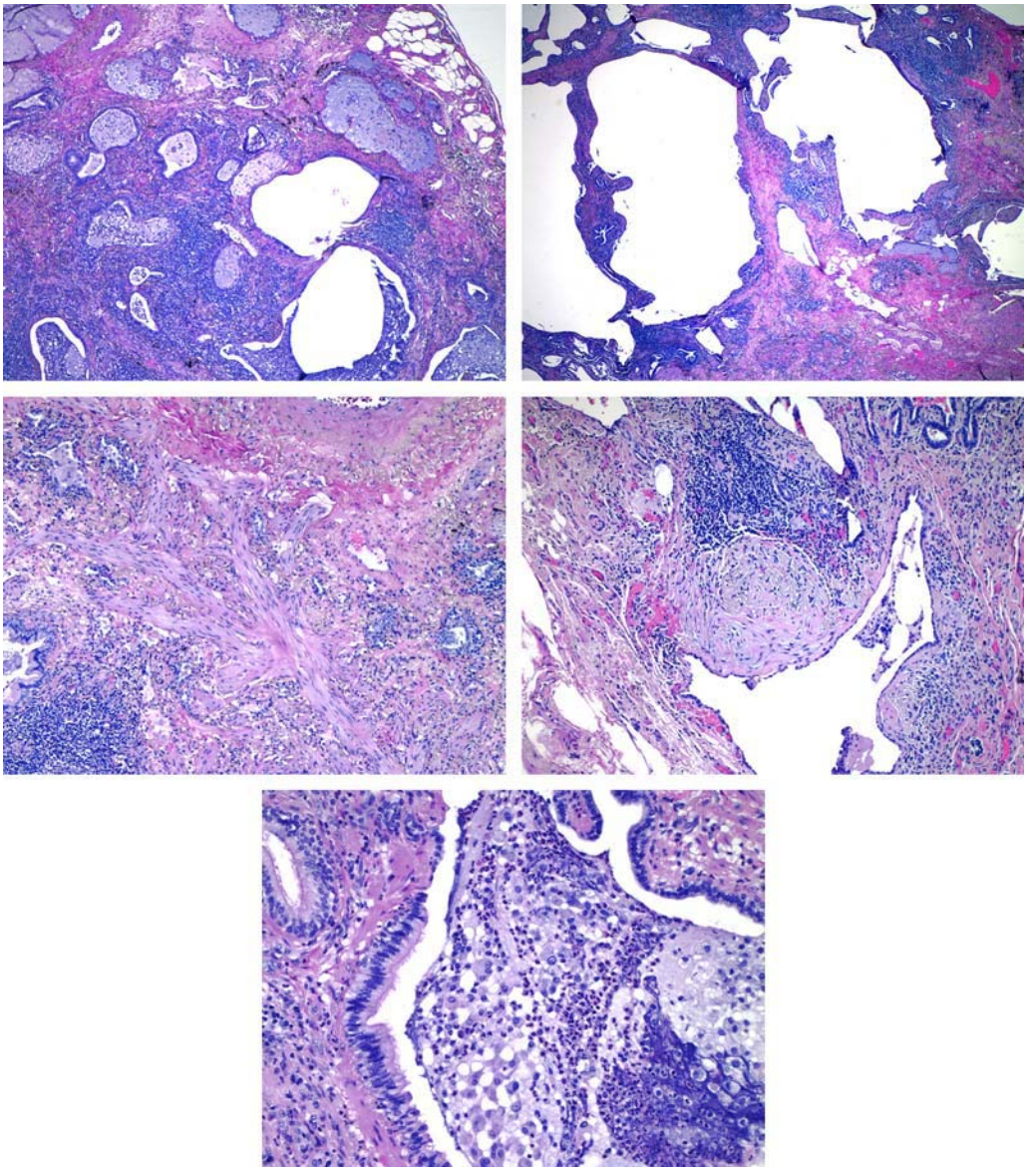
Diagnosis: Lung, open biopsies: Subpleural end-stage fibrosis with honeycomb change, cause uncertain, ? advanced UIP, ? other.

The lung consists of ectatic airspaces filled with pus and mucus. No normal intervening lung parenchyma is present. Rather, the ectatic air spaces are separated by old coarse fibrosis with hyperplasia of smooth muscle. The changes constitute honeycomb fibrosis, which is end-stage. This is in agreement with your interpretation.

Lung atrophy and subpleural fatty replacement suggest restrictive lung disease. This aspect together with the end-stage fibrosis suggests UIP as the statistically most likely diagnosis, and this diagnosis becomes more probable with the reported clinical diagnosis of diffuse interstitial lung disease. Another clinical possibility is central bronchiectasis with secondary bronchiolar obliteration and peripheral scarring, and I cannot exclude this possibility from the slides alone, but such patients do not generally have a clinical diagnosis of diffuse interstitial lung disease. Sarcoidosis cannot be absolutely excluded, but small circular scars of the size of granulomas often are still seen in patients with sarcoidosis even when end-stage honeycomb fibrosis has developed, and such scars are not present. I detect no significant amount of dusts and do not believe this is a pneumoconiosis. A final consideration is BOOP that has resulted in subpleural honeycomb fibrosis. This is very uncommon in patients with BOOP but can occasionally occur.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7164 (Chapter 3 – Interstitial Lung Disease)

Case 6681

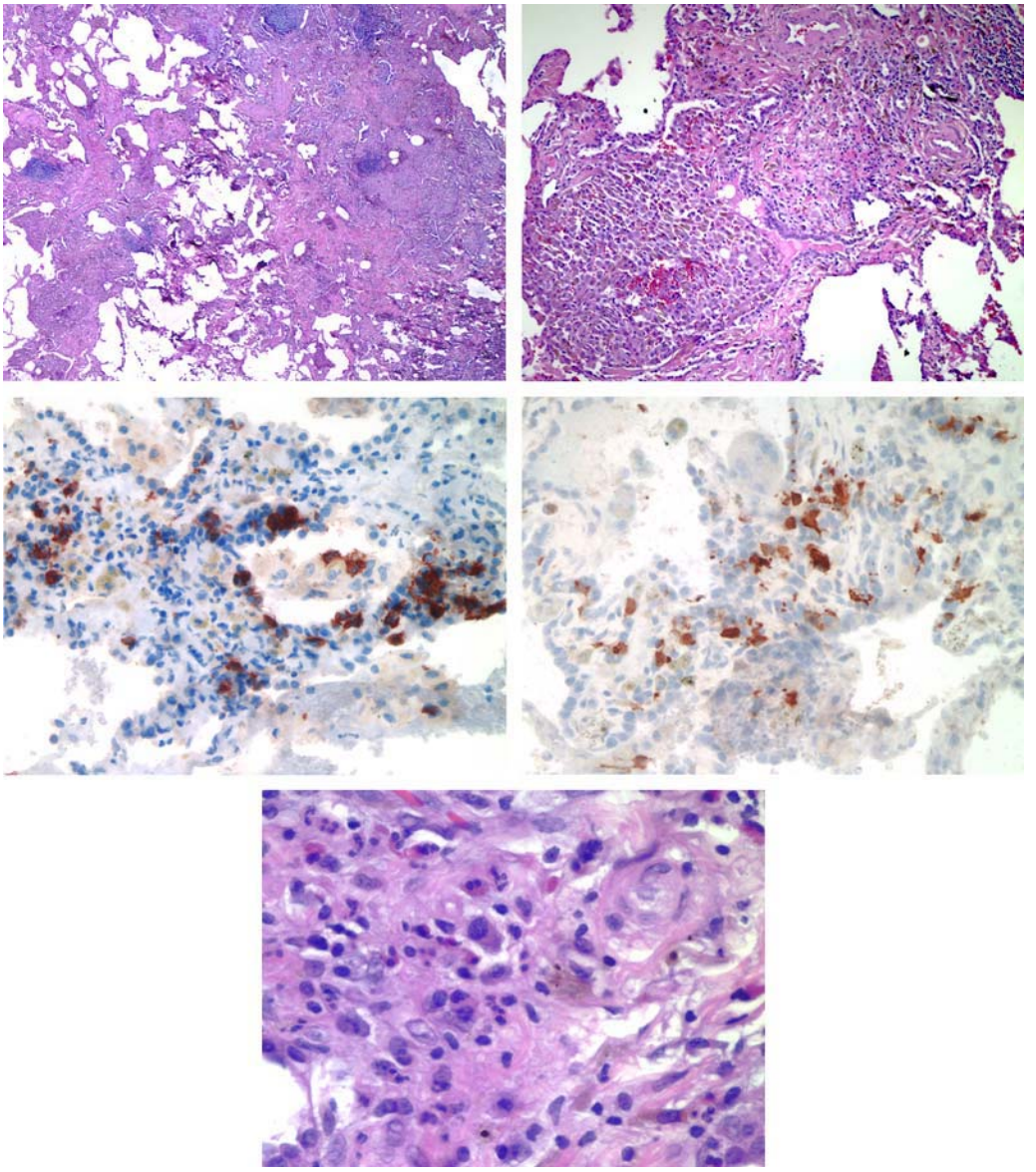
Diagnosis: Lung, open biopsy: EG.

Cellular nodules are composed of aggregated histiocytes with large convoluted nuclei typical of Langerhans' cells admixed with eosinophils. Although the stellate characteristic of the nodules of EG is not well established here, the cellular constituents suffice for the diagnosis. There is extensive DIP-like reaction around the nodules. This is an ancillary finding in many cases of EG. Regions of OP obscure the EG in some areas. There is no evidence of malignancy.

I have performed histochemistry and immunochemistry to confirm the diagnosis. In particular, large aggregates of the histiocytes stain positively for S-100 antigen and CD-1a. The chest radiograph is consistent with the diagnosis of EG.

Thank you for referring this case in consultation. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6681 (Chapter 3 – Interstitial Lung Disease)

Case 6792

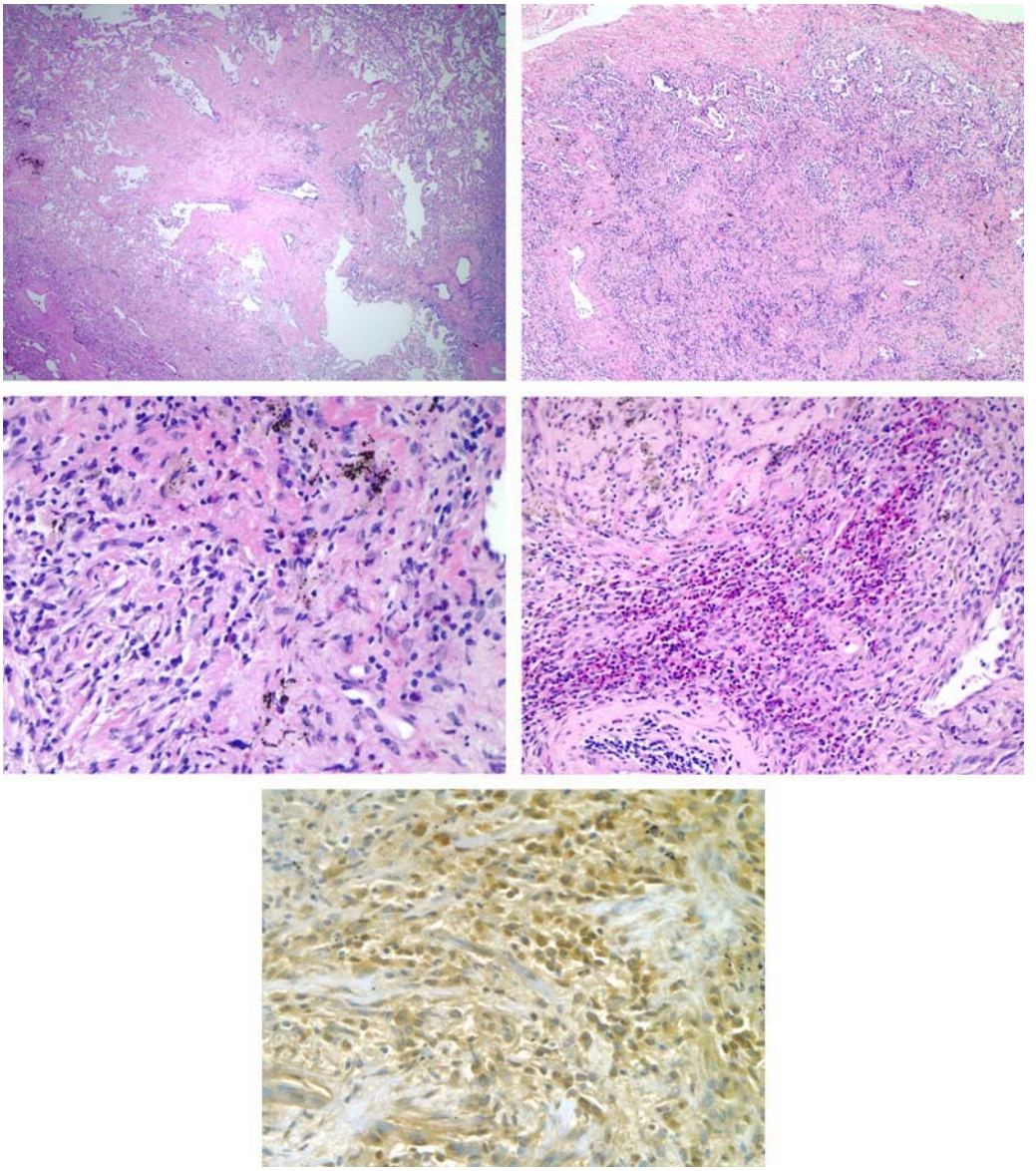
Diagnosis: Lung, open biopsy: EG.

Nodules of inflammation have scarring with hyperplasia of pneumocytes. No necrosis is present. Some of the more advanced scars have a stellate configuration. Some of the more cellular regions have sheets of histiocytes with large convoluted nuclei which characterize Langerhans' cells. Eosinophils are sprinkled in small numbers throughout and form an abscess in one region. I believe the constellation of changes characterizes EG of the lung. Since most cases of EG are associated with cigarette smoking, and since this patient has rather extensive scarring, cessation of cigarette smoking is particularly indicated. Your stains for organisms show none. There is no evidence of malignancy or fungal disease.

I have reviewed your immunopathological studies and also performed additional studies here. I interpret your S-100 stain as showing Langerhans' cells with additionally nonspecific staining of pneumocytes. I interpret our S-100 stain as showing aggregates of Langerhans' cells with large convoluted nuclei. I have enclosed a copy of our stains as you requested.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6792 (Chapter 3 – Interstitial Lung Disease)

Case 6705

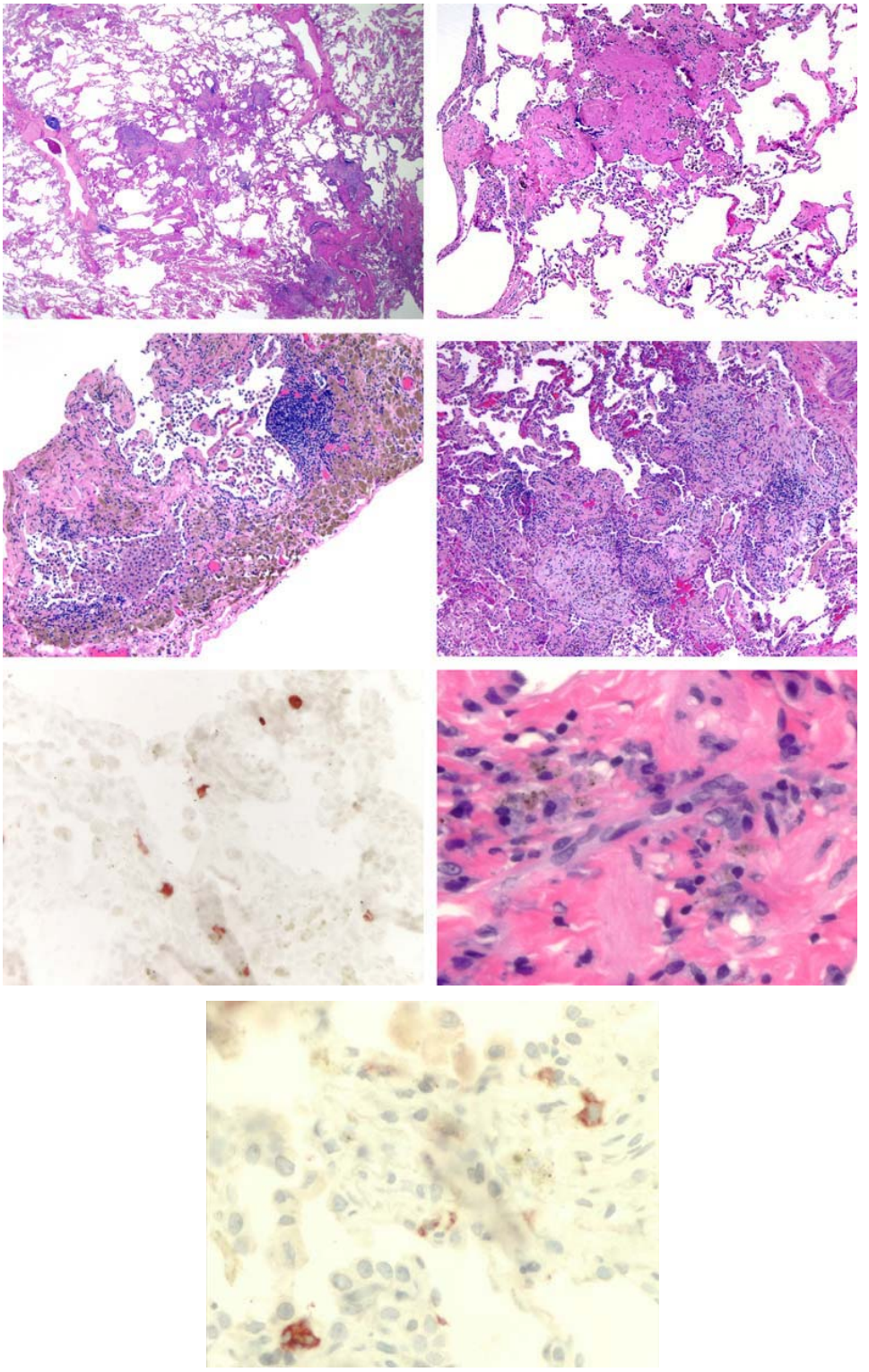
Diagnosis: Lung, open biopsy: EG.

This case is difficult. The majority of the specimen is normal. Scattered through the slides are a few stellate nodules whose low power configuration suggests EG. Tufts of myxoid fibrous tissue obstruct a few respiratory bronchioles and alveolar ducts. Pigmented histiocytes around and within these nodules support the diagnosis in that they are consistent with a DIP-like reaction seen with nodules of EG. A few scattered convoluted nuclei in the midst of the stellate nodules are consistent with Langerhans' cells. The differential diagnosis therefore is between EG and a form of bronchiolitis with elements of RB and BO.

To further establish the diagnosis, I examined tissue which you kindly provided and also studied the computerized tomograms of the chest. Stains for Langerhans' cells (S-100, CD1a) show small numbers of Langerhans' cells. Only about five Langerhans' cells lie together in their greatest concentration. This is borderline between Langerhans' cell hyperplasia and EG. However, the computerized tomograms show nodules and early small cysts suggestive of EG. I believe the diagnosis of EG can be established on the combination of the pathology and the radiology. Although the disease is slight on the tissue, it is relatively advanced on the X-rays. Because the disease on the X-rays is heterogeneous, it seems that the worst disease has not been sampled in the specimens. Cigarette smoking is the most common cause of this disease.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6705 (Chapter 3 – Interstitial Lung Disease)

Case 7077

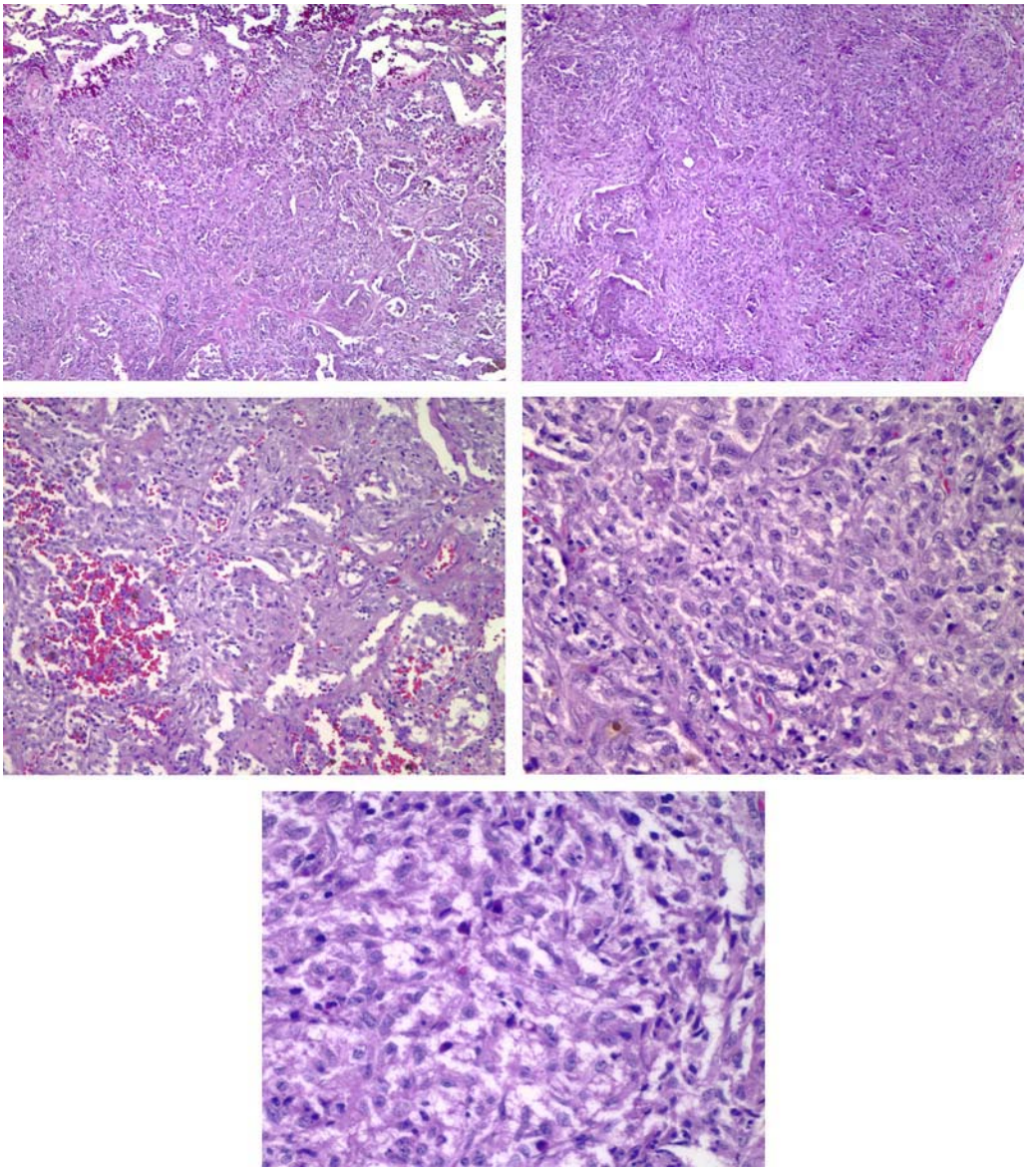
Diagnosis: Lung, open biopsy: EG, cellular and early scarring phases.

Nodules are composed of masses of histiocytes which have complex and indented nuclei indicative of Langerhans' cells. To confirm their nature, I have performed stains for Langerhans' cells (S-100), and it shows that the cells stain for this marker. The combination of these histiocytes with eosinophils and early cyst formation characterizes the early cellular and scarring phases of EG. Your radiographic studies of the chest are consistent with that interpretation, in that they show extensive cysts and nodules in all lobes.

In the differential diagnosis I considered Wegener's granulomatosis and lymphomatoid granulomatosis. These are not common differentials for EG. The eosinophils can be seen in both conditions, but Langerhans' cells do not comprise the diffuse granulomatous tissue of WG. There is insufficient nuclear pleomorphism and no angiodestructive behavior to further support a diagnosis of lymphomatoid granulomatosis.

These interpretations are essentially in agreement with your interpretation. Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7077 (Chapter 3 – Interstitial Lung Disease)

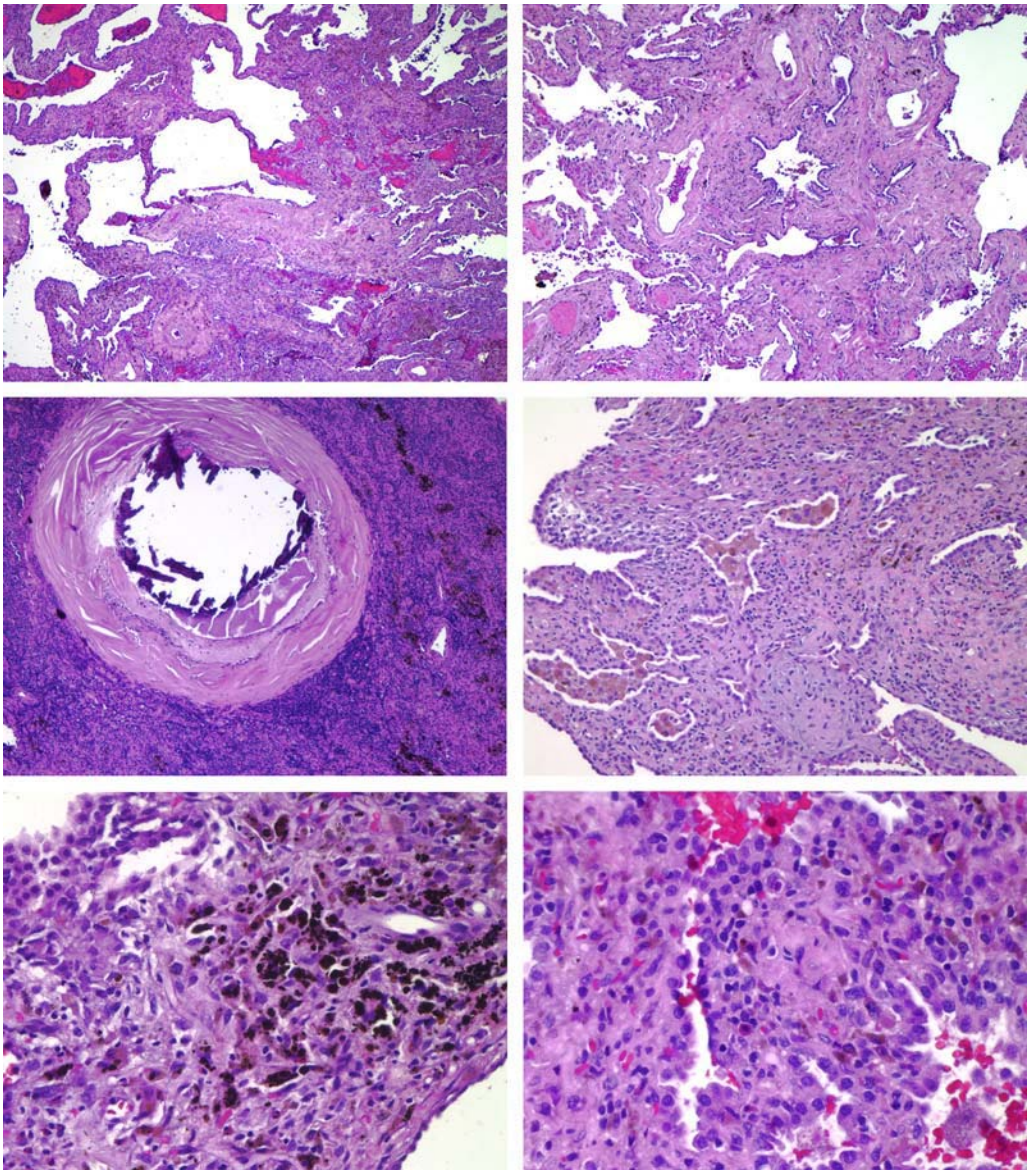
Case 6914

Diagnosis: Lung, open biopsy: EG, principally interstitial, with active and scarring disease.

This case is challenging. There is a cellular infiltrative process which widens interstitium and creates ectatic airspaces. In the more cellular regions of interstitial thickening, the cells are Langerhans' histiocytes with large convoluted nuclei. There is a small number of admixed eosinophils. This characterizes EG in one of its guises, that of relatively diffuse interstitial disease, since the classic stellate or starfish appearance is not readily apparent. The presence of many pigment-laden histiocytes around and within the lesions of EG support the diagnosis. A few older stellate scars could represent burned-out EG. The lung also contains a moderate amount of inhaled dust, including carbon and iron-encrusted carbon. One of the resected lymph nodes contains a calcified granuloma probably representing old mycobacterial or fungal disease in a quiescent state. I do not believe the pathology is that of sarcoidosis or UIP.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6914 (Chapter 3 – Interstitial Lung Disease)

Case 6743

Diagnosis: Lung, open biopsy: EG, old and active.

The biopsy, in aggregate, shows a diversity of stages of EG. The most diagnostic lesion, because it has the highest number of Langerhans' cells, is present in slide B2. In this slide, the stellate architecture characteristic of EG is appreciated. Adjacent to the cellular lesion is another stellate scar much older in time with broad bands of collagen and hyperplasia of smooth muscle. Other slides show intermediate stages in the histogenesis of EG, including bronchiolar destruction and early cyst formation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
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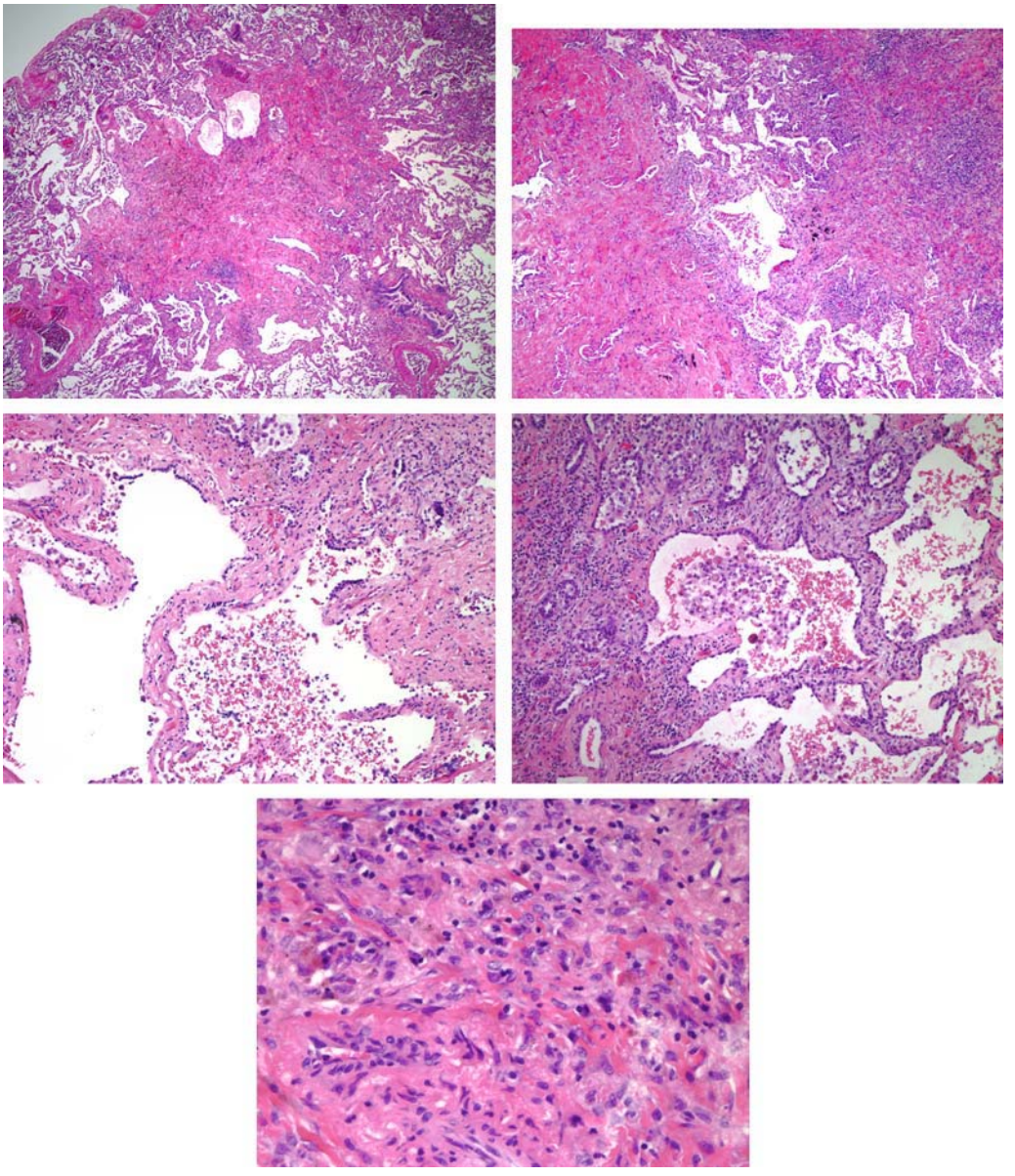


Case 6743 (Chapter 3 – Interstitial Lung Disease)

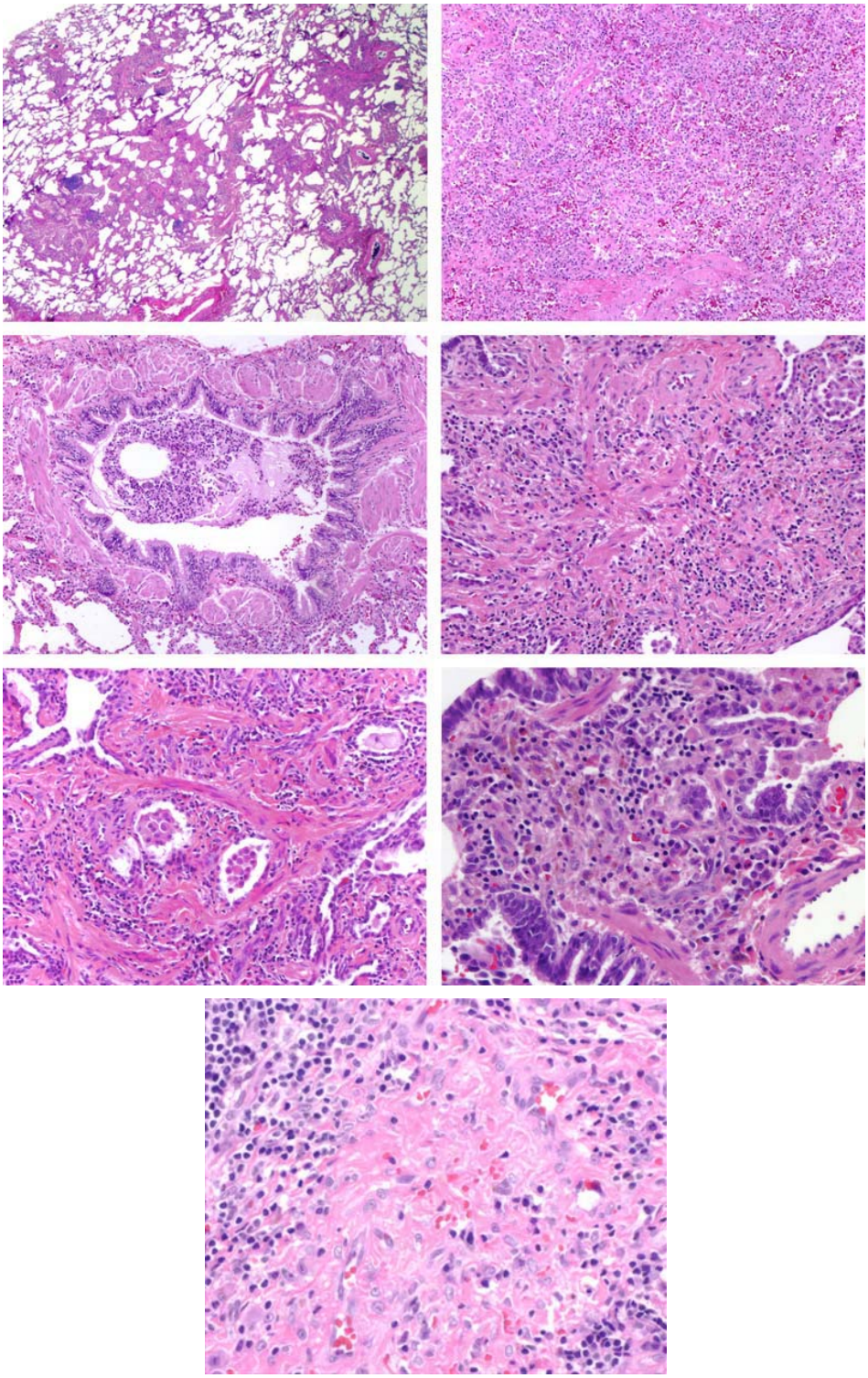
Case 6586

Diagnosis: Lung, open biopsy: EG, cellular and scarring phases.

A lymphohistiocytic proliferation forming stellate nodules at low power with central sclerosis and numerous eosinophils indicate EG. The disease is in a relatively late stage in that Langerhans' cells are not numerous, but I believe they are sufficient in number to make the diagnosis on slides stained with hematoxylin and eosin. The DIP-like reaction around some of the nodules and pigment-laden histiocytes within the scars of the EG are further evidence in favor of the diagnosis. One bronchiole is plugged with eosinophils and histiocytes, but I do not believe this represents bronchocentric granulomatosis.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6586 (Chapter 3 – Interstitial Lung Disease)

Case 7116

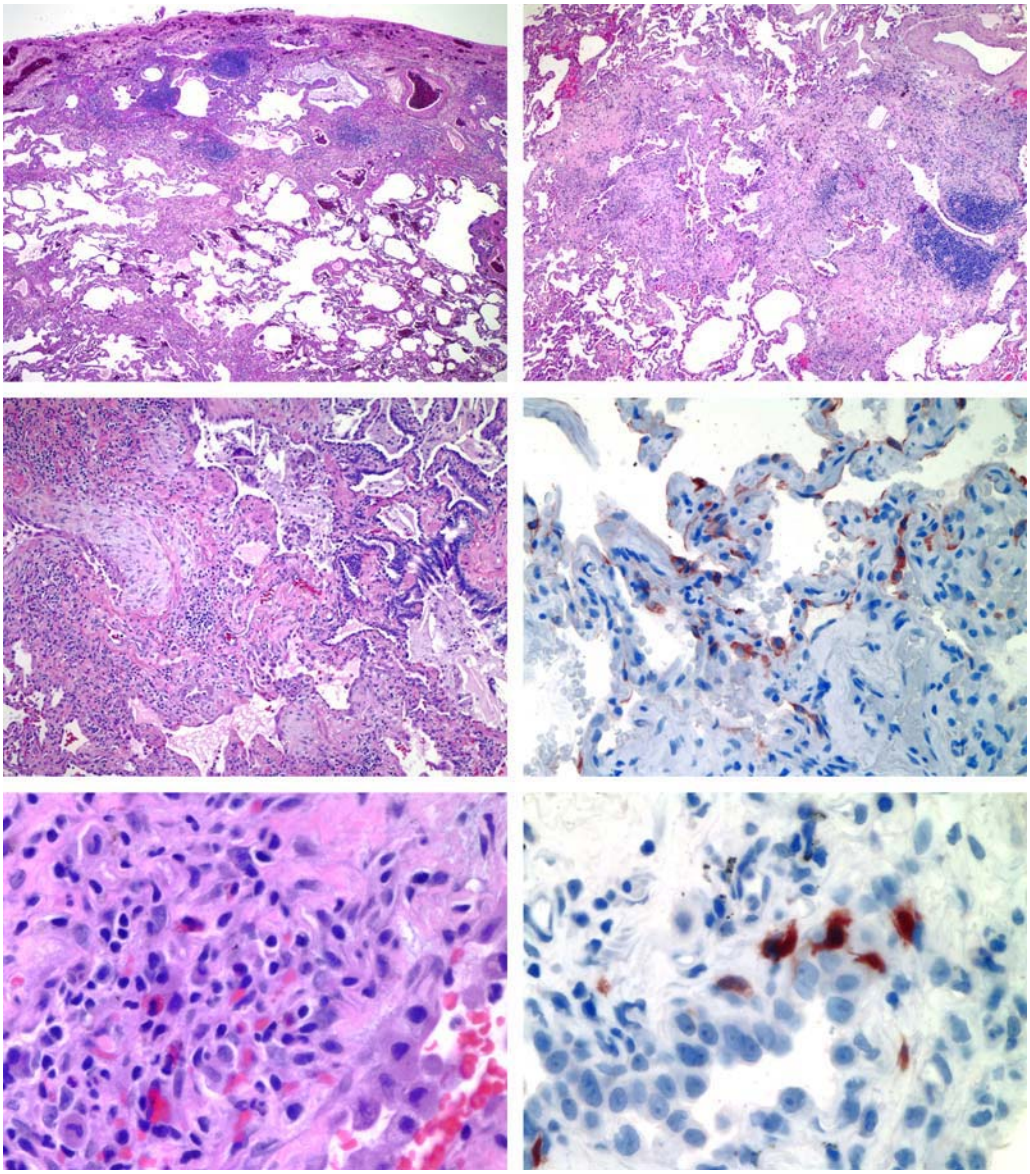
Diagnosis: Lung, open biopsy: Focal and diffuse interstitial fibrosis with patchy lymphocytic infiltrate, stellate scars, eosinophilia and honeycomb fibrosis, ? late phase of EG.

The honeycomb fibrosis with mucus plugging, as well as more diffuse fibrosis and foci of active alveolar fibrosis, makes the diagnosis of UIP the initial consideration. A second option is that this represents BOOP with focal scarring and eosinophils, and I cannot absolutely exclude that possibility, but the stellate scars are not typical of the scars associated with BOOP, and no distinct bronchiolitis is present. The presence of many eosinophils in some areas, as well as stellate scars with histiocytes, raises the alternative diagnosis of a late resolving phase of EG, which is the diagnosis I prefer. For this reason, we have performed additional stains for Langerhans' cells and reviewed the chest radiographs, which show multiple small nodules and linear scarring in all lung fields. Honeycomb fibrosis is not apparent. Computerized tomograms might be useful in further evaluation.

There are increased numbers of Langerhans' cells on slides stained for S-100 antigen and CD1a. The cells are relatively small in number, at the most, five or ten together, but they lie in regions of stellate scars that are suspicious for EG and serve to confirm the suspicion. Trichrome, elastic, Giemsa and periodic acid-Schiff stains portray the cells and the scarring. Iron stains show no hemosiderin.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7116 (Chapter 3 – Interstitial Lung Disease)

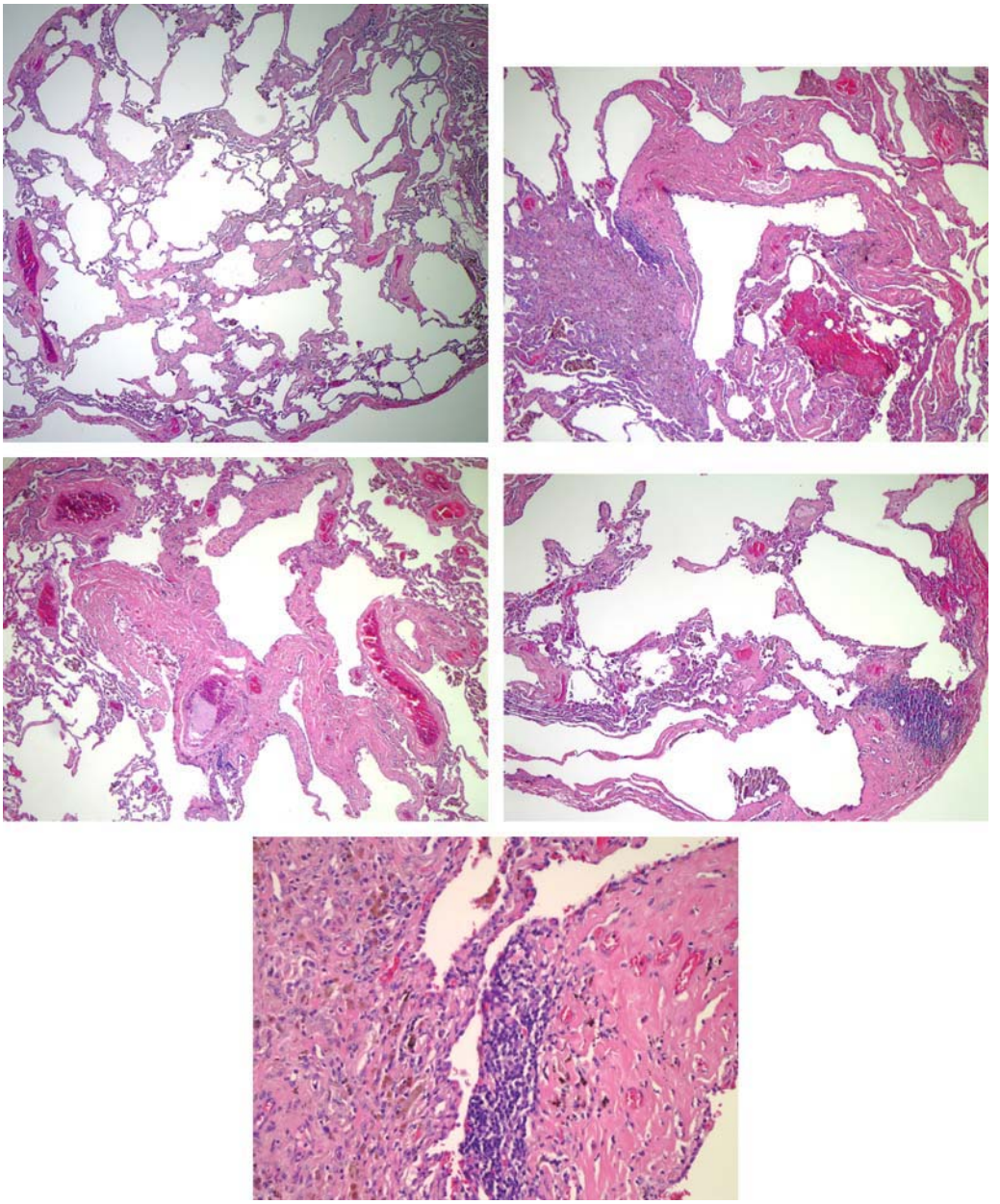
Case 6624

Diagnosis; Lung, open biopsy: Few stellate scars, ? burned-out phase of EG.

A few small stellate scars are associated with cysts beneath the pleura. The shape of one scar in particular and also other smaller jagged scars suggest this diagnosis. In the late burned-out stage of EG, Langerhans' cells may not be demonstrable in abnormal numbers, and I suspect that is the case here. The biopsy does not show lymphangioleiomyomatosis. In the clinical and radiographic setting of possible EG, I favor this interpretation. I have seen several such instances of so-called burned-out disease, so I am willing to suggest the possibility even when the pathology by itself would not permit the diagnosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6624 (Chapter 3 – Interstitial Lung Disease)

Case 6779

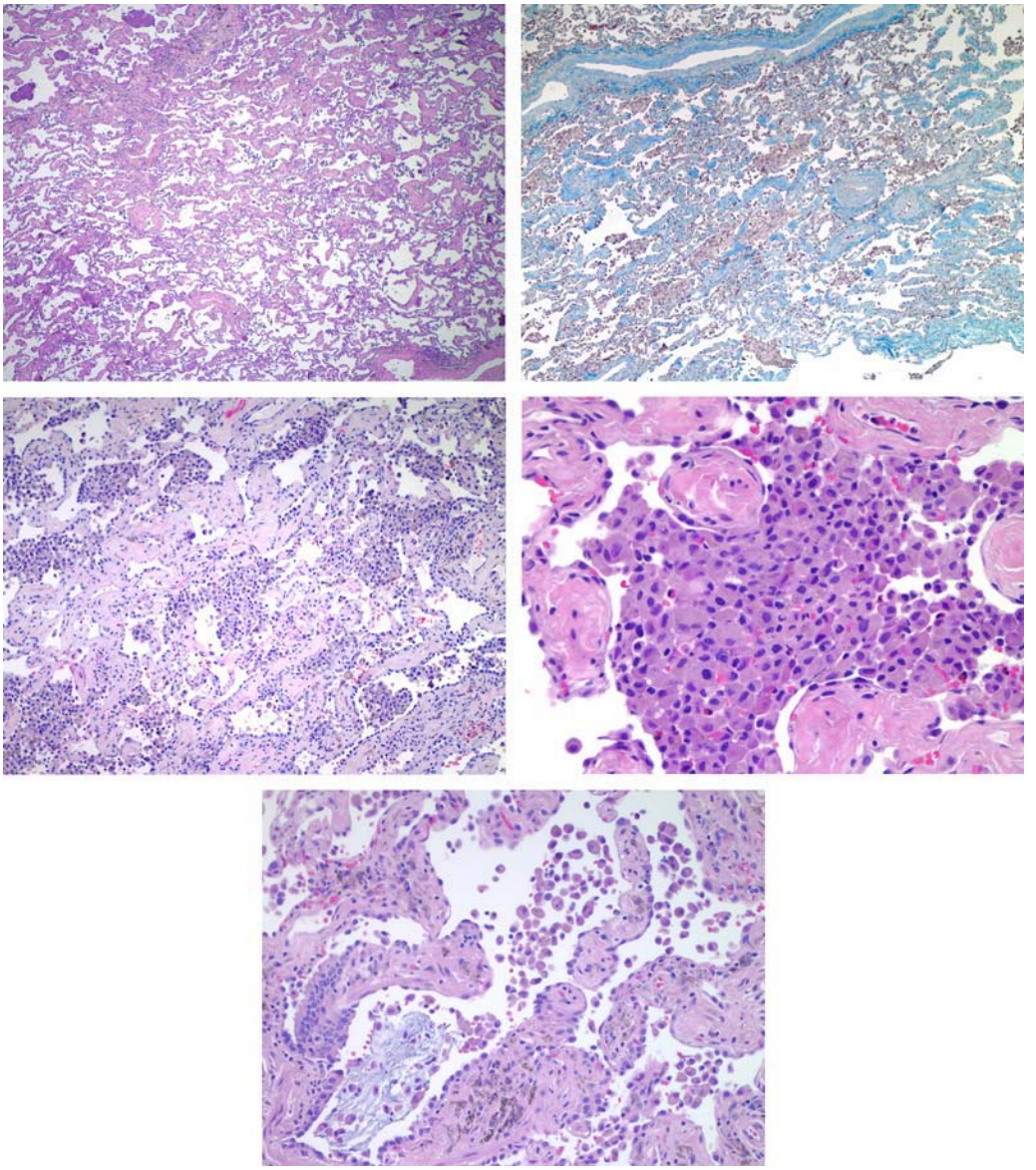
Diagnosis: Lung, open biopsy: DIP.

There is an alveolar filling process associated with old interstitial fibrosis of alveolar walls beneath the pleura. Pigmented histiocytes in alveoli outnumber lymphocytes in the interstitium. Thus, this histology is more in keeping with DIP than with UIP, despite the established interstitial fibrosis. Noteworthy is the absence of honeycomb fibrosis beneath the pleura. I would expect honeycomb fibrosis to be already established with this degree of interstitial fibrosis if it were UIP. Occasional eosinophils amidst the histiocytes are in keeping with DIP. The active tufts of alveolar fibrosis seen in UIP are not present.

DIP is now often associated with RB, and the two diseases are sometimes considered on a continuum as DIP/RB. In this case, however, the DIP falls into the context of an interstitial process separable from UIP as originally described by Dr. Liebow. The prognosis of DIP is generally favorable. In this case there is more fibrosis than usually encountered (trichrome stain), and this patient may not respond as well to therapy as other patients with the condition.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6779 (Chapter 3 – Interstitial Lung Disease)

Case 6826

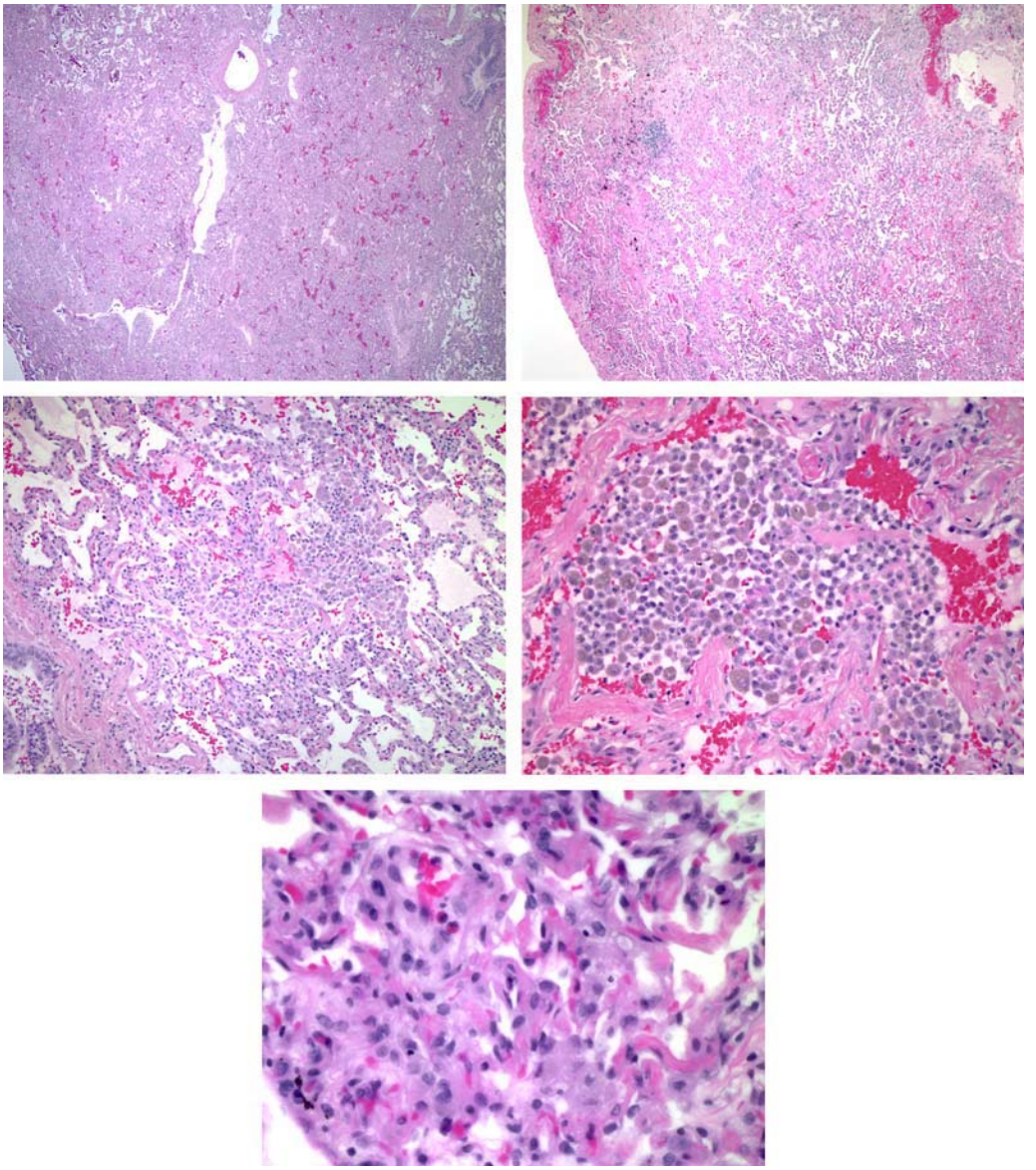
Diagnosis: Lung, open biopsy: Interstitial pneumonitis, consistent with DIP.

The principal pathology is alveolar filling by pigmented histiocytes, which contain finely granular iron and are admixed with eosinophils. There is also interstitial fibrosis in some regions as you indicate. A unifying diagnosis is DIP, and this is the diagnosis I favor. However, the alveolar filling is too focal for me to make that diagnosis unequivocally. The eosinophils are helpful in establishing the basic nature of the process. The principal differential diagnosis is RB with interstitial lung disease. Some pathologists consider DIP and RB as very similar diseases and on a continuum. I cannot exclude RB with interstitial lung disease, but I believe the changes are, for the most part, lobular (intra-alveolar) and involving respiratory bronchioles to only a minor degree. Other than from a semantic or categorical distinction, the importance of separating DIP from RB is that the latter generally is due to the smoking of cigarettes, while the former has some other cause. I believe the changes here are more marked than the usual case of RB and probably are a pneumonitis that is occurring apart from the smoking.

In the differential diagnosis, we also considered pulmonary hemosiderosis due to congestive heart failure, interstitial fibrosis associated with rheumatoid disease, and histiocytic inflammation as part of a hypersensitivity reaction. We do not favor these interpretations.

Thank you for referring this complicated case. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6826 (Chapter 3 – Interstitial Lung Disease)

Case 7134

Diagnosis: Lung, open biopsy: DIP.

This specimen shows extensive alveolar filling by pigmented histiocytes as well as regional interstitial fibrosis and a sparse interstitial lymphocytic infiltrate in regions of more coarse fibrosis. There is abundant granular brown pigment, which is in part formalin (polarizeable), in part iron (demonstrable on your iron stain), and in part so-called tobacco-pigment. I believe the hemorrhage is operative. No source of bleeding is evident in this specimen, and the patchy character of the alveolar blood without distention of the alveolar airspaces suggests that the blood is due to technical factors during operation.

The differential diagnosis is between DIP and respiratory bronchiolitis with associated interstitial lung disease (RB-ILD). There is an element of bronchiolar disease due to cigarette smoking. This bronchiolar disease includes mucus plugs as well as pigmented histiocytes filling the bronchioles, and these features alone would dictate a diagnosis of RB-ILD. However, the degree of the alveolar filling is more than expected for that condition, and the clinical features and severity of disease are also more in keeping with DIP than with RB-ILD.

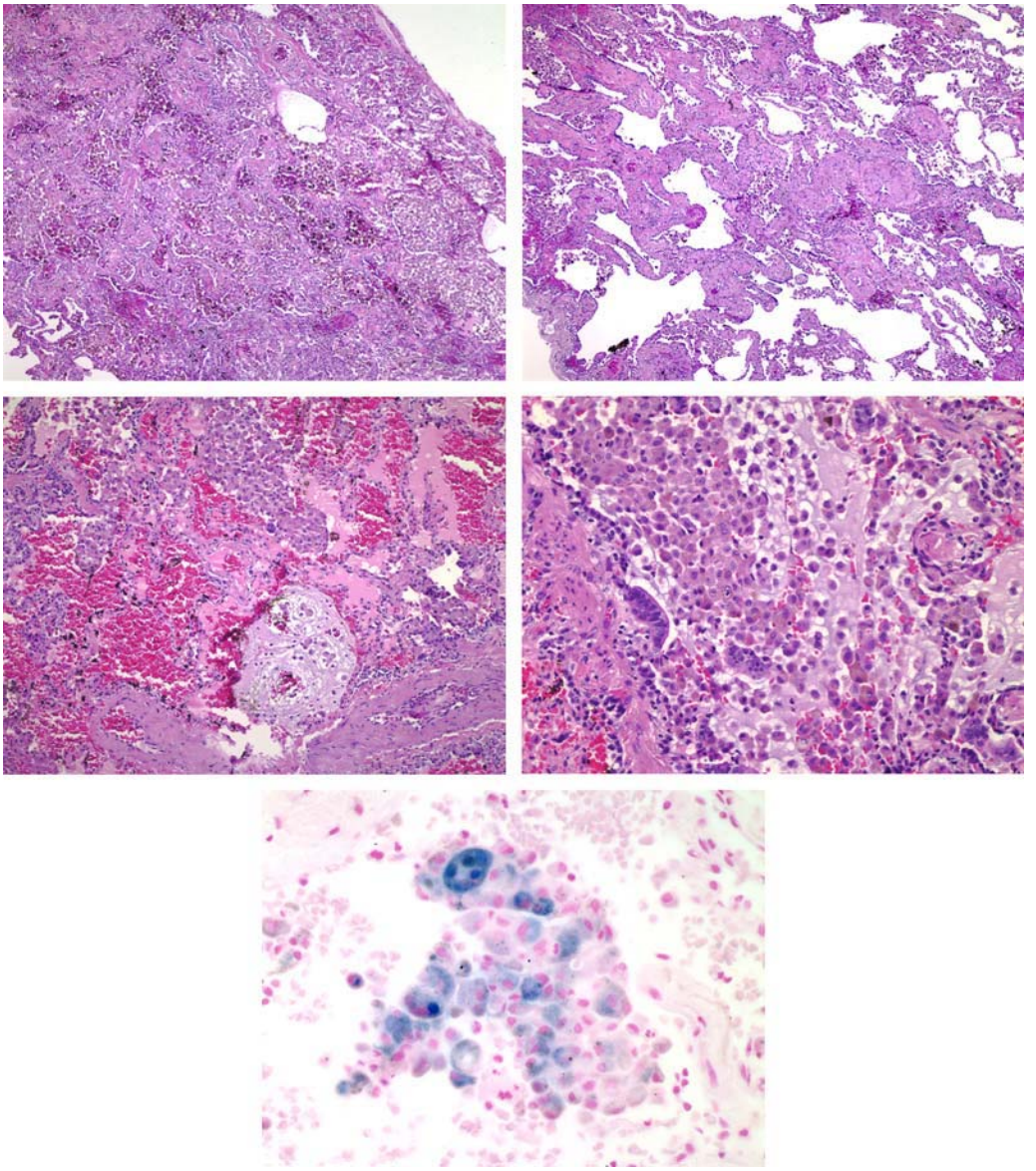
There is some controversy as to the relationship between RB-ILD and DIP. This controversy includes whether or not these are related or separate diseases. The two conditions can coexist. Both diseases occur principally in patients who smoke cigarettes. Cessation of cigarette smoking is important in the therapy of either condition.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989;64:1373–1380.



Case 7134 (Chapter 3 – Interstitial Lung Disease)

Case 7015

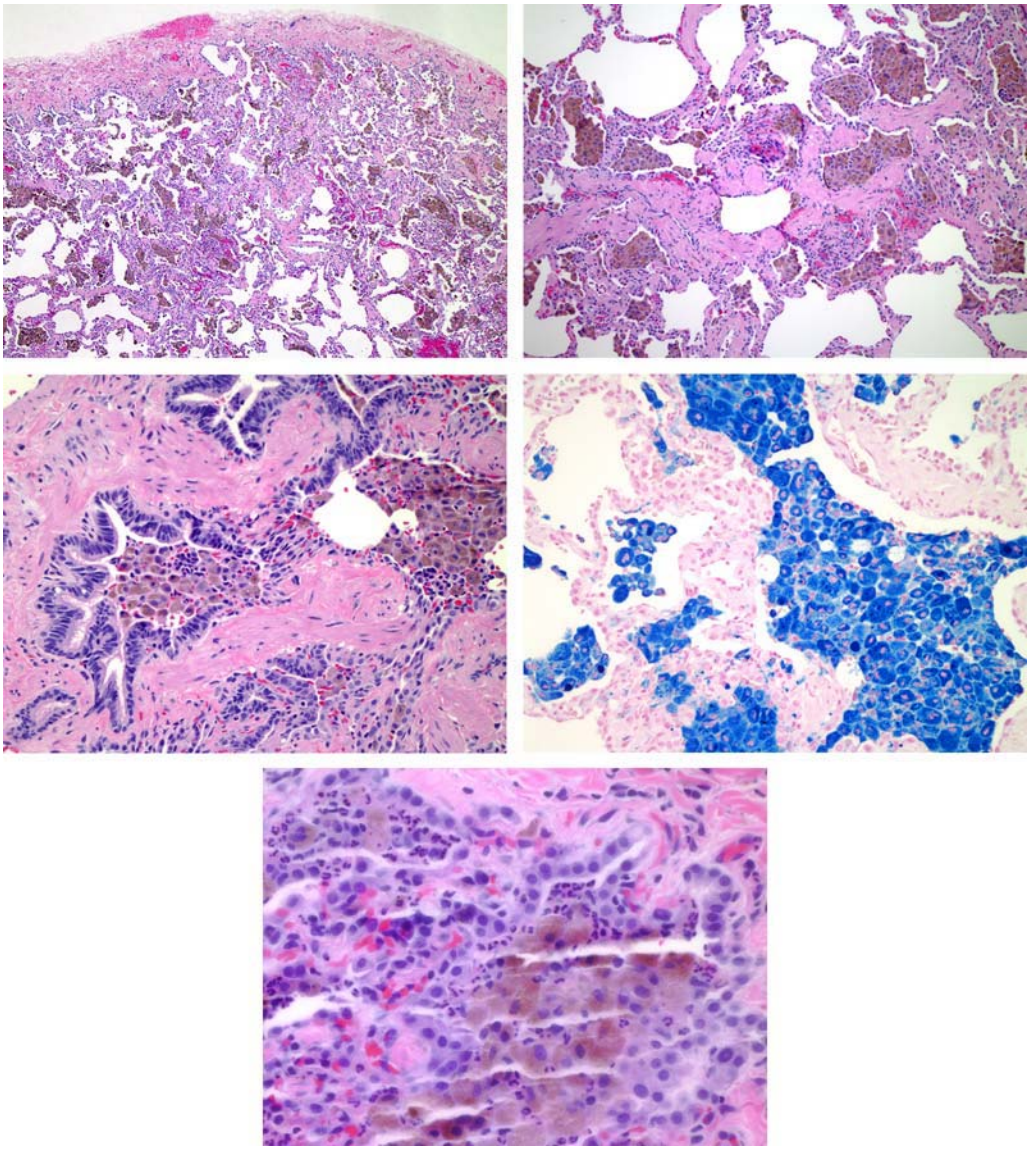
Diagnosis: Lung, open biopsy: Alveolar filling by pigmented histiocytes with extensive iron, ? DIP, ? hemosiderosis.

The predominant finding is alveolar filling by pigmented histiocytes and slight but old interstitial fibrosis without honeycomb change beneath the pleura. Some bronchioles are also plugged by the pigmented histiocytes. The pathology is most consistent with DIP. The chest radiographs including the computerized tomograms show extensive albeit regional ground glass densities, which are suggestive of DIP. The clinical story with progressive lung disease and clubbing is also consistent with DIP. In one study, 44% of patients with DIP had clubbing.

Your iron stain shows extensive, finely granular iron pigment in the pigmented histiocytes. The amount of iron is in excess of what is commonly encountered in DIP but can occur. Coarse granules of hemosiderin are present but in smaller measure. Because of the extensive iron, we considered mitral lung disease, idiopathic pulmonary hemosiderosis, and quiescent vasculitic disease including Goodpasture's syndrome and WG and lupus erythematosis. The radiographic studies do not disclose abnormal pulmonary arteries or enlarged left atrium. Idiopathic pulmonary hemosiderosis is a diagnosis of exclusion. We find a few microabscesses in a few alveoli. These could represent a facet of WG, which should be considered and further evaluated by testing for antineutrophil-cytoplasmic antibody, but I doubt this interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7015 (Chapter 3 – Interstitial Lung Disease)

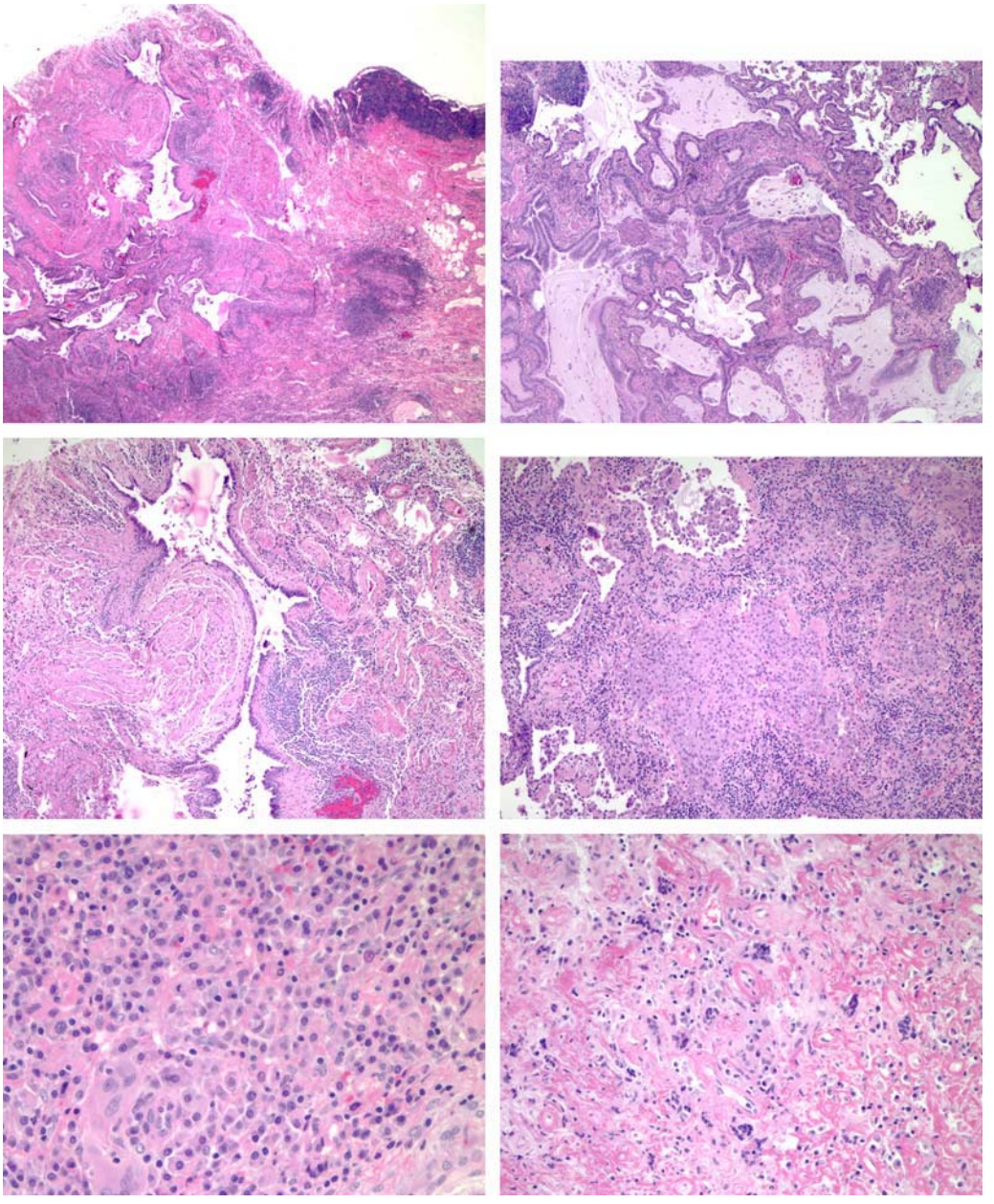
Case 6581

Diagnosis: Lung, open biopsy: Honeycomb fibrosis, end-stage.

This specimen consists of ectatic airspaces lined by hyperplastic respiratory epithelium and surrounded by old fibrosis with smooth muscle hyperplasia and a marked plasmacytic infiltrate. No normal lung or early alveolar or interstitial fibrosis is present. All of the scarring is advanced and irreversible in this specimen. There is atrophy of lung with fatty replacement. This appears to have occurred in the tip of a lobe which was sampled. The most common disease which results in this histology is UIP, and the clinical history and reported radiographic findings are consistent with that interpretation. There is a prominent DIP-like reaction within some of the airspaces, but in this case the DIP-like reaction probably relates to inspissation of mucus. Approximately 10% of patients with UIP have some histological overlap with DIP, but I would not place this specimen into that category because of the advanced nature of the disease. The other condition which enters into the differential diagnosis pathologically is bronchiectasis with honeycomb fibrosis beneath the pleura, but the clinical history in this case does not support that interpretation. Unusual morphologically are many multinucleated histocytes or mesothelial cells entrapped within the subpleural scar.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6581 (Chapter 3 – Interstitial Lung Disease)

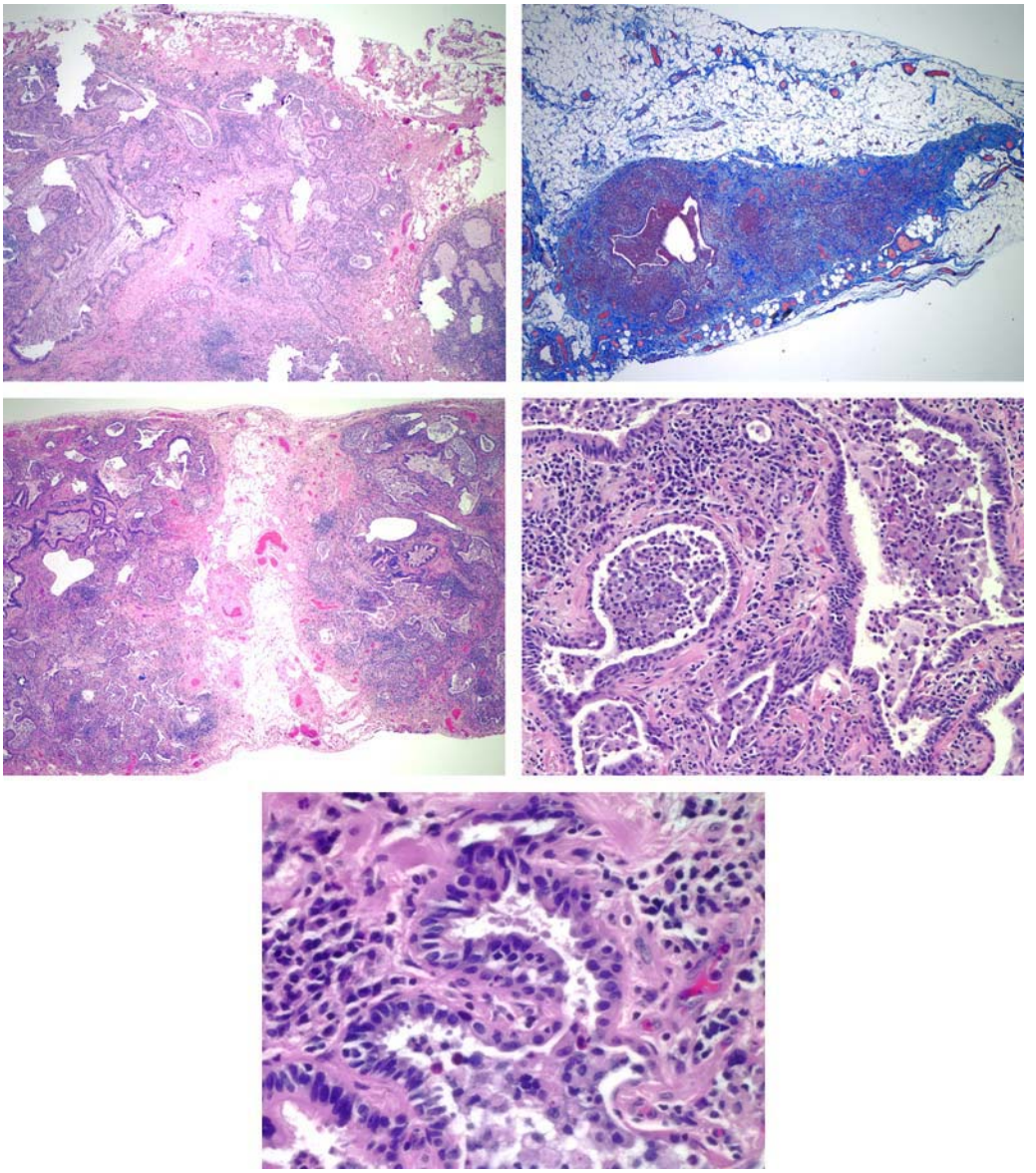
Case 6746

Diagnosis: Lung, open biopsy: Honeycomb fibrosis, end-stage.

The lung has bronchiolectasia forming honeycomb fibrosis not only beneath the pleura but in the entire specimen. There is marked mucus plugging with neutrophils. Because only end-stage disease is present, I cannot determine the etiology from the pathology alone. The statistically most likely condition based on the pathology and the reported clinical and radiographic history is UIP. This is essentially in agreement with your interpretation. Bronchiectasis resulting in peripheral honeycomb fibrosis can produce this pathology, and I cannot exclude this eventuality. Involvement of multiple lobes is more in keeping with UIP than with bronchiectasis as a primary diagnosis. No granulomas or nodular scars are present to suggest sarcoidosis. No inorganic particles are apparent. I believe the epithelial changes are reactive and due to the inflammation and fibrosis. I agree that there is a particularly prominent lobular pattern, produced not only by scar but by adipose tissue in lobular septa. The adipose tissue indicates lung atrophy (trichrome stain), but the creation of the lobular pattern is indeed unusual.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6746 (Chapter 3 – Interstitial Lung Disease)

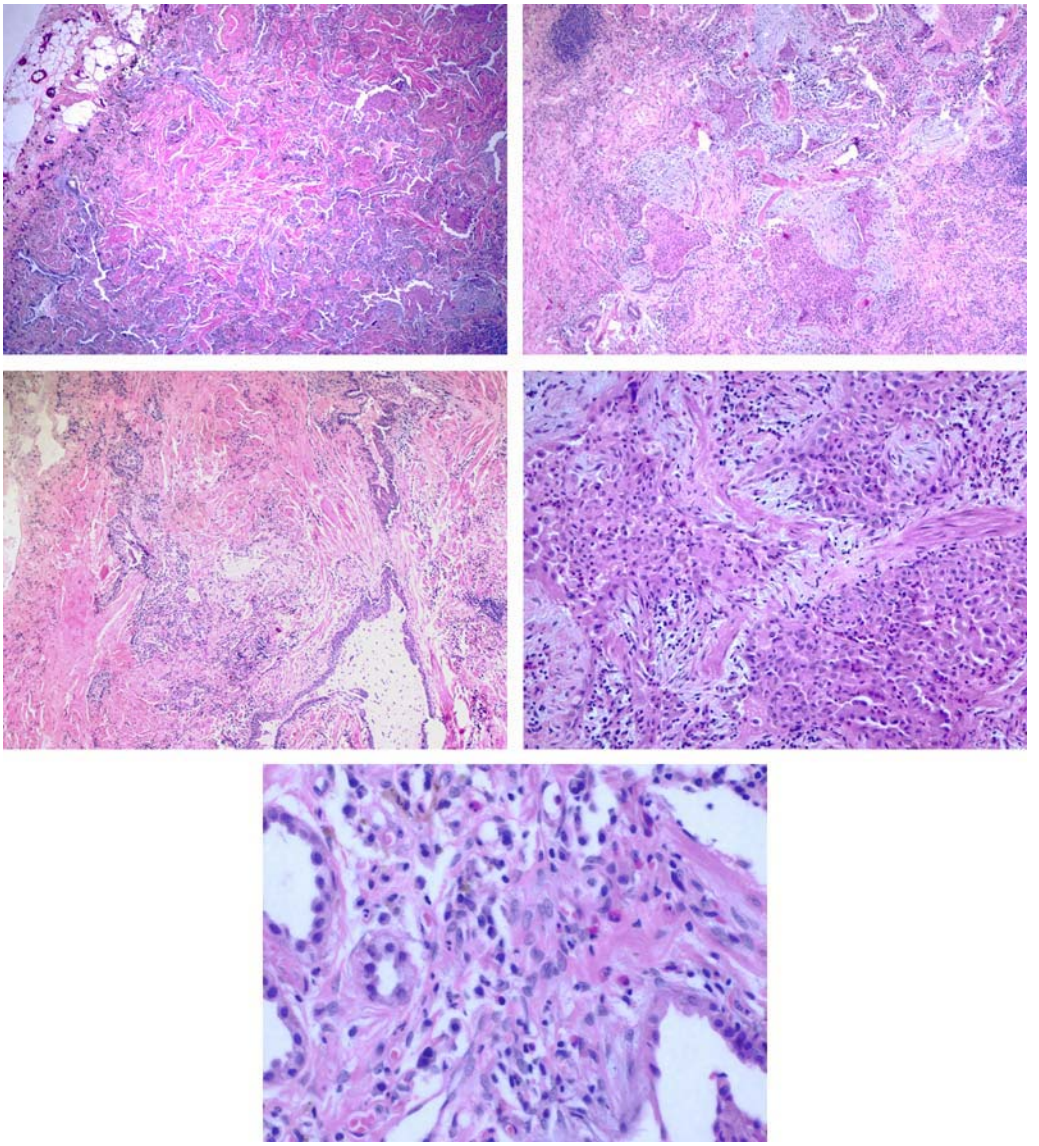
Case 6602

Diagnosis: Lung, open biopsies: Honeycomb fibrosis, end-stage, ? UIP, ? other.

Well established honeycomb fibrosis is associated with hyperplasia of smooth muscle and lung atrophy with fatty replacement. These changes are end-stage and have been termed muscular cirrhosis in the literature. The most common cause of end-stage interstitial fibrosis is UIP, which is the diagnosis I favor. The proliferative alveolar fibrosis in some regions is consistent with that interpretation and suggests the accelerated phase of UIP. I cannot exclude DIP, which overlaps histologically with UIP in approx 10% of cases of UIP. There is prominent alveolar filling with pigmented histiocytes and admixed eosinophils, which would be highly suggestive of DIP were it not for the prominent old and ongoing fibrosis. I also cannot exclude a late stage of EG because there are collections of eosinophils and occasional Langerhans' cells in the interstitium. EG can eventuate into honeycomb fibrosis, but the proliferative fibrosis is against that interpretation. The stellate architecture of early lesions of EG and aggregated Langerhans' cells are absent. The pathology does not suggest silicosis or silicatosis. The amount of birefringent particles seen with polarized light is within normal limits.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6602 (Chapter 3 – Interstitial Lung Disease)

Case 6772

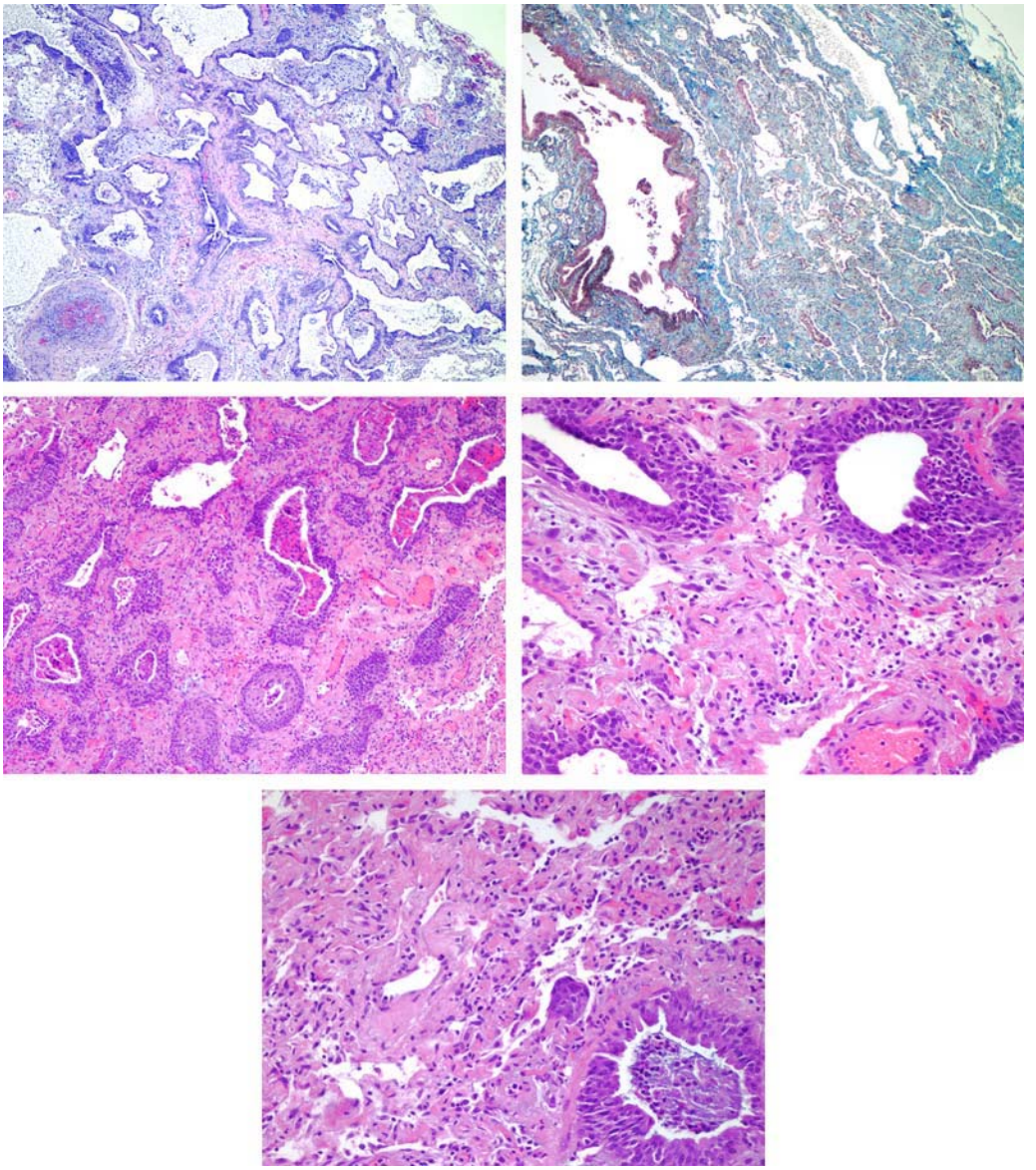
Diagnosis: Lung, open biopsy: Subpleural honeycomb fibrosis and organizing interstitial and alveolar fibrosis, nondiagnostic, with superimposed mucus plugging and acute inflammation.

This case is difficult because there is acute inflammation superimposed upon old fibrosis (trichrome stain) and new ongoing fibrosis. Because one of the common causes of subpleural honeycomb fibrosis is UIP and because there is active ongoing myxoid fibrosis in alveoli with incorporation into interstitium, I believe this is a possible scenario. I could not make a diagnosis of UIP with certainty in this case, however, for the following reasons: 1) the clinical history is not suggestive of UIP; 2) the clinical implications of that diagnosis are ominous; 3) so much of this specimen has very advanced disease; 4) active fibrosis is relatively limited in quantity. UIP is one form of rheumatoid lung disease, and I do not know whether the reported arthritis is rheumatoid. Central bronchiectasis is another condition that can cause subpleural honeycomb fibrosis. In this specimen the honeycomb fibrosis is restricted to the subpleural zone, and deeper lung is relatively normal.

There are many neutrophils within mucus and within metaplastic squamous epithelium lining areas of bronchiolectasis. The neutrophils could be reacting to inspissated mucus with possible superinfection. The pathology is not that of an acute or chronic organizing pneumonia. Neutrophils within mucus plugs in honeycomb fibrosis are common, but the neutrophils are more numerous here than usually encountered in that situation. There is one blood vessel with recent organizing thrombus or thromboembolus (trichrome stain). The squamous metaplasia is marked with focal atypia.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6772 (Chapter 3 – Interstitial Lung Disease)

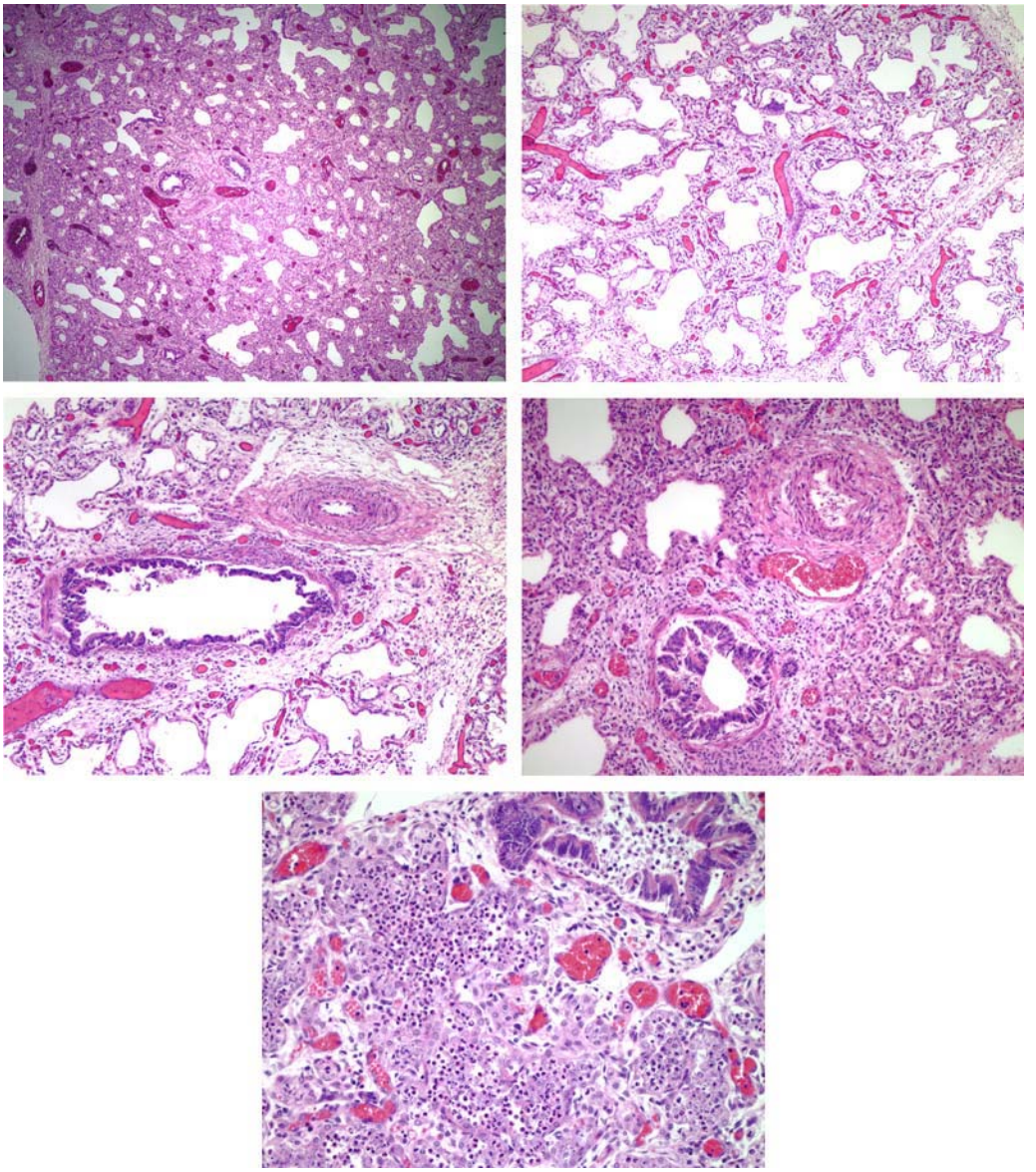
Case 6728

Diagnosis: Lung, autopsy: Interstitial fibrosis and capillary proliferation, cause undetermined.

This case is difficult. Capillaries and venules are numerous, and because of their numbers, the alignment is not normal. On the other hand, there is an extensive subacute proliferation of fibroblasts. One explanation for the proliferating blood vessels is that they are a part of the fibrosing process. I favor this interpretation. Because the fibrosis appears histologically approximately the same age as the length of life (16 d), a unifying diagnosis would be fibrosis first and vascular proliferation second. Although I cannot exclude the syndrome of alveolar capillary dysplasia, I do not believe this is the case. Pulmonary arteries have intimal and medial thickening comparable to fetal lung and suggest persistent pulmonary hypertension of the newborn. Part of the abnormal architecture is the circularity of the airspaces due to mechanical ventilation. Terminal fibrinous and purulent bronchopneumonia is present.

Thank you very much for sharing this case with me. With all best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6728 (Chapter 3 – Interstitial Lung Disease)

Case 6731

Diagnosis: Lung, open biopsy:

1. **Interstitial pneumonitis and fibrosis, nondiagnostic.**
2. **Foreign body giant cell reaction, ? aspiration; ? mucus plugging, ? both.**

An interstitial pneumonitis is present in portions of the lung, where the lymphocytic infiltrate is associated with interstitial widening due to early fibrosis as well. There is honeycomb change in at least one section. I do not know what is causing this disease. Early UIP is possible based on the polymorphous character of the infiltrate and the interstitial fibrosis. However the changes and the reported radiographic findings are not typical of that condition. Eosinophils are present in some regions. A drug reaction or a hypersensitivity reaction is possible.

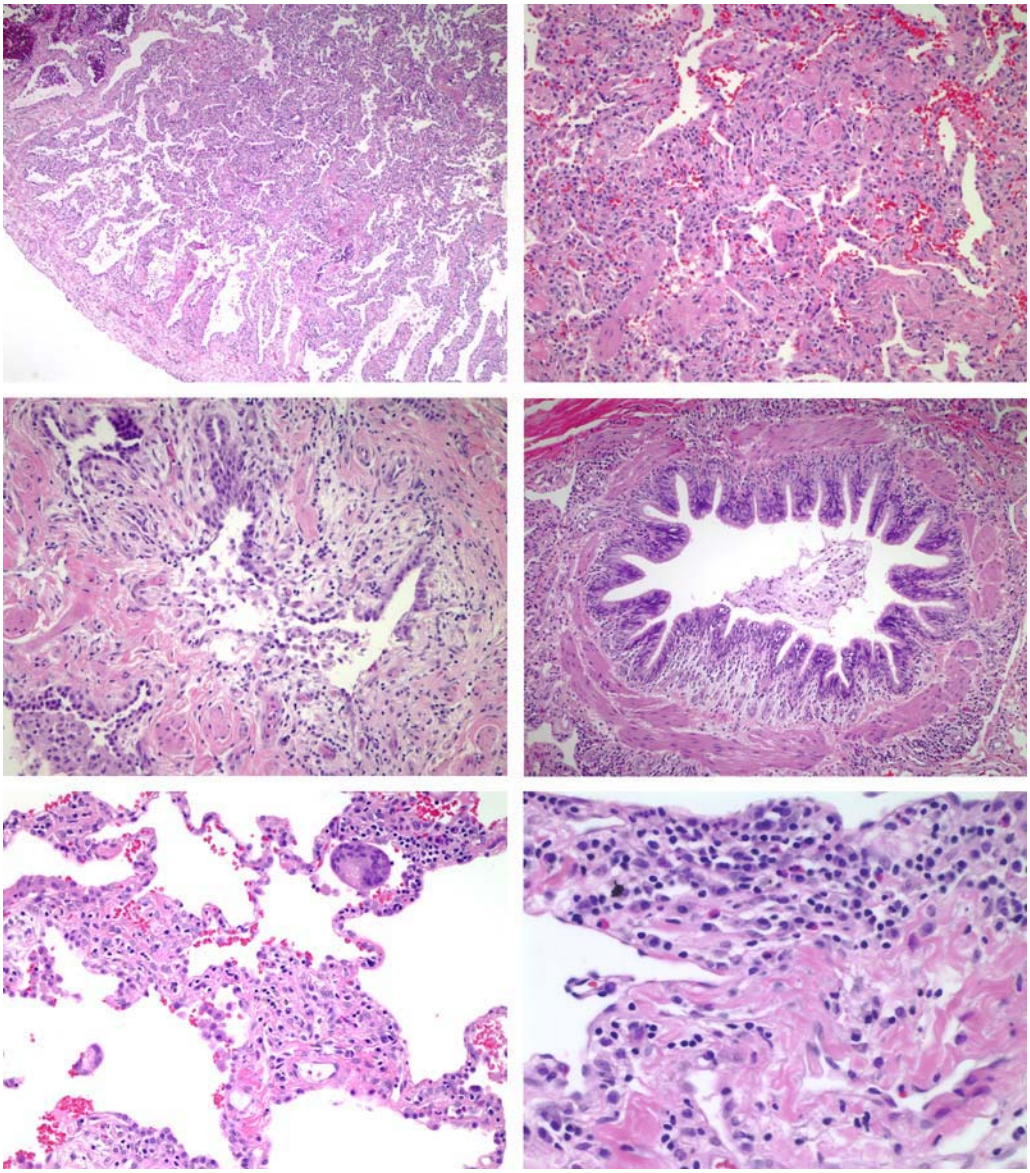
A few regions have fibrosis in alveolar ducts and alveoli. This may represent an element of bronchiolitis, but overall the pathology is not that of BOOP. BO rarely is associated more with interstitial fibrosis than with OP, and this situation is possible in this case.

Also present are occasional multinucleated histiocytes of giant cell type. The multinucleated histiocytes raise the possibility of aspiration. One sizable piece of foreign material is present in an occluded bronchiole (on gram stain). Other histiocytes react to mucus or contain cholesterol clefts. I cannot exclude aspiration as the cause for all of the changes.

I detect no marked changes of pulmonary arterial hypertension or venous hypertension. The blood in the specimen is operative. There is a small amount of hemosiderin.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6731 (Chapter 3 – Interstitial Lung Disease)

Case 7061

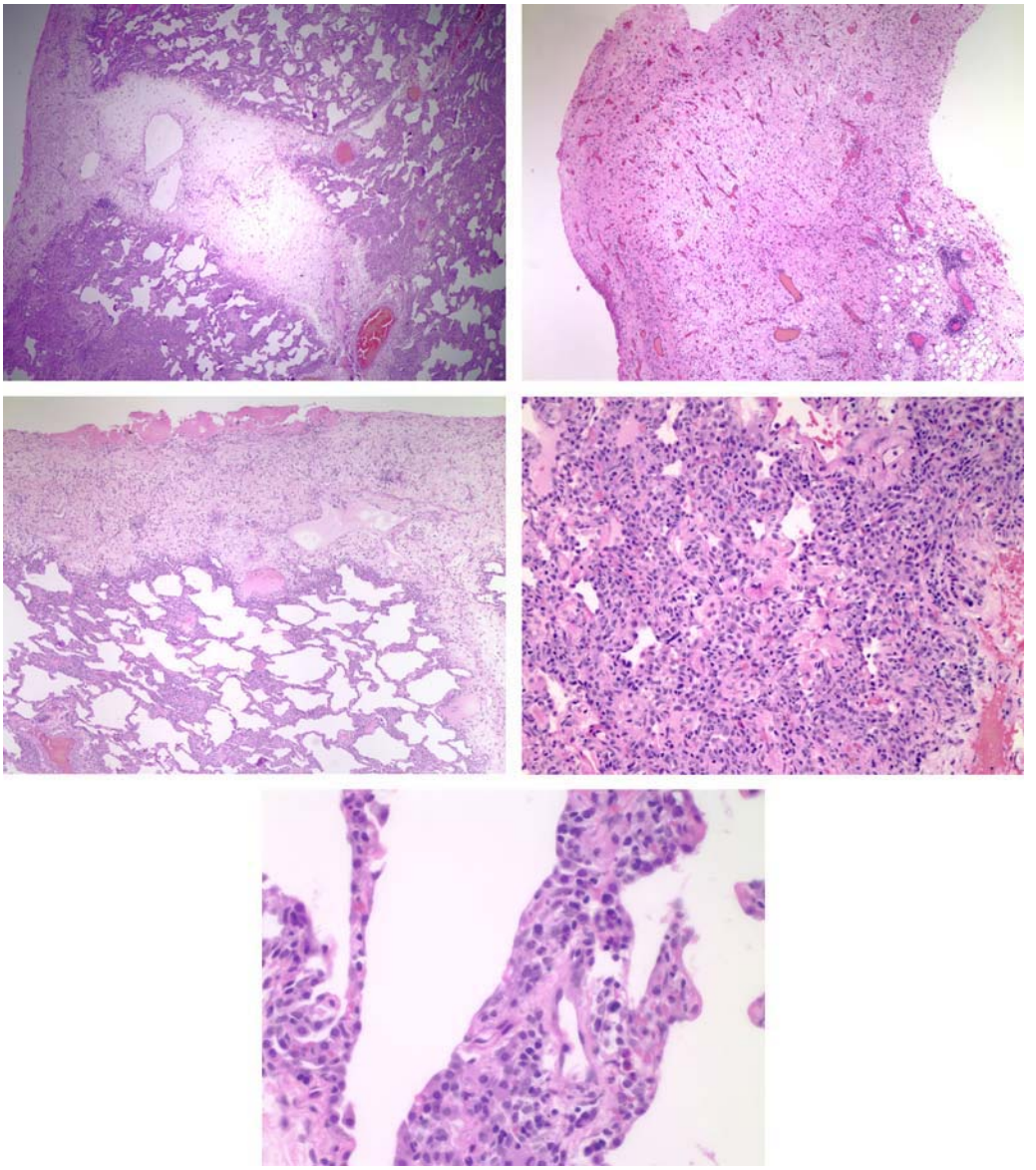
Diagnosis: Lung, open biopsy: Diffuse interstitial pneumonitis, interstitial and alveolar edema, and organizing fibrinous pleuritis, ? viral, ? collagen-vascular disease, ? other.

Pericardium, stripping: Organizing fibrinous pericarditis.

This active and ongoing disease has a lymphohistiocytic and plasmacytic infiltrate spread diffusely through alveolar walls and associated with marked edema and fibrinous pleuritis. The uniformity of the process temporally and spatially exclude UIP, and the pleuritis would not be in keeping with that interpretation. Occasional eosinophils are present. I do not know what is causing the pneumonitis, pleuritis and pericarditis. An infectious etiology is possible, including particularly virus. The diagnosis of viral pleuritis and pericarditis is more often suggested than proven. Collagen-vascular disease could produce this pathology. I considered a hypersensitivity reaction or drug reaction, but that would not well explain the pericarditis or the marked interstitial edema. Lymphangiectasia is present, and this made me consider a primary extrapulmonary problem, such as a mediastinal mass that might cause lymphatic obstruction. The absence of hyaline membranes means that this not DAD. We considered EG because some of the infiltrate is histiocytic and includes Langerhans' cells. Stains for Langerhans' cells could be performed to further quantitate them, but the overall process, as well as the pleuritis and pericarditis, are not at all characteristic of histiocytosis X in the adult.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7061 (Chapter 3 – Interstitial Lung Disease)

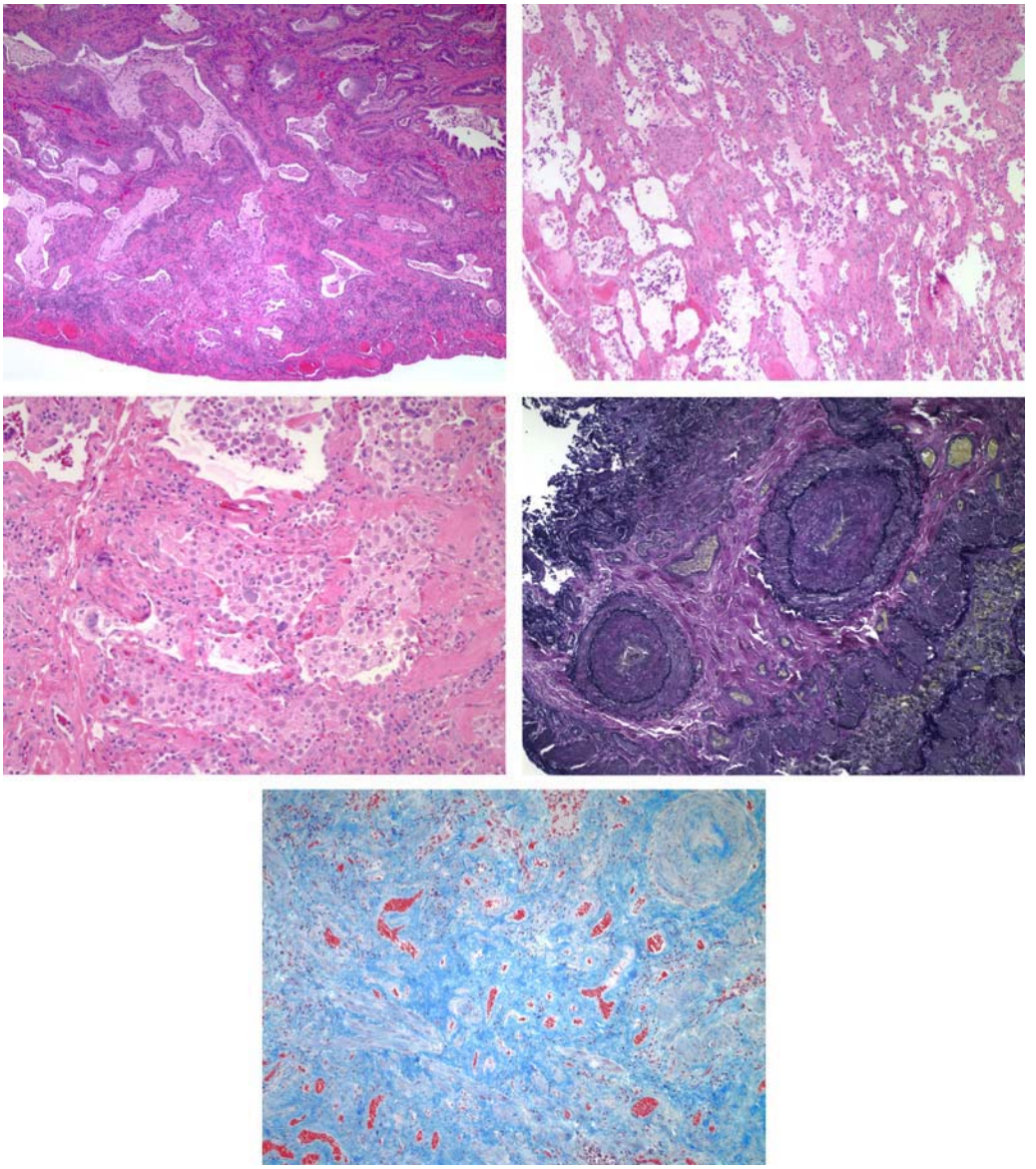
Case 6523

Diagnosis: Lung, open biopsy: Interstitial fibrosis, old, extensive, end-stage, consistent with lupus erythematosis.

Extensive old interstitial fibrosis involves virtually all of the specimen. In some regions the alveoli are normal in size but have rounded contours indicative of early interstitial expansion. Other regions have coarse collagen forming extensive scarring (trichrome stain) with bronchiolectasis and early subpleural honeycomb fibrosis. I cannot make a diagnosis of UIP in this specimen because of the absence of a lymphocytic infiltrate and the absence of the temporal and spatial heterogeneity typical of that condition. However, I suspect that UIP, one of the common forms of lung disease in patients with lupus erythematosis, was the inflammatory disease which led to the fibrosis. There is grade 3/4 arterial hypertension (elastic stain) involving principally muscular pulmonary arteries. The degree of pulmonary hypertension is consistent with the interstitial fibrosis. Necrotizing vasculitis and capillaritis as seen in patients with acute lung disease due to lupus erythematosis are not present. Other features of lupus erythematosis in the lung (pleuritis, bronchiolitis, lymphoid hyperplasia) are not present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6523 (Chapter 3 – Interstitial Lung Disease)

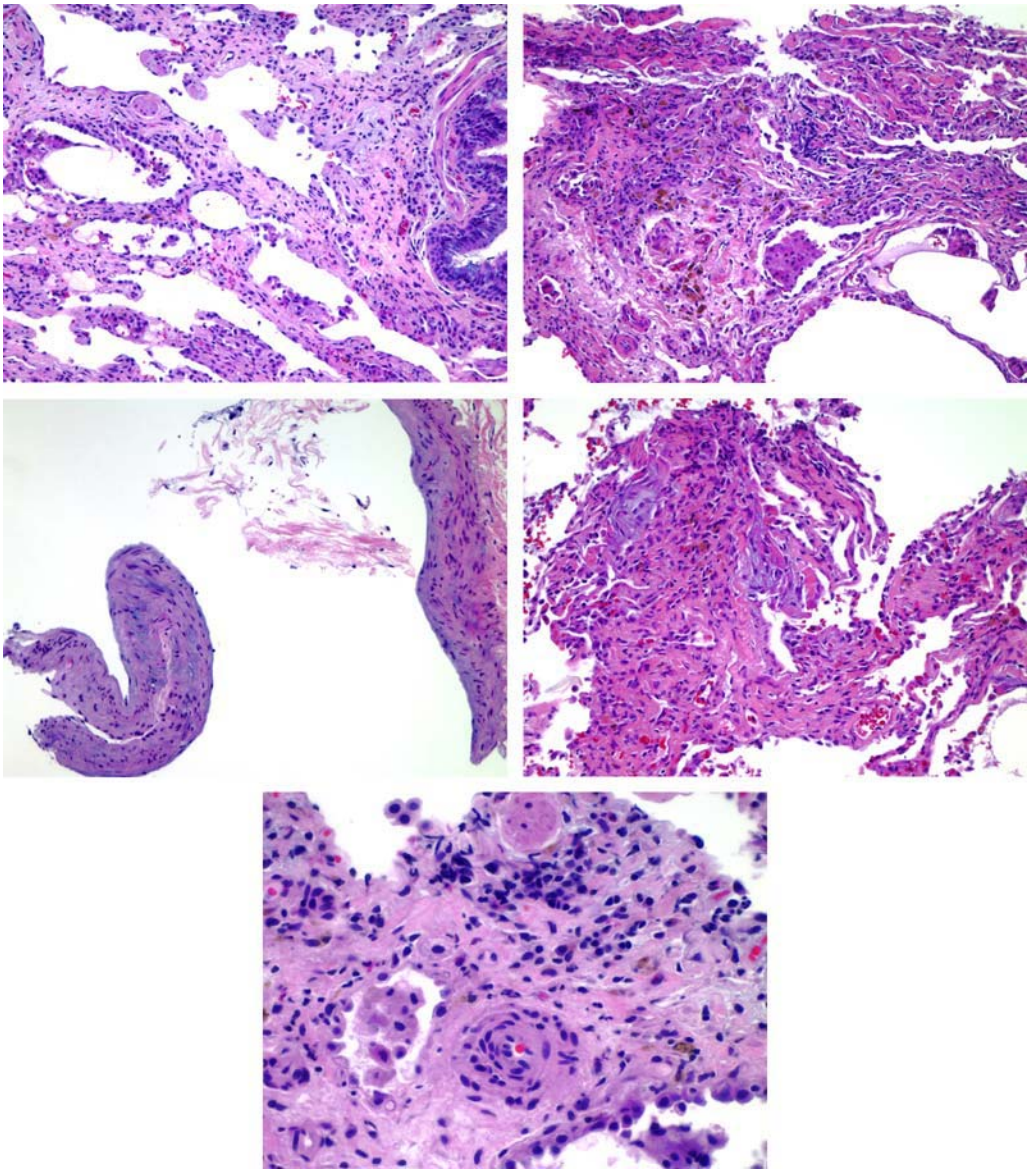
Case 7167

Diagnosis: Lung, bronchoscopic biopsy: Interstitial inflammation and fibrosis and arteriolar hypertensive changes, nondiagnostic, ? interstitial pneumonitis secondary to scleroderma.

This case is difficult. There is definite but delicate interstitial thickening by old fibrosis and small foci where myxoid fibrosis indicates active disease. A sparse lymphocytic infiltrate is also present. Such changes could represent UIP, but the biopsy is too small to further evaluate the spatial and temporal diversity characteristic of UIP. The interstitial pneumonitis and fibrosis in collagen-vascular disease generally has the morphology of UIP. Additionally, intimal and medial hyperplasia of arterioles are of moderate to marked degree. Collagen-vascular disease, including particularly scleroderma, can produce pulmonary hypertensive change of this degree. I understand that this patient has morphological evidence of scleroderma in a biopsy of the skin and has myositis in a biopsy of the muscle and a clinical diagnosis of scleroderma. The changes in this biopsy could represent pulmonary manifestations of scleroderma.

Thank you for referring this case in consultation. Please keep me informed of any follow-up.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7167 (Chapter 3 – Interstitial Lung Disease)

Case 7159

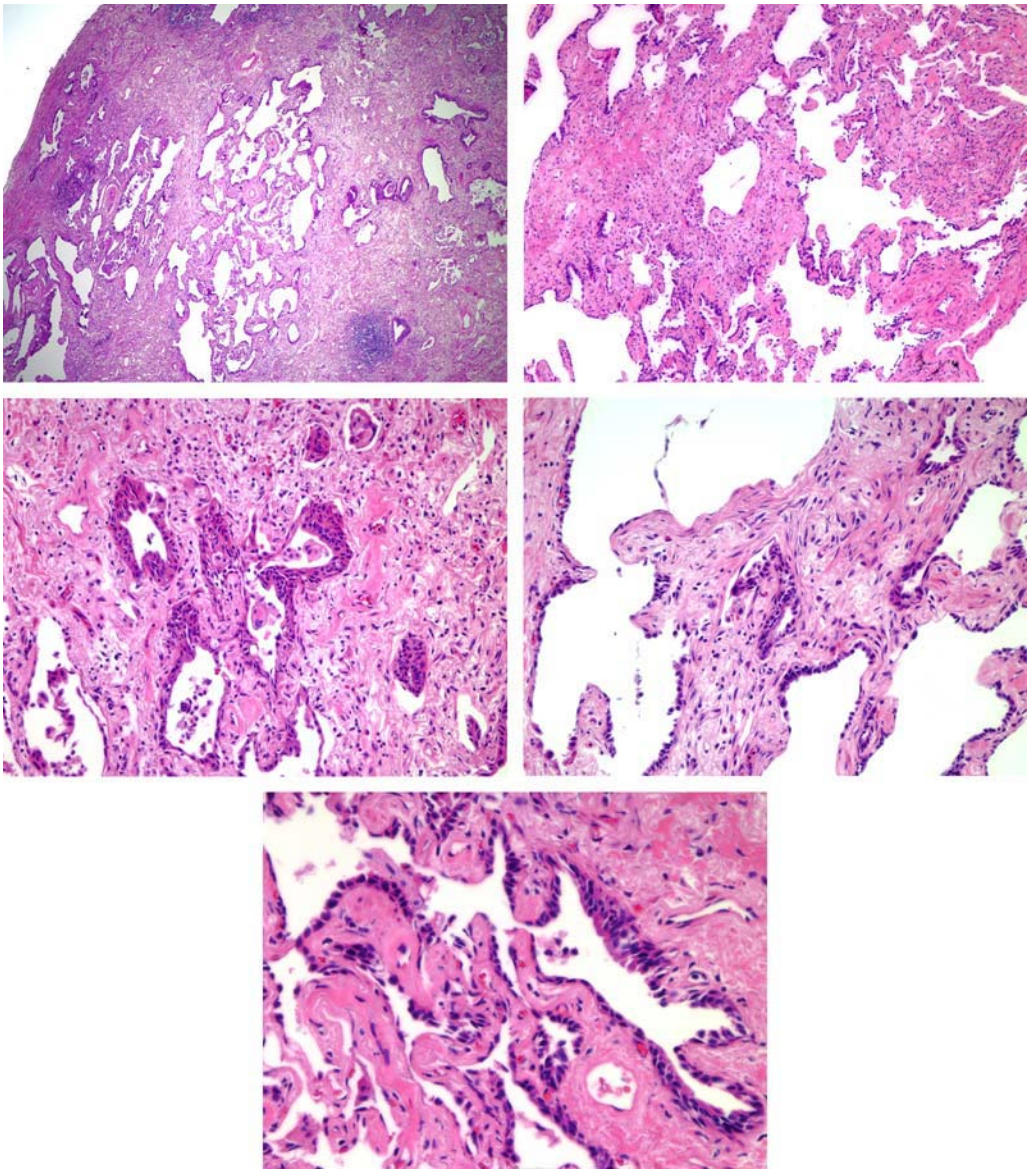
Diagnosis: Lung, open biopsy: Interstitial fibrosis, extensive, cause undetermined, ? late stage UIP, with atypical epithelial proliferation.

The interstitial fibrosis is extensive and old but relatively delicate in some areas. Two old nodular scars are present, but subpleural honeycomb fibrosis is not apparent in this specimen. The most common cause of this form of fibrosis is UIP, which I favor on a statistical basis; however, the reported diagnosis of atypical pneumonia is an unusual clinical impression for a patient with UIP. A definite diagnosis of UIP cannot be made because there is little lymphocytic inflammation, no active fibroblastic foci, and no acute alveolar injury. UIP in patients with longstanding collagen-vascular disease can sometimes result in this form of UIP. Another possible explanation for such interstitial fibrosis is bronchiectasis that has resulted in diffuse linear scarring in regions of the lung, and I cannot exclude this possibility, but I do not favor it.

The interstitial fibrosis is associated with extensive squamous metaplasia and atypical epithelial proliferation including foci with a few markedly atypical cells. I considered a well differentiated adenocarcinoma of bronchioloalveolar subtype arising in association with diffuse interstitial fibrosis, but I cannot find invasion, and the degree of nuclear change is not sufficient for a diagnosis of malignancy. Nevertheless, I would be concerned about this possibility in other areas of the lung not sampled either now or later in the patient.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7159 (Chapter 3 – Interstitial Lung Disease)

Case 6877

Diagnosis: Lung, bronchoscopic biopsy: Granulomatous bronchiolitis and pneumonia, cause undetermined, ? methotrexate pneumonitis.

There is organizing bronchiolitis with bifurcating tongues of fibrous tissue in small conducting airways associated with organizing fibrin and early fibrosis in alveoli, superimposed upon which are multinucleated histiocytes and poorly formed granulomas. The generic category of granulomatous bronchiolitis and pneumonia usually implies hypersensitivity reaction, drug reaction, aspiration, or infection. I detect no foreign particulates or birefringent material. No organisms are present on your silver or periodic acid-Schiff stains.

Methotrexate pneumonitis is raised into the differential diagnosis here because of the clinical history. There is a range of histological features for methotrexate pneumonitis, but BO with organizing pneumonia (OP) and granulomatous pneumonitis have both been described, either individually or combined. Methotrexate pneumonitis can develop after relatively low doses of the drug. Therefore, one must consider methotrexate as a very possible etiological agent in this case. Alveolar consolidation has been described radiographically in some patients with this process.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

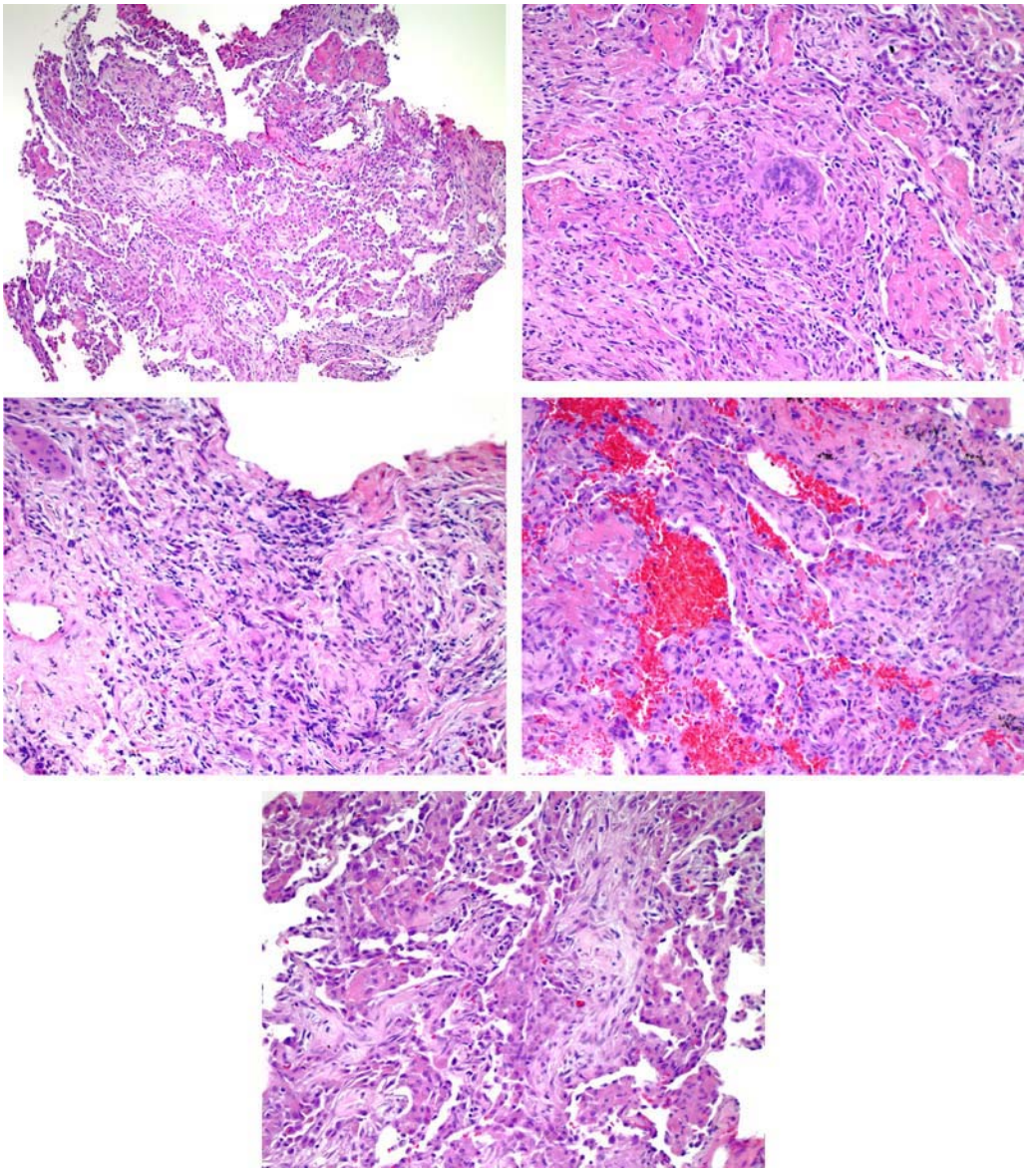
Sincerely yours,
Eugene J. Mark, M.D.

References:

Clarysse AM, Cathey WJ, Cartwright GE, Wintrobe MM. Pulmonary disease complicating intermittent therapy with methotrexate. JAMA 1969;209:1861–1864.

Leduc D, De Vuyst P, Lheureux P, Gevenois PA, Jacobovitz D, Yernault JC. Pneumonitis complicating low-dose methotrexate therapy for rheumatoid arthritis. Discrepancies between lung biopsy and bronchoalveolar lavage findings. Chest 1993;104:1620–1623.

Goldman GC, Moschella SL. Severe pneumonitis occurring during methotrexate therapy. Report of two cases. Arch Derm 1971;103:194–197.



Case 6877 (Chapter 3 – Interstitial Lung Disease)

Case 6610

Diagnosis: Lung, open biopsy: Interstitial pneumonitis with organizing fibrinous pneumonia and granulomatous inflammation, ? methotrexate pneumonitis, ? other.

An interstitial pneumonitis in some regions of the lung is predominantly fibrosing with coarsening of alveolar architecture, particularly beneath the pleura. The differential diagnosis for this portion of the pathology is broad and might include usual interstitial pneumonitis. However, there is also a focal organizing fibrinous pneumonia with histiocytic inflammation in aggregates, the latter representing granulomatous inflammation. In the context of a patient receiving methotrexate, and because methotrexate pneumonitis can be granulomatous, I am concerned that this interstitial pneumonitis may indeed be induced by methotrexate. Another differential diagnosis is a form of BPOP, and I cannot exclude this possibility. Methotrexate has caused the histological pattern of BPOP. The polymorphous nature of the inflammation including fibrin and neutrophils is not typical for the usual BPOP. I cannot absolutely exclude infection, but I doubt that interpretation. I find no viral inclusions. Drug-induced pneumonitis due to methotrexate has occurred in patients being treated for both immunological and neoplastic disease.

I have reviewed the chest X-ray which you kindly forwarded. The changes on the X-ray are consistent with an alveolar filling process.

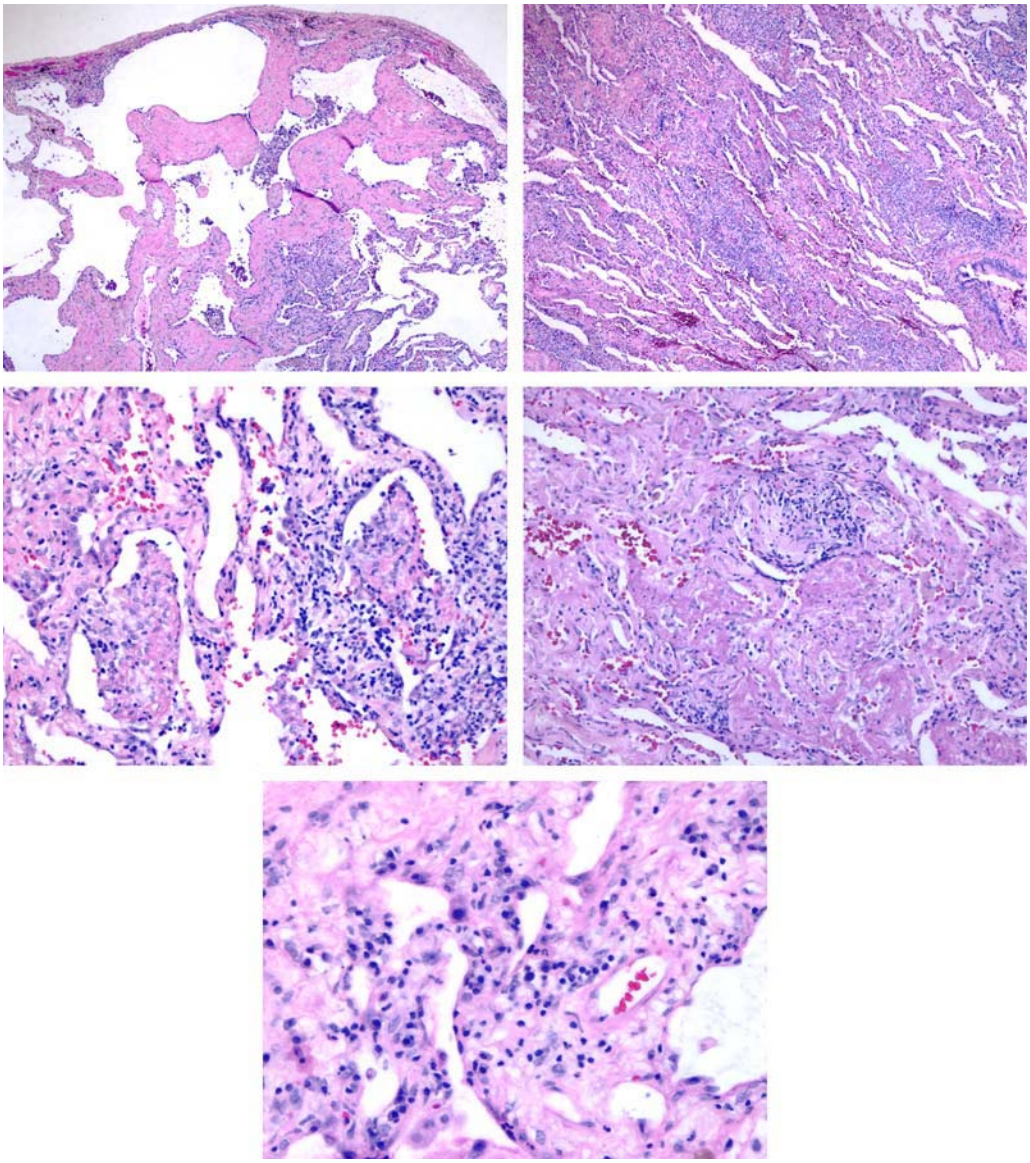
Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

Whitcomb ME, Schwarz IM, Tomey DC. Methotrexate pneumonitis: case report and review of the literature. Thorax 1972;27:636–639.

Leduc D, De Vuyst P, Lheureux P, Gevenois PA, Jacobovitz D, Yernault JC. Pneumonitis complicating low-dose methotrexate therapy for rheumatoid arthritis. Discrepancies between lung biopsy and bronchoalveolar lavage findings. Chest 1993;104:1620–1623.



Case 6610 (Chapter 3 – Interstitial Lung Disease)

Case 6953

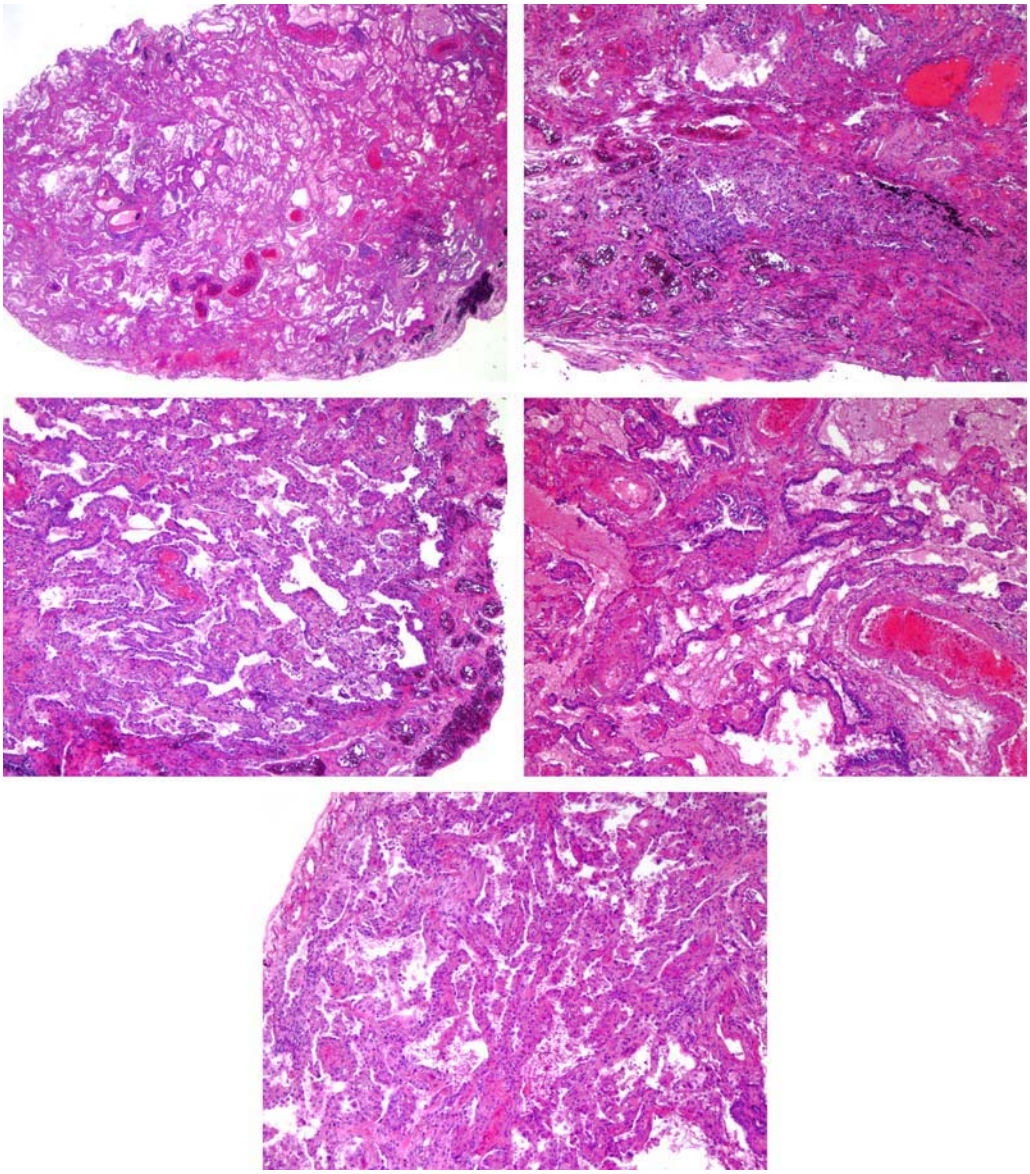
Diagnosis: Lung, open biopsy: Interstitial pneumonitis and fibrosis, nonspecific.

The lung is diffusely abnormal but in a nonspecific manner, in that the more common causes of interstitial pneumonitis or diffuse inflammatory lung disease (UIP, DIP, BPOP) are not present. Specifically, the temporal diversity of UIP is not present; the alveolar histiocytic component of DIP is not present; and the nodularity of BPOP is not present. Although this specimen could represent an early and mild stage of UIP, the active fibroblastic proliferation of that condition is not present. Organizing pleuritis with mesothelial hyperplasia is present.

Etiological considerations for this histology include drug-reaction, hypersensitivity reaction, collagen-vascular disease, quiescent resolving infectious pneumonia, and other. No honeycomb fibrosis is present beneath the pleura. No granulomas are present. No malignancy is present. No vasculitis is present. No bronchiolitis is present. There is Lamberthosis (distal extension of respiratory epithelium along alveolar walls) to suggest some prior bronchiolar scarring. Some of the process appears fibrotic and fixed, whereas other portions are inflammatory and potentially reversible.

The above observations are essentially in agreement with your interpretation. Please keep me informed of any follow-up and call if you have questions. Thank you for sending this case in consultation. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6953 (Chapter 3 – Interstitial Lung Disease)

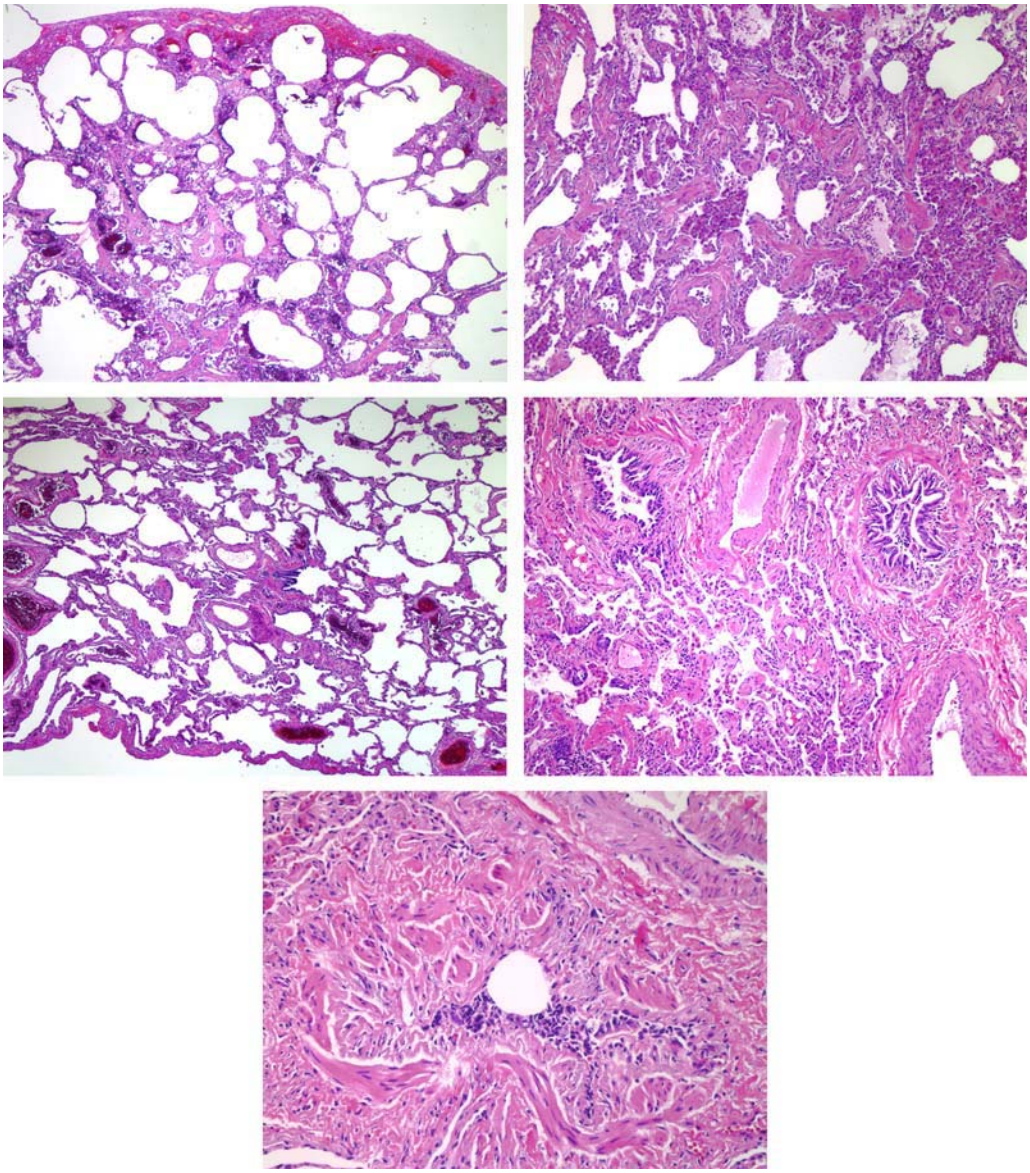
Case 6929

Diagnosis: Lung, open biopsy: Interstitial fibrosis, diffuse, extensive, cause and significance uncertain.

There is fibrous thickening of alveolar walls, as you indicate, and the thickening is quite extensive with simplification of architecture and overexpansion of alveoli. This fibrosis is old and associated with a few regions of smooth muscle hyperplasia as additional evidence of chronicity. I do not know the cause nor the significance of the fibrosis. The first consideration based on the clinical and pathological findings would be UIP, but there is no pneumonitis, no active fibrosis, and no subpleural honeycomb change. In the absence of these processes, a diagnosis of UIP cannot be made. However, UIP is possible. Some observers might describe this biopsy as NSIP, and I agree that it is nonspecific, but the lymphocytic infiltrate is minimal. There is also prominence of terminal bronchioles due to fibrosis of lamina propria and adventitia. This bronchiolar thickening might be related to the smoking of cigarettes, but I do not favor bronchiolar disease as a principal diagnosis, and it would not account for the diffuse interstitial fibrosis. Scleroderma and other collagen-vascular diseases can sometimes create interstitial fibrosis such as this without apparent pneumonitis. It is difficult to prognosticate from biopsies such as this, which do not fall into a clear pattern. In the differential diagnosis we also considered lymphangioleiomyomatosis and DIP, but we do not favor these interpretations.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6929 (Chapter 3 – Interstitial Lung Disease)

4 Histological Patterns Consistent With Pulmonary Infectious Disease

CONTENTS

INTRODUCTION

The purpose of this chapter is not to present an exhaustive list of lung infections or agents causing these infectious processes. Such an atlas has recently been published by the American Registry of Pathology and the Armed Forces Institute of Pathology in Washington, DC. Instead, examples of a select group of pulmonary infections seen in a consultative format are illustrated here. More importantly, various cases are presented to help the pathologist identify histological patterns that should trigger consideration of a diagnosis of infection of the lung even though stains for specific organisms may have been negative or, in a consultative format, unavailable. Furthermore, cases with nonspecific histological findings that could have followed infectious processes are instructive when indications for culture techniques and special stains are defined.

To emphasize the broadness of the range of histological findings that are consistent with pulmonary infection, cases illustrated in other chapters of this monograph in which infection is relevant to differential diagnoses are listed in Table 1. These cases are hyperlinked on the accompanying disk to facilitate the reader's ability to refer to them. Most of these challenging cases fall under the topic of alveolar disease. However, infectious processes involve small airways and the interstitium as well. Furthermore, granulomatous and necrotizing processes resulting from infection may involve geographic areas of lung. Finally, postinfectious remodeling of lung may not be organism-specific.

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

Table 1

Cases in Other Chapters in Which Infection is Relevant to Differential Diagnoses

Case number	*Histological pattern*	*Possible organism*
Chapter 1: Airway Disease		
6764	BO	not specified
6750	BO	viral
6904	peribronchiolitis	Pertussis
Chapter 2: Alveolar Disease		
4439	DAD	viral; Gram neg. sepsis
7022	DAD	late organizing phase sequel to viral
7146	? resolving phase of DAD	sequel to viral
6514	BPOP with neutrophils, eosinophils, granulomatous features	not specified
6513	focal, organizing fibrinous and purulent pneumonia	not specified
6679	BPOP, with purulent inflammation	not specified
6550	organizing fibrinous pneumonia; ?BPOP	not specified
6707	BOOP	resolving infection
6846	necrotizing BOOP	viral, bacterial, mycoplasma
6700	BOOP	not specified
6578	BOOP	not specified
6998	BOOP	not specified
6558	BOOP	not specified
7168	interstitial pneumonitis, bronchiolectasis with mucus plugging, lymphohistiocytic inflammation with giant cells and eosinophils	not specified
6763	organizing fibrinous pneumonia with bronchiolitis and eosinophils; ? BOOP	mycoplasma, chlamydia
6699	organizing pneumonia, subacute, with edema and eosinophils	mycoplasma, chlamydia
6863	organizing pneumonia, ulcerated respiratory epithelium with neutrophils and eosinophils	not specified
6729	organizing fibrinous pneumonia	not specified
7019	organizing fibrinous and histiocytic bronchiolitis and pneumonia	resolving infection, possible Legionella
7012	organizing pneunonia with interstitial fibrosis, ? resolving BPOP or late resolving phase of DAD	not specified
6916	consistent with subacute and COP	not specified
6923	? unusual organizing pneumonia	resolving viral, mycoplasma, Legionella

(continued)

Table 1 *(continued)*
Cases in Other Chapters in Which Infection is Relevant to Differential Diagnoses

Case number	*Histological pattern*	*Possible organism*
Chapter 3: Interstitial Lung Disease		
6800	UIP; BOOP, active	not specified
7061	diffuse interstitial pneumonitis, interstitial and alveolar edema	viral
6953	Interstitial pneumonitis and fibrosis, nonspecific, quiescent resolving infection	not specified
Chapter 5: Granulomatosis		
6804	Wegener's granulomatosis intracellulare	mycobacterium avium
6518	consistent with Wegener's granulomatosis, tumefactive form	blastomycosis
6829	consistent with Wegener's granulomatosis	mycobacterial, fungal
	necrotizing granulomatous nodule with prominent	mycobacterial, fungal dirofilarial, nocardial,
6937	squamous metaplasia and vascular thrombosis	actinomycotic, aspergillosis
7072	necrotizing granulomatous inflammation	aspergillus, tuberculosis, other fungal
6548	consistent with lymphomatoid granulomatosis American blastomycosis	fungal, such as North
6623	consistent with sarcoidosis	schistosomiasis, mycobacteria, histoplasmosis
6540	compact granulomas and granulomatous inflammation, extensive	atypical mycobacterial, aspergillus
7030	few compact noncaseating granulomas in bronchial mucosa	myobacterial, fungal
Chapter 7: Miscellaneous Pulmonary Disease		
6687	interstitial lymphocytic infiltrate with fibrin, vacuolated histiocytes, and rare, poorly formed granulomas microgranulomatous	unusual, such as psitticosis
6924	peribronchiolitis and pneumonitis	aspergillus
6950	lymphcytic interstitial infiltrate and fibrinous pneumonia chlamydia	unusual: viral, mycoplasma,
7013	histiocytic-eosinophilic infiltrate	schistosomiasis
6962	compact granuloma with focal slight central necrosis;eosionphilic infiltrate in lamina propria Whipple's disease,	not specified
7004	proliferation of clear epithelioid cells with marked PAS-positivity	mycobactium avium intracellulare

BO, bronchilitis obliterans; DAD, diffuse alveolar damage; BPOP, bronchiolitis with patchy organizing pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; COP, cryptogenic organizing pneumonia; PAS, periodic acid-Schiff.

DIFFERENTIAL DIAGNOSES OF HISTOLOGICAL PATTERNS CONSISTENT WITH INFECTION

- Hypersensitivity reaction
- Rheumatoid nodule
- Beryllium disease
- Sarcoidosis
- Collagen-vascular disease
- Chronic eosinophilic pneumonia
- Drug reaction
- Asthma
- Aspiration
- Graft-vs-host disease

SUGGESTED READINGS

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LETTERS

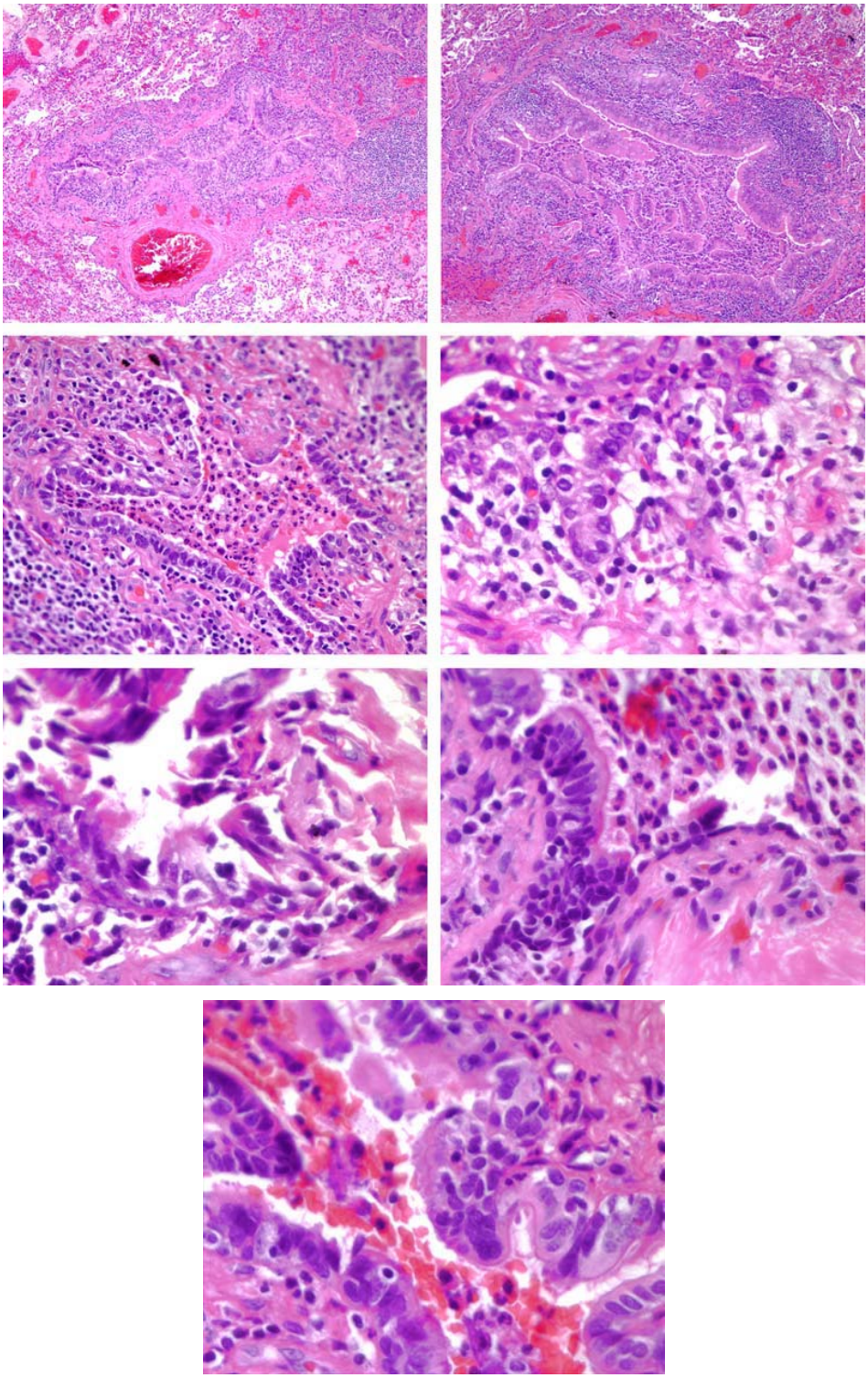
Case 7008

Diagnosis: Lung, open biopsy: Diffuse panbronchiolitis, with associated acute bronchiolitis and epithelial cell necrosis of probable infectious etiology.

I am very much in agreement with your interpretation that this represents diffuse panbronchiolitis complicated by infection. The marked and cellular thickening of all layers of the bronchial wall associated with clusters of prominently vacuolated histiocytes in the lung characterizes diffuse panbronchiolitis. There is bronchiectasis both radiographically and pathologically, but I would view this as part of diffuse pan-bronchiolitis and not make a second diagnosis. However, the epithelial cell necrosis in the bronchiolar epithelium is not necessarily a part of the process. This, in conjunction with neutrophils in the lumens and neutrophils percolating through the epithelium, make me suspicious that there is an infection complicating the diffuse panbronchiolitis. The infection probably is viral by virtue of the individual cell necrosis, although bacteria or chlamydia cannot be excluded. I detect no fungi. Multinucleated epithelial cells in two bronchi made me question measles, which is statistically unlikely, but to be considered if the patient had an immunosuppressed state. Individually necrotic epithelial cells made me also consider adenovirus. More common viruses would include parainfluenza or respiratory syncytial virus.

Thank you for sharing this very instructive case with us. With all best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7008 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

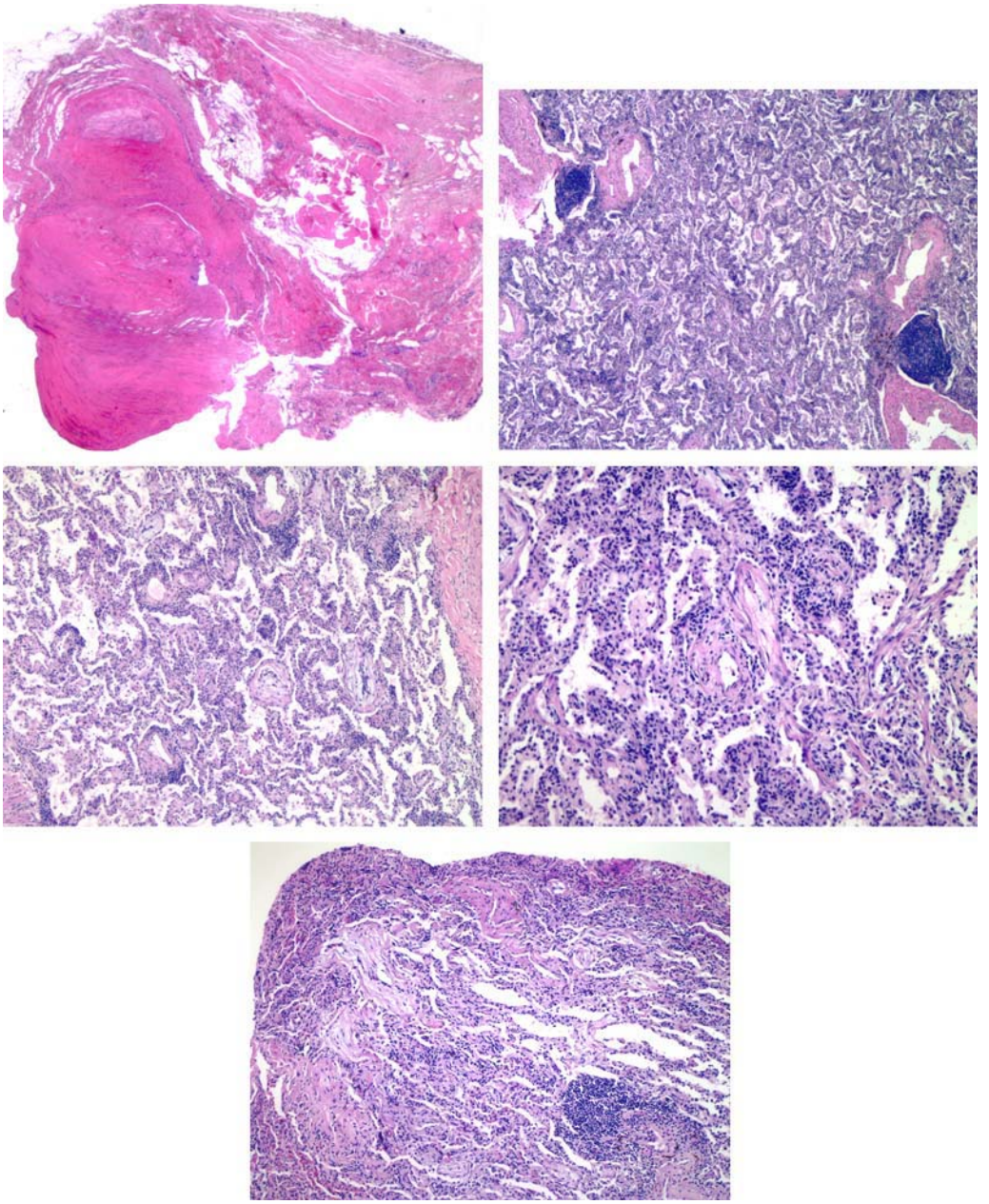
Case 4426

Diagnosis: Lung, open biopsy: Focal organizing pneumonia with lymphocytic interstitial pneumonitis-like reaction, cause undetermined, ? resolving infection, ? hypersensitivity reaction.

Lymphoid hyperplasia involves the bronchus-associated lymphoid tissue and extends into alveolar walls in a manner similar to a recently reported Case Record (Case 23–1993, N Engl J Med 1993; 328:1696–1704). The major question is whether this patient has a primary lymphoid hyperplasia as might be seen with viral infection (EBV, HIV, other), or whether it represents a less specific rection to a prior bronchiolar infection or hypersensitivity reaction. I favor the latter because of the associated alveolar inflammation and fibrosis. I agree that the process is benign. Little scarring has yet occurred. One slide consists of a separate pleural hyaline nodule.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 4426 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

Case 6726

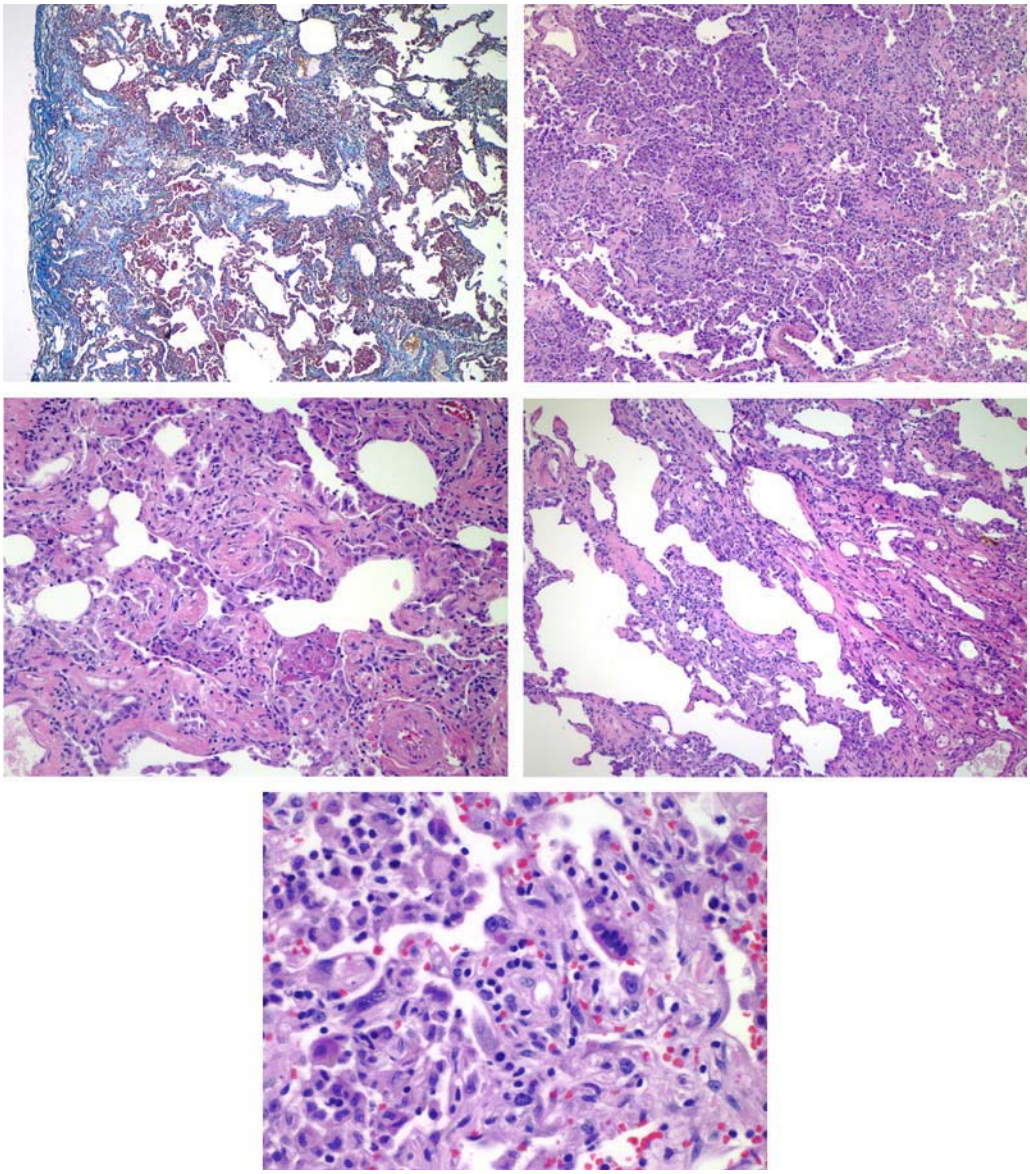
Diagnosis: Lung, open biopsy: Subacute organizing pneumonia (OP) with occasional large epithelial cells, cause undetermined.

The lung has lobules with organizing fibrin and histiocytes in alveoli associated with enlarged and occasionally multinucleated epithelial cells in alveolar ducts and alveoli, a lymphocytic infiltrate, and patchy fibrosis. There is also old interstitial fibrosis of modest degree beneath the pleura (trichrome stain), the significance of which is uncertain but probably not significant clinically for the current disease.

The cause of the subacute OP is not apparent. From a pathological standpoint, I would favor an infection and include viruses that occasionally cause multinucleated epithelial cells (for example, respiratory syncytial virus, adenovirus, parainfluenza, parvovirus). I cannot exclude hypersensitivity reaction. The pathology is not characteristic for bronchiolitis obliterans organizing pneumonia (BOOP) and is not that of usual interstitial pneumonitis (UIP). Blood vessels are normal.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6726 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

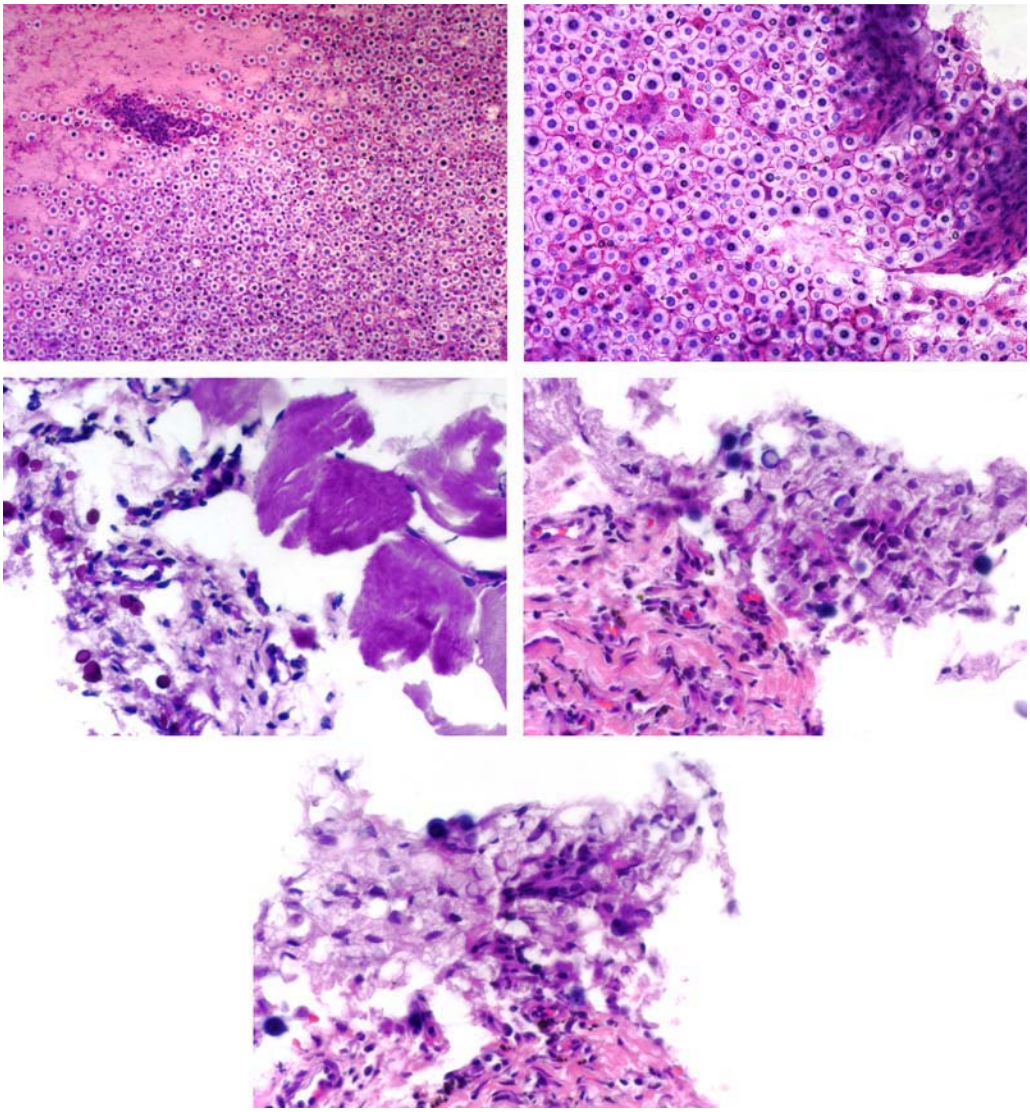
Case 6986

Diagnosis: Lung, needle aspiration biopsy: Cryptococcoma.

A small tissue fragment has clear cells with vacuolar cytoplasm. In the differential diagnosis of clear cell lesions is fungal infection and particularly fungal infection due to cryptococcus. Your special stains and smears nicely show the yeast with halos typical of cryptococcus. The sheets of cryptococcus on the smears are unusual in my experience and suggest that there was a necrotic area filled with fluid or pus and exuberant growth of cryptococcus. Immunosuppressed state might be considered. No malignant cells are present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. I have retained one slide and one smear and hereby return the remainder. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6986 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

Case 7154

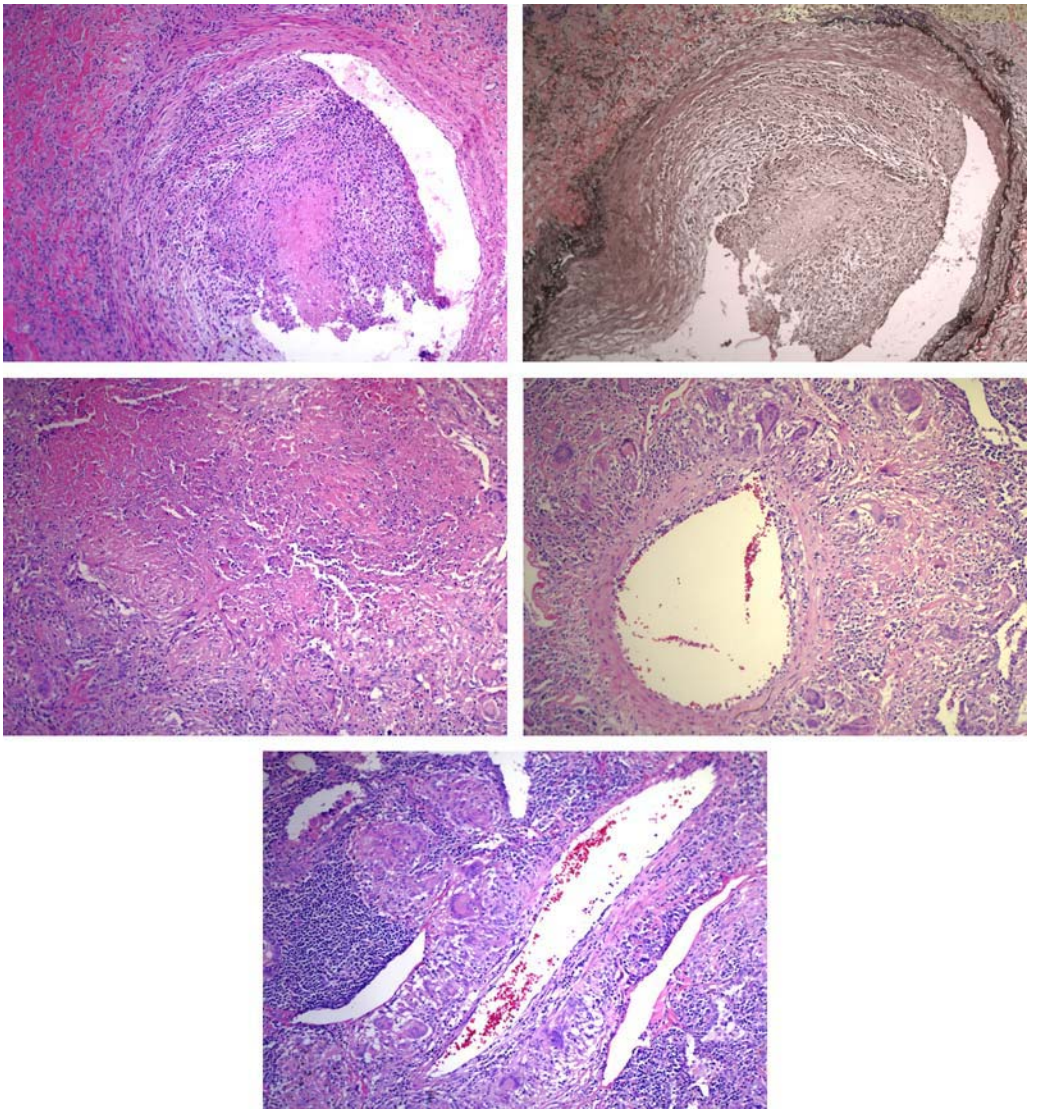
Diagnosis: Lung, open biopsy: Compact granulomas with focal necrosis and granulomatous vasculitis, forming nodules, ? infection, ? necrotizing sarcoidal granulomatosis, ? other.

This case is challenging. In favor of tuberculosis or other mycobacterial or fungal disease is the microfocal fibrinoid necrosis in parenchyma surrounded by multinucleated histiocytes and the clinical history of prior treatment for a positive PPD. In favor of necrotizing sarcoidal granulomatosis is the extensive granulomatous involvement of large arteries (elastic stain) and veins. Fibrinoid necrosis of some large vessels is atypical for either condition and raises the possibility of Wegener's granulomatosis (WG), but the numerous compact granulomas of tuberculoid or sarcoidal type are against WG. Serological studies for WG can be performed if clinically indicated.

Your silver and acid-fast stains show no organisms. I repeated additional stains for organisms. Acid-fast, silver, periodic acid-Schiff, mucicarmine, and Brown-Hopps stains on two bocks of tissue show no organisms. Nevertheless, I am still suspicious of an infectious etiology.

Thank you for referring this case in consultation. Please keep me informed of any follow-up, and call if you have questions. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7154 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

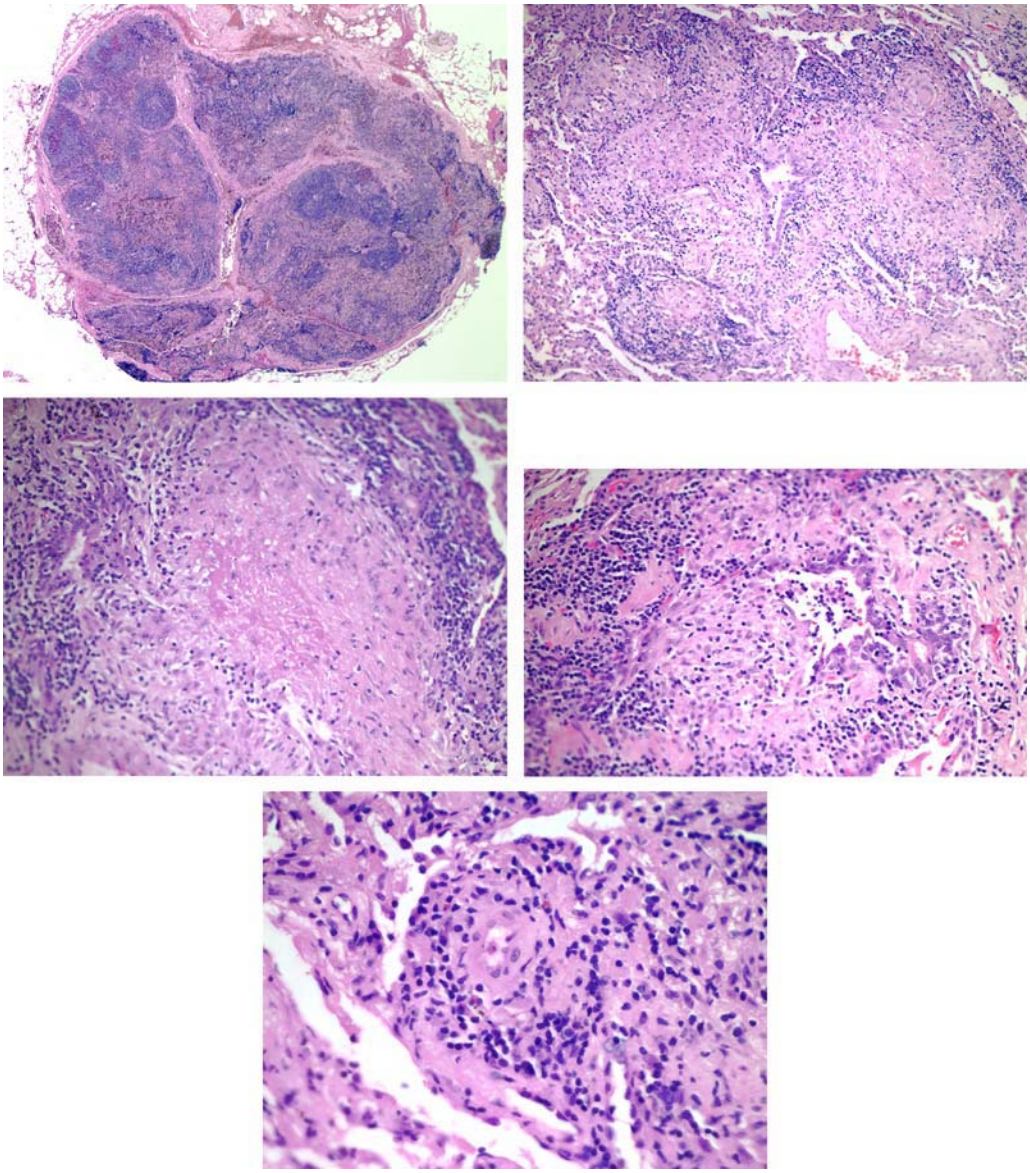
Case 7018

Diagnosis: Lung, open biopsy: Granulomatous bronchiolitis and pneumonitis, cause undetermined, ? infection, ? aspiration, ? hypersensitivity reaction, ? other.

The principal pathology consists of ill-defined granulomas, which involve and even destroy some bronchioles and also are distributed in alveoli. There is a moderate lymphocytic infiltrate and a rare eosinophil. Sarcoidosis enters into the differential because some of the granulomas are relatively discrete and juxtabronchiolar, but the clinical history of disease confined to one region of one lobe and the luminal occlusion by the granulomas would be highly unusual for sarcoidosis. The hilar lymph nodes are devoid of granulomas; this is against sarcoidosis but does not exclude it. Infection is possible, particularly because there is a small amount of necrosis. Mycobacteria and fungi are the leading candidates, including atypical mycobacteria. We had a recent similar case of atypical mycobacerial bronchiolitis due to a contaminated hot tub. I understand that your stains for organisms are negative. If this is not infection, the changes could represent aspiration or hypersensitivity. Aspiration, including that which has caused bronchial obstruction, could produce this pathology in one lobe. Hypersensitivity reaction would be unusual as a localized density. The character of the granulomas would fit that diagnosis, but the necrosis would be unusual.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7018 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

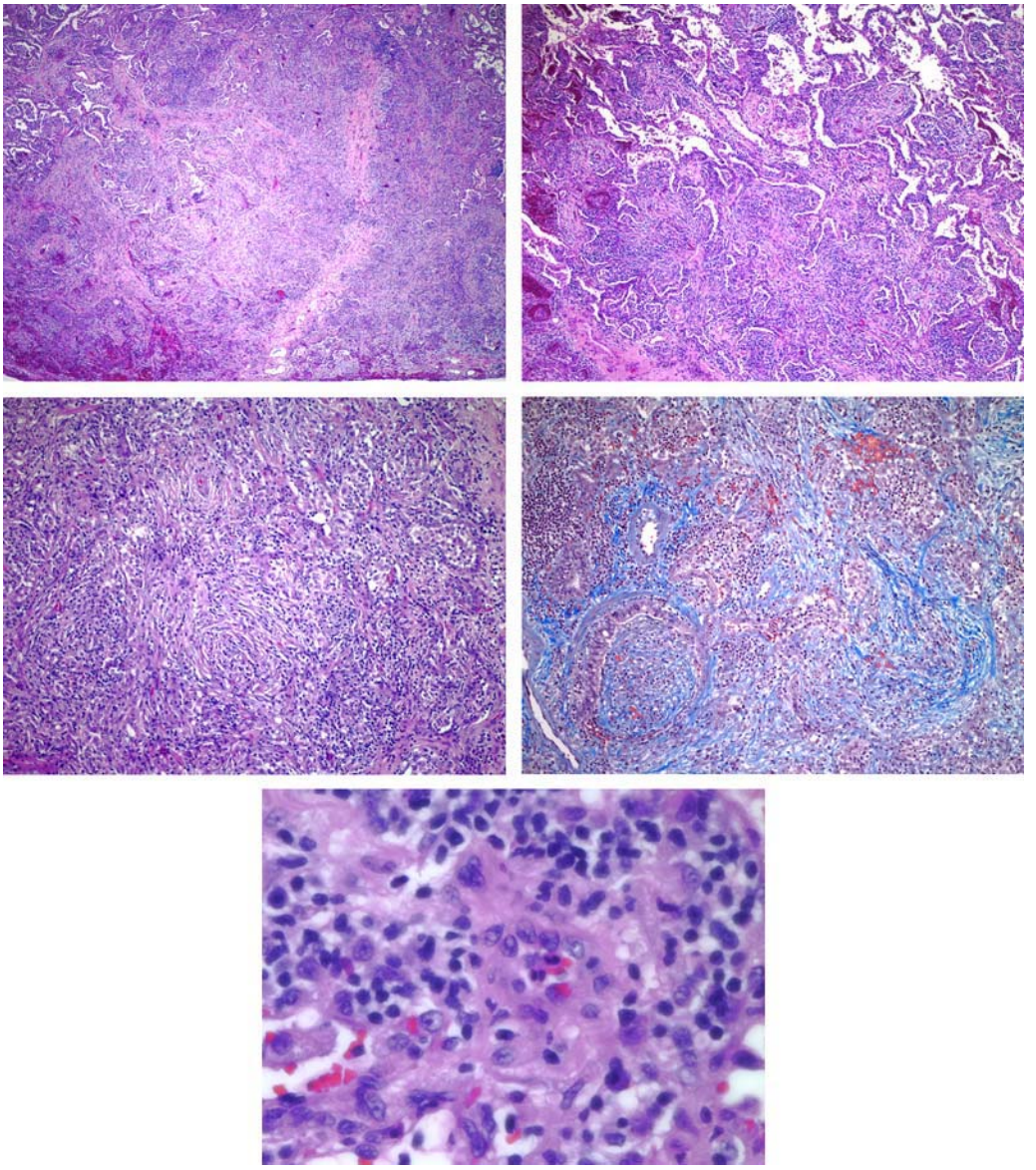
Case 7056

Diagnosis: Lung, wedge resection: OP with granulomatous features and rare eosinophils, cause undetermined.

The principal process is an OP with fibrohistiocytic proliferation that fills conducting airways and alveoli (trichrome stain). If this histology produced one or a small number of tumefactive nodules in the lung, I would make a diagnosis of inflammatory pseudotumor of OP subtype. If this is multifocal with many small nodules that wax and wane, a clinical-pathological diagnosis of BOOP would be appropriate. The granulomatous features are generally not found in OP as seen with inflammatory pseudotumor and raise the possibility of an infectious cause. Mycobacterium avium intracellulare and other organisms have been found in cases of inflammatory pseudotumor. The presence of eosinophils raises yet another diagnostic possibility, that is, WG producing an inflammatory pseudotumor. Serum assay for antineutrophil cytoplasmic antibody could be accomplished. I considered necrotizing sarcoidal granulomatosis but do not favor this intepretation. I do not believe this is a lymphoproliferative disorder, and thus I do not believe this is malignant lymphoma of lymphomatoid granulomatosis type, even though other clinical features suggest that the patient might have a lymphoproliferative process. I am obtaining additional stains for completeness and will report this in an addendum when the slides are completed.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7056 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

Case 4424

Diagnosis: Lung, excision of nodule: Cryptococcoma.

This fibrocaseous nodule has the appearance of an old infectious granuloma now hyalinized. Your silver stain discloses yeast. Interpretation is difficult because round spherules of calcium also take the silver stain. I repeated these stains from tissue which you kindly provided. The yeast stain positively with methenamine silver, Fontana Masson, and mucicarmine. On the PAS stain, one can see retraction of a capsule as the mucin adheres to the yeast wall. The morphology indicates Cryptococcus.

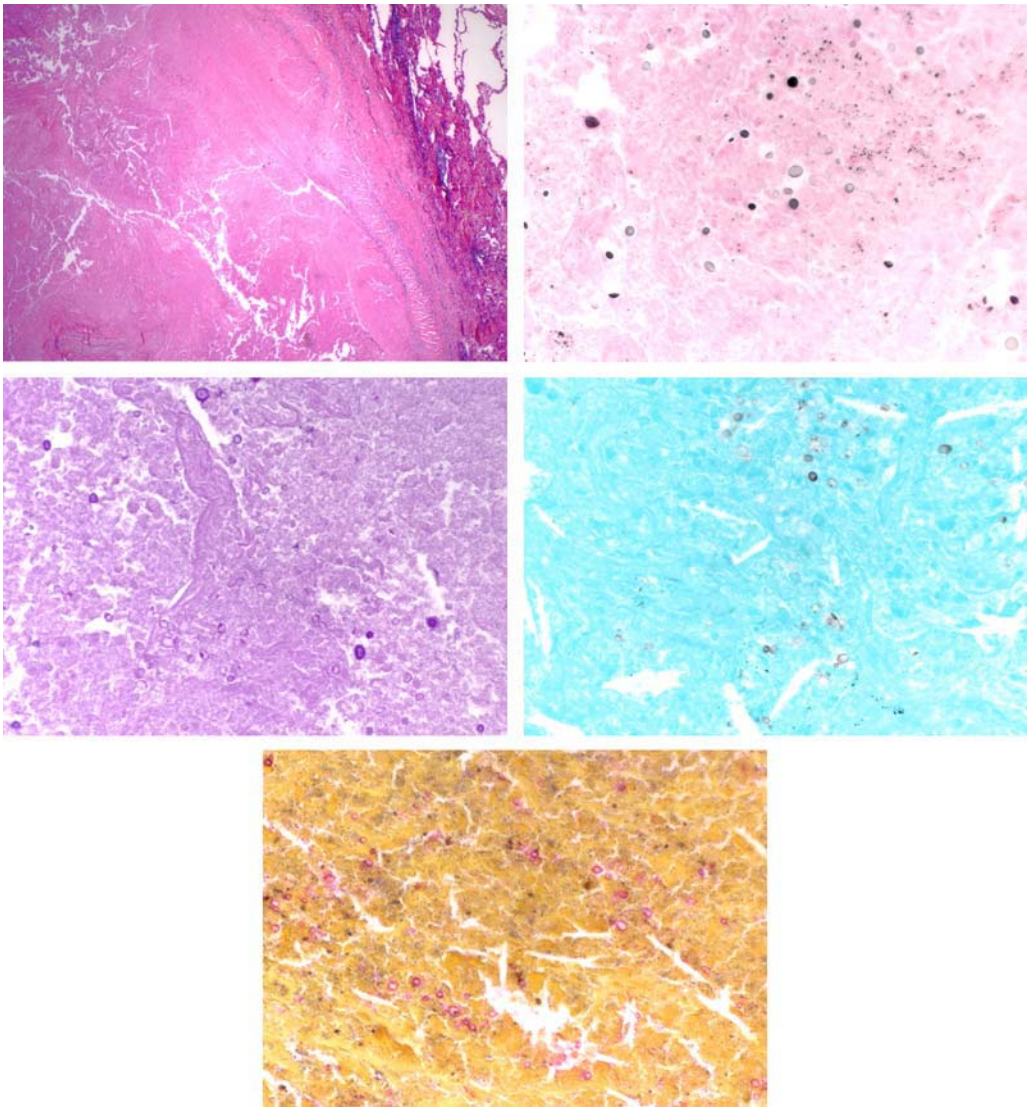
The histology of cryptococcal disease depends on duration and host response. An unusual form in the lung and elsewhere are fibrocaseous nodules of residual disease previously undetected. This patient seems to fit into that category.

Thank you for referring this case in consultation. Your special stains and paraffin blocks are hereby returned. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D

Reference:

Gordon SM, Gal AA, Amerson JR. Granulomatous peritoneal cryptococcomas. An unusual sequela of disseminated cryptococcosis. Arch Pathol Lab Med 1994;118:194–195.



Case 4424 (Chapter 4 – Histological Patterns Consistent With Pulimonary Infectious Disease)

Case 6587

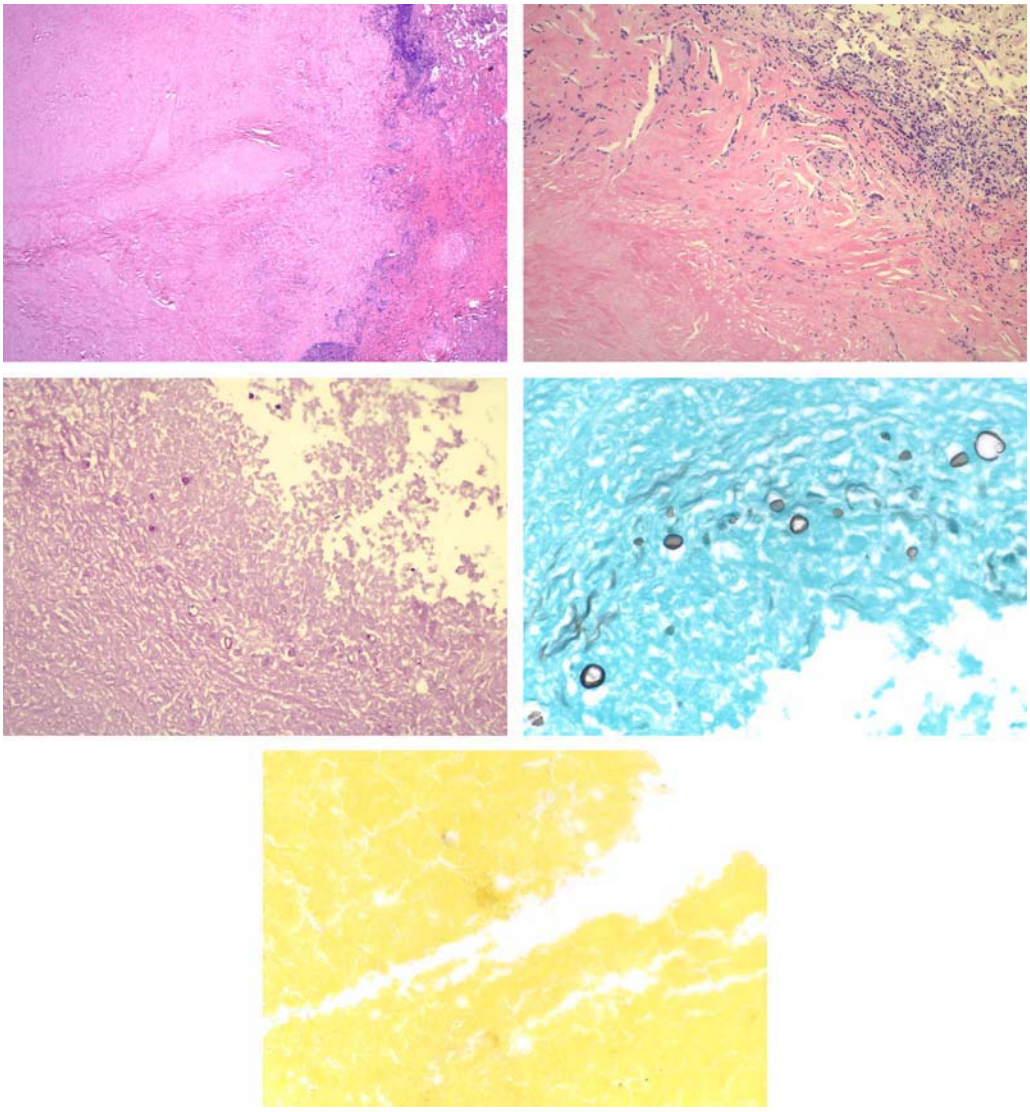
Diagnosis: Lung, wedge resection: Fungal granulomatous nodule, ? coccidioidomycosis, ? other.

A necrotic and hyalinized nodule is surrounded by granulomatous inflammation. Your periodic acid-Schiff stain shows a multinucleated histiocyte which contains an ovoid structure with a distinct capsule and internal chromatin-like material indicative of an organism.

I have obtained additional special stains. At the edge of an area of necrosis, several large yeast are visible on our stains with silver and periodic acid-Schiff. Because of their size, I favor coccidiodomycosis. However, I find no internal sporulation, so I cannot make that diagnosis with certainty. Degenerate yeast of cryptococcus and North American blastomyces can also occasionally achieve this size. Mucicarmine stain is not decisive. One could attempt to search for endosporulation by making additional sections on any tissue not yet embedded or deeper sections on other blocks of tissue in paraffin.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. Your original periodic acid-Schiff and acid-fast stains are returned as well as our silver stain. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6587 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

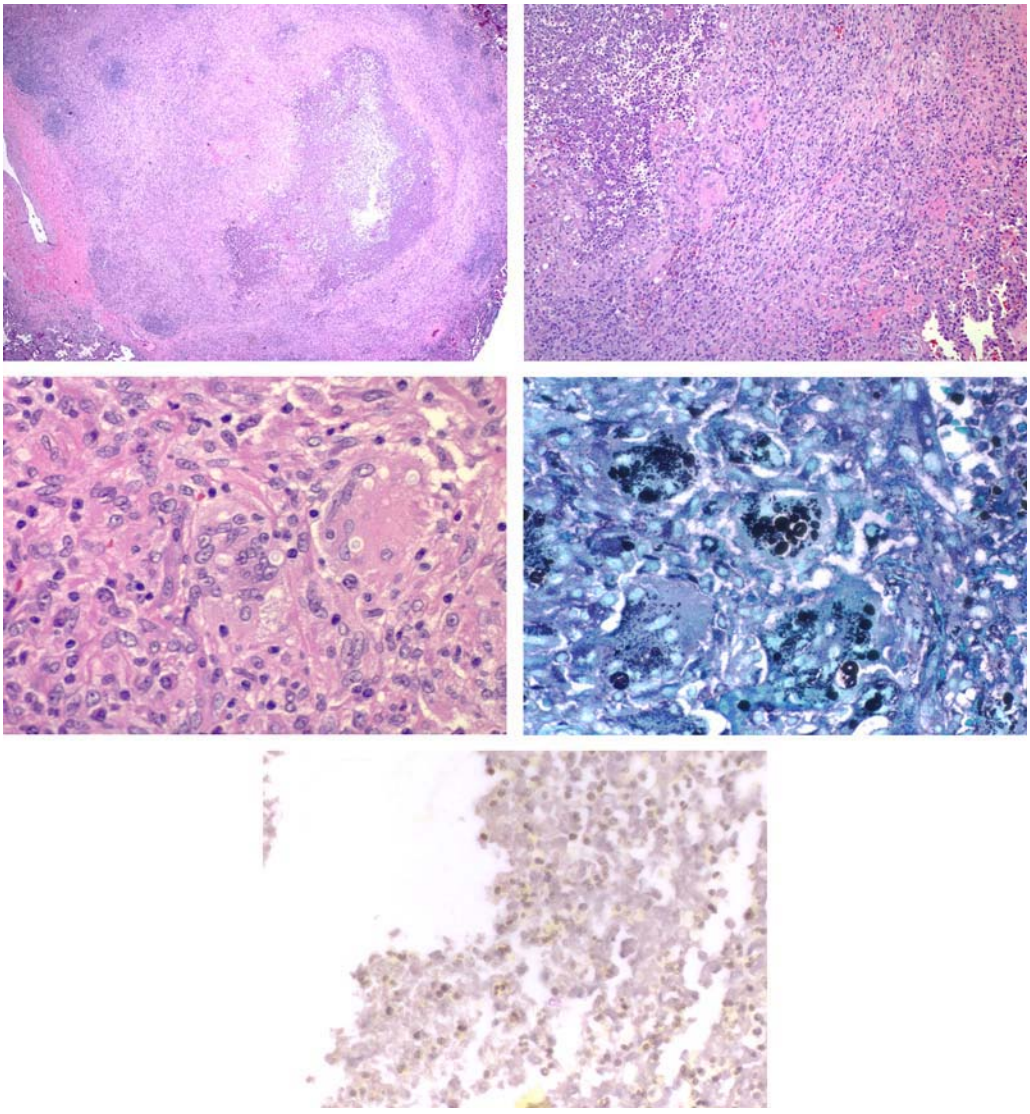
Case 6906

Diagnosis: Lung, resection of nodule: Cryptococcoma.

The nodule has a purulent center and a granulomatous rim with fibrosis. Many multinucleated histiocytes lie within the granulomatous inflammation, and some of these contain large vacuoles with distinct circular structures representing yeast. To prove this interpretation I performed some histochemical studies. The yeast stain with periodic acid-Schiff and silver, and there is also a mucus capsule around many of them with mucicarmine stain. Thus, these yeast are cryptococci, and the lesion is a cryptococcoma with purulent necrosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. Your slides and blocks are enclosed under a separate cover. I have also included the positive mucicarmine stain. This is a confirmation of my earlier telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6906 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

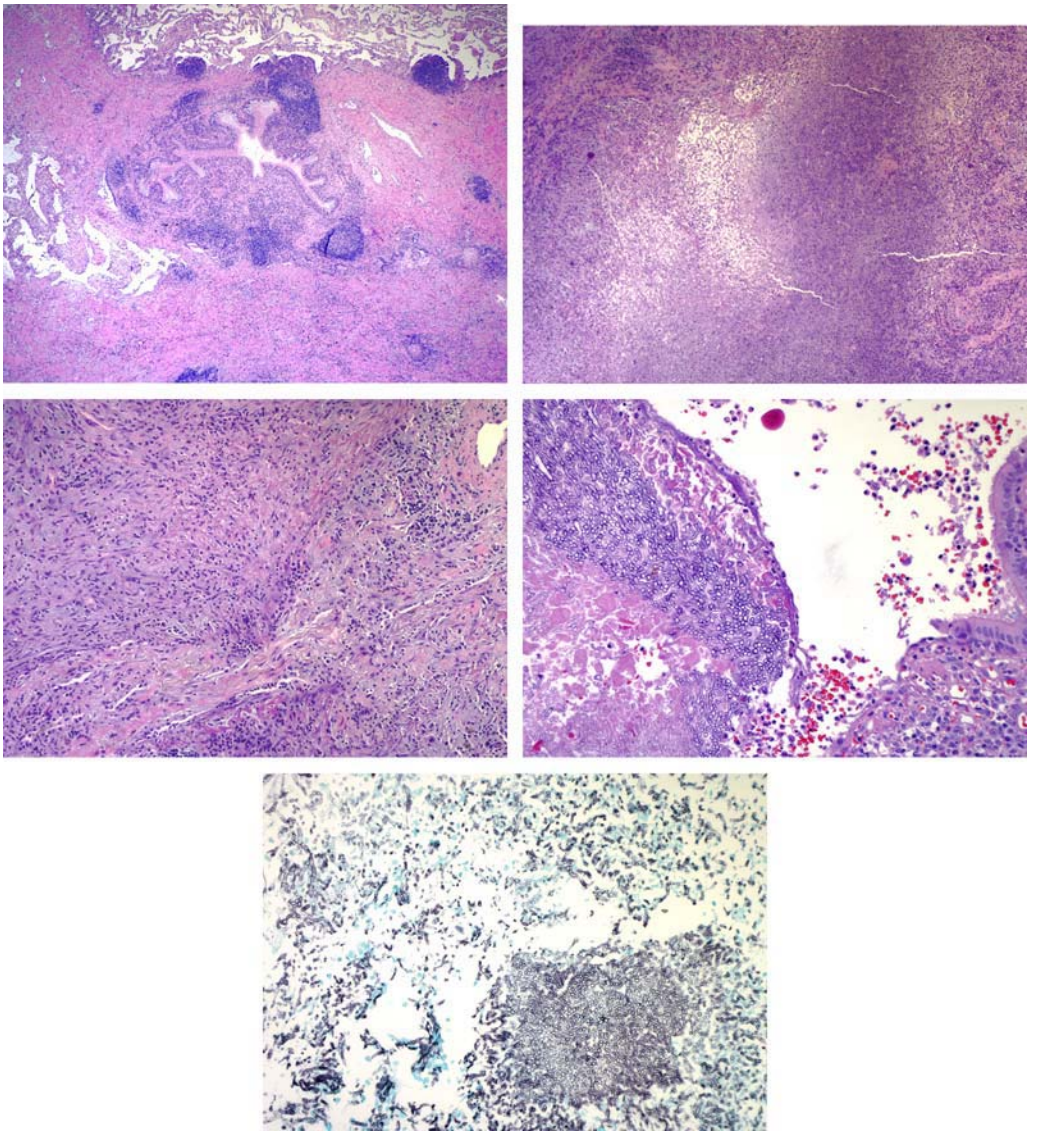
Case 6949

Diagnosis: Lung, wedge resection: Bronchiectasis, with extensive sclerosis, mucus plugging, abscess formation, acute bronchopneumonia, intrabronchial aspergillus, and single aspergillus granuloma.

The extensive scarring around an abscess and ectatic bronchioles suggest that the original process was bronchiectasis, which has now proceeded to abscess formation as well as acute purulent bronchopneumonia with necrosis. The cause of the original bronchiectasis is unclear. Some of the bronchioles are necrotic, and we considered bronchocentric granulomatosis or allergic bronchopulmonary aspergillosis as diseases related to bronchiectasis. In the process of searching for aspergillus, we found one single granuloma with a colony of aspergillus (silver stain) surrounded by multinucleated histiocytes and two bronchioles filled with pus and aspergillus. Aspergillus granuloma is an infrequently encountered form of aspergillus and implies relatively good host response. Invasive aspergillosis is not present, but in the context of abscess elsewhere in the slide, I would be concerned that this could have progressed to a more invasive form of aspergillus infection if it had not been removed. I believe the above is essentially in agreement with your interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6949 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

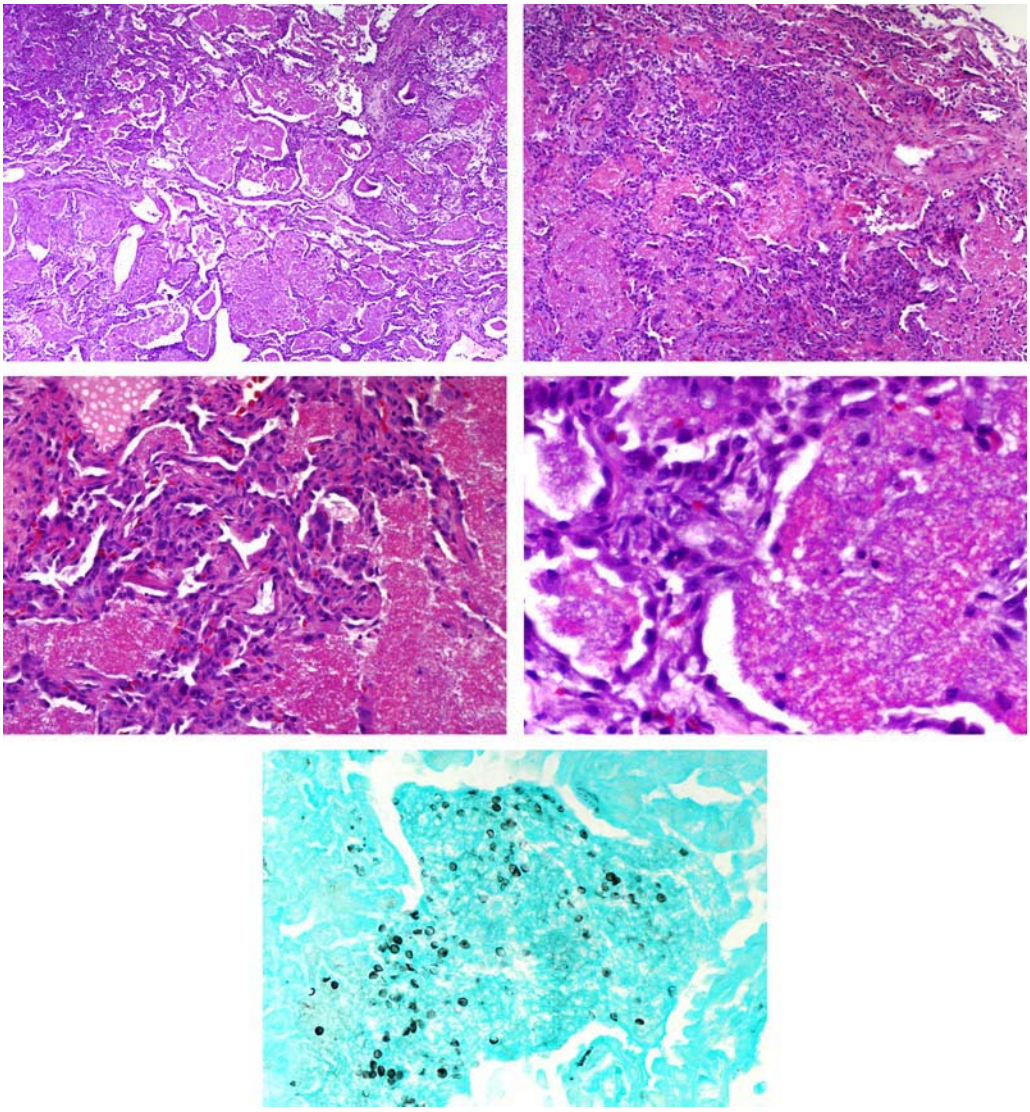
Case 7092

Diagnosis: Lung, open biopsy: Pneumocystis carinii pneumonia.

Alveoli are filled and lobules consolidated by frothy eosinophilic fluid. Within this material on the slides stained with hematoxylin and eosin are blue dots, which represent the trophozoite form of pneumocystis. Your silver stain shows many of the spherules of pneumocystis. There is a moderate interstitial lymphocytic response in this pneumonia. The frothy fluid represents fibrin and immunglobulins as part of the pneumonia. We searched for other diseases which might appear in a patient with Pneumocystis carinii pneumonia and reported HIV infection. We find no cytomegalovirus, no herpesvirus, no fungi, no toxoplasma, and no Kaposi's sarcoma.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7092 (Chapter 4 – Histological Patterns Consistent With Pulmonary Infectious Disease)

5 Granulomatosis

CONTENTS

INTRODUCTION

The diagnosis of Wegener's granulomatosis (WG) began with a clinicopathological triad of necrotizing granulomatous inflammation of the upper and lower respiratory tracts, angiitis, and necrotizing glomerulonephritis based on tissue examined at autopsy. However, only one-half of the patients in the initial series of Godman and Churg had the complete triad. Limited and ulcerative or tumefactive forms can occur in many organs. Initial biopsy diagnosis of established disease was followed by the early histological diagnosis of limited disease. This was followed by diagnosis on the basis of anti-neutrophilic cytoplasmic antibody (ANCA) without tissue confirmation. Today, therapy prevents most cases from progressing to multi-organ involvement. The most common cause of death is renal failure resulting from glomerulonephritis, and this can occur with days or even hours, so the pathological evaluation of a lung biopsy for WG is a medical emergency. Pulmonary and cardiovascular complications of the disease are much less common causes of morbidity or mortality. The evolution of the ANCA test has provided substantiating evidence for cases with equivocal histology and for separation of WG from microscopic polyangiitis and from other forms of disseminated vasculitis.

WEGENER'S GRANULOMATOSIS

Ground Rules

- Affects all anatomic compartments (vessels, airways, interstitium, pleura)
- Thus, not just a vasculitis
- Variety of pulmonary symptoms (hemoptysis, cough, dyspnea)

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

- Panoply of radiographic findings: airspace, interstitial, nodular)
- Can pathology integrate this variety?

General Approach to the Lung Biopsy

- Necrosis of collagen, but not infarction
- Granulomatous inflammation, but no granulomas (always exclude infection)
- Microabscesses, but not bronchopneumonia
- Inquire as to involvement of other organs
- Evaluation of ANCA and ANA
- Medical emergency if diffuse inflammation or hemorrhage; but not so for solitary nodule or bronchiolitic forms

WG **(6804)** has many histopathological facets in the lung. It can involve the various anatomic compartments: arteries, veins, capillaries, bronchioles, interstitium, and pleura. The intrinsic lesion is necrosis of collagen, including collagen in vascular walls, which may be mediated by mechanisms that do not necessarily occur in other forms of vasculitis or ischemia; however, the vasculitis receives so much attention that pathologists are reluctant to make the diagnosis in its absence. Subsequent writings dealt with the concept of superficial mucosal necrosis of bronchi as well as mucosa of the nasal sinuses, larynx, and trachea and with delineation of capillaritis and its relationship to diffuse hemorrhage. Bronchioles may be selectively involved, either in a relatively specific form of mucosal necrosis resembling bronchocentric granulomatosis **(7072)** or in a nonspecific healing form of bronchiolar damage resulting in bronchiolitis obliterans (BO) **(6471)**.

Variant (Nonvasculitic) Anatomic Forms in the Lung

- Capillaritis with hemorrhage **(6541)**
- Hemosiderosis (treated or resolved) **(6911)**
- Purulent pneumonia (microabscesses) **(6829)**
- Bronchiolitis with pneumonia (bronchiolitis obliterans organizing pneumonia [BOOP]-like) **(6905)**
- Bronchocentric granulomatosis (BCG)-like **(7072)**
- Eosinophilic pneumonia **(7177)**
- Bronchiolitis fibrosa (treated) **(6905)**
- Usual interstitial pneumonitis (UIP)-like **(6900)**
- Lipid pneumonia **(6998)**
- Giant cell pneumonia **(7154)**
- Inflammatory pseudotumor (IPT)-like **(6518)**
- Cavitated tumor

Variant nonvasculitic anatomic forms of WG in the lung can be tied together conceptually and considered, in part, to be stages in the natural history of the disease based on principles of general pathology as well as on the anatomic compartment involved in the lung. Extensive neutrophilic infiltrates and microabscesses were described years ago; however, their significance in the absence of necrotizing vasculitis had been uncertain, although made less so after the systematic application of ANCA.

Natural History (Histogenesis) in the Lung Over Time

- Collagen necrosis
- Microabscesses or vasculitis

- Palisading granuloma
- Geographic necrosis with palisading histiocytes
- Bronchiolitis fibrosa with hemosiderin
- Nodular or interstitial fibrosis with hemosiderin
- Inflammatory mass
- Cavitation

Vasculitic Forms

Vasculitic forms vary in appearance depending on the size of blood vessel involved and on the stage of progression of disease. The relationship between capillaritis and more obvious forms of necrotizing arteritis and venulitis remains unclear because many cases with capillaritis do not have arteritis or phlebitis. Whether capillaritis in the absence of arteritis or phlebitis has a particular significance has not been quantified. By current criteria, it is part of WG, but these patients tend to be quite ill and the disease particularly fulminant. This occurrence is not surprising when one considers that the patients have diffuse pulmonary hemorrhage. It has always been popular to categorize vasculitides by the size of blood vessel involved. WG does not fit this mold well because vessels from the size of large elastic arteries down to capillaries and even veins may be involved.

Arteritis (or Phlebitis) Over Time

- Fibrinoid necrosis
- Leukocytoclastic arteritis
- Multinucleated histiocytes in arterial wall (giant cell arteritis)
- Lymphocytic (inactive, nonnecrotizing) arteritis
- Focal mural scars

Some of the reactions are diagnostic of hyperacute or active disease, whereas others are suspicious for residual or treated disease or spontaneous resolution. Muted forms of untreated WG occur as the superficial protracted phase in the upper airways or in limited forms in the lungs and other organs. The chronic forms may have subtle forms of vasculitis, necrosis, neutrophilic infiltrate, and scarring. Effective treatment leads to distinctive as well as nonspecific scarring, which is permanent. A longitudinal and histological evaluation of untreated classic WG is unlikely to occur now that there is effective therapy. On the other hand, the relation between atypical forms of WG and other ANCA-positive disease still requires biopsy and remains relatively unexplored.

COLLAGEN NECROSIS

The serological identification of ANCA has provided a noninvasive way to suspect or confirm the diagnosis, but a positive ANCA *per se* does not mean WG or vasculitis. Thus, it might be expected that vasculitis need not be found in every patient. The nondetection might be due to sampling, to the stage of disease, to effects of treatment, or to its absence. Because so many other facets of WG are now appreciated, the absence of necrotizing or inflammatory arteritis or phlebitis need not dissuade one from the diagnosis. However, necrosis of epithelium and, particularly, necrosis of collagen are seen in virtually all of the forms. Their purest representation lies in the superficial protracted phase, where collagen of lamina propria beneath epithelium is necrotic in bronchial or sinus mucosa in the absence of detectable vasculitis. Fresh hemorrhage and rare multinucleated histiocytes are important ancillary findings in such cases. If this approach is accepted, then one

can conceive that the primary event is necrosis of collagen, whether that collagen is in lamina propria of mucosa, wall of blood vessel, wall of bronchus, alveolar wall, or pleura.

In the most florid form of collagen necrosis, one finds geographic areas of basophilic granular material which has lost any fibrillar component, even with elastic or trichrome stains. Therefore, the absence of the fibrillar component is different from what one sees in some cases of tuberculosis or pulmonary infarction, where one may find preserved elastica, suggesting that the collagen necrosis might be a primary event. This form of collagen necrosis without cause was described by Dr. Robert Fienberg as pathergic necrosis.

GRANULOMATOUS INFLAMMATION

The histiocytic inflammation **(7177)** in WG can at times be puzzling and yet helpful in diagnosis. One of the less appreciated forms is diffuse granulomatous tissue, in which sheets of histiocytes fill alveoli and may form destructive masses. When this pattern occurs in the absence of other features, the inflammation may be dismissed as resulting from bronchial obstruction, which may indeed be a mechanism for the change; but there may also be some other mechanism related more directly to histiocytes. The same considerations apply to the rare case with the picture of endogenous lipid pneumonia. Similar widespread histiocytic inflammation accounts for the development of granulomatous bronchiolitis and granulomatous pleuritis.

The palisading granuloma **(7177)** is a term used for microfocal necrosis bounded by multinucleated histiocytes. The palisading granuloma is presumably an early lesion. It may have fibrinoid necrosis in its center without any inflammation or have neutrophils as the only inflammatory component; furthermore, it is small, of the order of a tubercle. The palisading granuloma may be small enough to be found within the wall of a large blood vessel. A well-developed and complete palisade of histiocytes is usually not apparent. In sinus mucosa or soft tissue, the palisading granuloma is the expected early form of granulomatous inflammation. The palisading granuloma does not have the solid aggregate of histiocytes typical of a granuloma of sarcoidal or tuberculoid type, and the two types are very distinct. The presence of a granuloma of sarcoidal or tuberculoid type is extremely helpful because it virtually excludes WG unless there is a coexistent sarcoidosis or aspiration, two relatively common diseases which have been seen in combination with WG.

A large necrotic nodule with eosinophilic necrosis surrounded by histiocytes is another item altogether. This is a form of WG that can persist for years with little change. It is encountered in patients with few symptoms, who on serial chest X-ray are found to have an expanding tumor or multiple nodules. This form is very difficult to distinguish from old tuberculosis, atypical mycobacterial infection, histoplasmoma, dirofilaria or rheumatoid nodule if there are no other distinguishing features, and in chronic WG there may be no other such features. Although this histology is sometimes described generically as a necrotic granuloma, compact tubercles are not present in the rim; nor are they present elsewhere in the lung. This histology is encountered in the limited form.

Granulomatous Forms Over Time

- Diffuse granulomatous tissue
- Granulomatous bronchiolitis
- Granulomatous arteritis and phlebitis
- Palisading granuloma
- Pathergic necrosis with palisading histiocytes
- Rheumatoid nodule-like **(6937)**
- Old fibrous scar with palisading histiocytes
- Never granulomas of sarcoidal or tuberculoid type

Diffuse Granulomatous Tissue

- Transformed histiocytes, epithelioid histiocytes in sheets, poorly defined aggregates
- Relatively clear cytoplasm
- Focal palisading
- Occasional multinucleated histiocytes
- No necrosis
- No nodularity

IMPORTANT EXTRAPULMONARY FORMS

The most serious organ involvement is the necrotizing glomerulonephritis, which is the principal cause of death in WG and the facet of the disease to be avoided by the rapid diagnosis based on serology or biopsy of other organs, particularly the lung, sinuses, or skin. Cutaneous forms are multiple and include involvement of larger vessels with necrotizing arteritis or phlebitis and capillaries with leukocytoclastic vasculitis. Cerebral involvement can take the form of angiitis in the meninges or choroid plexus. There can also be primary collagen necrosis and necrotizing granulomatous inflammation resembling rheumatoid nodule in the dura. Tumefactions resulting from WG occur in the breast, mediastinum, and retroperitoneum. Diffuse granulomatous tissue and vasculitis can involve the oral mucosa.

CONDITIONS CLOSELY RELATED TO WG

Churg-Strauss granulomatosis (CSG) **(7177)** is a clinicopathological condition which differs from WG clinically by the prevalence of myocarditis, myositis, polyneuropathy, and particularly by the coexistence of asthma. The pathology of CSG is essentially that of WG with the addition of mucus plugging, mucinous metaplasia, peribronchiolar scarring, and smooth muscle hyperplasia as seen in asthma. Peripheral blood eosinophilia of CSG can be manifest as a marked eosinophilic infiltrate in the lung, including eosinophilic pneumonia or eosinophilic vasculitis; however, these phenomena can be seen in WG and, therefore, are not defining features of CSG.

Microscopic polyangiitis is principally a renal disease with involvement of vessels larger than capillaries and positive for p-ANCA (anti-MPO) rather than c-ANCA (anti-PR3). When it involves the lung, one does not find the extravascular components or the extensive necrotizing granulomatous inflammation.

OTHER "GRANULOMATOSES"

Sarcoid and chronic berylliosis **(6623)** have granulomas which are arrayed in a lymphangitic pattern around bronchovascular bundles and in the interlobular septa and pleura. Granulomas may be present in hilar lymph nodes when they are absent in the lung. In early disease, a lymphocytic infiltrate may be prominent both in the air spaces and in the interstitium. In late stage, granulomas may be represented only by small circular hyaline scars, which are more clearly seen in lymph nodes than in markedly fibrotic lung. Some cases of berylliosis lack granulomas, and distinction from UIP may be impossible histologically. Calcium oxalate/carbonate crystals are common in mutinucleated histiocytes in sarcoid and may be misinterpreted as talc or other inspired particles.

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LETTERS

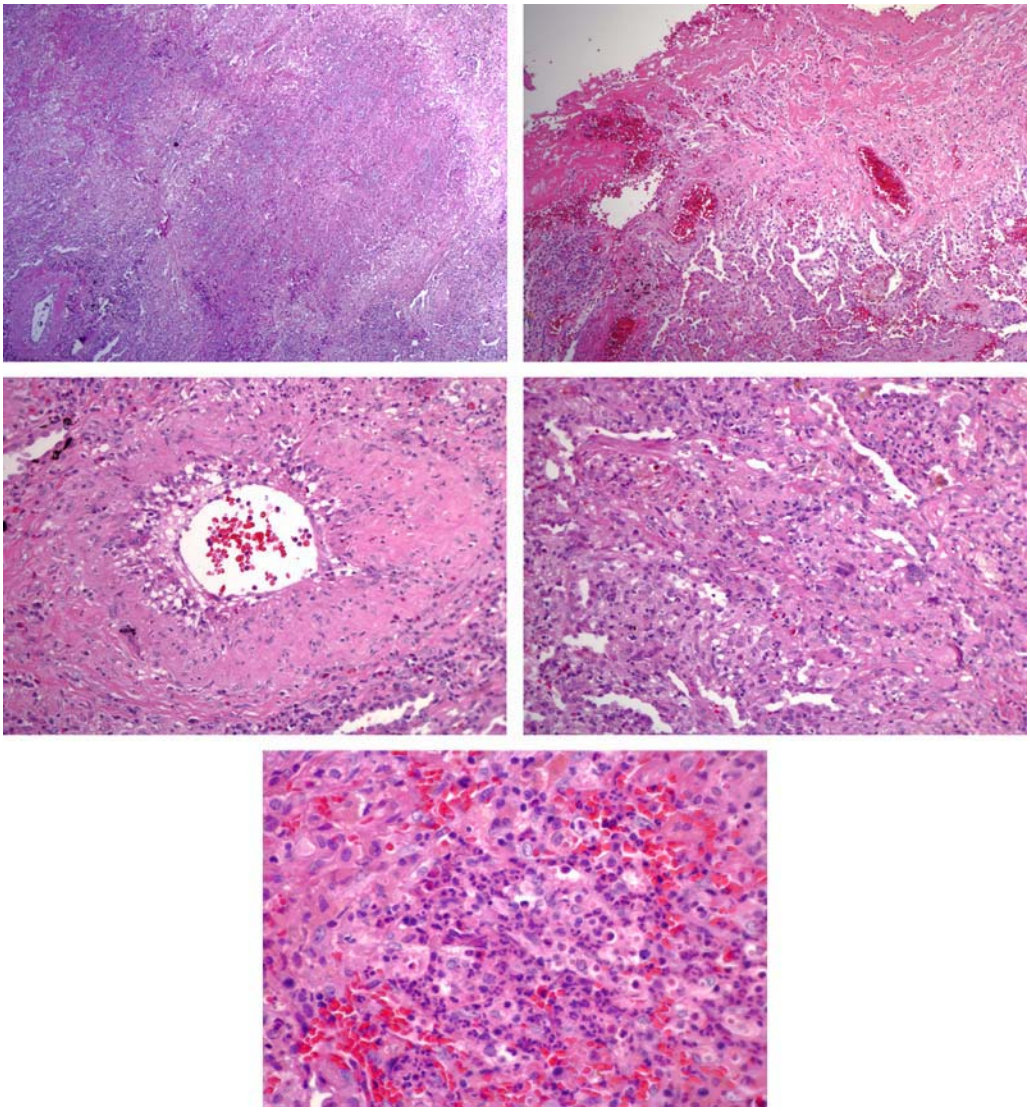
Case 6804

Diagnosis: Lung, open biopsy: WG.

This case has most of the characteristic features of WG (diffuse granulomatous tissue, isolated multinucleated histiocytes, geographic necrosis, eosinophils, micro-abscesses, pathergic necrosis, and necrotizing arteritis). Unusual is marked pleuritis. It is hard for me to suggest an alternative diagnosis. Mycobacterium avium intracellulare (MAI) infection is sometimes the most difficult disease to separate from WG, but MAI infection would not explain the necrotizing vasculitis in this case.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6804 (Chapter 5 – Granulomatosis)

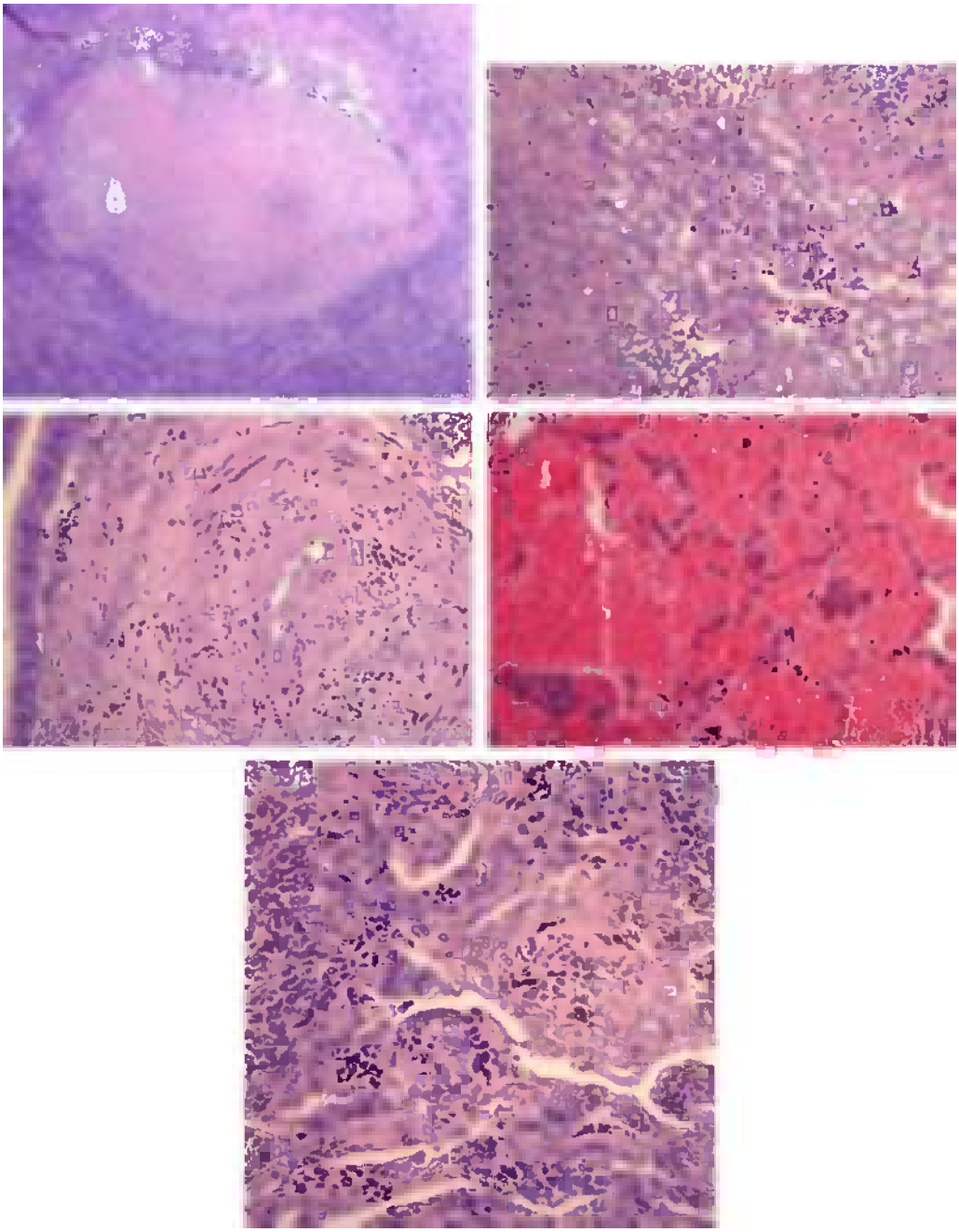
Case 6620

Diagnosis: Lung, open biopsy: WG.

Necrotizing nodules have palisaded histiocytes surrounding pools of neutrophils as well as microabscesses distributed throughout diffuse granulomatous tissue. This histology suggests WG, but bronchocentric granulomatosis remains in the differential diagnosis were it not for fibrinoid necrosis of arteries in one section. I believe the totality indicates WG despite the reportedly negative test for ANCA. In my experience a history of arthritis, considered clinically as rheumatoid arthritis, is relatively common in patients who subsequently develop WG and probably indicates involvement of synovial tissue by the disease.

Thank you for referring this case in consultation. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6620 (Chapter 5 – Granulomatosis)

Case 6518

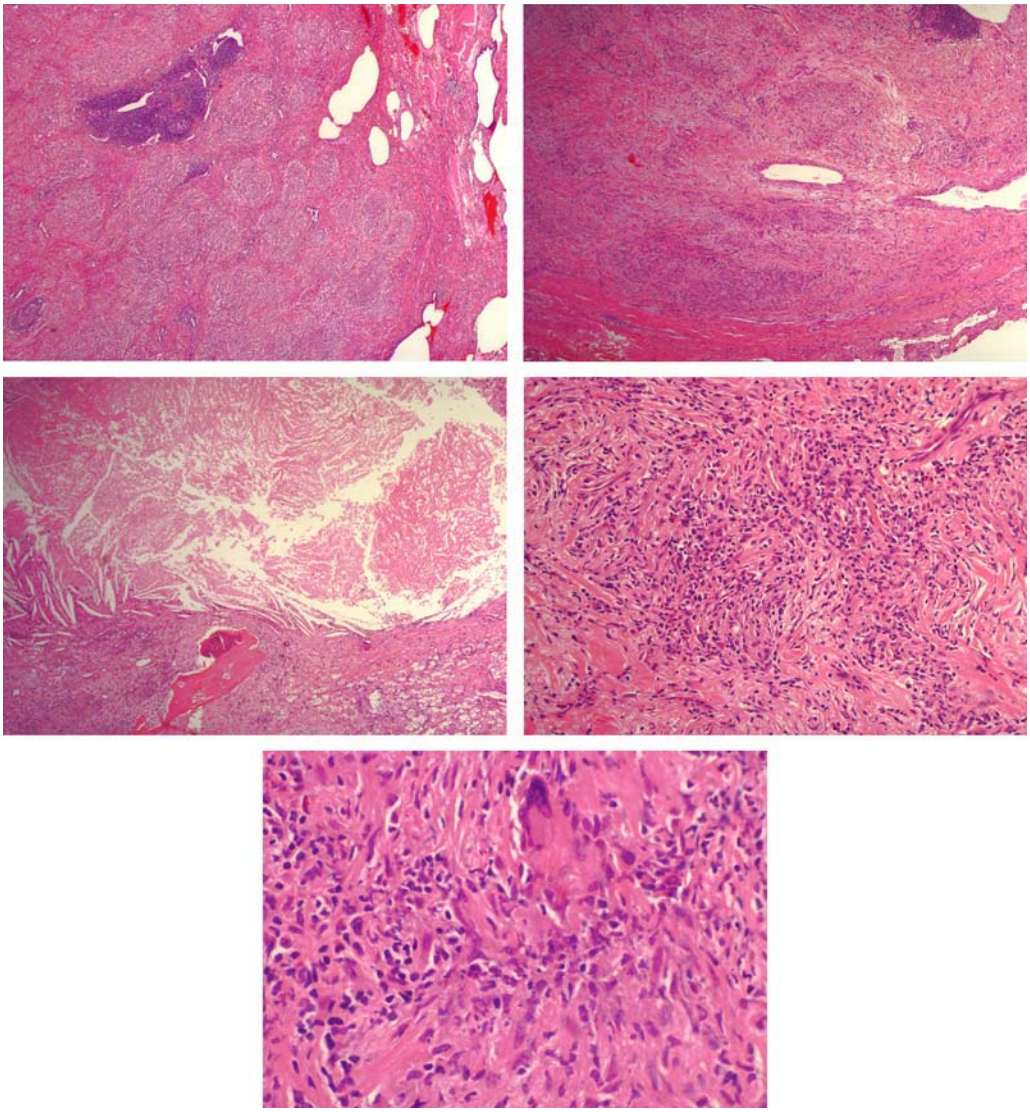
Patient: 25-yr-old female

Diagnosis: Lung, excision of nodule: Granulomatous nodule, consistent with WG in tumefactive form.

The differential diagnosis is inflammatory pseudotumor, unusual granulomatous infection, and WG. I believe the changes best fit with WG: (1) miliary microabscesses; (2) eosinophils; (3) diffuse granulomatous tissue; (4) occasional multinucleated histiocytes; (5) absence of compact granulomas of sarcoidal type. A vague storiform pattern makes me consider inflammatory pseudotumor, but I would not be able to explain the other features with that diagnosis. I have seen this form of WG in extrapulmonary sites such as breast and mediastinum. It is certainly not the typical form of WG in the lung. Interesting is that the mass involves pleura and adjacent soft tissue of chest wall although it is principally in the lung. The clinical history is consistent with limited WG. Infection should be excluded by special stains on tissue, looking particularly for Blastomyces, even though culture of lavage fluid has been negative.

Thank you for the opportunity to review this case.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6518 (Chapter 5 – Granulomatosis)

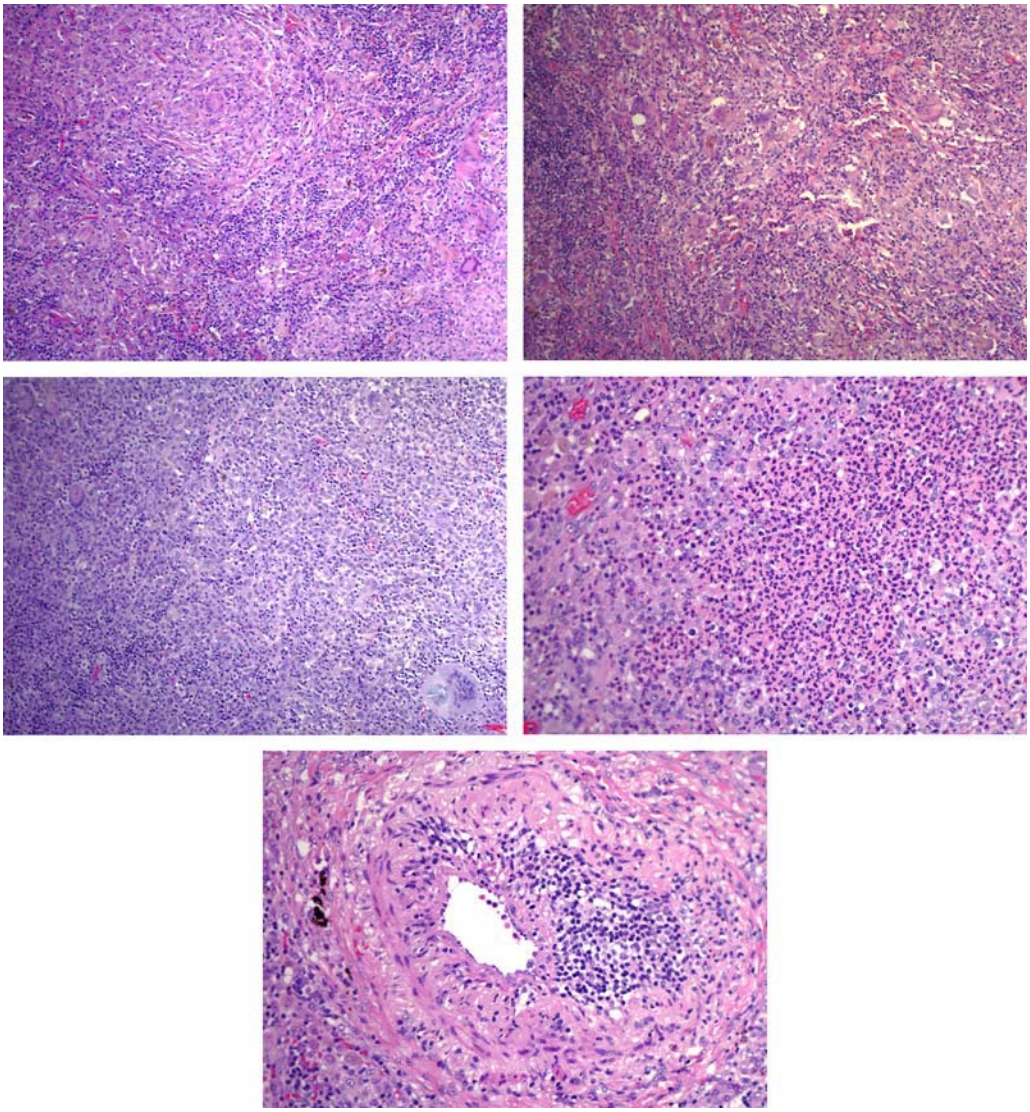
Case 6829

Diagnosis: Lung, open biopsy: Granulomatous inflammation with microabscesses and diffuse granulomatous tissue, consistent with WG.

This histology falls into the general category of granulomatous inflammation with necrosis, as you indicate. The absence of compact granulomas of tuberculoid or sarcoidal type is against the usual mycobacterial or fungal infection. An infectious etiology cannot be definitely excluded despite your negative stains for mycobacteria and fungi, and this histology might be mimicked by infection in an immunosuppressed patient. However, the diffuse granulomatous tissue and microabscesses (particularly well seen in slide AS-1), as well as numerous histiocytic giant cells in the absence of compact granulomas, is highly suggestive of WG, which is the diagnosis I prefer. There is a chronic vasculitis with lymphocytic inflammation and scarring of blood vessels, but I detect no acute necrotizing vasculitis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6829 (Chapter 5 – Granulomatosis)

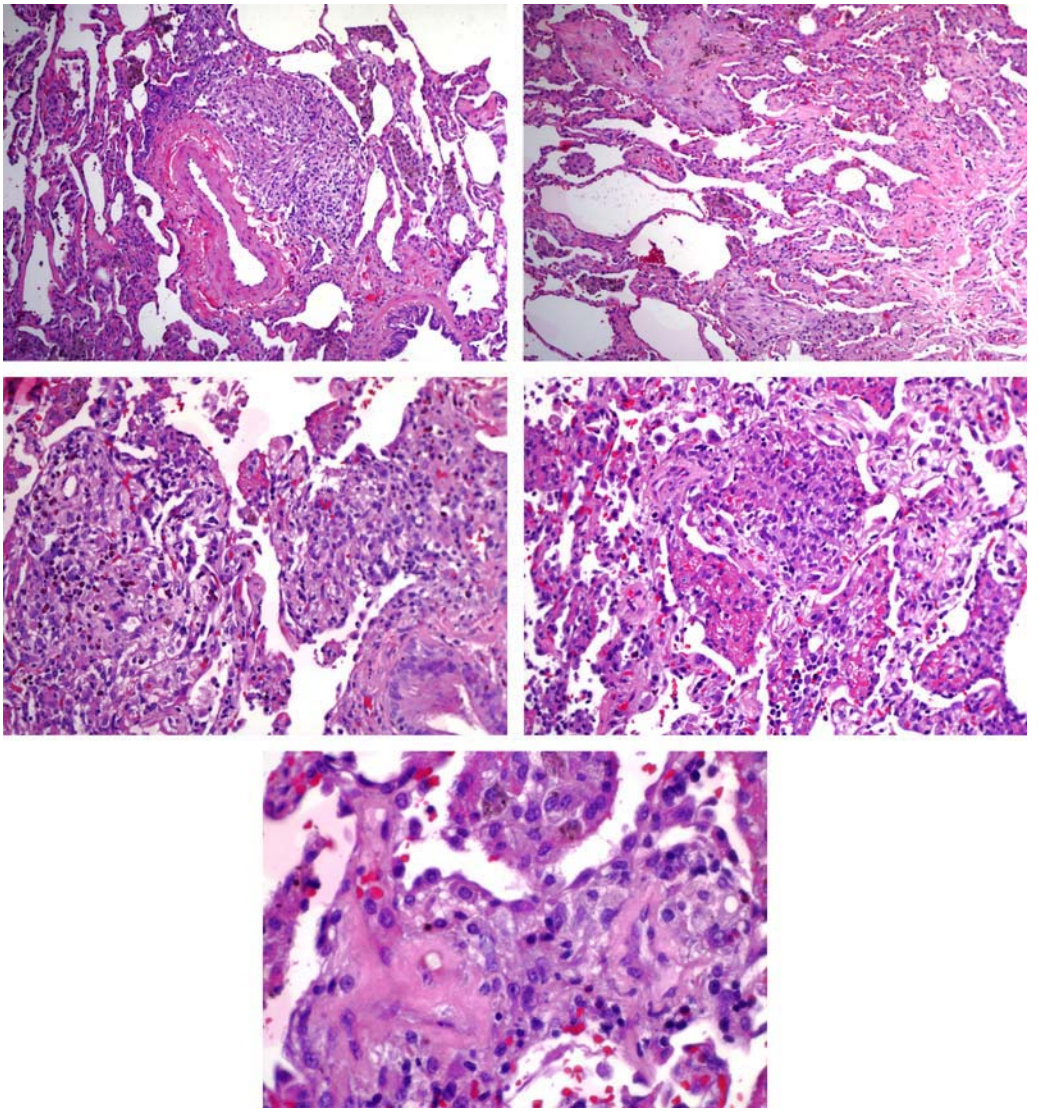
Case 6905

Diagnosis: Lung, open biopsy: BOOP-like pattern with eosinophils and focal granulomatous tissue, consistent with treated WG.

This case is complicated. The first assessment is BOOP associated with eosinophils, and this combination could be explained by the overlap syndrome of BOOP and chronic eosinophilic pneumonia (CEP). Unusual for that condition is the hemosiderin. Furthermore, there are aggregates of histiocytes in a few of the slides, including perivascular aggregates of same. These histiocytic aggregates could be a focal representation of the phenomenon we describe as diffuse granulomatous tissue. With this in mind, I suspect that the disease we are seeing is WG that has been treated. I cannot absolutely exclude an infection causing the process or a coexisting infection, but I doubt this. We searched for necrotizing bronchiolitis and vasculitis but find none. In some areas the granulomatous tissue has slight palisading in the manner of a palisading granuloma, but no necrosis is present, and there is nothing I can specifically designate as palisading granuloma. If I could, then my diagnosis of WG would be more definite.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6905 (Chapter 5 – Granulomatosis)

Case 7177

Diagnosis: Lung, open biopsy: Palisading granuloma, diffuse granulomatous tissue, fibrinous pneumonia, microabscesses and eosinophils, ? WG, ? other.

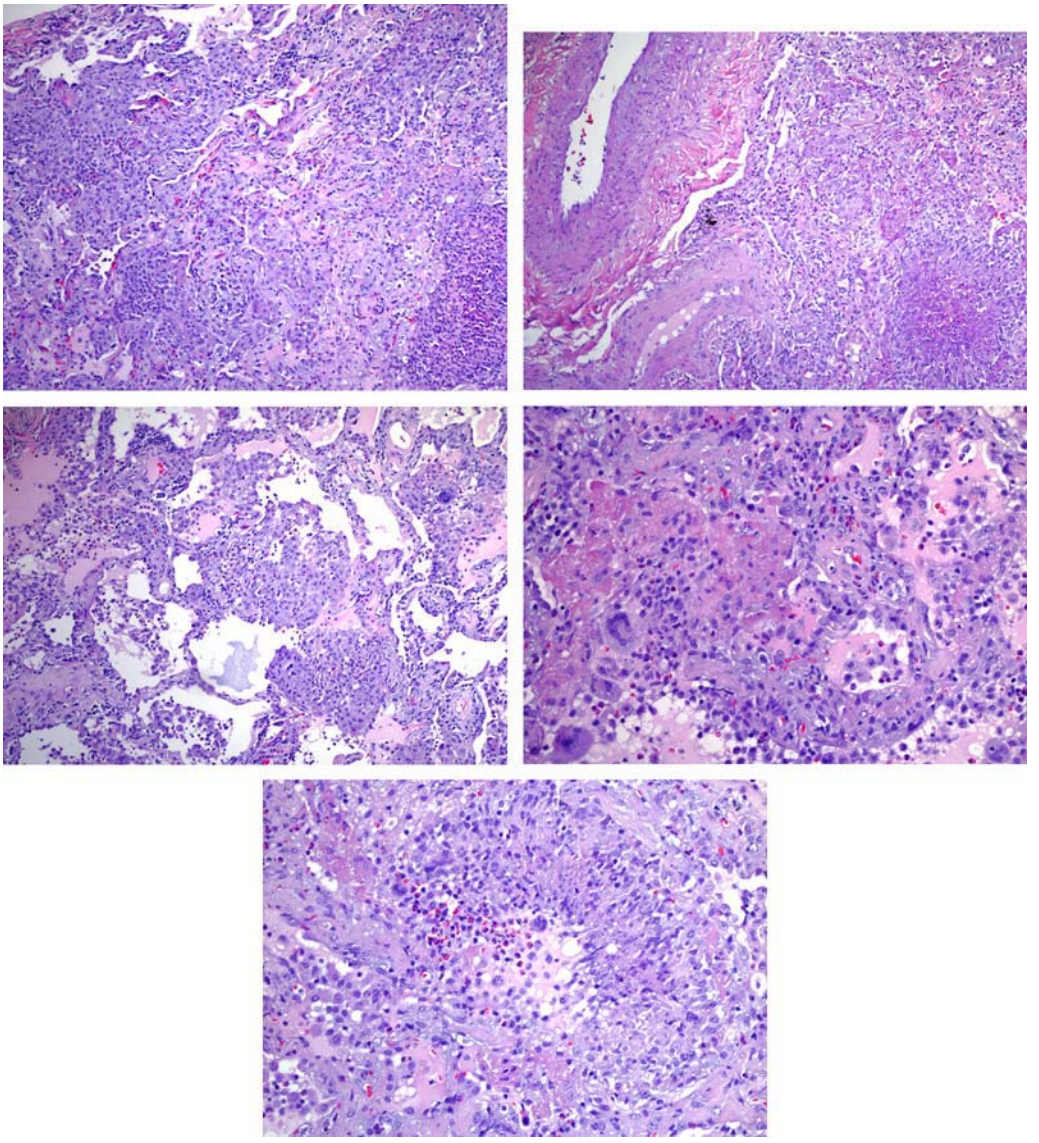
This case is relatively unique in my experience and quite distinctive. Foci of fibrinoid necrosis are surrounded by distinct palisades of histiocytes. These have the characteristics of the palisading granuloma, which is a marker of WG in early phase. No compact granulomas of sarcoidal or tuberculoid type are present. Strands of histiocytes constitute diffuse granulomatous tissue, another facet of WG. Microabscesses and eosinophils also add to the picture. Absent in these slides is distinct necrotizing vasculitis. For this reason and because of the somewhat unusual presentation, I refrain from a definite diagnosis of WG but favor that interpretation. We believe that Churg-Strauss syndrome is essentially a facet of WG in an asthmatic. Patients with Churg-Strauss syndrome can have many eosinophils in the lung similar to this case. The last possibility is a very unusual infection, such as mycobacterial disease in a markedly immunosuppressed patient. I doubt this interpretation, but special stains for organisms and special stains for vessels will be performed by me when I receive paraffin blocks. I do not believe this pathology characterizes a radiation reaction or drug reaction. No carcinoma is present.

I have received a paraffin block and performed the following special stains: acid-fast, methenamine silver, Brown-Hopps, periodic acid-Schiff, elastic, and trichrome. I detect no bacteria, mycobacteria, fungi, or pneumocystis on special stains for organisms. I detect no viral inclusions. I detect no necrotizing vasculitis on the elastic and trichrome slides. I understand that serum tests for antineutrophil cytoplasmic antibody are negative. I understand that no renal abnormality has been found.

I do not know what is causing this process. Approximately 10% of patients who have WG do not have positive test for ANCA. Infections that can mimic WG include tularemia, which should be considered in the clinical differential diagnosis despite the negative stains for organisms in tissue. Other infections cannot be absolutely excluded.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. I will issue a supplemental report when I have performed the above mentioned additional stains.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7177 (Chapter 5 – Granulomatosis)

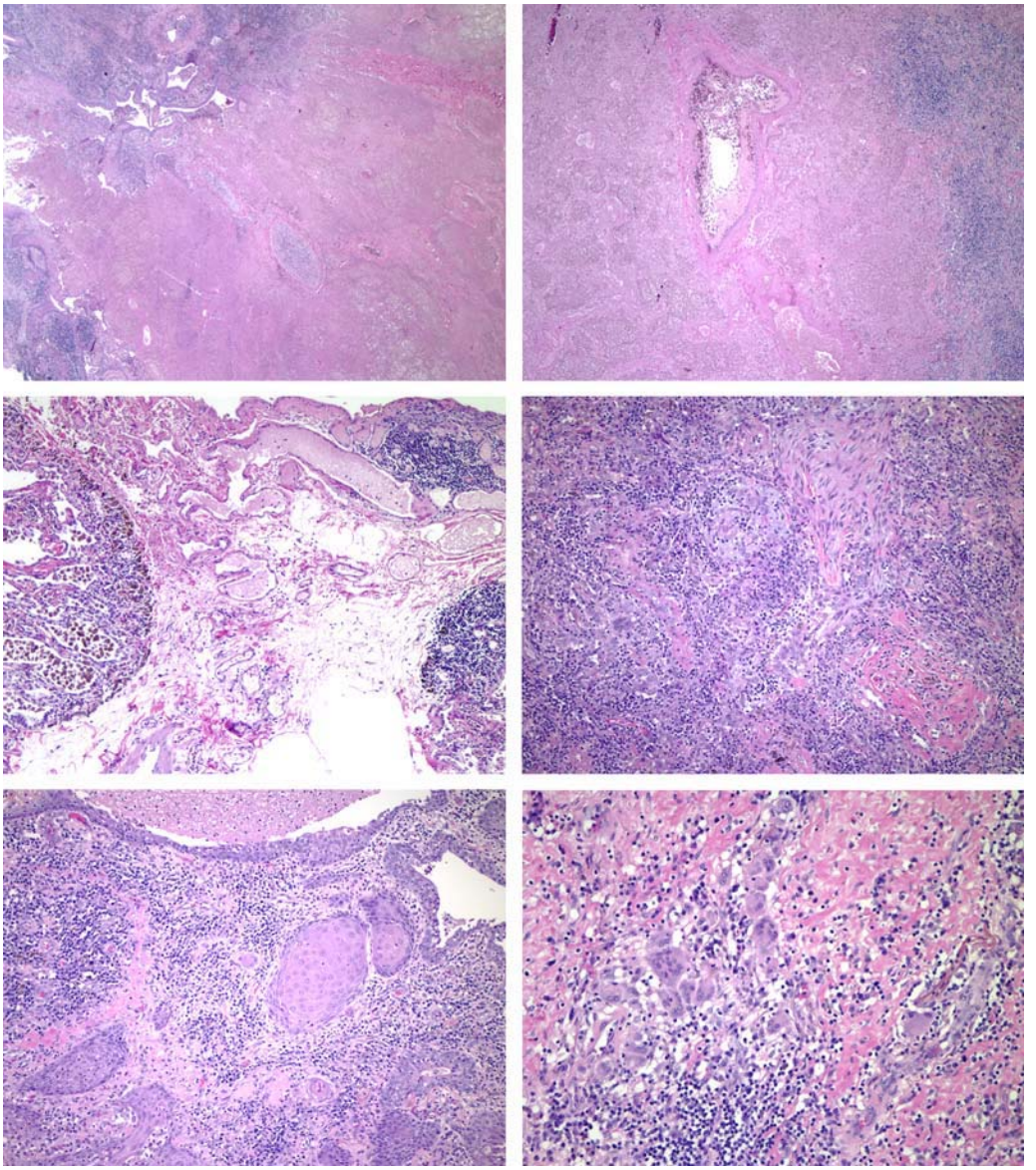
Case 6937

Diagnosis: Lung, lobectomy: Necrotizing granulomatous nodule with prominent squamous metaplasia and vascular thrombosis, etiology undetermined, ? rheumatoid nodule, ? old infection, ? other.

This dramatic case has necrotizing granulomatous inflammation with palisading histiocytes but other perplexing aspects. First is the marked squamous metaplasia, which suggests a preexistent scar and possibly preexistent bronchiectatic cavity. Second is the extensive thrombosis of arteries and veins in the vicinity of the nodule. The thrombosis is weeks to months in age. It could be secondary to the inflammation. Palisading of histiocytes in some regions, concurrent pleuritis, and organizing bronchiolitis and pneumonia in the vicinity of the nodule make me consider rheumatoid nodule. A second possibility is mycobacterial or fungal infection, but your stains reportedly show no organisms, and the presence of only a few poorly formed granulomas is against this interpretation. Another possibility is WG, and an ANCA test may be indicated, but the absence of microabscesses, diffuse granulomatous tissue, palisading granuloma, necrotizing vasculitis and eosinophils are all against that interpretation. If this were WG presenting as a solitary nodule, it is possible that the ANCA test might be negative, but I do not favor this diagnosis. In the differential diagnosis we also considered an unusual form of infarction, dirofilaria, nocardial or actinomycotic infection, or aspergillosis occurring in a preexistent cavity, but we do not favor any of these interpretations and cannot prove them. The absence of mucoid impaction of bronchioles is against BCG.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6937 (Chapter 5 – Granulomatosis)

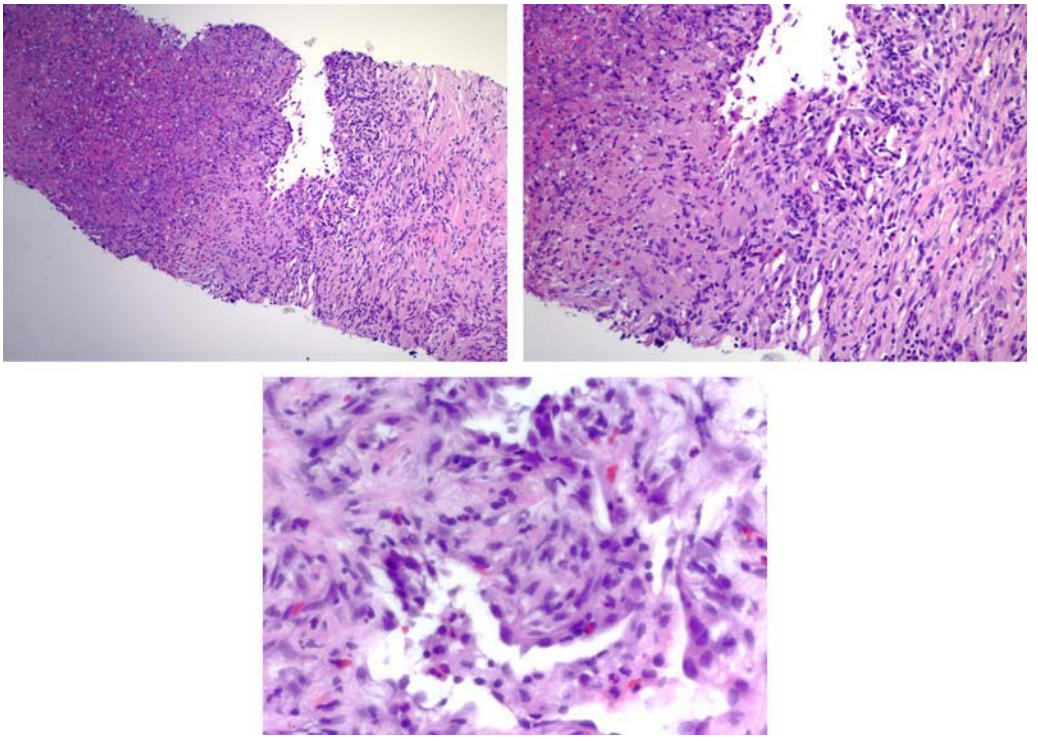
Case 7072

Diagnosis: Lung, needle biopsy: Necrotizing granulomatous inflammation, cause undetermined, ? BCG, WG, ? infectious, ? other.

A nodule of necrosis is surrounded by vaguely palisaded histiocytes. Lung adjacent to the necrosis has fibrosis and eosinophils. The differential diagnosis for this process includes BCG with or without aspergillus, WG, tuberculosis, fungal infection, and other more unusual conditions. Additional tissue will be necessary for more precise morphological diagnosis. I agree that your special stains for organisms (periodic acid-Schiff, silver, acid-fast) are negative.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7072 (Chapter 5 – Granulomatosis)

Case 6548

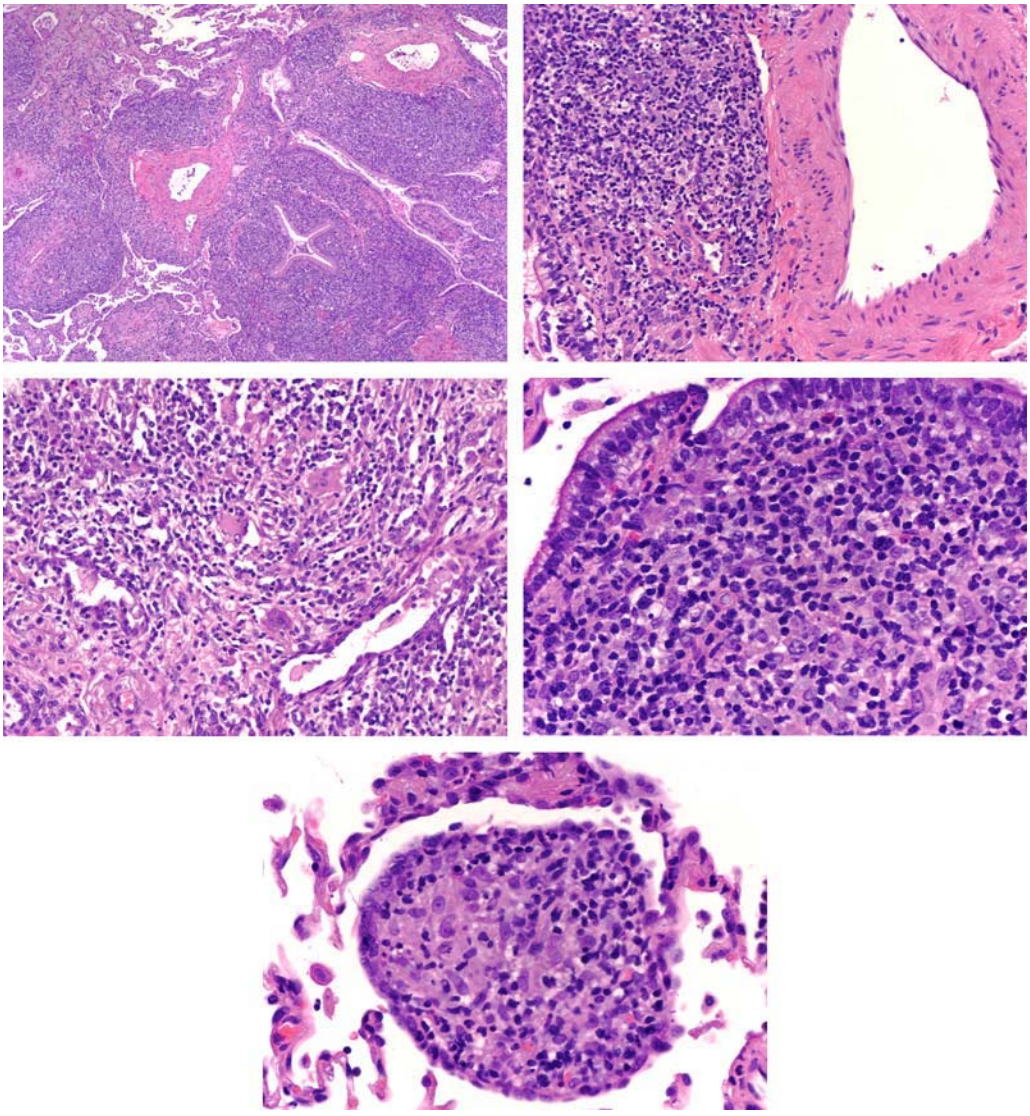
Diagnosis: Lung, open biopsy: Lymphohistiocytic inflammation, marked, with lymphangitic distribution and granulomatous features, consistent with lymphomatoid granulomatosis (LYG).

Large nodules of massed lymphocytes and histiocytes are associated with focal necrosis and many multinucleated histiocytes. The magnitude of the infiltrate and its distribution suggests a low grade malignant lymphoma and in particular malignant lymphoma of LYG type. I cannot make a diagnosis of malignant lymphoma in this case, however, because there is a virtual absence of atypia. Furthermore, the inflammation is peribronchiolar and perivascular but not destructive of these structures. Low grade malignant lymphomas of this sort cannot generally be demonstrated to have a monocloncal population of cells. I will obtain lymphoid markers and report the results separately.

The principal differential diagnosis is WG, because there is diffuse granulomatous inflammation and a small amount of necrosis, but no micro-abcesses or pathergic necrosis is present. However, the principal process seems to be lymphoproliferative rather than necrotizing. I also considered a fungal infection such as North American blastomycosis. I repeated stains for organisms on the block which you provided, and no organisms are present. I cannot absolutely exclude fungal pneumonia, but I do not favor that interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and all if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6548 (Chapter 5 – Granulomatosis)

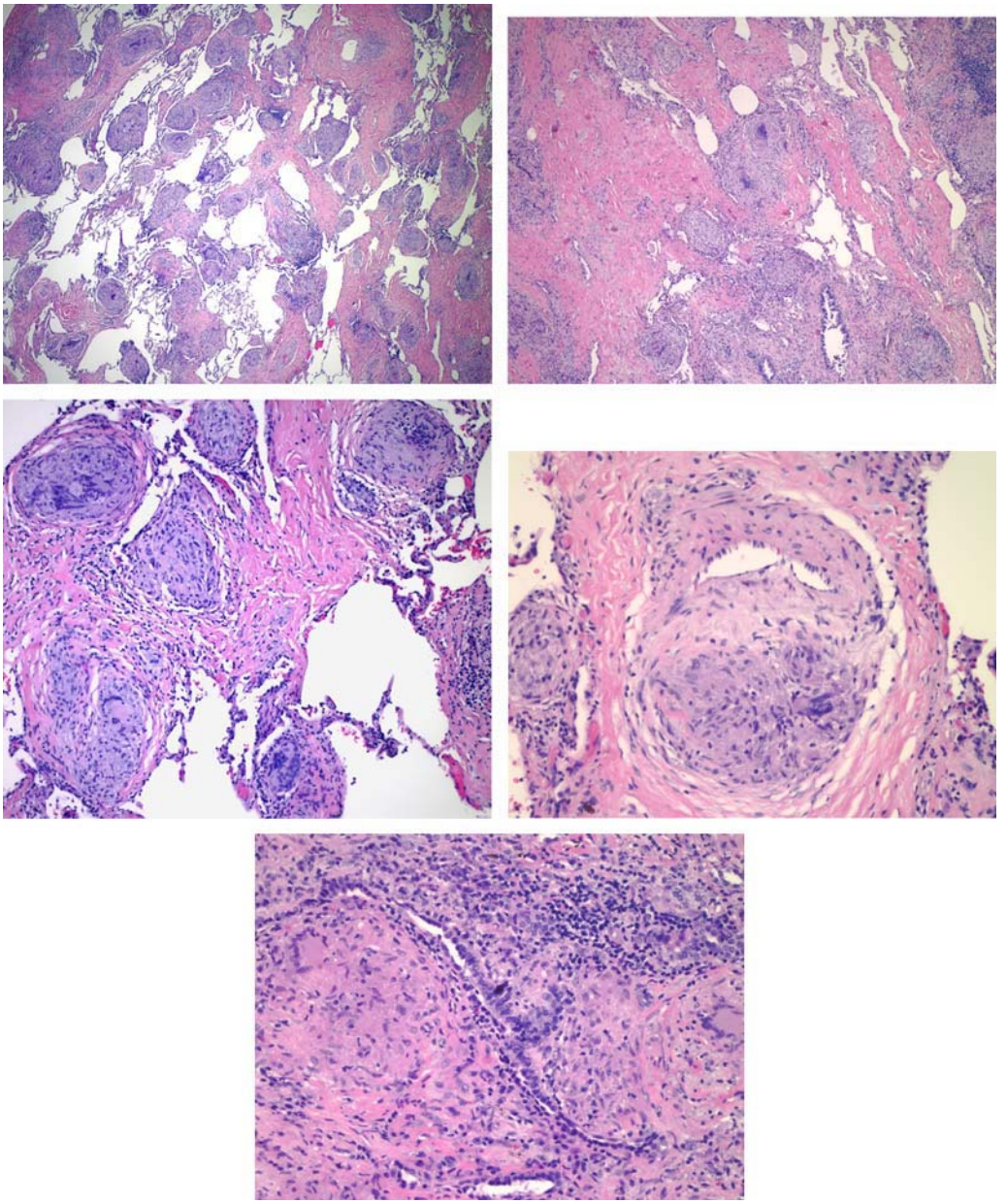
Case 6623

Diagnosis: Lung open biopsy: Compact non-necrotizing granulomas, with bronchiolar and vascular involvement, in part in lymphangitic distribution with extensive linear sclerosis, consistent with sarcoidosis.

I reviewed the slides of your recent open lung biopsy and also the radiographic studies. The character of the granulomas and their distribution are typical for sarcoidosis. As we discussed, chronic beryllium disease and schistosomiasis are two considerations in biopsies which otherwise are typical for sarcoidosis. Infection, including tuberculosis or histoplasmosis, is always a possibility in a patient with a biopsy having these finding, but the absence of necrosis, the negative silver stain for fungus, and the negative acid-fast stain for mycobacterium are all against that interpretation. Results of the culture of the biopsy are the gold standard for evaluation of an infectious etiology. Histopathologically, the disease is approximately equal parts of cellular granuloma and of old fibrotic scarring. The fibrosis has produced both linear and nodular scars. However, no honeycomb fibrosis is present.

In summary, I believe the biopsy shows granulomatous disease consistent with sarcoidosis of a moderately severe form pathologically. Please let me know if I can be of further assistance now or in the future. With all best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6623 (Chapter 5 – Granulomatosis)

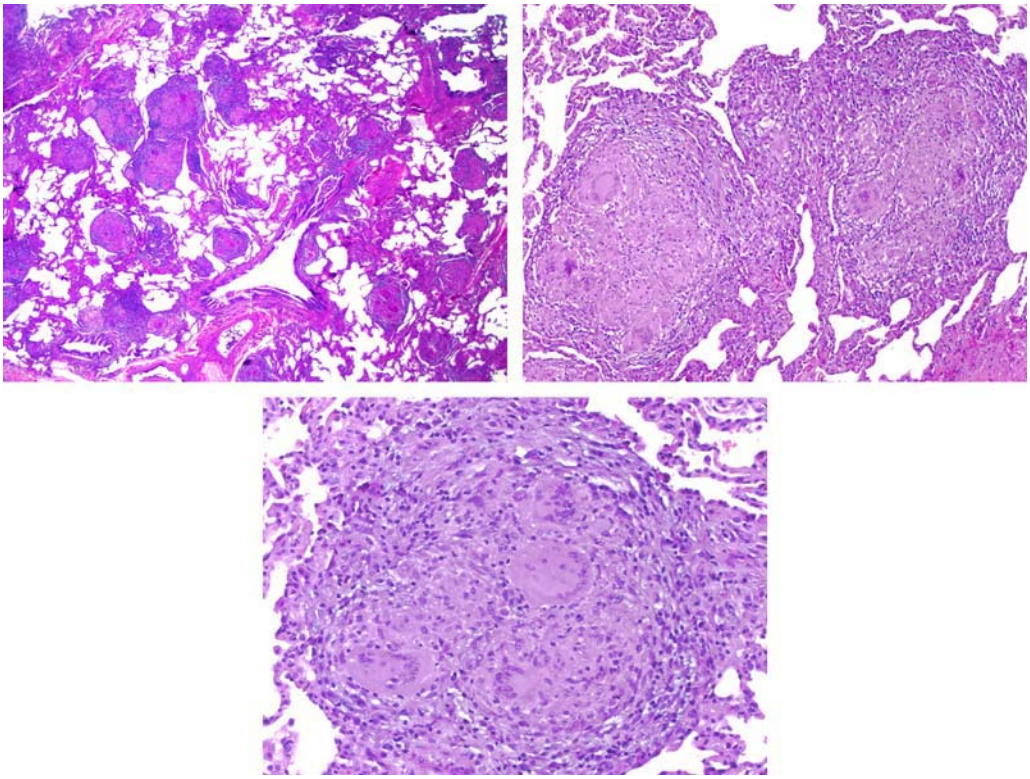
Case 6540

Diagnosis: Lung, open biopsy: Compact granulomas and granulomatous inflammation, extensive, ? sarcoidosis, ? atypical mycobacterium infection, ? hypersensitivity reaction, ? other.

The compact character of the granulomas raises sarcoidosis into the differential diagnosis immediately. I favor this diagnosis with the realization that sarcoidosis is not common in a 10 yr old but has been described in children many times. Against sarcoidosis, is the absence of a distinct lymphangitic distribution of the granulomas. A second possibility and important for prognosis is atypical mycobacterial infection, which can mimic sarcoidosis and be difficult to identify by culture or staining. Hypersensitivity is possible, including hypersensitivity to inhaled particles, such as particles from a fire, but I am reluctant to accept this explanation because the granulomas are unusually numerous and compact for hypersensitivity reaction and do not appear to represent acute disease. Allergic aspergillosis also might be considered in a child, particularly if there were any history of wheezing or eosinophilia. The compact nature of the granulomas effectively excludes WG. Chronic beryllium disease would be considered in an adult with the proper occupational exposure.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6540 (Chapter 5 – Granulomatosis)

Case 7030

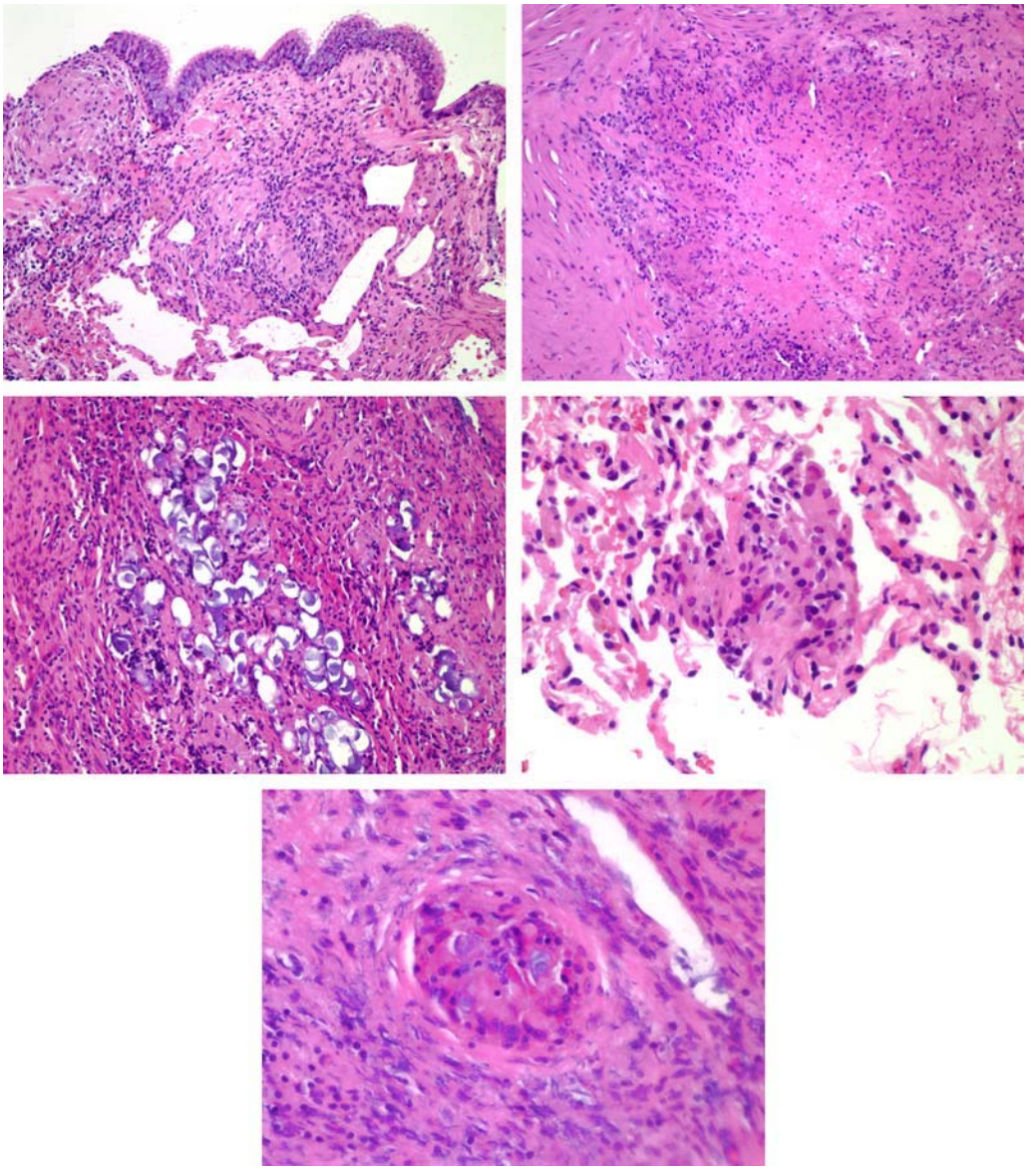
Diagnosis: Lung, transbronchial biopsy: Few compact noncaseating granulomas in bronchial mucosa, ? sarcoidosis.

Sinus mucosa, biopsy: Compact granulomas, confluent, with slight necrosis and moderate sclerosis, ? sarcoidosis.

Both the lung and the sinus mucosa have compact granulomas of sarcoidal type. In areas of confluent granulomas in the nose, there is a small amount of necrosis. Infection cannot be absolutely excluded. Your special stains (acid-fast, methenamine silver, periodic acid-Schiff) for organisms are negative in both the lung and the sinus mucosa. The sinus mucosa contains inspissated globules of mucus which elicit a small amount of multinucleated histiocytic reaction on their own. Sarcoidosis would be a principal diagnosis on a statistical basis for patients living in this area. The compact nature of the granulomas is very much against the diagnosis of WG. I searched for allergic mucus and hyphae in the sinus specimen and find none.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. I have retained two slides stained with hematoxylin and eosin for our permanent teaching collection in pulmonary pathology and hereby return all of the remainder, including all of your special studies. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7030 (Chapter 5 – Granulomatosis)

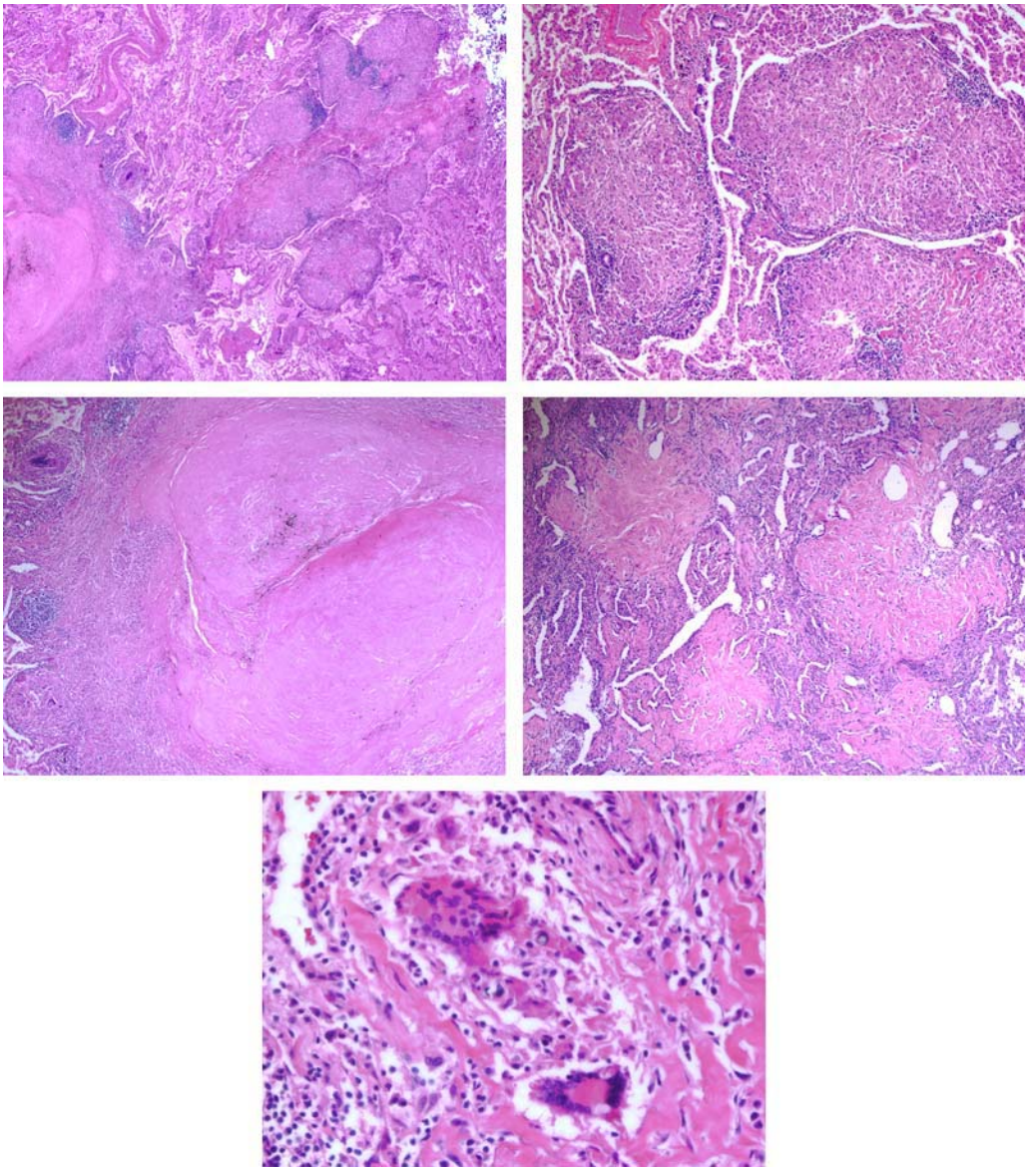
Case 6638

Diagnosis: Lung, open biopsy: Compact granulomas in lymphangitic distribution with focal nodular hyalinization, ? sarcoidosis.

The compact character of the granulomas and their lymphangitic distribution are suggestive of sarcoidosis. The lymphangitic distribution is manifested by peribronchial and septal accentuation of the granulomas, as you indicate. This distribution is typical for sarcoidosis, and the relative uniformity of the granulomas in size and age is also consistent with that interpretation. Some of the granulomas are aggregated into small nodular scars. Some of the scars have anthracotic pigment, but I do not believe these granulomas represent a pneumoconiosis. Whether or not sarcoidosis is related to environmental factors is conjectural, but I know of no specific inhalational disease with this pathology except for chronic beryllium disease, which could be further investigated by a detailed and directed occupational history. I cannot absolutely exclude infection, but I doubt that interpretation because of the character and distribution of the granulomas as indicated above, the absence of necrosis even where granulomas are aggregated enough to form nodular scars, and your negative stains for mycobacteria and fungi.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6638 (Chapter 5 – Granulomatosis)

Case 6611

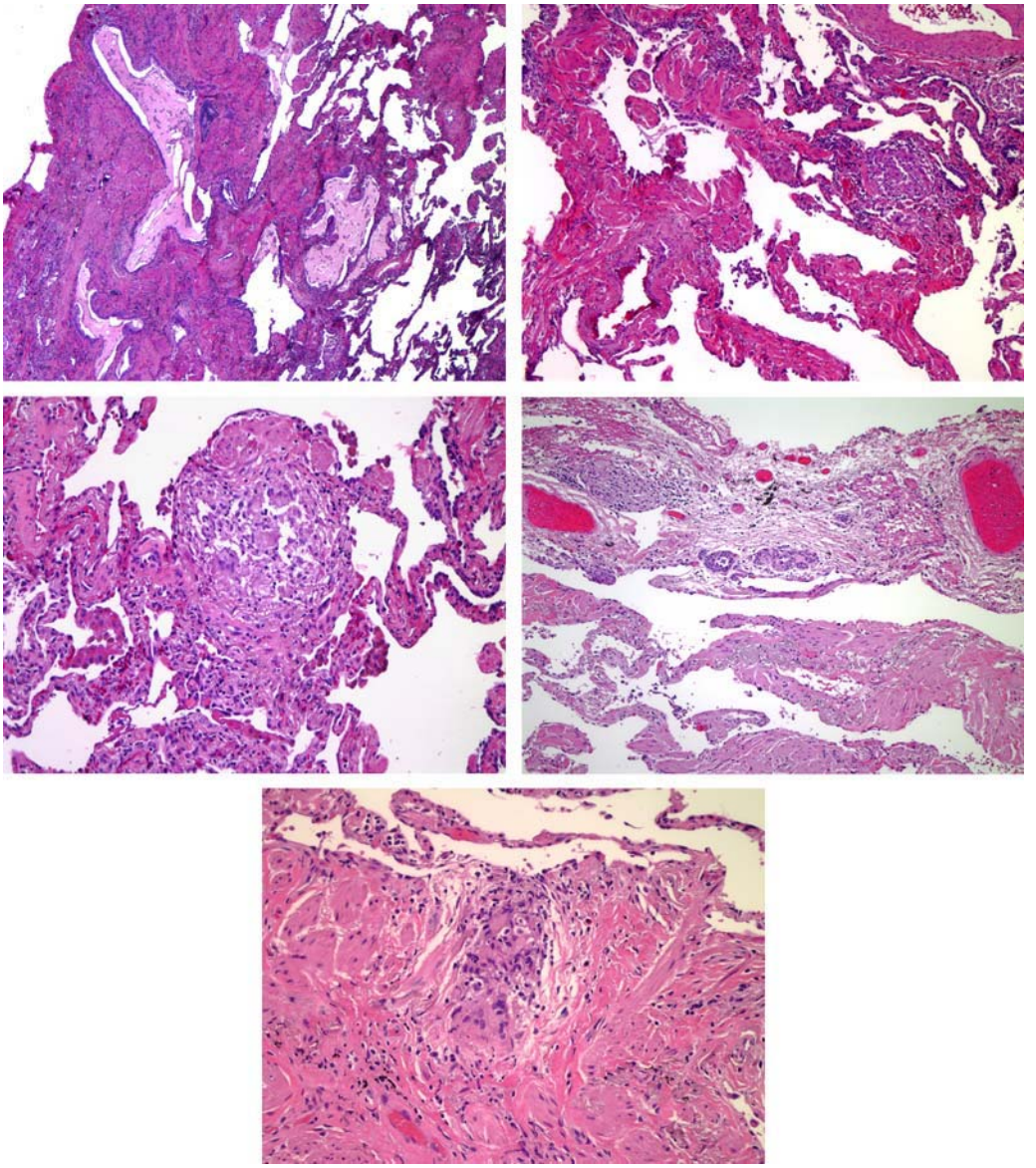
Diagnosis: Lung, open biopsy: Extensive interstitial fibrosis and compact granulomas of sarcoidal type, consistent with end-stage sarcoidosis.

The lung has extensive old interstitial fibrosis with smooth muscle hyperplasia and early honeycomb fibrosis beneath the pleura. A relatively small number of compact granulomas of sarcoidal type are scattered through the scar at a concentration of approximately two per slide. This combination suggests the unusual untoward sequel of sarcoidosis eventuating into honeycomb fibrosis, which is the interpretation I prefer. Although UIP would be statistically a more probable diagnosis, the granulomatous inflammation in UIP (when it occurs) usually does not contain such compact granulomas. There is little active fibrosis as seen in UIP, the interstitial lymphocytic infiltrate here is meager, and there is no desquamative interstitial pneumonitis-like reaction as seen in cases of UIP with honeycomb fibrosis and mucus plugging. I find the very numerous granulomas in the lymph node, all of which are approximately the same age, very suggestive of sarcoidosis. I cannot absolutely exclude an infection, but I understand that your stains are negative, and I do not favor this interpretation.

Peculiar are nested ovoid cells in a pleural adhesion. These seem to be the histologic expression of the mesothelial/histiocytic excrescences sometimes observed in pleural or pericardial effusions.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6611 (Chapter 5 – Granulomatosis)

Case 7000

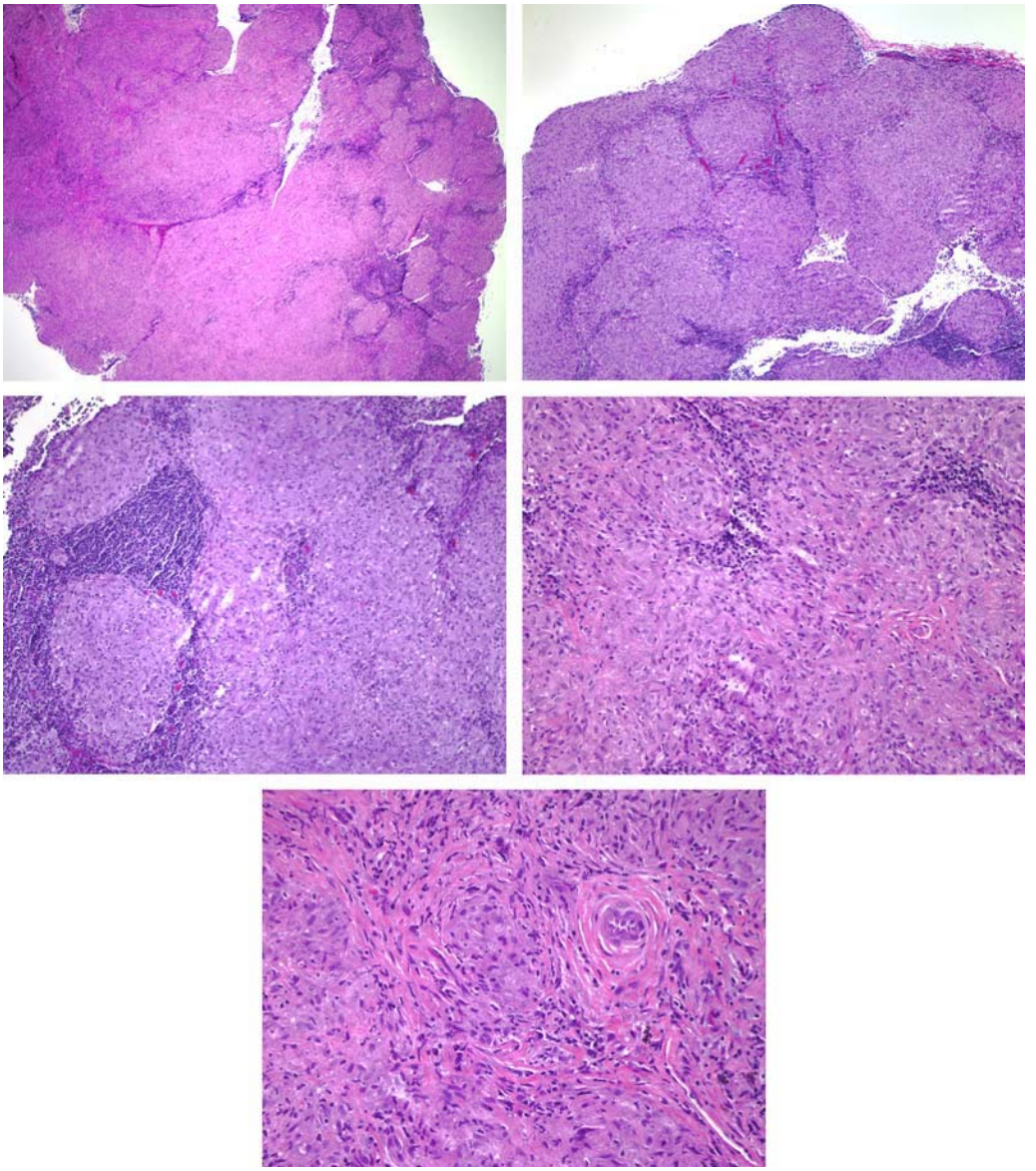
Patient: 49-yr-old female with mediastinal lymphadenopathy.

Diagnosis: Lymph node (mediastinal), biopsy: Compact confluent non-necrotizing granulomas.

The character of the granulomas, the absence of necrosis, the fact that the granulomas are all of approximately the same age, and their confluence all suggest sarcoidosis. Infection cannot be absolutely excluded, but your silver and acid-fast stains demonstrate no orgaisms, and I doubt that this is an infectious process. This is essentially in agreement with your interpretation. Another very remote consideration is chronic beryllium disease.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7000 (Chapter 5 – Granulomatosis)

6 Pulmonary Vascular Disease

Contents

ARTERIAL AND ARTERIOLAR HYPERTENSION

Hypertensive changes are usually ancillary to other pulmonary pathology, although biopsies may be done in patients with subacute cor pulmonale or congenital heart disease specifically to identify the type and degree of hypertension. Hypertensive changes occur in pulmonary blood vessels of all sizes but are usually quantified in small muscular arteries. The grading of pulmonary hypertension in musuclar arteries used here is a modification of the system used by Heath and Edwards and by Wagenvoort and Wagenvoort. The description of Heath and Edwards includes six grades. Because grades 4–6 are closely related in their pathogenesis and clinical significance and because grade 6 precedes grades 5 and 4, all three are grouped together here into a single grade. Plexogenic arterial hypertension (grade 4) usually occurs in only severe and untreated congenital heart disease and in severe and rapidly progressive idiopathic pulmonary hypertension. A subdivision of classic grading as applied to preoperative lung biopsies from patients scheduled for corrective surgery for congenital heart disease is discussed separately. Each higher grade of pulmonary hypertension incorporates the changes of the lower grades as well.

Medial Hypertrophy (Grade l)

The blood vessels most readily examined in an open biopsy are those which have the most characteristic changes of pulmonary hypertension; namely, the muscular arteries have an external diameter from approx l mm, ranging down to 0.l mm. The earliest and most common manifestation of hypertension is medial hypertrophy. The medial hypertrophy is defined as an increase in thickness between the internal and external elastic laminae, best demonstrated with an elastic tissue stain. The thickening is the result of an increase in both size and number of smooth muscle cells. The nuclei are oriented both

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

parallel to and tangential to the long axis of the artery. Pulmonary hypertension generally indicates a mean medial thickness of l0% or more of the external diameter. With hypertension, the mean medial thickness may increase to l5% in adults and to 25% in infants. With hypertension, arterioles may acquire a mean medial thickness up to 35%.

Ideally, a specimen of lung should be inflated with formalin through the bronchial tree prior to quantification of thickness of pulmonary vessels. In practice, post-vital arterial collapse contributes little to the thickening of the media in cases of hypertrophy. The lung should not be inflated through the arteries, as this produces post-vital, artifactual arterial dilatation. It is more important to prevent collapse of the air spaces and thereby the arteries than to forcibly expand the arteries.

Another facet of medial hypertrophy is extension of muscle distally into arterioles. A continuous muscular media normally ceases when the vessel tapers to an external diameter of l00 μ. In pulmonary hypertension, muscle fibers can be seen down to an external diameter of 20 μ. At this level, the muscle cells are best appreciated in cross-section as circular nuclei surrounded by clear rims of cytoplasm beneath the endothelium.

Medial arterial hypertension is common and often extensive in emphysema, chronic bronchitis, bronchiectasis, and diffuse pulmonary scarring of any cause. It is also an early stage of hypertension in congenital heart disease with left-to-right shunt.

Intimal Hyperplasia (Grade 2)

Intimal hyperplasia follows medial hypertrophy if pulmonary hypertension develops slowly. Intimal hyperplasia may appear without medial hypertrophy if pulmonary hypertension develops rapidly in infants with some types of congenital heart disease and in adults with some cases of diffuse alveolar damage (DAD). The intimal cells are increased in size and number. As they encroach upon the lumen, they tend to be oriented radially rather than concentrically. Abundant, clear, ground substance may separate the intial nuclei. It will stain positively with the Alcian blue stain. The boundary between intima and media may be partially effaced. Over time, the myxoid character of the stroma is lost. It becomes hyalinized. Intimal hyperplasia can be seen in hypertension of both congenital heart disease and diffuse pulmonary scarring. In the latter instance, it is usually associated with clinically severe disease and tends to be most marked in the midst of the scarring.

Concentric intimal hyperplasia should be distinguished from eccentric bolsters of intimal cells at bifurcation points. The bolsters may appear to partially occlude arteries when cut at odd angles. The bolsters are a phenomenon of aging and are common in open lung biopsies from elderly patients. The bolsters are not indicative of hypertension.

Intimal Fibroelastosis (Grade 3) (6502)

Deposition of fibers of collagen and elastica in the hypertrophic intima defines the next stage of pulmonary hypertension. Both the fibers and the nuclei form concentric lamellae. Because concentrically arranged fibers are seen in both medial and intimal hypertrophy, it may not be clear whether these lamellae are the result of medial and/or intimal hyperplasia without an elastic tissue stain. The intima becomes eosinophilic as the content of collagen increases. Eventually, the intima becomes hyalinized and has few nuclei. In severe disease, the hyperplasia comes to occlude the arteries and arterioles. Whereas arteries with an external diameter of l00–300 μ are primarily involved in grade 2 pulmonary hypertension, larger arteries up to 500 μ in diameter are involved as well in grade 3 pulmonary hypertension. Associated with the intimal changes is an increase in the medial hyperplasia and in the distal extension of smooth muscle cells.

Intimal fibroelastosis indicates permanent vascular damage. In congenital heart diseae, it suggests a poor prognosis. In adults, intimal fibroelastosis may be eccentric as well as concentric and associated with focal fibrous scars in both the intima and media. It is uncommon and then focal in most types of pulmonary fibrosis. It can be extensive, however, in patients with scleroderma, lupus erythematosus, and rheumatoid disease.

Occlusive intimal fibroelastosis should be distinguished from organizing pulmonary emboli, which produce secondary hypertension with a different histogenesis. In organizing or organized emboli, one may see remnants of laminated fibrin, multiple serpentine capillaries reflecting recanalization, and extensive elastosis and obliteration of the intimal-medial interface. Arterial and arteriolar hypertension with concentric intimal fibroelastosis has a single central lumen, if any lumen remains, whereas hypertension on the basis of organizing emboli has eccentric fibrosis and a single, large, residual, crescentic lumen or multiple small channels within the occlusive intimal fibrosis.

Plexiform Arteriopathy (Grade 4)

In the most severe form of pulmonary hypertension, the muscular pulmonary artery or arteriole undergoes fibrinoid necrosis. The necrosis is often segmental, usually associated with nuclear dust, and progresses to aneurysmal rupture. This is followed by hemorrhage into the interstitium or alveoli and later by hemosiderosis. The local reparative structure that re-establishes the continuity of the flow of blood is the plexiform lesion, the benchmark of grade 4 pulmonary hypertension. The fibrin clot which forms after vascular rupture is organized by an ingrowth of fibroblasts and capillaries. A congeries of endothelial lined channels within the wall of the artery at the point of rupture and external to it connects the artery directly to nearby venules and veins.

There is considerable variation in the appearance of plexiform lesions. Easiest to overlook are those which, in a given cross-section, are within the original confines of the artery. Easiest to spot are those external to the artery, which produce an abnormal hump on the artery. Plexiform lesions may be as big as l mm in diameter. The lumens of the plexiform lesion may be narrow and slit-like and vaguely resemble Kaposi's sarcoma. The endothelial cells may produce a cellular nodule resembling a glomus tumor adjacent to the artery. At other times, the lumens of the plexiform lesion may be widely patent, and the lesion then resembles an arteriovenous malformation. If the lumens contain fibrin clot, the lesion must be distinguished from an organizing embolus. Even in clinically severe pulmonary hypertension, the plexiform lesion is usually not frequent. Only one or two may be present per slide, and at least 10 blocks of tissue should be examined before concluding that no plexiform lesions exist.

Often associated with the plexiform lesion is the dilatation lesion. This is a segment of ectatic vessel in which the media seems to have vanished. The segment of dilated vessel may be straight and fusiform, or it may become coiled and resemble a cavernous hemangioma, sometimes referred to as an angiomatoid lesion. Or it may appear as a localized, thin-walled, bulbous swelling resembling an aneurysm. Dilatation lesions are thought to be a result of proximal luminal narrowing by intimal fibrosis and post-stenotic dilatation. They are thought to be a direct result of necrotizing arteritis. Occasionally, dilatation lesions are observed in association with lesser degrees of pulmonary hypertension in the absence of plexiform lesions.

Plexiform arteriopathy, in distinction to lesser grades of pulmonary hypertension, generally is seen in clinically severe disease. It is not, however, an etiological diagnosis. It is a common finding in children or adults dying with severe and untreated congenital

heart disease with a large left-to-right shunt. It is also seen in primary pulmonary hypertension, which is classically a rapidly progressive disease in young women. The plexiform lesion has been observed in patients who have ingested the apetite-suppressant drug aminorex. It is rarely seen in patients with hepatic cirrhosis. A similar lesion has been seen in pulmonary schistosomiasis. Plexiform arteriopathy is seldom seen in all other types of pulmonary hypertension and is thus an important feature in differential diagnosis, even though it does not supply an etiology.

Fibrinoid necrosis and plexiform lesions are usually not seen in children under 2 yr of age, even though there may be physiologically high pressures. In this age group, recognition of the obliterative changes is more important than the fibrinoid or plexiform changes. A marked reduction in the number of small arteries and arterioles can be observed qualitatively, but a slight or moderate reduction requires quantitative methodology.

VASCULITIS

Pulmonary Capillaritis: Histological Features

- Neutrophils and nuclear dust in interstitium and along alveolar walls
- Blood in alveoli with few neutrophils
- Capillary thrombosis
- Fibrin nodules on alveolar walls
- Fibrinoid necrosis of alveolar walls and loss of alveolar walls
- Advanced cases with alveolar filling by neutrophils ("alveolitis")

Pulmonary Capillaritis: Causes

- Wegener's granulomatosis
- Lupus erythematosus
- Microscopic polyangiitis
- Acute rheumatoid disease
- Henoch-Schoenlein purpura
- Goodpasture's disease
- Plexogenic hypertension
- Artifact resulting from instrumentation

Leukocytoclastic

Nuclear dust in and around blood vessels and hemorrhage define leukocytoclastic vasculitis. Fibrinois necrosis is often visible in larger vessels but hard to detect in capillaries and venules. Leukocytoclastic capillaritis is not commonly documented histologically in the lung. This is owing to the difficulty in appreciating nuclear dust and blood in interalveolar septa because the interstitial space is so thin. Further difficulty resides in interpretation of the significance of nuclear dust and hemorrhage once they have entered the air space, where often they are assumed to represent leukocytoclastic or hemorrhagic pneumonia.

Leukocytoclastic vasculitis in the lung may be a facet of systemic vasculitis or may be primarily pulmonary. Examples of systemic leukocytoclastic vasculitis with pulmonary involvement include drug reactions, Henoch-Schonlein purpura, lupus erythematosus, and rheumatoid disease. The kidney and skin are often biopsied in preference to the lung in these conditions. Other immune complex diseases may be primarily pulmonary. In contrast to leukocytoclastic pneumonias, in leukocytoclastic vasculitis, the amount of

nuclear dust is relatively less and the hemorrhage relatively more. Leukocytoclastic vasculitis and unexplained pulmonary hemorrhage are the prime indications for study of lung biopsies by direct immunofluorescence to detect immunoglobulins and complement in walls of blood vessels. Not all cases of immunologically mediated pulmonary hemorrhage exhibit leukocytoclastic vasculitis.

Early Gram-negative sepsis may produce a neutrophilic infiltrate in capillary walls and in the interstitium of interalveolar septa and pleura. This event occurs early in the course of the sepsis when the diagnosis may not be clinically obvious. In *Pseudomonas vasculitis*, one observes swarms of Gram-negative bacilli in the interalveolar septa, associated with leukocytoclasis, vascular thrombosis, and hemorrhagic necrosis. In embolic sepsis, intravascular emboli contain organisms. Lobar pneumonia produces arteritis, capillaritis, and phlebitis with disintegrating neutrophils. The lobar consolidation surrounding the vessels is obvious. Neutrohils and red blood cells in the pleura may be the result of rough or prolonged handling of the lung at thoracotomy prior to biopsy.

Wegener's disease may produce a leukocytoclastic vasculitis involving arteries, veins, and capillaries. The capillaritis is uncommon but, if observed, serves to distinguish Wegener's disease from infection. Polyarteritis nodosa produces leukocytoclastic vasculitis of pulmonary arteries and veins. Because of the larger size of the vessels, fibrinoid necrosis is much more apparent than in leukocytoclastic capillaritis. The necrosis is usually segmental both in longitudinal and cross-sectional dimensions. Granulomatous inflammation in and around the blood vessels serves to distinguish Wegener's disease and pulmonary polyarteritis nodosa from purer examples of leukocytoclastic vasculitis.

Severe or accelerated pulmonary hypertension produces segmental or circumferential fibrinoid necrosis of musuclar arteries and arterioles with nuclear dust and hemorrhage. Distinction from polyarteritis is based on the presence of plexiform and dilated lesions and on the intimal and medial changes of milder degrees of pulmonary hypertension in other arteries.

Eosinophilic

Eosinophils in the walls of blood vessels define eosinophilic vasculitis. Eosinophils in arteries are seen in eosinophlic granuloma. The disease is diagnosed by other characteristics, and the presence of eosinophils in blood vessels is not an important diagnostic feature. The interstitial infiltration of eosinophils in chronic eosinophilic pneumonia or in interstitial eosinophilic pneumonitis associated with asthma includes eosinophils in walls of capillaries and veins. Eosinophilic vasculitis in these conditions rarely has nuclear dust or fibrinoid necrosis even though the wall of the vessel may be thickened and the lumen occluded. Thus, the pathogenesis of eosinophilic vasculitis is different from leukocytoclastic vasculitis.

Lymphocytic Vasculitis

Lymphocytes are commonly seen within vessel walls in lymphoproliferative disorders whether they are benign, premalignant, or malignant. The vessel wall is infiltrated, thickened, and the lumen is obliterated. The vessel in this sense is destroyed, but fibrinoid necrosis does not occur. The term lymphocytic vasculitis indicates an observation but, unlike leukocytoclastic vasculitis, it implies no pathogenic mechanism.

Leukocytic vasculitis occurs in Wegener's disease but forms a small portion of the diagnostic histology. A relatively pure example of lymphocytic vasculitis in the lung

occurs in Behcet's diease, a syndrome of recurrent oral and genital ulcers in which there is rarely pulmonary vasculitis with hemorrhage.

Mycobacterial and fungal infections may induce an obliterative vasculitis with lymphocytes in the wall of the vessel. Veins are involved more than arteries. Dirofilariasis elicits a marked infiltration of lymphocytes and plasma cells into the wall of the artery adjacent to but also distant from the embolic filaria. Plasma cell vasculitis in an inflammatory nodule should prompt a search for a dead filaria in other sections. A pulmonary syphilitic gumma has a plasma cell vasculitis.

Discrete and compact granulomas of sarcoidal type occur in arteries and veins in sarcoid, necrotizing sarcoidal granulomatosis, and tuberculosis. Granulomas with birefringent foreign material in giant cells occur in and around arteries in intravenous drug abuse. Granulomatous inflammation with aggregated or palisaded histiocytes and multinucleate giant cells in walls of arteries and veins occur in bronchocentric granulomatosis, Wegener's disease, and pulmonary polyarteritis nodosa. Granulomas in veins have been observed in veno-occlusive disease.

VENOUS HYPERTENSION

Venous hypertension in the adult usually arises from left-sided cardiac failure and particularly from mitral stenosis. The earliest change is medial hypertrophy with increase in the number of smooth muscle fibers. This is followed by intimal hyperplasia and adventitial fibrosis. Thickening of the walls of veins is more difficult to appraise than thickening of arteries because veins have irregular contours owing to collapse in histological sections, whereas arteries tend to retain a more circular contour. Elastic fibers in veins, normally distributed throughout the media, become condensed into internal and external elastic laminae. This condensation is termed arterialization. The vessel may become histologically indistinguishable from an artery except with regard to the anatomic location of the vessel. In severe venous hypertension, paucicellular intimal fibrosis may deform and even occlude the lumen. Intra-parenchymal varices rarely develop. Lymphatics are diffusely dilated.

In addition to the changes in the veins, the interstitium is first edematous and then fibrotic in severe venous hypertension. Hemosiderin is deposited within alveoli and interstitium. The result is brown induration of the lung. In most instances, arteriolar hypertension is found along with venous hypertension.

VENO-OCCLUSIVE DISEASE (6831)

Primary pulmonary veno-occlusive disease is a poorly understood condition of both sexes and all ages in which the pulmonary venules and veins become occluded in the absence of left-sided cardiac failure. The disease may be preceded by a febrile episode and has interstitial inflammation. Suggested etiologies include viral infection, immune complex disease, and drug effect. The disease is rare and usually diagnosed only at autopsy.

Many to most medium and small veins are occluded by myxoid intimal hyperplasia. Fibers of collagen and elastica may also be present within the intima. Elastic fibers may be calcified. The media may be normal, thickened, or arterialized with creation of internal and external elastic laminae. The lumen may contain an organizing thrombus which progresses to fibrous septation. Large pulmonary veins and bronchial veins also may be involved. Pulmonary arteries may show moderate degrees of medial and intimal hyper-

trophy. Pulmonary veins undergo progressive mural thickening with age, so the diagnosis must be made with caution in the elderly. The occlusive changes should be widespread and occur within the clinical context of a dyspneic patient who has radiological signs of congestion, pulmonary arterial hypertension, and a normal pulmonary wedge pressure.

Adventitial fibrosis extends from the veins into interlobular or interalveolar septa. Hemorrhage and hemosiderin may be scarce or abundant. The combination of diffuse interstitial fibrosis and hemosiderin creates histology resembling idiopathic pulmonary hemosiderosis. Around large veins, the interstitial fibrosis may be more nodular than diffuse. An interstitial lymphocytic and histiocytic infiltrate is found in the majority of cases, and the histology may then resemble usual interstitial pneumonitis (UIP). Veno-occlusive disease generally will go undiagnosed without an elastic tissue stain.

ARTERIOVENOUS MALFORMATION

Microscopic collections of anomalous arterial vessels leading into patulous venous vessels are occasional incidential findings in lobectomy specimens. Walls of the vessels often have a structure which is typical neither for arteries nor veins but intermediate between them. Most congenital arteriovenous malformations are found away from the bronchial tree. Histologically, they often have local hemorrhage, hemosiderin, and fibrosis.

Arteriovenous shunts are normal in the periphery of the lung. They occur after an embolism. They appear in the pleura in cirrhotic patients and are analogous to spider angiomas of the skin. Anastomoses between bronchial and pulmonary circulations are normal. Increased numbers occur in sickle cell anemia and in pulmonic stenosis.

Arteriovenous malformations may be small or large, single or multiple, central or peripheral. They may communicate with a systemic artery. They may have anomalous venous drainage to the vena cava or to the right atrium. Multiple, large, radiologically detectable, arteriovenous malformations occur in Osler-Weber-Rendu and Sturge-Weber syndromes. Isolated lesions may represent congenital anomalies, hamartomas, or benign neoplasms. Patients with large lesions are hypoxemic owing to shunting of blood and may cough up blood.

Malformations may affect bronchial arteries. A congenitally dysplastic artery in the bronchial mucosa with an irregularly thickened and cellular wall may rupture and cause massive hemoptysis. Acquired hypertrophy of bronchial arteries in bronchiectasis may appear similar.

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LETTERS

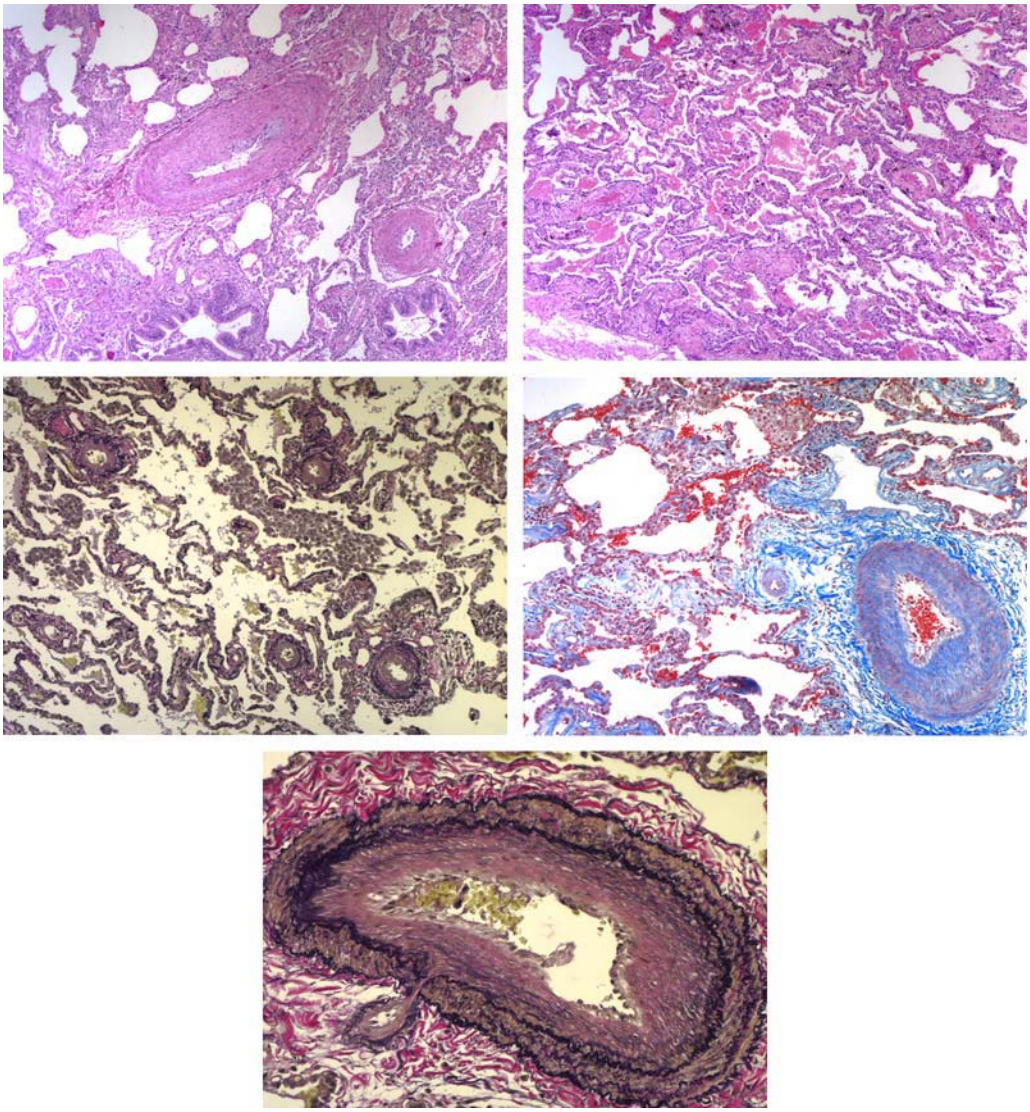
Case 6502

Diagnosis: Lung, open biopsy: Interstitial fibrosis and marked arterial hypertension, cause undetermined.

Although the lung is aerated, the circularity of the alveoli in most of the specimen indicates interstitial fibrosis involving the majority of the specimen. The pathology could represent UIP, but I cannot be sure of that diagnosis because the lymphocytic infiltrate is slight. I do not feel the changes are specific. Other authors might call this nonspecific interstitial pneumonitis. The small muscular pulmonary arteries and arterioles (elastic stain) have marked intimal proliferation approaching onion-skin change. This corresponds to grade III/IV pulmonary arterial hypertension. These changes (trichrome stain) are seen particularly in scleroderma and to a lesser extent in other collagen-vascular diseases. Another remote possibility is mitral lung disease, because there is focal hemosiderin and interstitial edema of lobular septa. I cannot relate the changes to Castleman's disease. I do not see disease that I would expect to be particularly responsive to corticosteroid therapy.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6502 (Chapter 6 – Pulmonary Vascular Disease)

Case 6656

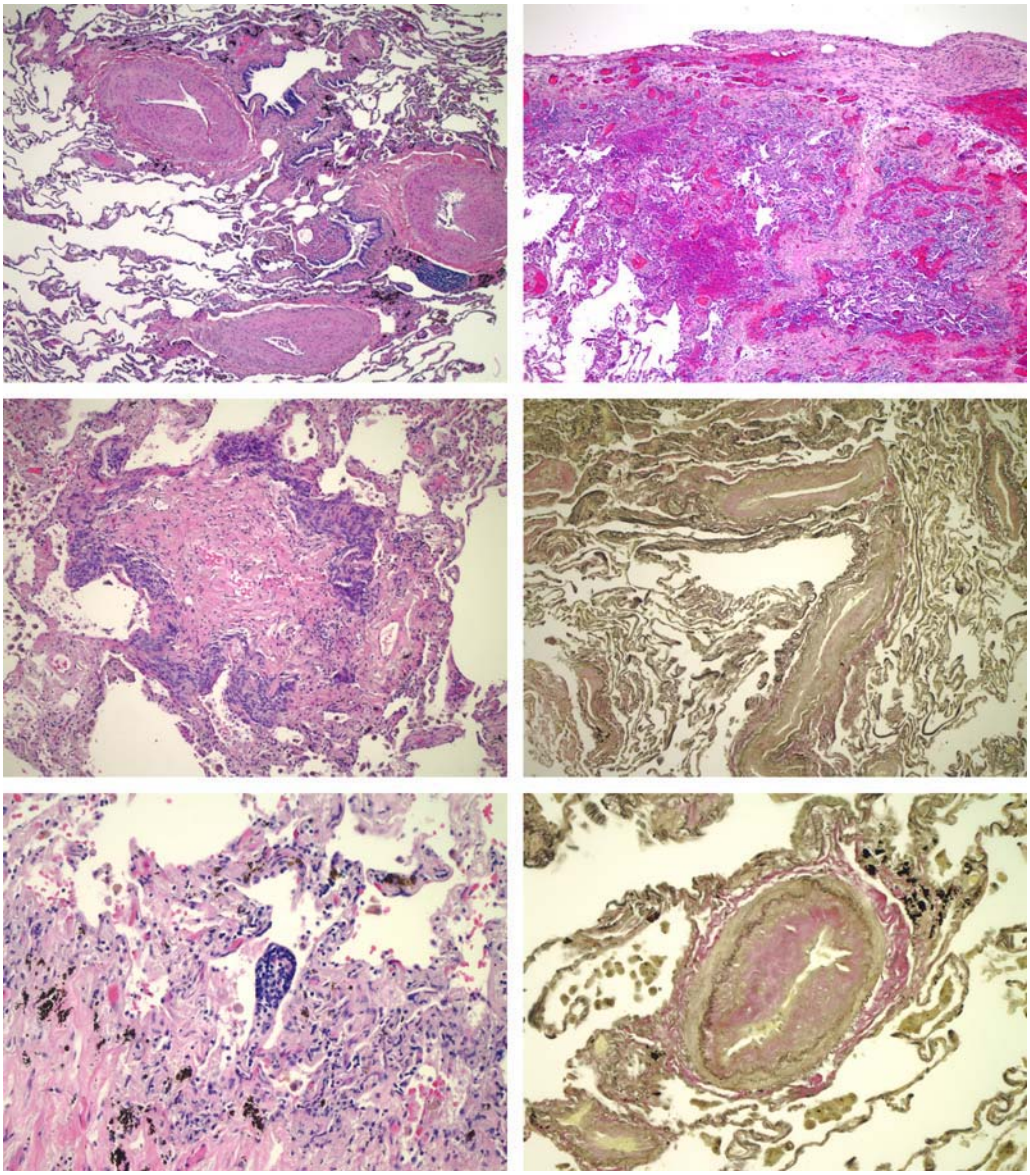
Diagnosis: Lung, open biopsy:

1. **Pulmonary arterial hypertension and pulmonary venous sclerosis and slight hemosiderin, nondiagnostic.**
2. **Organizing fibrinous pleuritis with pleural adhesions.**

Considerable compression and atelectasis make interpretation difficult. I see no cause for nodular lung disease. There is moderate (grade 3/4) arterial hypertension with intimal and medial hypertrophy (elastic stain). There is also venous sclerosis. In combination with mild interstitial inflammation and hemosiderin, the possibility of veno-occlusive disease arises. I don't know whether there is any clinical evidence of that condition. Venous sclerosis can be an aging phenomenon and might simply reflect the patient's age. Veno-occlusive disease usually results in more hemosiderin than is present here. A chemodectoma is present. Organizing fibrinous pleuritis is present. One microscopic focus of organizing pneumonia is present. The reportedly migratory masses with hemoptysis might make one consider arteriovenous malformations, but I see no evidence for this morphologically.

Thank you for referring this case in consultation. Please keep me informed of any follow-up, and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6656 (Chapter 6 – Pulmonary Vascular Disease)

Case 6831

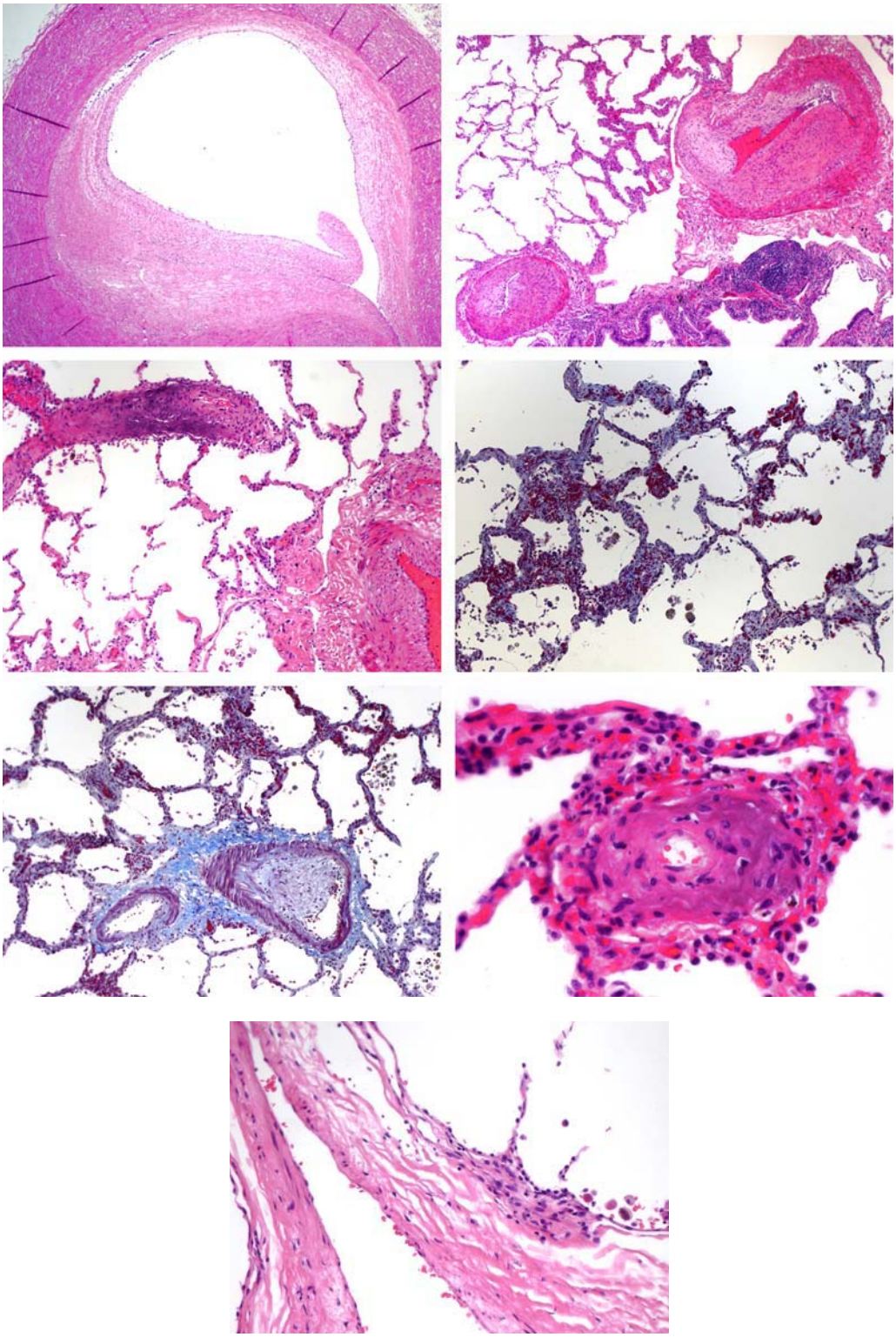
Diagnosis: Lungs, pneumonectomies:

1. **Veno-occlusive disease, with marked pulmonary arterial hypertension, focal interstitial fibrosis, and hemosiderin.**
2. **Chronic bronchitis with mucus plugs.**

The most striking pathology is pulmonary arterial hypertension of grade 3/4 (marked medial and intimal proliferation without plexogenic arteriopathy). The focal interstitial fibrosis with ectasia of capillaries is unusual for primary arterial hypertension and more in keeping with veno-occlusive disease, which is the diagnosis I prefer. Many of the thickened and scarred blood vessels (trichrome stain) cannot be precisely categorized as arteries or veins, but I believe some seen linearly and longitudinally in septa are definitely veins, and some of these veins have mural sclerosis and luminal narrowing or obliteration. There is also inflammation, including possible histiocytic inflammation, around some of the veins. Granulomatous inflammation in veno-occlusive disease has been described. The overlap of arterial hypertension due to arterial disease versus arterial hypertension due to venous disease becomes complex, but it is easier to explain the interstitial process by virtue of venous disease than arterial disease in this case. Endogenous pneumoconiosis (encrustation of blood vessel walls by calcium) is prominent. Hemosiderin (trichrome stain) is modest. The large pulmonary artery shows atherosclerosis with lymphocytic inflammation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6831 (Chapter 6 – Pulmonary Vascular Disease)

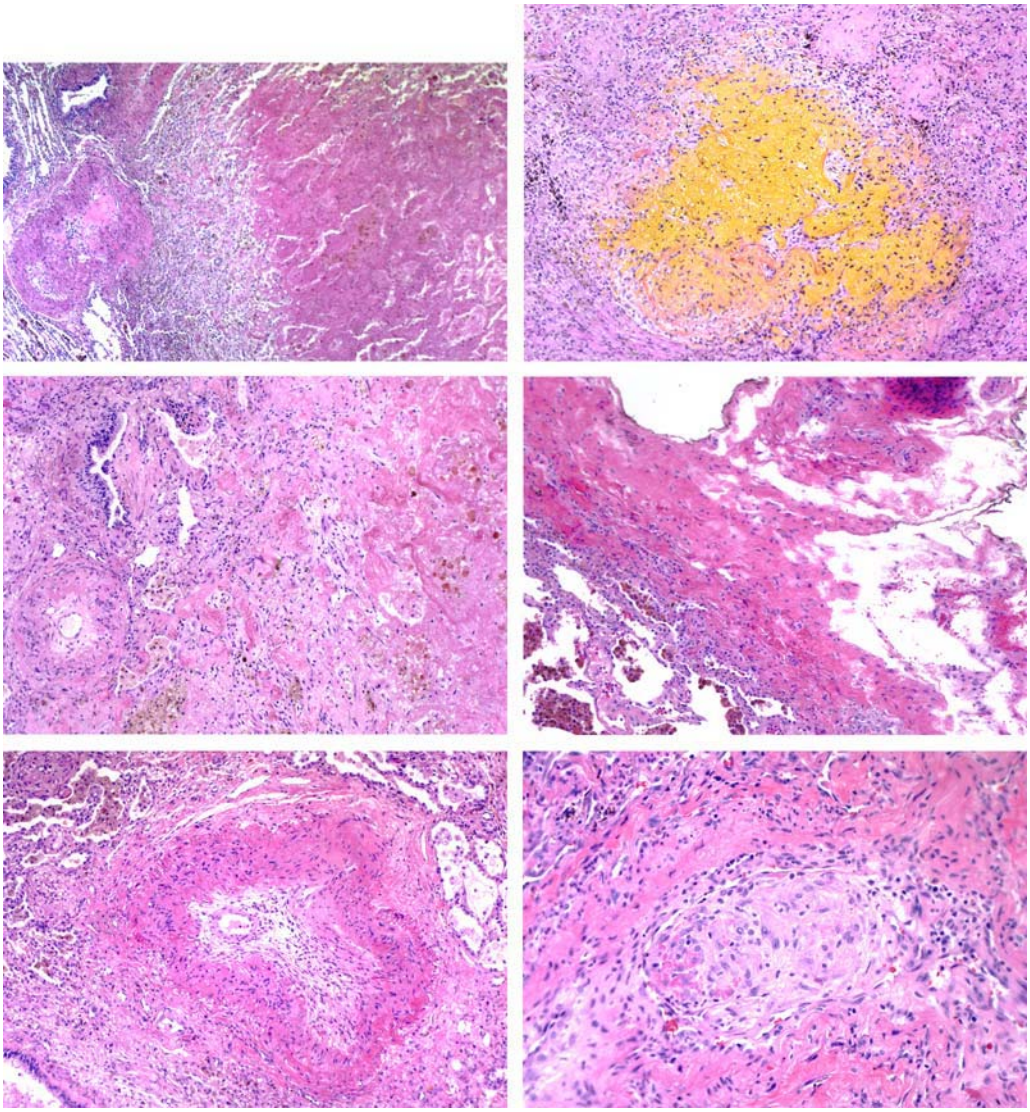
Case 6775

Diagnosis; Lung, wedge resection: Organizing thromboemboli with pulmonary infarction.

An area of necrosis and hyalinization is surrounded by fibrosis, which is in part older and in part active with alveolar organization. There is hemosiderin and capillary proliferation. Also present are organizing thromboemboli in many muscular and elastic pulmonary arteries. The emboli are in part eccentric and in part occlusive. The emboli are in part organizing blood clot and in part fibrous. The combination of the thromboemboli and the necrosis constitutes thromboembolic pulmonary infarction. There is organizing fibrosing pleuritis overlying the infarction. A small focus of hematoidin pigment is present in an area of necrosis in one slide. Hematoidin appears on rare occasions in pulmonary infarcts. I see no vasculitis and no malignancy.

Thank you for the opportunity to review this case. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6775 (Chapter 6 – Pulmonary Vascular Disease)

Case 6889

Diagnosis: Lung, autopsy:

1. **Pulmonary thromboemboli, subacute and organizing (days).**
2. **Bronchiolitis obliterans organizing pneumonia (BOOP), acute and organizing.**
3. **Pleuritis, recent and old, cause undetermined.**

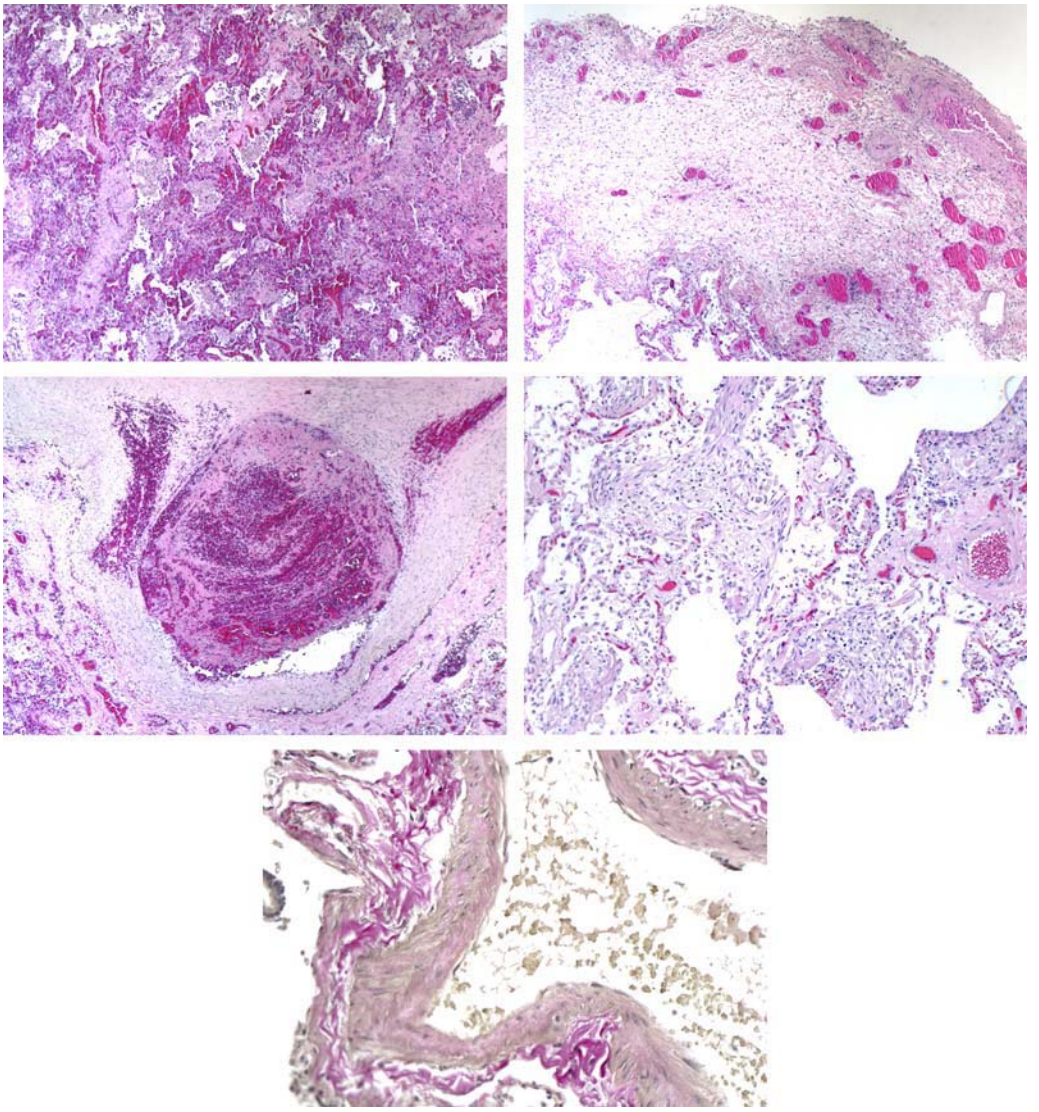
I cannot answer all of the questions or establish a precise scenario and time line in this case. The pulmonary thromboemboli provide for relatively precise dating, with ingrowth of capillaries traversing the entire width of pulmonary arteries a few millimeters in diameter. Thus, these emboli are approx 5–7 d in age. I detect no definite old eccentric fibrous occlusion indicative of old thromboemboli. There is a moderate amount of medial and intimal sclerosis of arterioles which can be categorized as pulmonary arterial hypertensive change, but such changes do not always correlate with physiologic hypertension and apparently do not correlate so in this case. I doubt significant mitral valve disease as a cause of the pulmonary vascular changes because of the virtual absence of hemosiderin.

The BOOP in this case is probably a BOOP-like change and not the clinicopathological entity of BOOP. However, the focality of the tufts of fibrous tissue and the absence of diffuse hyaline membranes or atypia of pneumocytes is more in keeping with BOOP than with DAD. The heavy weight of the lungs might then be related to pulmonary edema or hemorrhage rather than to DAD. One section shows hemorrhage and marked congestion and probable early ischemic damage consistent with an early infarction or near infarction as well as older fibrosis indicating a healing process. The cause of the BOOP is unknown. It is possible that this patient developed a viral infection over the last few days of life. The BOOP is recent with remnants of fibrin and no advanced fibosis.

The pleuritis includes fibrous organization weeks or months in age as well as more recent organizing fibrin. I do not know the cause of either the old or the recent pleuritis. Enigmatic causes in general include viral pleuritis, collagen-vascular diseases and drug reactions. Pulmonary infarcts can cause pleuritis, but in this case the pleuritis is older than the pulmonary emboli and not spatially associated with them, so I do not favor that interpretation.

Thank you for referring this case in consultation. Please call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6889 (Chapter 6 – Pulmonary Vascular Disease)

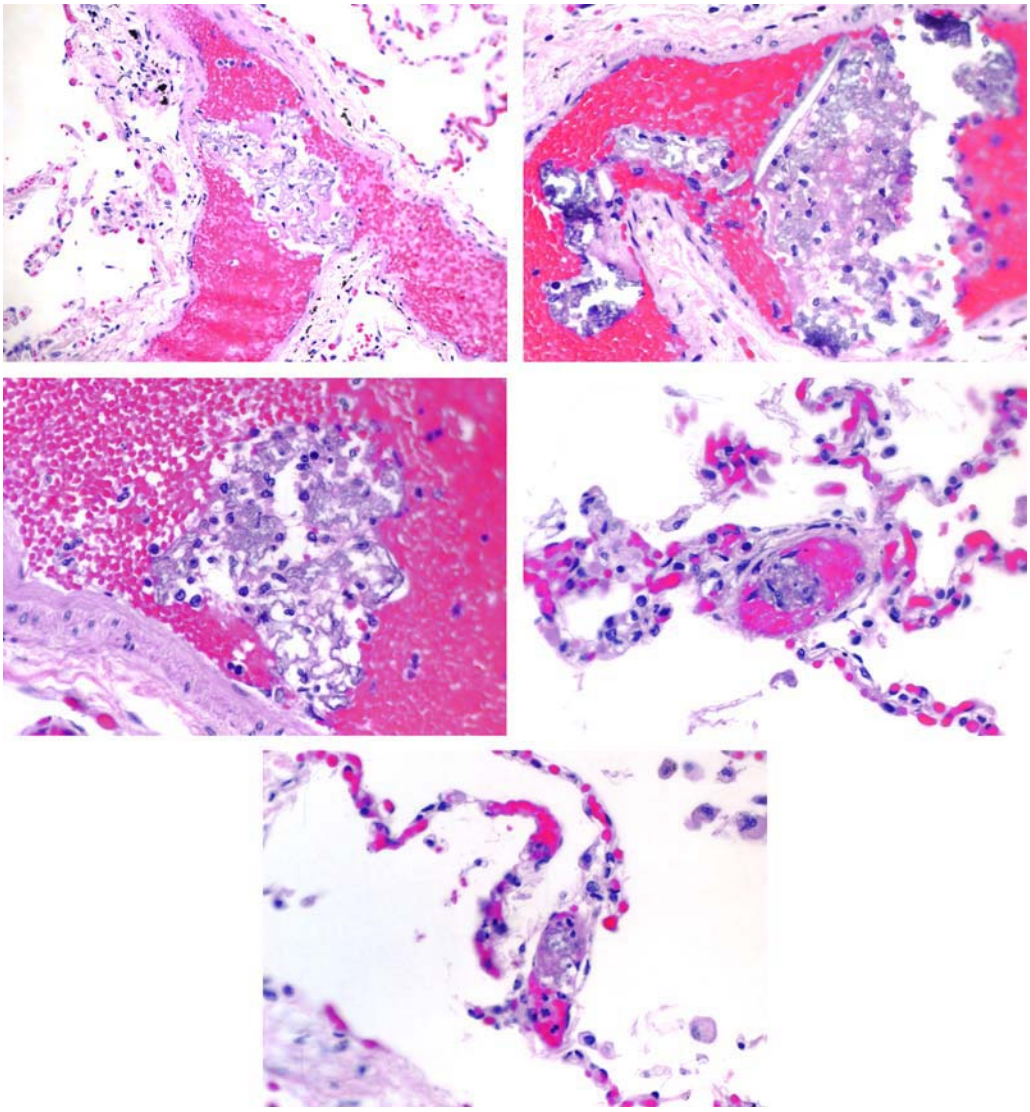
Case 6732

Diagnosis: Lung, autopsy: Embolic necrotic material, probably necrotic fatty bone marrow.

Many small pulmonary arteries and arterioles and capillaries contain clumps of basophilic material with admixed nuclei, as you indicate. I do not know for sure what this material represents. I favor necrotic fat as a manifestation of necrotic bone marrow. Because some pieces of recognizable bone marrow are present, I suspect that the basophilic masses are necrotic bone marrow. The oval or contorted nuclei in the basophilic material could represent either lymphoid cells or fibroblasts, both of which survive longer than erythroid and myeloid precursors in embolic bone marrow. Embolic fat can arise from administration of corticosteroids, vertebral compression fracture, other bone fracture, fatty liver, pancreatitis or necrotic tumor. I cannot definitely attribute the necrotic material here to surgery. I have seen embolic fat in patients who have sustained or exacerbated fractures during surgery, including fractures of long bones, in the process of manipulation. I cannot exclude necrotic retroperitoneal fat as a source for this material, but I do not know of a precedent in the literature for this interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6732 (Chapter 6 – Pulmonary Vascular Disease)

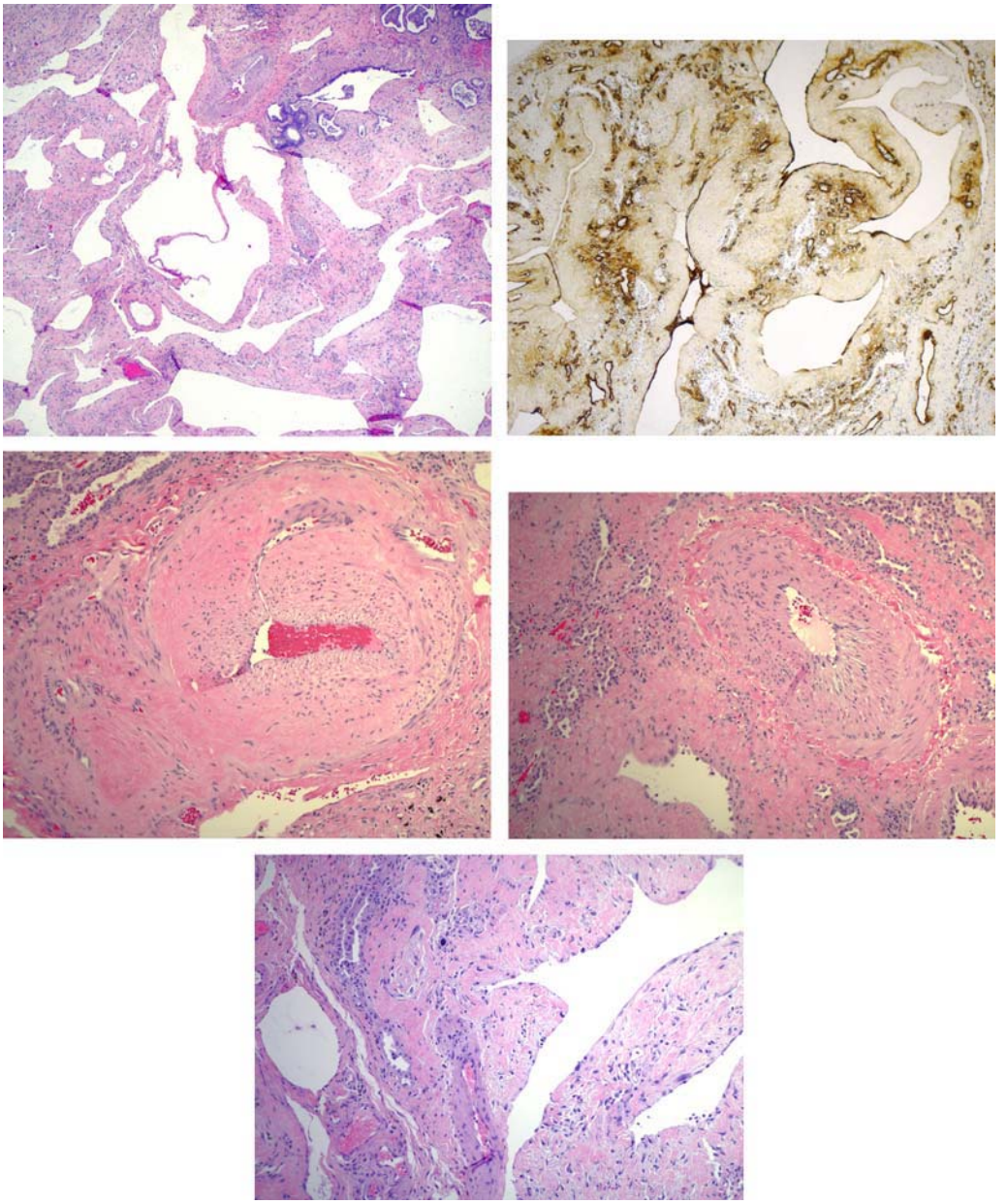
Case 6565

Diagnosis: Lung, wedge resection: Vascular malformation, ? arteriovenous, ? lymphatic.

Dilated spaces have thick fibrous walls and are lined by flat and inconspicuous cells. The differential diagnosis is honeycomb lung vs a vascular malformation, as you indicate. Your special stains show that the large spaces are indeed lined by endothelial cells rather than epithelial cells. Further proof of the vascular origin of this process are hypertrophic arteries with eccentric thickening of their walls and abnormal contour. Such vessels tend to be found around arteriovenous malformations and not in honeycomb fibrosis. More rarely they can occur around lymphangiomas. The distinction of blood vessel versus lymphatic malformation is important in the lung since the former are often multiple, either synchronously or metachronously, and may bleed, while the latter are generally incidental findings. I cannot distinguish the two in this case. The absence of hemosiderin indicates no prior bleeding and thus favors lymphangioma. The above is essentially in agreement with your interpretation. Your observation is an excellent one because it would be very easy to pass this off as honeycomb change. It appears that this lesion is not related to the patient's current problem of reportedly acute respiratory distress syndrome. I have performed elastic and trichrome stains on the block of tissue which you kindly provided, and these accentuate the mural changes in the abnormal blood vessels.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6565 (Chapter 6 – Pulmonary Vascular Disease)

Case 7175

Diagnosis: Lung, open biopsy: Capillary hemangiomatosis in pleura and interstitial lymphocytic inflammation, consistent with pulmonary capillary hemangiomatosis.

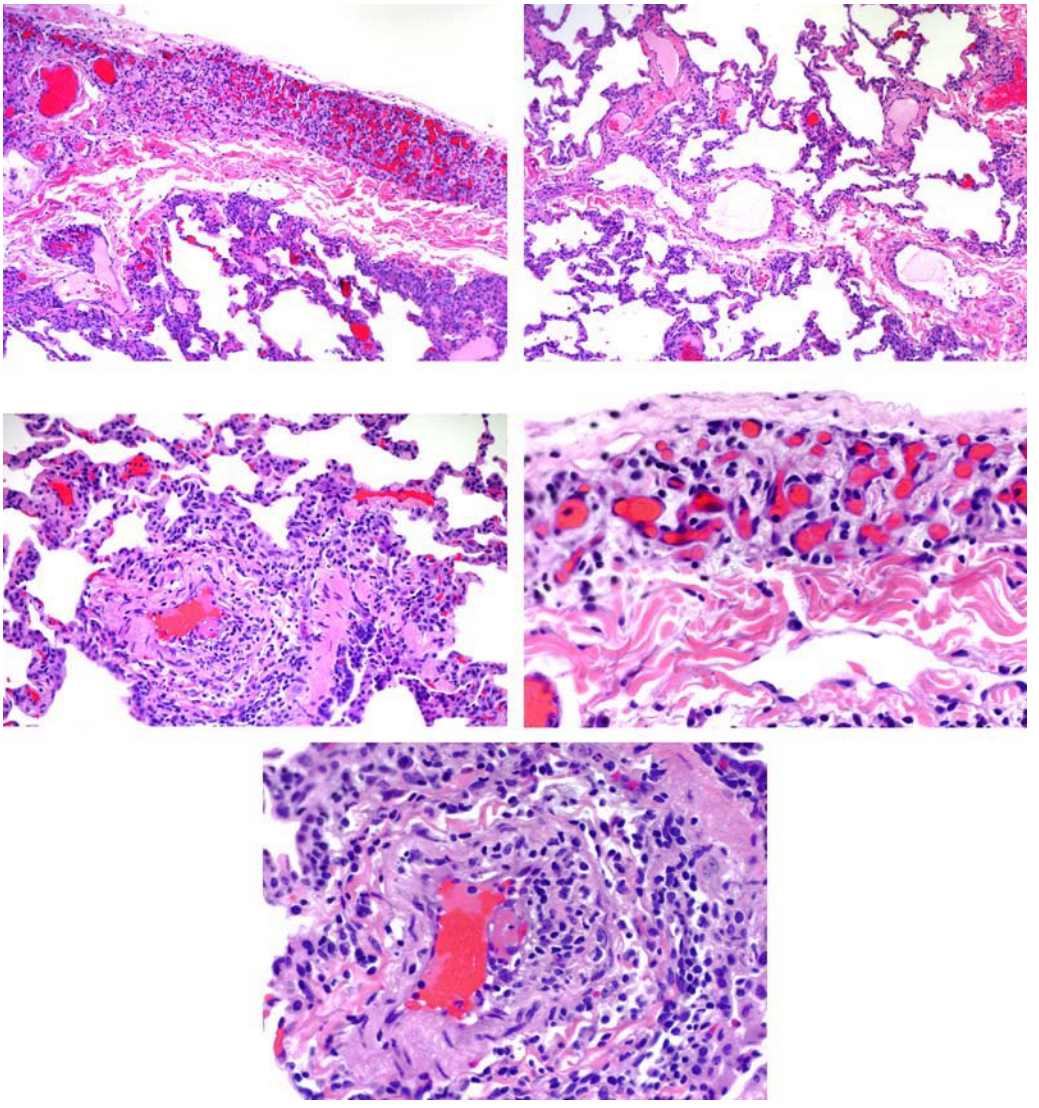
There is a marked and extensive proliferation of capillaries in the pleura. I agree that this is a primary proliferative process and not part of an organizing pleuritis or adhesion. I searched for congestive vasculopathy as a cause of this hemangiomatosis but find no hemosiderin or venous sclerosis or secondary pulmonary hypertensive change. Based on the pathology alone in the absence of capillary proliferation in lung parenchyma, I would not know whether this is an incidental finding or the patient's disease.

After our telephone conversation, I understand that subsequent radiographic studies have shown nodular densities in the lung with changes on angiograms suggestive of arteriovenous malformations. Therefore, I believe this capillary hemangiomatosis is related to that finding and represents the patient's disease rather than an incidental finding. This would also correlate with the reported rubbery appearance of the lung at surgery.

The lymphocytic infiltrate around some conducting airways and blood vessels includes occasional histiocytes, and lymphocytes and histiocytes are in one small artery with organizing fibrin partially obstructing the lumen. Because a common cause of clubbing in children is Crohn's disease, I considered pulmonary manifestations of Crohn's disease in the differential diagnosis. With the knowledge of the angiographic findings, I believe this lymphoid infiltrate is secondary to the vascular process and not the primary issue.

Thank you for the opportunity to review this case. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7175 (Chapter 6 – Pulmonary Vascular Disease)

7 Miscellaneous Pulmonary Disease

CONTENTS

INTRODUCTION

In this chapter, a series of cases is presented that have provoked significant thought on the part of the consulting and consulted pathologists. Most of these cases don't fall neatly into the context of other chapters in this volume. A number of these cases illustrate patterns of pulmonary disease that are not diagnostic and challenge the pathologist to offer an intelligent differential diagnosis. A brief discussion of some of these relevant diagnoses follows.

HYPERSENSITIVITY PNEUMONITIS

Sometimes termed extrinsic allergic alveolitis, hypersensitivity pneumonitis exhibits bronchiolitis, lymphohistiocytic infiltrate, eosinophils, and multinucleated histiocytes. An offending agent often is never identified. Many cases have the histology of a nonspecific interstitial pneumonitis (NSIP) if no bronchiolitis or giant cells are present.

DRUG REACTION AND HEMORRAGE

Drug reactions **(6764)** depend on the drug and may be chronic or acute, interstitial or alveolar, and marked or slight. There may or may not be eosinophils, pleuritis, bronchiolitis, or granulomatous inflammation depending on the drug. Because of the common use of amiodarone and because of some more specific features, amiodarone constitutes a special case. Usual interstitial pneumonitis (UIP) with amiodarone effect must be considered in the differential diagnosis.

The most common differential diagnosis for pulmonary capillaritis is an acute bacterial or viral pneumonia that has caused extensive hemorrhage without capillaritis. Filling of the alveoli and bronchioles with neutrophils and microabscesses suggest infection. Hyaline membranes suggest viral infection, as was illustrated in Chapter 4. Hyaline

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

membranes also raise the possibility of diffuse alveolar damage (DAD), which occasionally exhibits more blood than hyaline membranes or atypia of pneumocytes and fibroblasts.

A bleeding diathesis leaves no telltale histological finding in the lung unless one also finds an intravascular leukemia that might be causing it. Arteriovenous malformations are generally difficult to identify unless angiography localizes them precisely. Even then, pulmonary arteriovenous malformations may destroy themselves when they rupture. There may be no way to prove that blood in an open lung biopsy has been aspirated from a proximal source, but often aspirated blood fills one lobule entirely and the adjacent lobule not at all. This is because blood is draining into one terminal bronchiole that bifurcates downward relative to gravity but does not enter the next terminal bronchiole that bifurcates upward relative to gravity.

Pulmonary hemorrhage occurs in a variety of pulmonary-renal syndromes. Some are well characterized, such as Goodpasture's syndrome (anti-basement membrane antibody disease) and IgA nephropathy. Other pulmonary bleeding may be poorly characterized and idiopathic. In our experience, a leukocytoclastic capillaritis is not recognized in the lung in Goodpasture's syndrome even when there is extensive hemorrhage.

Hemosiderosis **(6911)** has more fibrosis relative to inflammation than UIP. Hemosiderosis may be diffuse or patchy. Small amounts of hemosiderin are occasionally seen in UIP. In cases of moderate amount, distinction may not be possible. Hemosiderosis secondary to mitral disease or to primary veno-occlusive disease is associated with changes of venous hypertension.

Idiopathic pulmonary hemosiderosis (IPH) is a diagnosis best avoided if at all possible. Although the histological features of interstitial fibrosis and extensive hemosiderin are easy to recognize, the pathological diagnosis does not have a consistent clinical presentation or natural history. There are probably several causes of the idiopathic form of the disease, one of which is a previous capillaritis and hemorrhage. IPH in these cases is the chronic sequel to the acute hemorrhage. Diagnoses of Wegener's granulomatosis (WG) and Goodpasture's syndrome have been established during later episodes of acute pulmonary hemorrhage in patients with a prior diagnosis of IPH.

Amiodarone Pneumonitis

- Drug-induced phospholipidosis
- Vacuolated macrophages and pneumocytes
- Birefringent particles
- Lamellar inclusions
- Interstitial pneumonitis (R/O UIP)
- Hyaline membranes
- Bronchiolitis
- ? reversible, ? honeycomb fibrosis

Pulmonary Hemorrhage in Open Lung Biopsy: Causes

- Operative effect
- Aspiration
- Bleeding diathesis
- Arteriovenous malformation
- DAD
- Infective pneumonia

- Goodpasture's disease
- IPH
- Capillaritis

Blood in Lung: Clues That It May Be Illusory

- Neutrophils around pleural venules
- One lobule involved but not another
- Intervening alveoli atelectatic
- Alveoli not expanded
- No hemosiderin

OTHER PULMONARY DISEASES

Asbestosis in late stage is primarily fibrosis, but in early stage, an interstitial lymphocytic infiltrate may be marked. Asbestosis in early stage may be accentuated around respiratory bronchioles and beneath the pleura. This localization is not part of UIP. One or more asbestos bodies per slide exclude UIP. Differentiation of asbestosis **(6867)** from silicatosis **(6917)** is based on the strong birefringence of silicates, which result from the combination of silicon dioxide with one or more cations, usually magnesium, calcium, and aluminum. Furthermore, ferruginated silicates differ in morphology from asbestos bodies, being broader, shorter, plate-like, and more irregular than asbestos bodies.

Occasional patients have a nonscarring lymphocytic interstitial infiltrate of moderate degree without granulomas and without accentuation around bronchioles. This entity may be seen primarily in children, where the clinical course has been benign and the children have recovered. It is possible that some cases represent viral stimulation of the immune system in the lung in a manner comparable to follicular bronchiolitis, which is the usual differential diagnosis clinically. Other cases in the literature may represent abnormal immature lung, in part or in whole.

UIP, desquamative interstitial pneumonitis (DIP), and lymphocytic interstitial pneumonitis (LIP) all occur in childhood. The same essential histological criteria are applied as in adults. However, the clinical significance of these diagnoses in children is less clear than in adults.

A few congenital anomalies of lung reviewed here reflect some diagnostic challenges to which the pathologist may be confronted. Congenital pulmonary lymphangiectasia **(6667)**, a usually fatal disorder in a neonate, is characterized microscopically by cystic dilatation of lymphatic vessels in interlobular septa and fanning out in the subpleural region of an entire lung or, rarely, a single lobe. The endothelial cells, which line the dilated vessels, may be lined by a loose myxoid or dense connective tissue. This entity is distinguished from interstitial pulmonary emphysema, in which dilated spaces lacking a cellular lining are limited to interlobular spaces.

Congenital cystic adenomatoid malformations, recently given the new name of congenital pulmonary airway malformations (CPAMs), are subclassified into five separate anomalies originating from regions of the airway extending from the tracheobronchial segment to the distal acinar region. CPAM type 2 **(6869)**, the intermediate cyst type, comprises 15–20% of CPAMs and may be associated with other anomalies. Microscopically, these lesions consist of dilated bronchioles which lie "back to back" and are separated by structures that resemble irregular alveolar ducts. They have been seen in up to

50% of extralobar sequestrations, which are segments of pulmonary parenchyma which are isolated from the tracheobronchial tree, with separate visceral pleura and arterial blood supply ususally from a branch of the aorta. Extralobar sequestrations, except those with embedded CPAMs **(6809)**, contain bronchioles, alveolar ducts, and alveoli which are uniformly dilated in uninflated specimens.

Mesenchymal hamartomatous nodules and cysts **(4408)** in the lungs can cause hemoptysis, pneumothorax, hemothorax, pleuritic chest pain, dyspnea of slight or moderate degree, or a combination of these signs and symptoms. They can be multifocal and bilateral. The nodules are composed of primitive mesenchymal cells subdivided into papillae by a plexus of small airways lined with respiratory epithelium. The nodules grow slowly in number and size over the years and apparently become cystic when they reach a diameter of about 1 cm. The cysts have a cambium layer of mesenchymal cells and are lined with normal or metaplastic respiratory epithelium. In general, the disease has an indolent course. Malignant transformation has been noted in one case.

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LETTERS

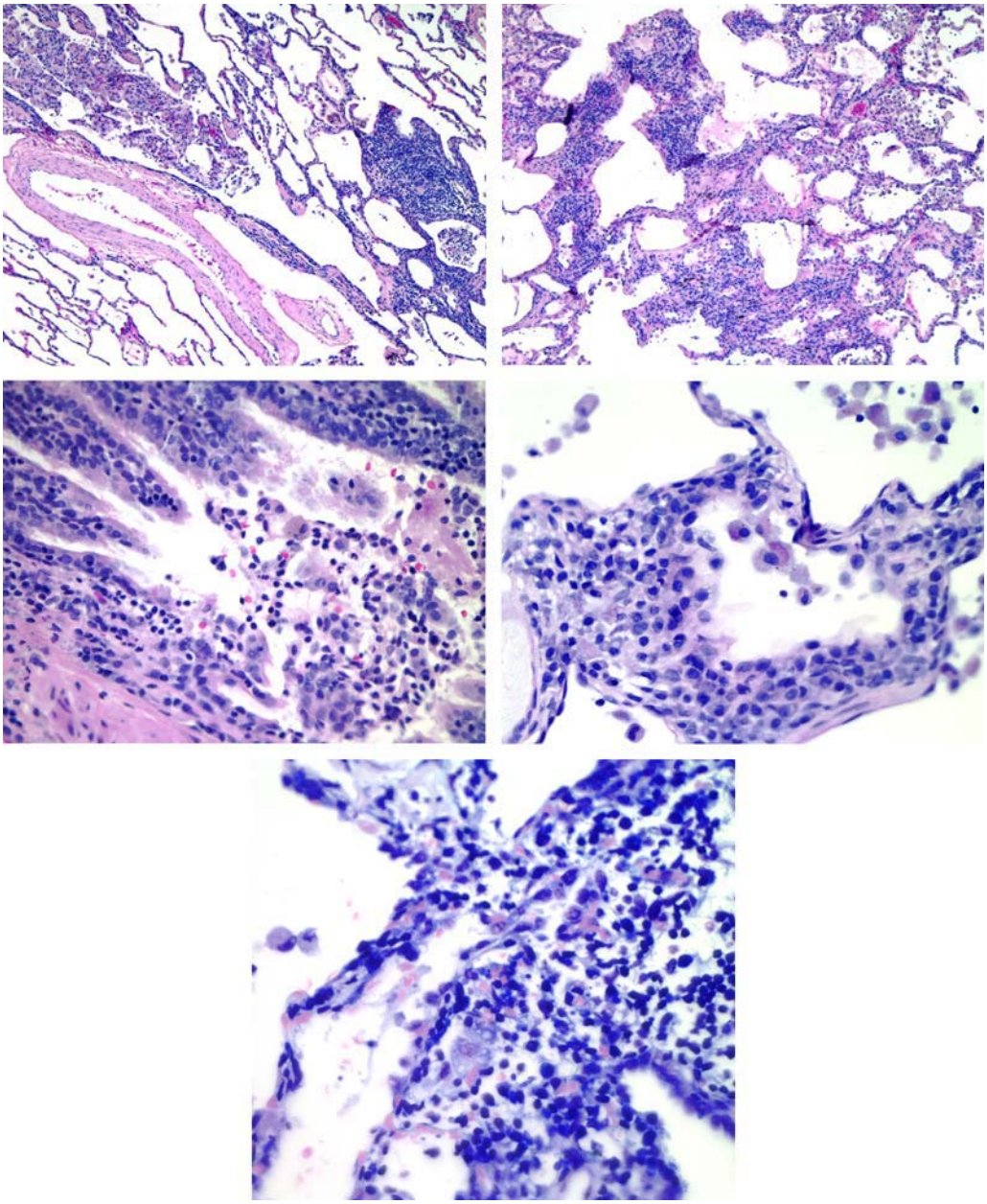
Case 7010

Diagnosis: Lung, open biopsy: Lymphohistiocytic inflammation, moderate, with peribronchiolar accentuation and scattered neutrophils in bronchioles, consistent with hypersensitivity reaction.

I essentially agree with your interpretation of hypersensitivity pneumonitis vs LIP. In my view LIP is a lymphoproliferative disorder, whereas in this case there are the added components of histiocytic inflammation around alveoli, neutrophils in bronchioles, and a few small aggregates of histiocytes. These features all suggest hypersensitivity pneumonitis, even though eosinophils and distinct granulomatous inflammation are lacking. The clinical history is also consistent with either of the two proposed clinical interpretations, but more in keeping with the history of intermittent seasonal disease. Lymphocytic hyperplasia or inflammation (Giemsa stain) also can occur with autoimmune and collagen-vascular diseases, and I cannot exclude that interpretation, but the histiocytes favor hypersensitivity reaction. I generally do not use the term NSIP as an entity but rather as the process which has many attributes of UIP but is not diagnostic of same. The absence of significant scarring in this case excludes a firm diagnosis of UIP, and I would not make a diagnosis of NSIP in this case.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7010 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 7170

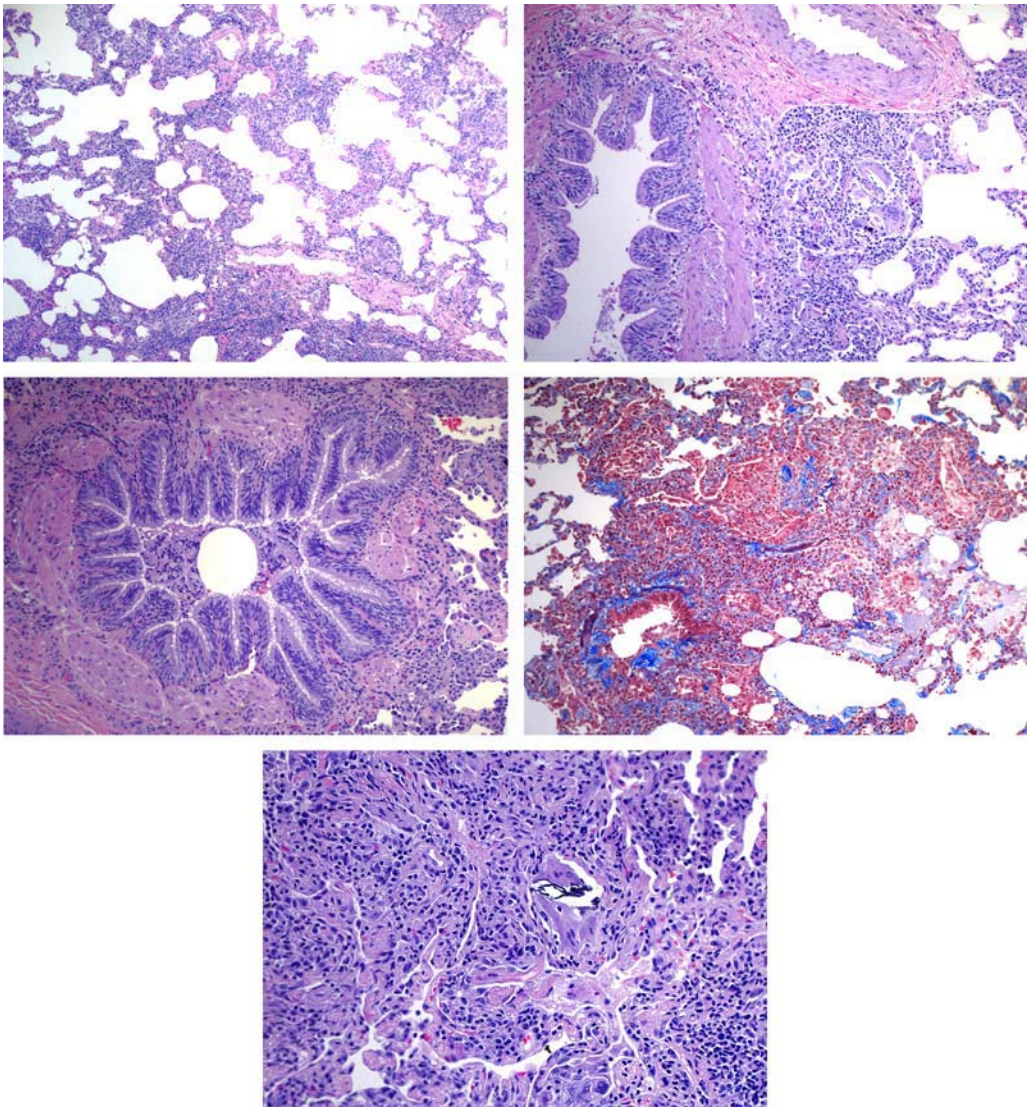
Diagnosis: Lung, open biopsy: Lymphohistiocytic and granulomatous inflammation, extensive, with refractile crystaline material in multinucelated histiocytes, ? hypersensitivity reaction, ? aspiration, ? other.

I have sectioned the four blocks of tissue which you provided and stained them with hematoxylin and eosin, elastic, trichrome, and periodic acid-Schiff. The majority of the lung is involved with a lymphohistiocytic infiltrate which is both interstitial and alveolar (trichrome stain). A small amount of bronchiolitis obliterans (BO) is present, but the pathology overall is not that bronchiolitis obliterans organizing pneumonia (BOOP). There are loosely aggregated histiocytes and several more compact aggregates of multinucleated histiocytes containing refractile and partially calcified material. Some histiocytes also have cholesterol clefts.

The etiology of this process is not clear. The crystalline material may represent aspiration, which could produce this histology. Hypersensitivity reaction is another possibility, but the absence of more extensive BO and the absence of eosinophils do not further support that interpretation. I cannot exclude a resolving infectious pneumonia, but I doubt it. No pus, compact granulomas of tuberculoid type, or necrosis are present. These features all serve to exclude an active infection. Acute sarcoidosis (Lofgren's syndrome) enters into the differential diagnosis. Elastic and trichrome stain show minimal fibrosis. The absence of temporal heterogeneity and the absence of advanced fibrosis such as subpleural honeycomb change are against UIP. To the degree that the process is principally cellular and minimally fibrotic, to that degree, one might hope for a favorable response to corticosteroid therapy.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7170 (Chapter 7 – Miscellaneous Pulmonary Disease)

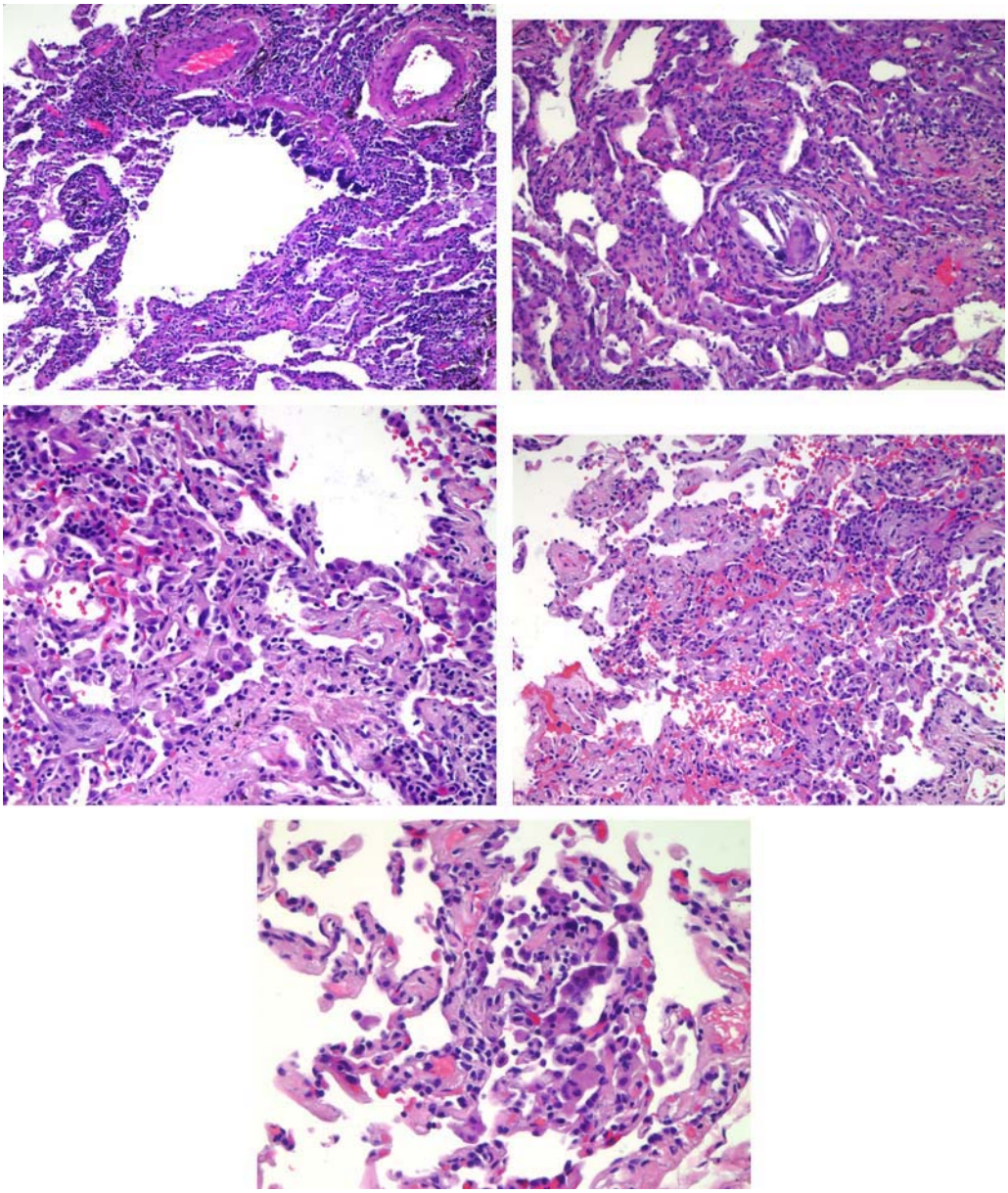
Case 6687

Diagnosis: Lung, open biopsy: Interstitial lymphocytic infiltrate with fibrin and vacuolated histiocytes and rare poorly formed granuloma, nonspecific, ? hypersensitivity pneumonitis, ? other.

The lymphohistiocytic infiltrate is well developed but unassociated with any significant old interstitial fibrosis or with active intra-alveolar organizing fibrosis. Multinucleated histiocytes and cholesterol clefts are present. Thus, the changes are not diagnostic of UIP (fibrosing alveolitis). Although I cannot exclude an early phase of that disease, I doubt that interpretation. The fibrin indicates active disease. The constellation of changes raises the possibility of a reaction to inhaled antigens or particles creating a hypersensitivity pneumonitis (extrinsic allergic alveolitis). This diagnosis would be more probable if bronchiolitis or eosinophils were present. There is a peribronchiolitis but no BO or organizing pneumonia (OP). Other etiologic considerations include drug reaction, aspiration, the inflammatory phase of sarcoidosis with a "lymphocytic alveolitis" and no sarcoidal granulomas, or an unusual infection, such as psitticosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6687 (Chapter 7 – Miscellaneous Pulmonary Disease)

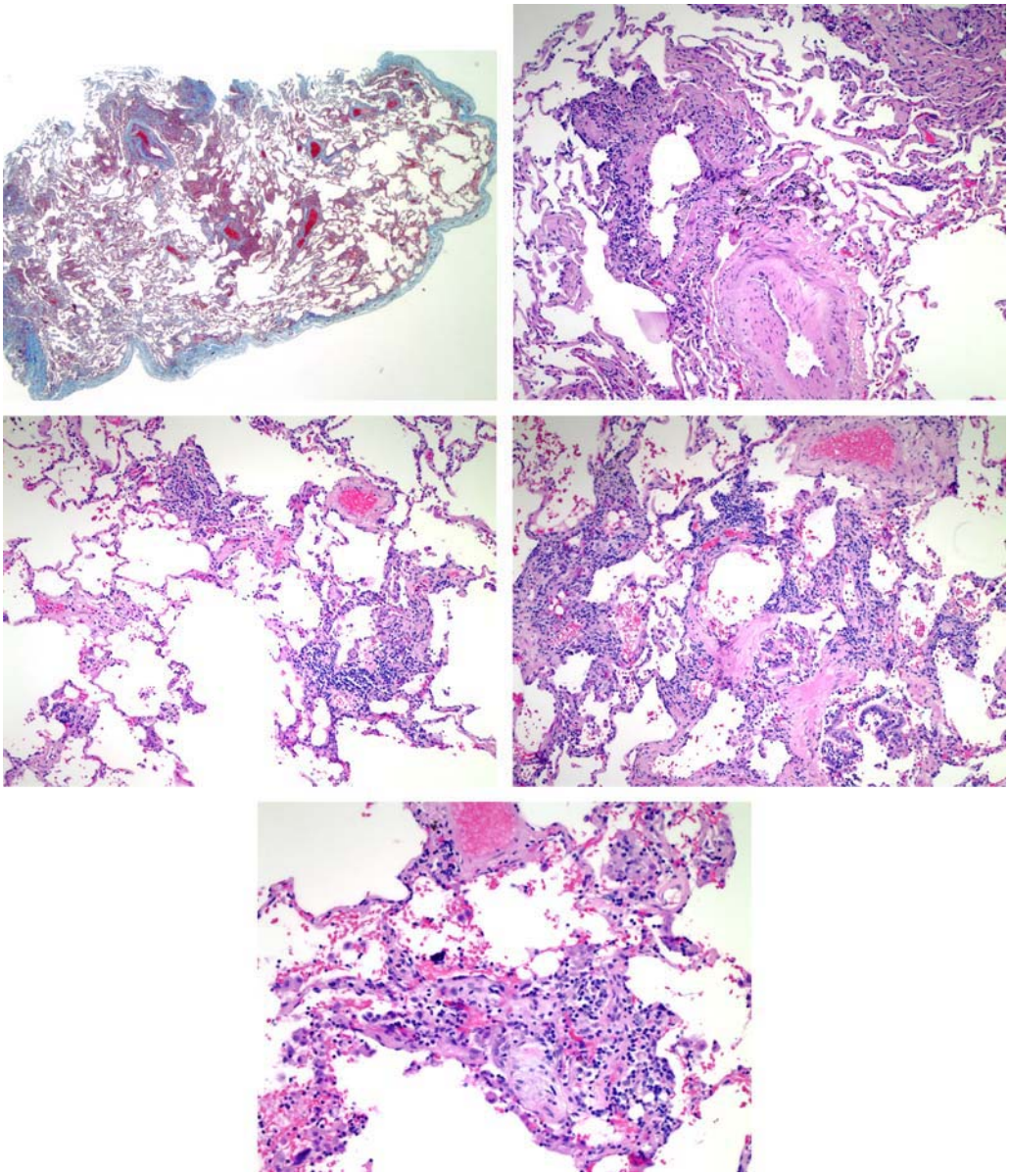
Case 6924

Diagnosis: Lung, open biopsy: Microgranulomatous peribronchiolitis and pneumonitis, ? hypersensitivity reaction, ? other.

The most specific facet of the biopsy are the histiocytic aggregates, which lie both in the adventitia of bronchioles and in the interstitium of alveolar walls. Descriptively this change can be termed microgranulomatous pneumonitis with a bronchiolar component. Microgranulomatous bronchiolitis has been associated with hypersensitivity reaction and collagen-vascular diseases. Extrinsic allergic alveolitis including that associated with aspergillus is one form of hypersensitivity reaction. Other cases remain enigmatic and idiopathic. I agree that the changes are not those of UIP. There is no old established interstitial fibrosis beneath the pleura, and the interstitial lymphocytic infiltrate is, for the most part, restricted to the granulomatous areas. I generally do not make a diagnosis of NSIP except to mean that a biopsy is not diagnostic for whatever reason. In the recent literature NSIP generally does not include granulomatous features. In this case, I have made a diagnosis emphasizing the granulomatous features and suggesting some possible etiologies.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6924 (Chapter 7 – Miscellaneous Pulmonary Disease)

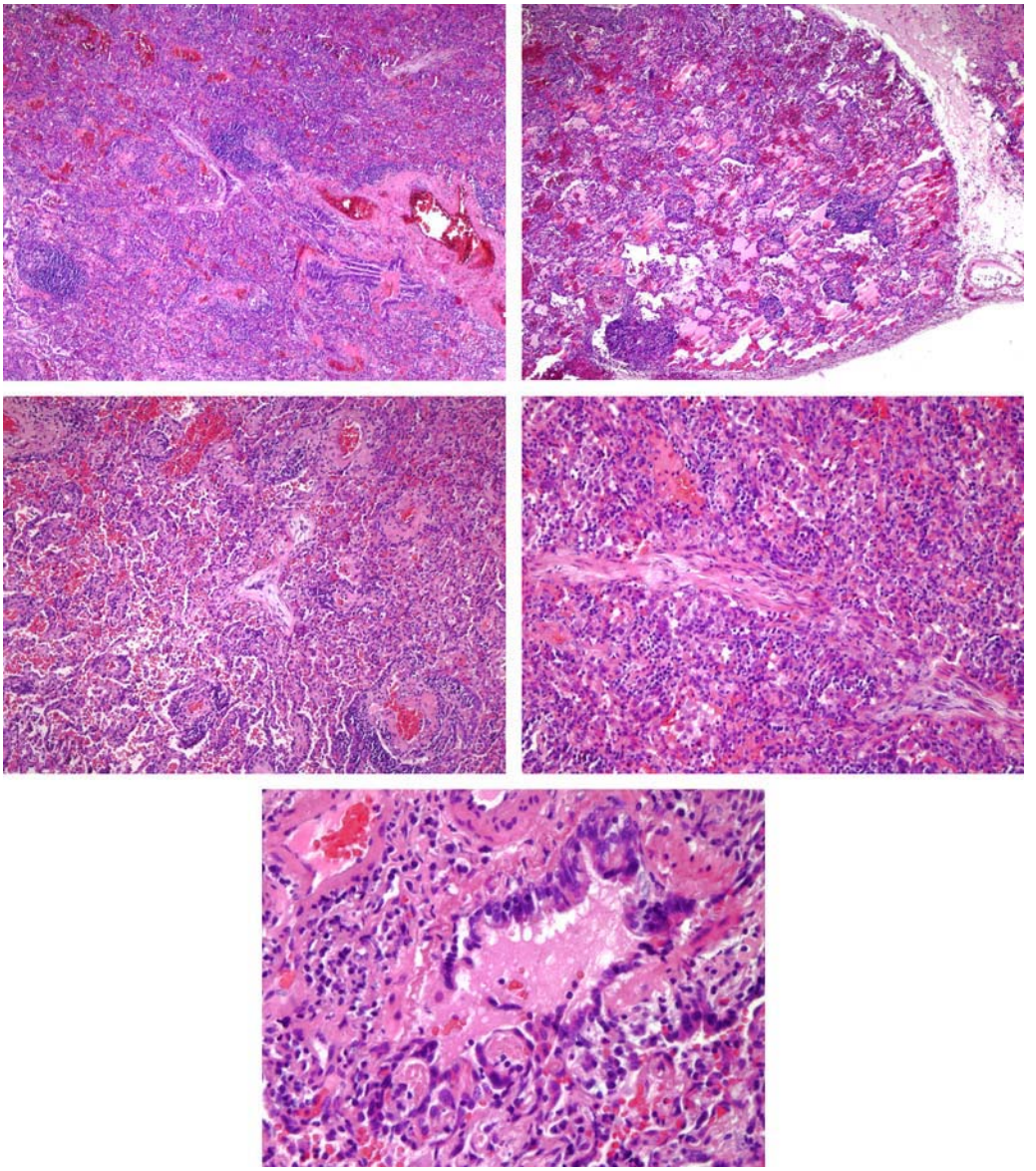
Case 6950

Diagnosis: Lung, open biopsy: Lymphocytic interstitial infiltrate and fibrinous pneumonia, etiology uncertain, ? hypersensitivity reaction, ? resolving infection, ? other.

I can describe this biopsy but cannot determine what has caused this process. The combination of hyperplastic lymphoid tissue around bronchioles with extension into alveolar walls simulates LIP, but that disease does not have the acute exudative character of alveolar fibrin and is not the correct interpretation. Hypersensitivity reaction would be further suspected if there were more bronchiolitis, but only a few bronchioles are occluded by fibrous plugs. However, an LIP-like change with edema has been seen in patients with hypersensitivity reaction. Another possibility is a slowly resolving unusual infection such as virus or mycoplasma or chlamydia. These agents might be further investigated by serologic or cultural studies. Collagen-vascular disease also can be considered because of the lymphoid hyperplasia and foci of chronic organizing pneumonia. I doubt toxic exposure. I am not sure whether or not the blood in the alveoli is real. Because of the extensive edema, some of it may represent leakage of capillaries. Because of the blood, we searched for a vasculitis, and we do find endothelial activation but no vascular necrosis, so vasculitis is not confirmed, and I doubt this interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6950 (Chapter 7 – Miscellaneous Pulmonary Disease)

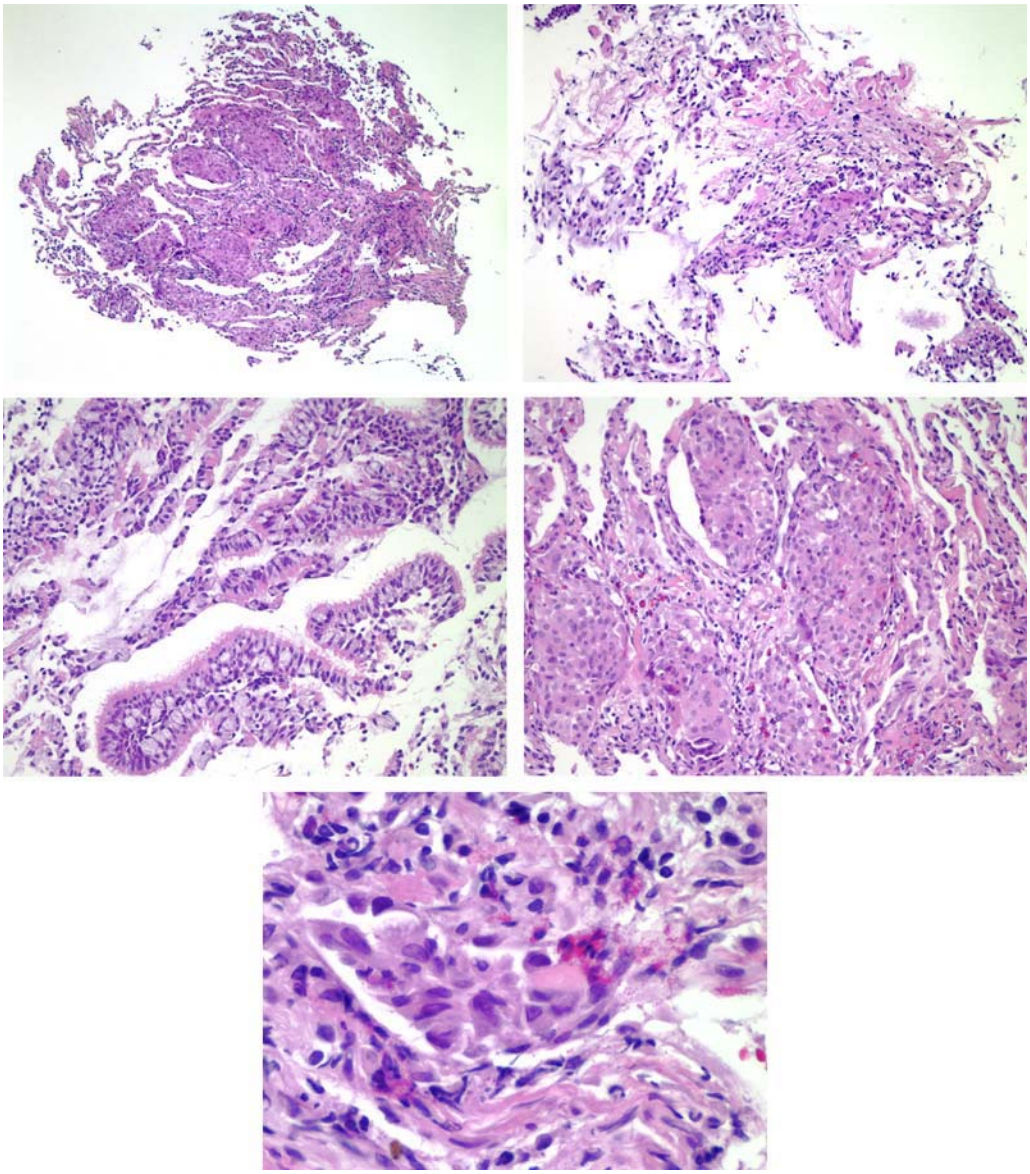
Case 7013

Diagnosis: Lung, transbronchial biopsy: Histiocytic-eosinophilic infiltrate, type and significance uncertain.

Aggregates of histiocytic cells vaguely resemble sarcoidal granulomas at low power, and multinucleated cells support a histiocytic origin, but the cells never form compact granulomas of sarcoidal type. The eosinophilic microabscesses are also unusual for sarcoid. The admixture of histiocytes and eosinophils raises the possibility of DIP or chronic eosinophilic pneumonia (CEP), but the histiocytic cells are not typical for either condition. The admixture of histiocytes and eosinophils and the positive stain for S-100 are consistent with eosinophilic granuloma (EG), but the large convoluted nuclei characteristic of Langerhans' cells are not apparent, and I doubt that this is EG. Occasionally histiocytic cells other than Langerhans' cells can stain for S-100, although staining here is very marked. The positive staining for S-100 made me think about metastatic malignant melanoma of the nevoid type, but this would not explain the eosinophils, and this process is not malignant in my opinion. In the etiologic differential diagnosis, I considered hypersensitivity reaction and schistosomiasis. This case is unusual and difficult in my opinion and in the opinion of several other senior pathologists in the department who have also reviewed the case. We do not know exactly what this biopsy represents.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. Additional tissue will be necessary for more precise morphological diagnosis in my opinion. I have retained one slide stained with hematoxylin and eosin for our permanent teaching collection in pulmonary pathology and hereby return all of the remainder including all of your special studies.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7013 (Chapter 7 – Miscellaneous Pulmonary Disease)

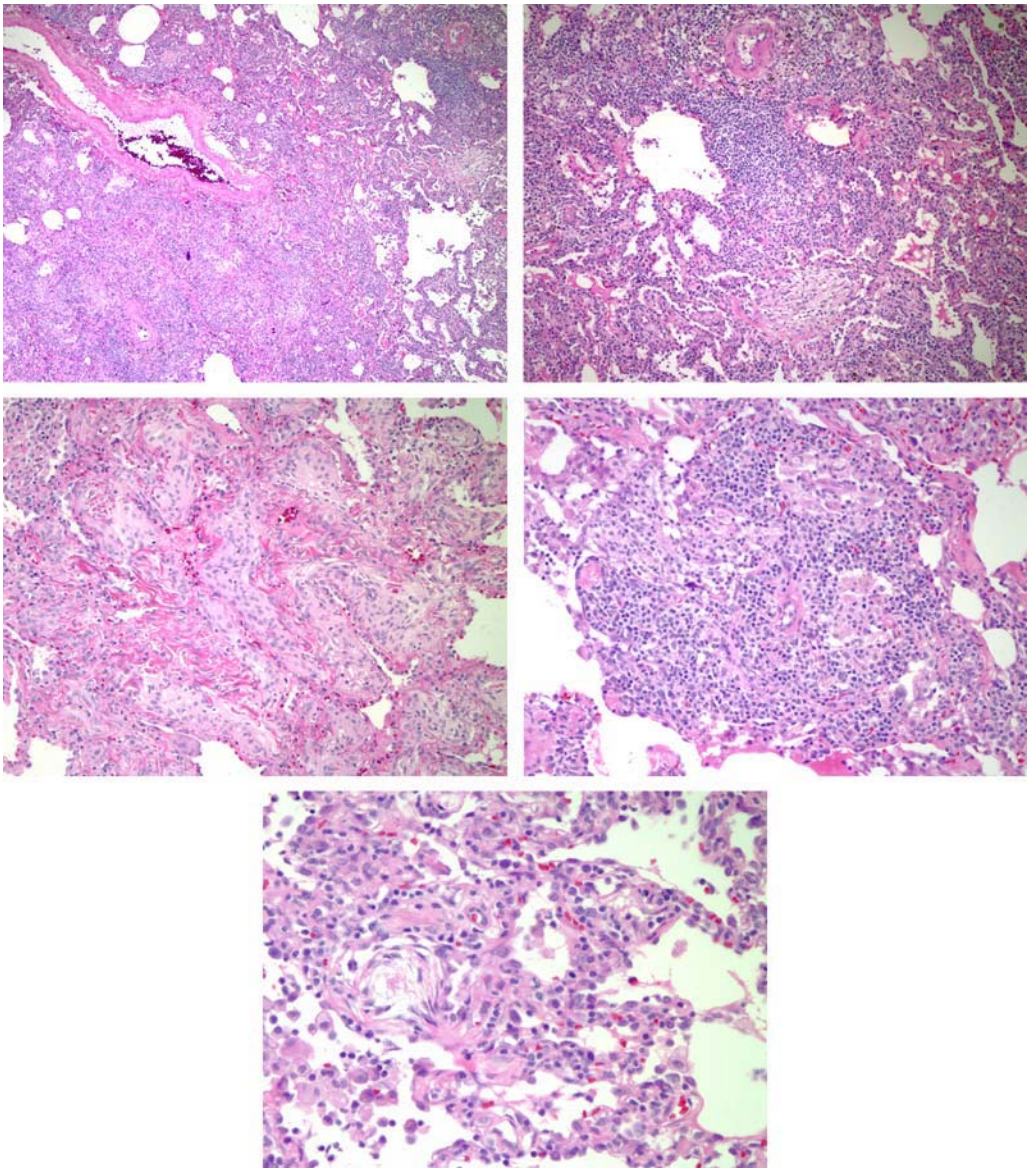
Case 6493

Diagnosis: Lung, open biopsy: Granulomatous pneumonitis with eosinophils.

A marked interstitial lymphohistiocytic infiltrate is associated with aggregated histiocytes sufficient to categorize this process as granulomatous. Eosinophils are present. Lymphocytes are prominent and include lymphoid nodules. Lymphoid hyperplasia of this degree can be seen in hypersensitivity pneumonitis, which I believe is the best etiologic diagnosis. This is in agreement with your suggestion of extrinsic allergic alveolitis, but I do not make the latter diagnosis pathologically because it is more a clinicopathological correlation requiring knowledge of what is extrinsic and what is allergic. Nevertheless, I suspect there is an antigenic cause for this patient's illness. I see no compact granulomas of sarcoidal type and do not favor sarcoidosis.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6493 (Chapter 7 – Miscellaneous Pulmonary Disease)

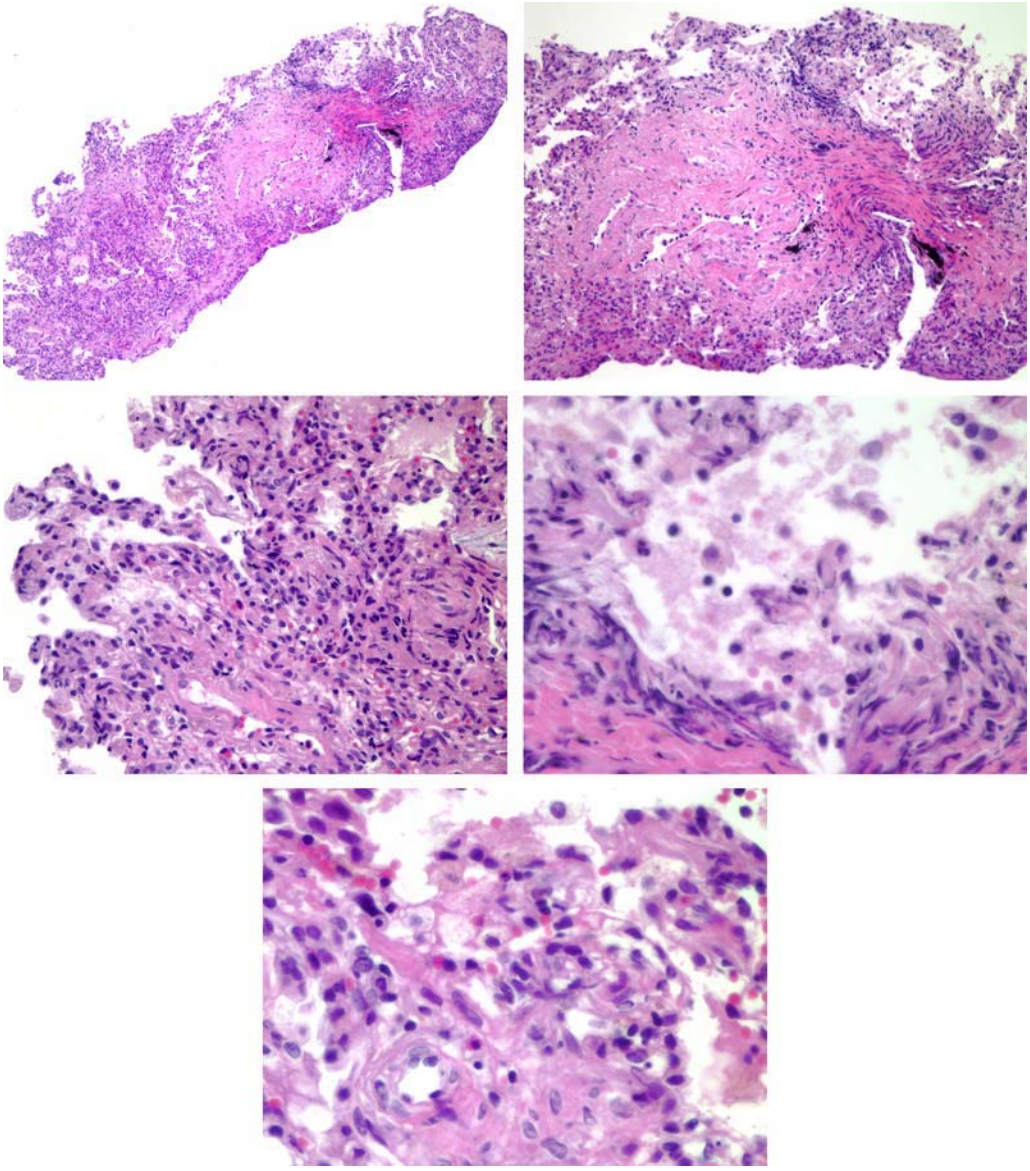
Case 6890

Diagnosis: Lung, transbronchial biopsy: Slight interstitial inflammation, vacuolated histiocytes, rare eosinophils and hypertrophic pneumocytes, nondiagnostic.

The specimen consists of approx 30 alveoli and an interlobular septum. A lymphohistiocytic infiltrate within the interstitium is associated with rare eosinophils. The differential diagnosis for these changes is broad and includes the interstitial pneumonitides, asthma, chronic eosinophilic pneumonia, bronchiolitis with patchy organizing pneumonia (BPOP), and other conditions. The vacuolated histiocytes probably represent an element of bronchiolar obstruction. There is probable slight fibrosis of lobular septa, but atelectasis and crush-effect preclude definite analysis of this. No malignancy is present. No granulomas are present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. More precise morphological diagnosis will require additional tissue, and the need for more precise morphological diagnosis depends upon clinical circumstances. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6890 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6962

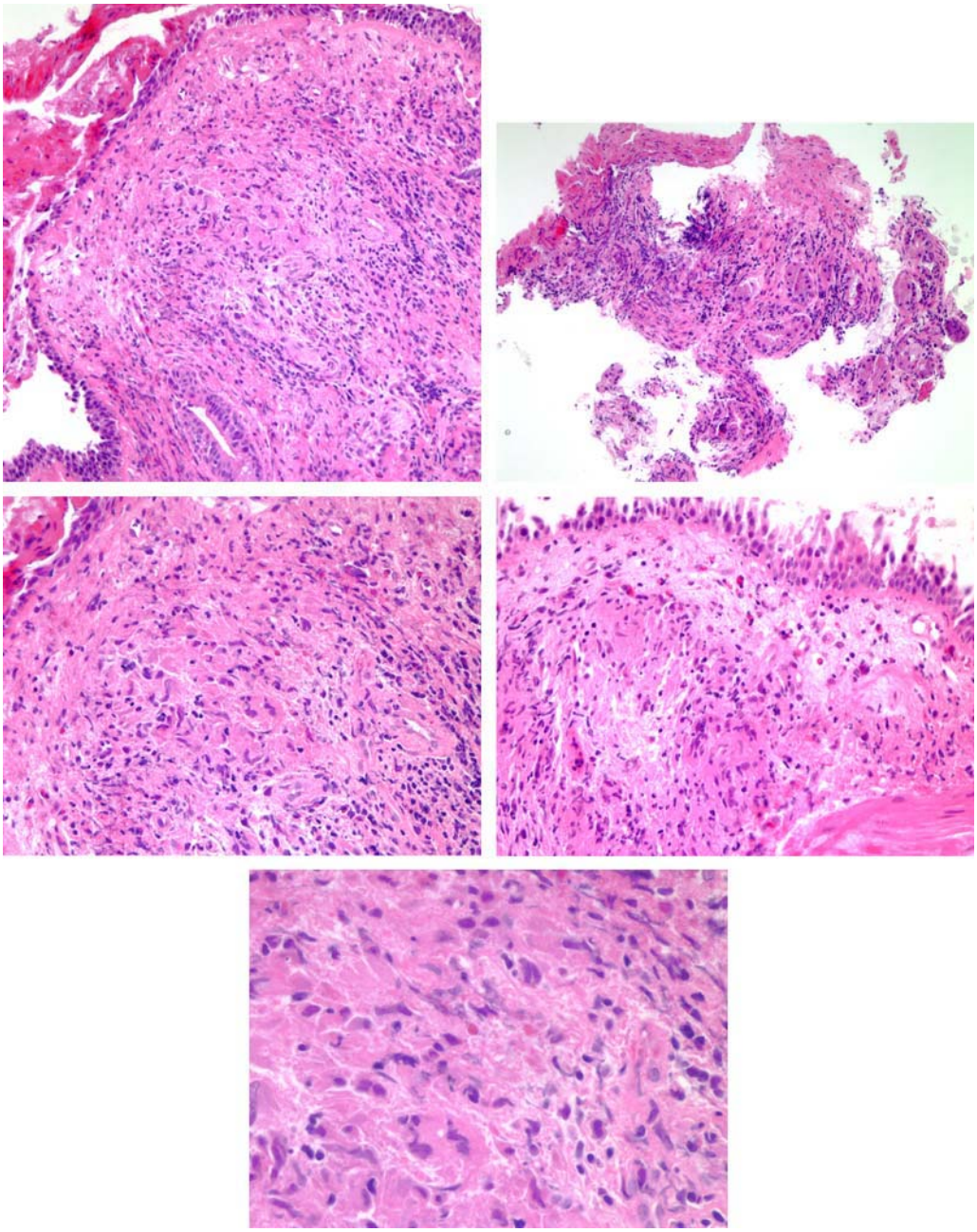
Diagnosis: Bronchus, bronchoscopic biopsy:

1. **Compact granuloma, with focal slight central necrosis, etiology undetermined.**
2. **Eosinophilic infiltrate in lamina propria.**

Two different processes are present, and I suspect that they represent two different diseases. The compact granulomas and their location in bronchial mucosa are consistent with sarcoidosis, but infection cannot be excluded despite the reportedly negative stains for organisms. The eosinophils in lamina propria most commonly would be seen in a patient with an asthmatic diathesis. CEP and other conditions of eosinophilic infiltrates cannot be excluded. Although granulomatous inflammation and eosinophils can both occur in bronchiolitis with hypersensitivity reaction and WG, I do not favor these interpretations.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6962 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 7150

Diagnosis: Lung, thoracoscopic biopsy: Hemosiderosis and capillary proliferation, consistent with congestive vasculopathy.

There is focal fibrous scarring, as you indicate, associated with moderate deposition of hemosiderin and pulmonary arterial hypertensive change (elastic stain). A few foci with proliferation of capillaries raise the possibility of pulmonary capillary hemangiomatosis as a cause of scarring and hemosiderin. In addition to increased numbers of capillaries in individual alveolar walls, there is intrusion of capillaries into walls of bronchioles and small blood vessels (PAS stain). Pulmonary capillary hemangiomatosis can be a condition which causes interstitial infiltrates on X-ray and pulmonary hypertension with cor pulmonale, it can be an incidental finding, or it can be a disease. To further substantiate the degree of capillary proliferation, I performed recut sections on a block of tissue in paraffin which you kindly provided and stained the recut sections with periodic-Schiff, elastic tissue, trichrome and Giemsa as well as prussian blue for iron. The periodic acid-Schiff stain, particularly, shows the excess number of capillaries. I then reviewed the chest radiograph which you provided. Marked cardiac dilatation in conjunction with the clinical history indicates that the capillary proliferation as well as the hemosiderosis is probably secondary to congestive vasculopathy in this patient.

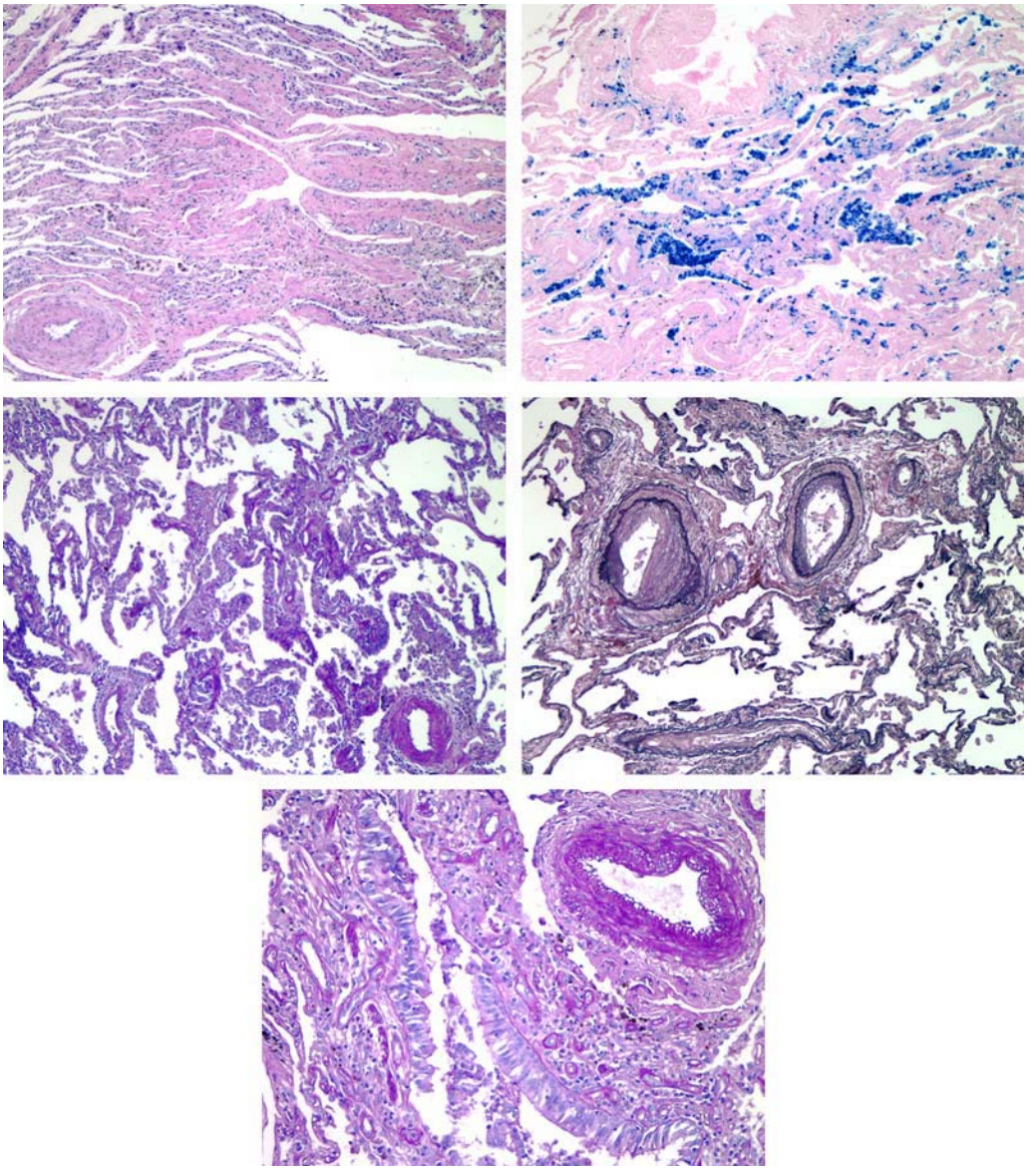
The permanent sections do not show any fungi or any necrosis or granulomatous reaction that might be associated with fungi. There are prominent fibers of elastica in the permanent sections, and it is sometimes very difficult on frozen sections to distinguish elastic fibers from hyphae. Degenerative elastica sometimes occurs in pulmonary vascular disease.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. Delay in reporting was due to the histochemical analysis as well as the review of the clinical and radiographic records and films. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Jing X, Yokoi T, Nakamura Y, et al. Pulmonary capillary hemangiomatosis. A unique feature of congestive vasculopathy associated with hypertrophic cardiomyopathy. Arch Pathol Lab Med 1998;122:94–96.



Case 7150 (Chapter 7 – Miscellaneous Pulmonary Disease)

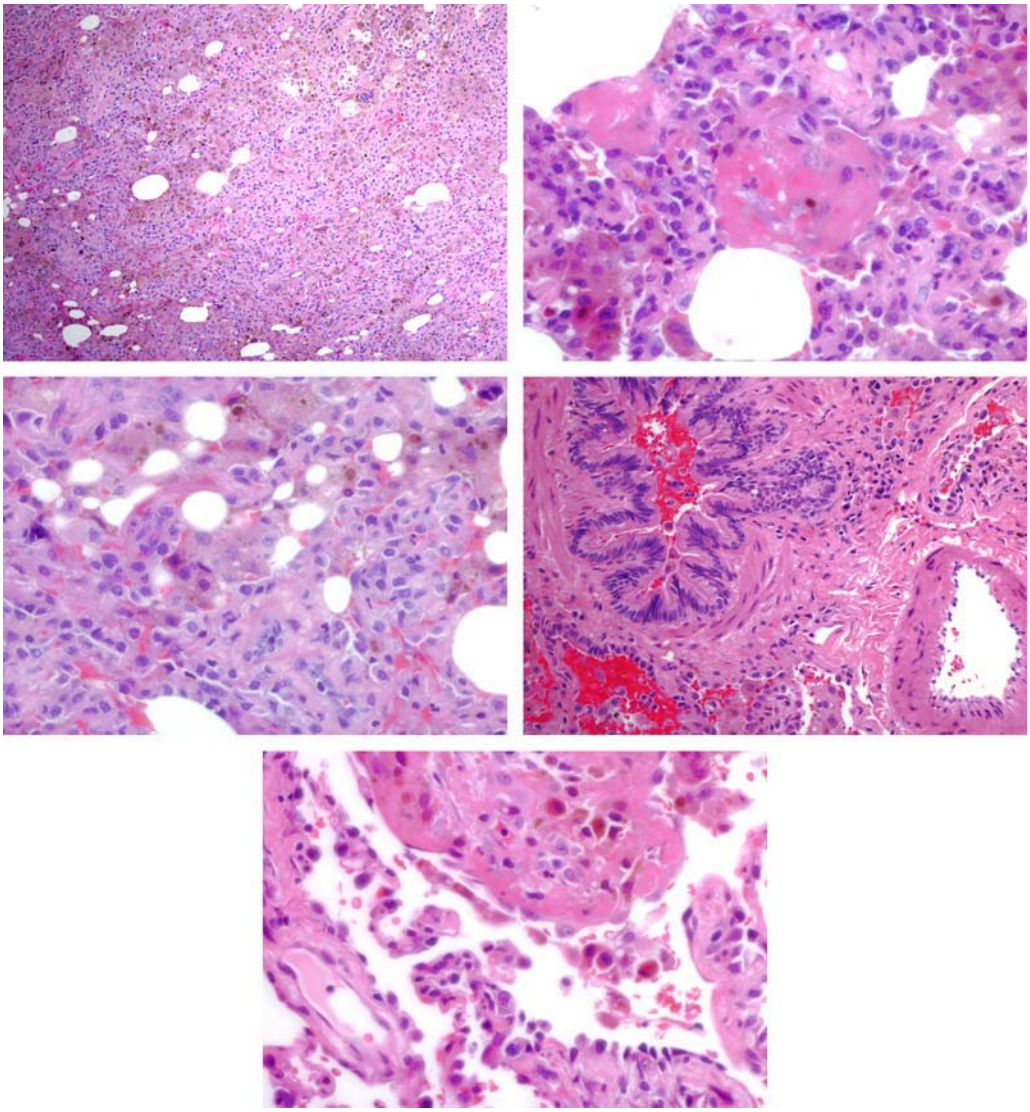
Case 6541

Diagnosis: Lung, open biopsy: Pulmonary hemorrhage and hemosiderosis, with probable capillaritis, and with DIP-like reaction.

Alveolar filling by histiocytes suggests DIP, but the abundant and coarse hemosiderin is not typical for that condition. Absence of eosinophils amidst the histiocytes is additional evidence against DIP. Therefore, I believe the better clinicopathological diagnosis is a pulmonary hemorrhage syndrome with DIP-like reaction. There is fresh blood in the lung. Although some may be operative, blood in terminal bronchioles suggests active flow and consequently real hemorrhage. There are collections of neutrophils with fibrin in a few alveoli and in interstitium of the type sufficient for me to suspect that there are now and have been episodes of capillaritis. I cannot make that diagnosis unequivocally because the neutrophils are spotty, not particularly associated with the fresh hemorrhage, and not associated with detectable fibrinoid necrosis of blood vessels or with fibrin thrombosis of capillaries. If one cannot prove capillaritis, the remaining diagnosis in this case would be IPH, but I believe the evidence for capillaritis is strong enough so that I suspect the bleeding is due to lupus erythematosis, WG, or one of the other less frequent causes of capillaritis. Goodpasture's syndrome usually does not produce capillaritis in the lung.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6541 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6911

Diagnosis: Lung, open biopsy:

1. **Hemosiderosis, cause uncertain, ? IPH.**
2. **Linear sclerosis, involving septa and pleura, significance uncertain, ? early dendriform ossification, ? veno-occlusive disease, ? other.**

We can diagnose hemosiderosis (iron stain) by virtue of the old and focal recent hemorrhage. No capillaritis is present. Pleural adhesions are present. IPH is possible, but I use this diagnosis only as a last resort and diagnosis of exclusion. WG and Goodpasture's syndrome could be assessed by serologic study because some cases of so-called IPH have ultimately proved to be one of these two diseases. Mitral lung would enter the differential diagnosis, but I understand that mitral valvular disease has already been excluded.

An enigmatic abnormality is the dense sclerosis involving lobular septa (trichrome stain) and the adventitia of small intralobular veins (elastic stain), as you indicate. This raises the possibility of veno-occlusive disease, but usually there is more inflammation and hemosiderin around the veins in that condition as well as luminal occlusion by fibrosis, which is not present either on your slides or in the elastic and trichrome stains which we performed on the block which you kindly provided. Secondary arterial hypertension often develops in patients with veno-occlusive disease, but in this case there is only mild medial thickening of some arteries. Focal ossification is present, and the ossification seems to develop in some of the fibrotic foci, leading to the possibility that this is a forme fruste of dendriform ossification of the lung. Dendriform ossification usually has been reported as an incidental finding. There have been associations with tuberculosis, mitral lung, heart failure, and pneumoconiosis. I am not aware of an association with pulmonary hemorrhage other than mitral valve disease.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is an elaboration of my telephone call. With best wishes,

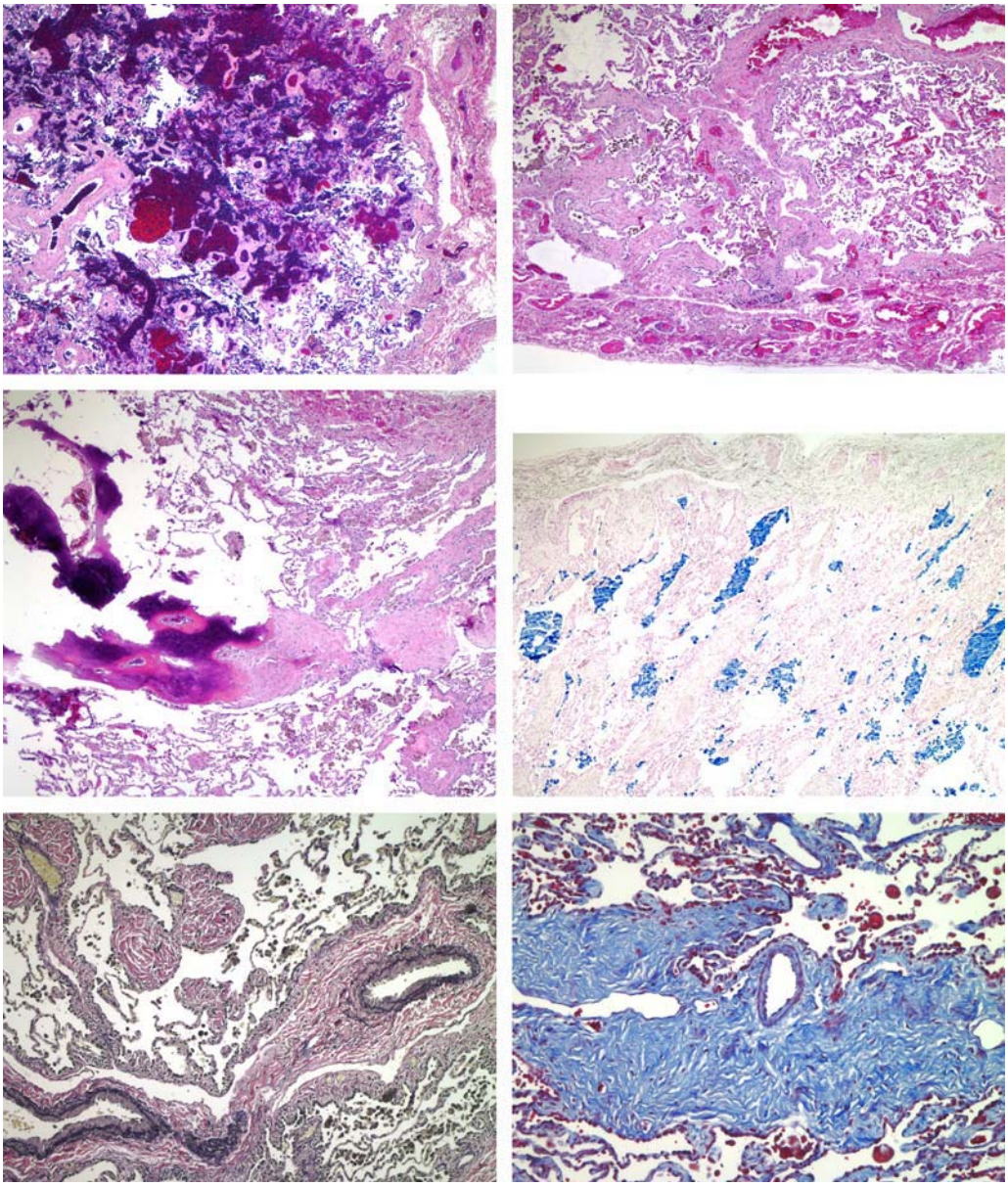
Sincerely yours,
Eugene J. Mark, M.D.

References:

Chow LTC, Shum BSF, Chow WH, Tso CB. Diffuse pulmonary ossification—a rare complication of tuberculosis. Histopathology 1992;20:435–437.

Fried ED, Godwin TA. Extensive diffuse pulmonary ossification. Chest 1992;102:1614–1615.

Jones RW, Roggli VL. Dendriform pulmonary ossification. Report of two cases with unique findings. Am J Clin Pathol 1989;91:398–402.



Case 6911 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 4432

Patient: 27-yr-old male

Diagnosis: Lung, resection of bullae: Subpleural bullae and focal destructive arterial lesions with hemorrhage, ? elastic tissue disease (? pseudoxanthoma elasticum, ? Ehlers-Danlos, ? other).

This patient had an unusual disease which I cannot categorize from the available information. However, I am fairly certain that this is some form of elastic tissue disease. The subpleural bullae can be seen in pseudoxanthoma elasticum, Ehlers-Danlos disease, and Marfan syndrome. Very little elastica stains on your elastic tissue stains, although wavy refractile elastic-like fibers are present in arteries and pleura. I am not sure whether this stain is technically in error or whether the apparent elastic tissue is chemically abnormal. However, degenerate clumped elastic fibers are visible due to their iron encrustation on the iron stain. Abnormal elastic fibers are present on one side of an artery, and elastic fibers are absent on the opposite side of the artery. The focal areas of hemorrhage with punctate acute necrosis, some regions of organizing hemorrhage a few days old, and extensive hemosiderin (iron stain) and fibrosis indicative of hemorrhage weeks or months old suggest that the bleeding has been due to repetitive arterial destruction and rupture rather than nonspecific hemorrhage from a ruptured bulla. These changes have been described previously in pseudoxanthoma elasticum and Ehlers-Danlos syndrome. Various other clinical findings might substantiate or refute these diagnoses. Elastic tissue diseases have many subcategories. Therefore, I do not know whether this patient fits into any clearly described entity. You might consider working this case up further, because it might be an initial manifestation of such a disease and possibly the subject of a case report.

We are currently studying elastic tissue in patients with Marfan syndrome. Although the clinical appearance of the patient suggests Marfan syndrome and these patients have repeated pneumothorax, we have not seen marked abnormalities in elastica nor significant pulmonary hemorrhage in patients with Marfan syndrome. I do not favor a diagnosis of Marfan syndrome.

Thank you for referring this case in consultation. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

Jackson A, Loh C-L. Pulmonary calcification and elastic tissue damage in pseudoxanthoma elasticum. Histopathology 1980;4:607–611.

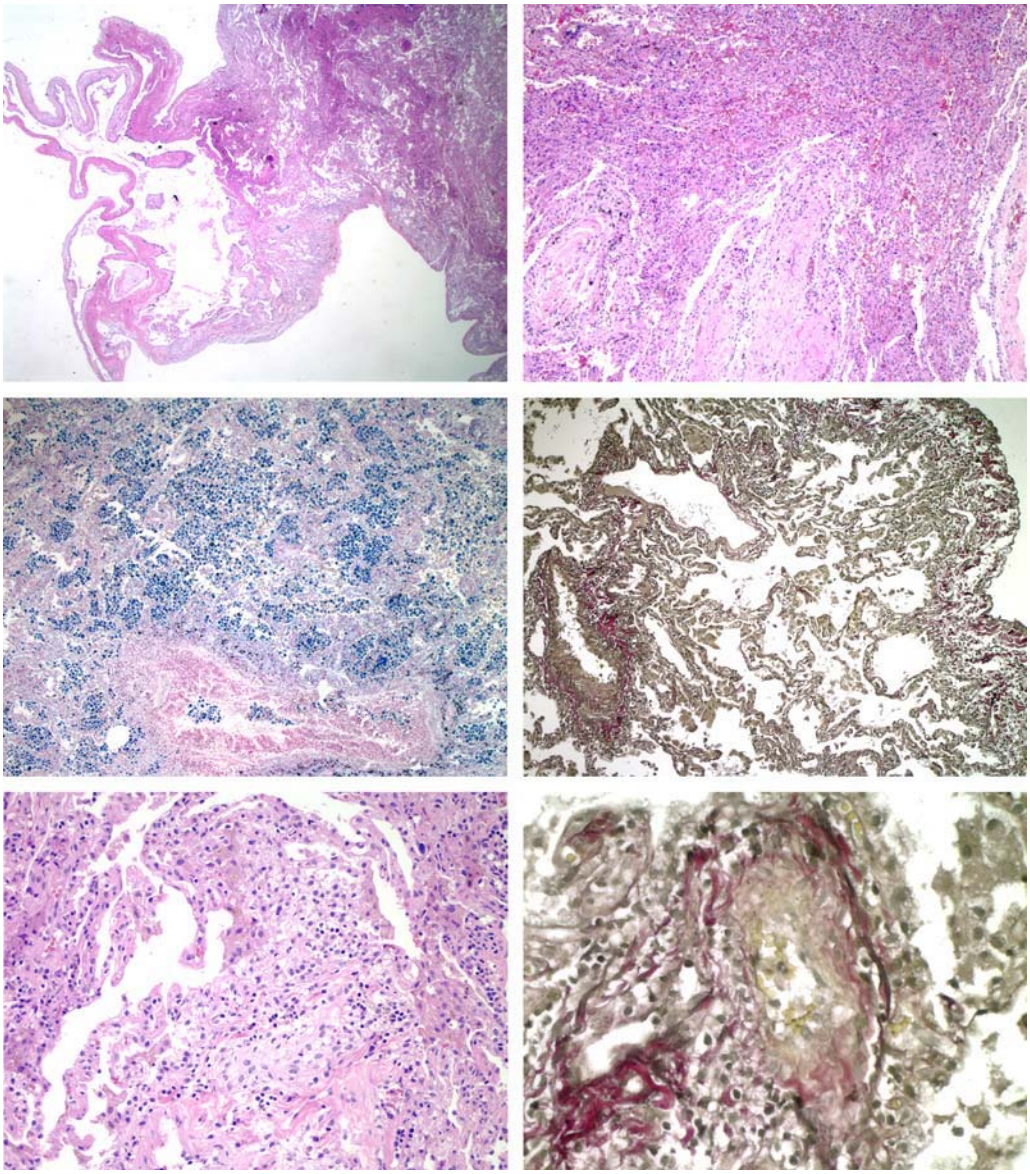
Huang S-N, Steele HD, Kuma G, Parker JO. Ultrastructural changes of elastic fibers in pseudoxanthoma elasticum. A study of histogenesis. Arch Pathol 1967;83:108–113.

Corrin B, Simpson CGB, Fisher C. Fibrous pseudotumours and cyst formation in the lungs in Ehlers-Danlos syndrome. Histopathology 1990;17:478–479.

McFarland W, Fuller DE. Mortality in Ehlers-Danlos syndrome due to spontaneous rupture of large arteries. N Engl J Med 1964;271:1309–310.

Haraguchi S, Fukuda Y. Histogenesis of abnormal elastic fibers in blebs and bullae of patients with spontaneous pneumothorax: ultrastructural and immunohistochemical studies. Acta Pathologica Japonica 1993;43:709–722.

Wood JR, Bellamy D, Child AH, Citron KM. Pulmonary disease in patients with Marfan syndrome. Thorax 1984;39:780–784.



Case 4432 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6549

Diagnosis: Lung, open biopsy: Pulmonary hemorrhage and hemosiderosis, ? collagen-vascular disease, ? other.

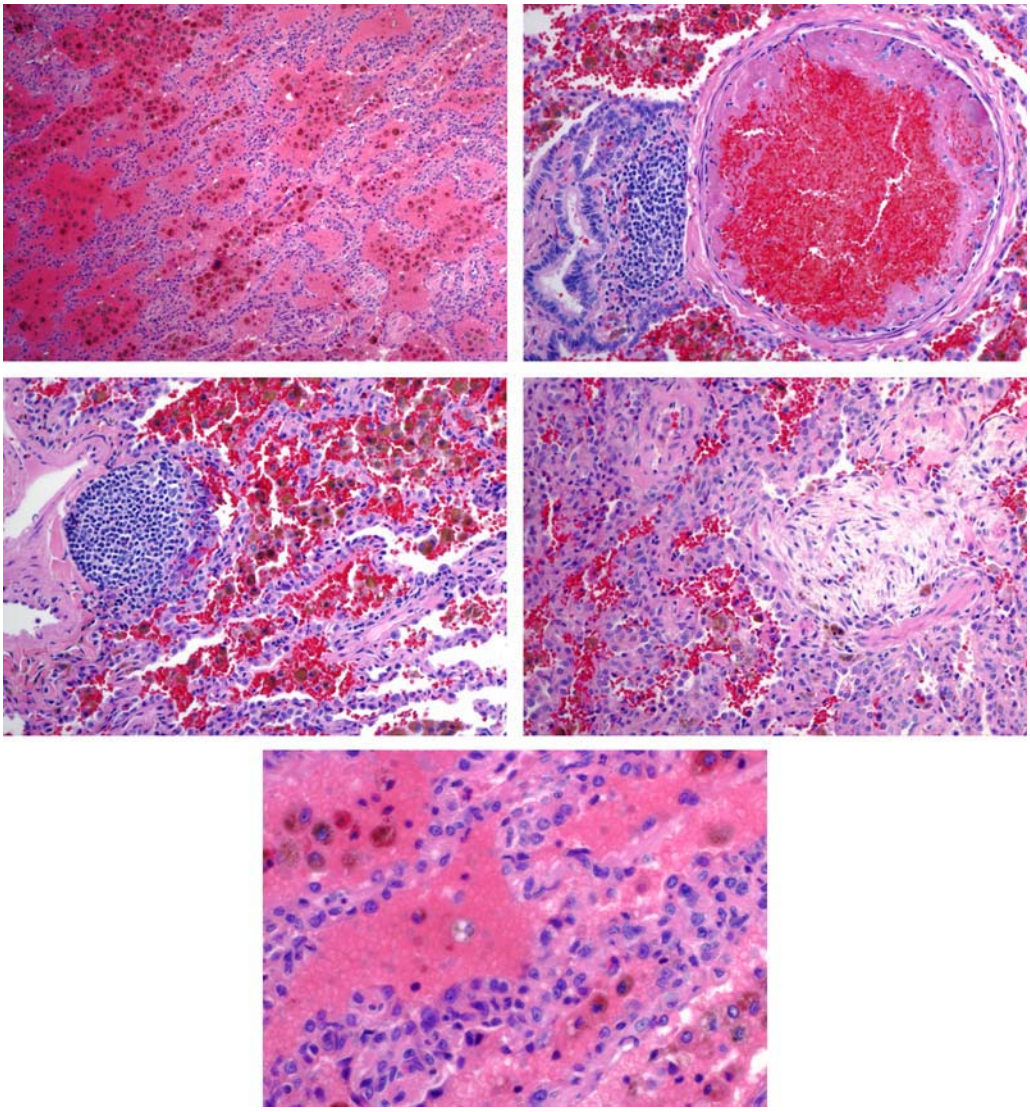
Extensive hemorrhage and hemosiderosis are associated with an interstitial thickening due to lymphocytes and probably fibrosis as well. The most common causes of this condition in our experience are WG, Goodpasture's syndrome, and lupus erythematosis. The slightly elevated ANA raises the possibility that the patient may have a variety of lupus erythematosis. WG could be further investigated by serum anti-neutrophilic cytoplasmic antibody (ANCA). Capillaritis would explain the hemorrhage, but I detect no capillaritis in this patient. Patients may have episodes of capillaritis without our ability to morphologically document it between episodes of active bleeding. I suspect that is the case in this patient. I detect no arteritis or phlebitis, but there is a recent thrombus with peripheral organization in one slide next to a terminal bronchiole. Acute and chronic hemorrhage and interstitial pneumonitis have been described with regularity at autopsy in patients who have used cocaine, and I cannot exclude this possibility. No birefringent particles are present within vessels.

Thank you referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Bailey ME, Fraire AE, Greenburg SD, Barnard J, Cagle PT. Pulmonary histopathology in cocaine abusers. Hum Pathol 1994;25:203–207.



Case 6549 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6867

Diagnosis: Lung, open biopsy:

1. **Adenocarcinoma, bronhioloalveolar subtype.**
2. **Asbestosis.**

Histopathologically, the open biopsy consists of lung which contains tumor. The largest piece of tissue is approx 5 mm in greatest diameter. The lung contains an adenocarcinoma. The malignant cells spread along walls of alveoli in a lepidic manner. Nuclei are hyperchromatic and oval with relative opacity of some of the nuclei and central clearing in other nuclei. Nucleoli are relatively inconspicuous. The malignant cells are cuboidal or columnar. Some of the malignant cells have snouts at the apex of the cytoplasm, typical of Clara cells. The alveolar walls have fibrous thickening. A slight lymphocytic infiltrate is present in the interstitium. In one piece the carcinoma cells form regular glands imbedded in more abundant fibrous stroma with elastotic scarring. The pathological findings indicate an adenocarcinoma of bronchioloalveolar subtype.

Histopathologically, the lung contains a moderate amount of carbon and many asbestos bodies. The asbestos bodies are long, brown, beaded, and have thin translucent cores. The asbestos bodies lie singly or in groups of two or three together. The asbestos bodies lie in interstitial fibrosis amidst tumor and in interstitial fibrosis away from tumor.

I quantify the asbestos bodies by optical microscopy. The asbestos bodies are present at a concentration of approx 10 per square centimeter of lung and tumor tissue. The combination of the interstitial fibrosis and the asbestos bodies constitutes parenchymal asbestosis.

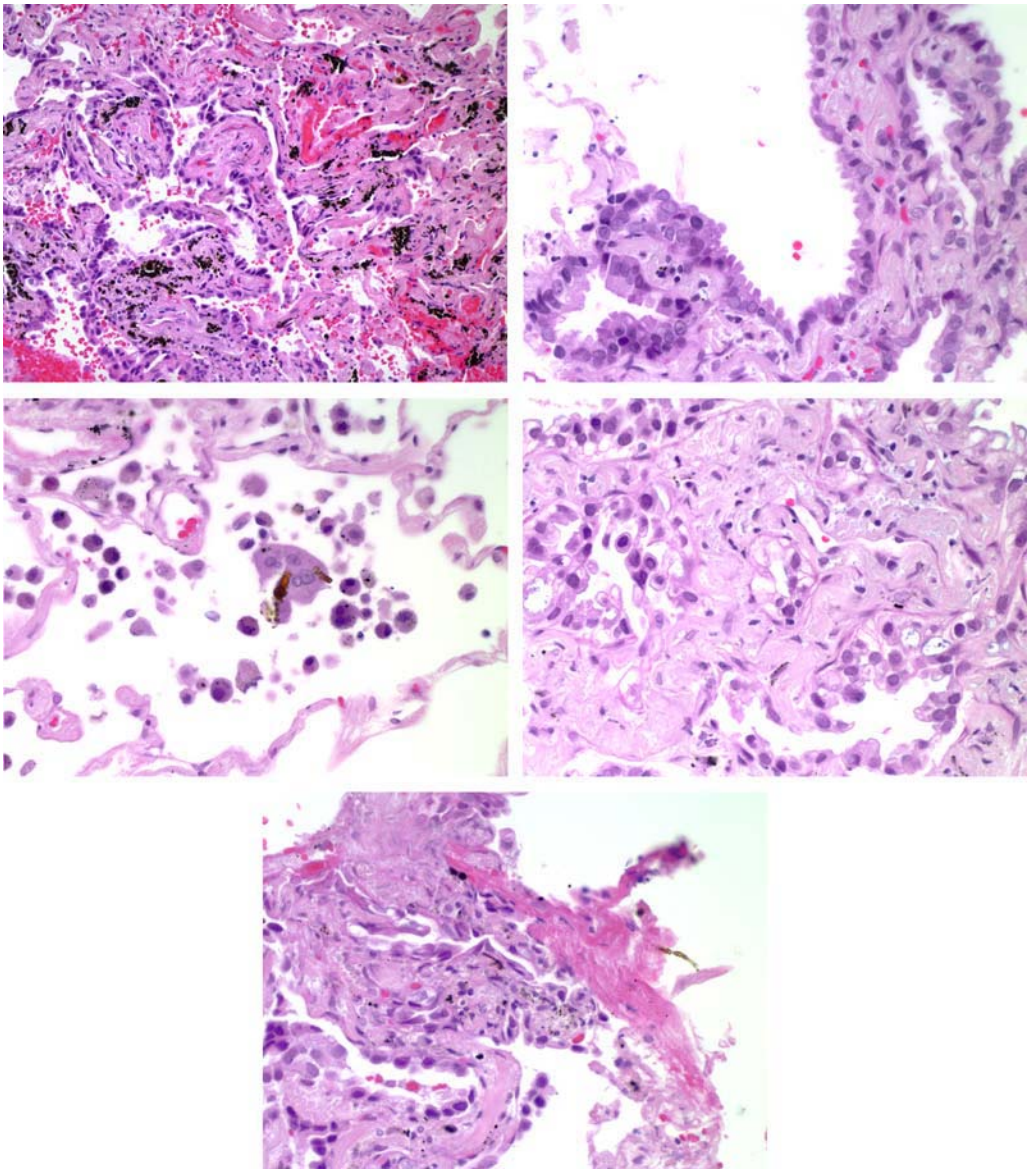
From a block of the tumor embedded in paraffin, I have obtained recut slides for histochemical studies. Trichrome stain delineates interstitial fibrosis amidst carcinoma and interstitial fibrosis away from carcinoma. Mucicarmine stain shows intracellular mucin in a small number of carcinoma cells. Prussian blue stain colors the asbestos bodies blue.

From the same block of the tumor embedded in paraffin, I have obtained recut slides for immunochemical studies. One slide has been stained for prostate specific antigen by the immunoperoxidase technique. A second slide has been stained for prostatic acid phosphatase by the immunoperoxidase technique. The malignant cells do not stain for prostatic acid phosphatase nor for prostate specific antigen. The histochemical and immunochemical results are consistent with an adenocarcinoma of bronchiolo-alveolar subtype that has arisen in the lung.

Cigarette smoke and asbestos each can cause carcinoma of the lung, including adenocarcinoma. Together, cigarette smoke and asbestos act in a synergistic manner to cause carcinoma of the lung. All of the types of asbestos can cause carcinoma of the lung. All of the exposures to asbestos which occur prior to the development of the carcinoma contribute to its pathogensesis.

I conclude that the patient developed an adenocarcinoma of bronchioloalveolar subtype that arose in the lung. I conclude that the patient inhaled asbestos. I conclude that the adeoncaricnoma of the lung caused death.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6867 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6917

Diagnosis: Lung, wedge biopsy:

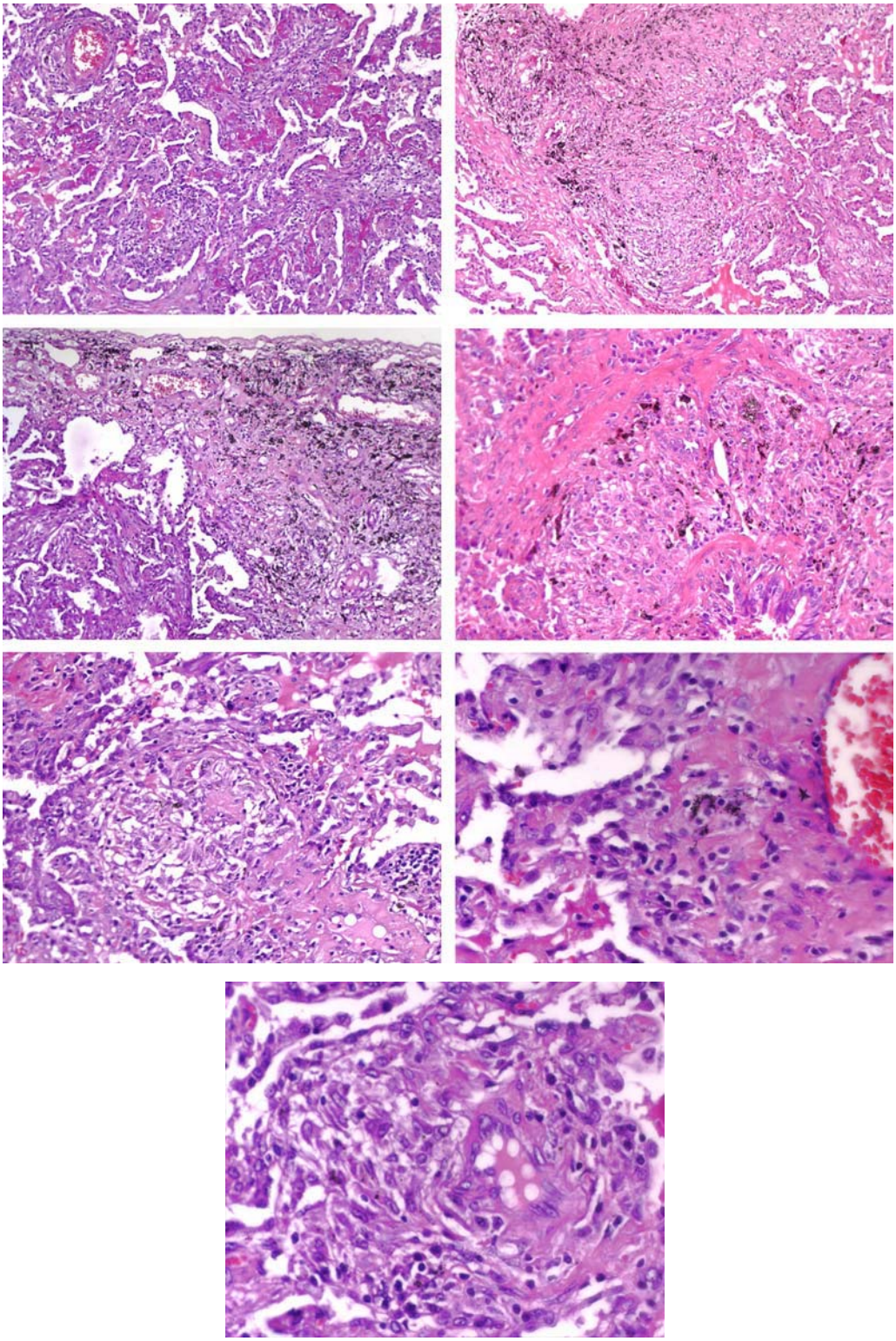
1. **Silicatosis, nodular and linear, extensive.**
2. **Organizing fibrinous pneumonia.**

I have examined microscopically approx 15 glass slides, the most salient of which are histological preparations of a wedge biopsy of the lung. The specimen was obtained at surgery in 1995. The slides of the wedge biopsy have been stained with hematoxylin and eosin.

Histopathologically, a diffuse histiocytic infiltrate arrranged in ill-defined nodules and linearly along lymphangitic pathways around bronchovascular bundles and in septa and in pleura. The histiocytic inflammation is, in large part, granulomatous. Extensive carbon pigment, as well as crystals of silicate, are present in the granulomatous inflammation. The silicate is seen with routine microscopy and with polarization microscopy. One region has central focal necrosis within fibrous scar of the type seen in silicosis. No asbestos bodies are present.

Histopathologicaly, the organizing fibrinous pneumonia is a separate and more recent process. A few hyaline membranes are present. The cause of the fibrinous pneumonia is uncertain based on the pathology materials alone.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6917 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6834

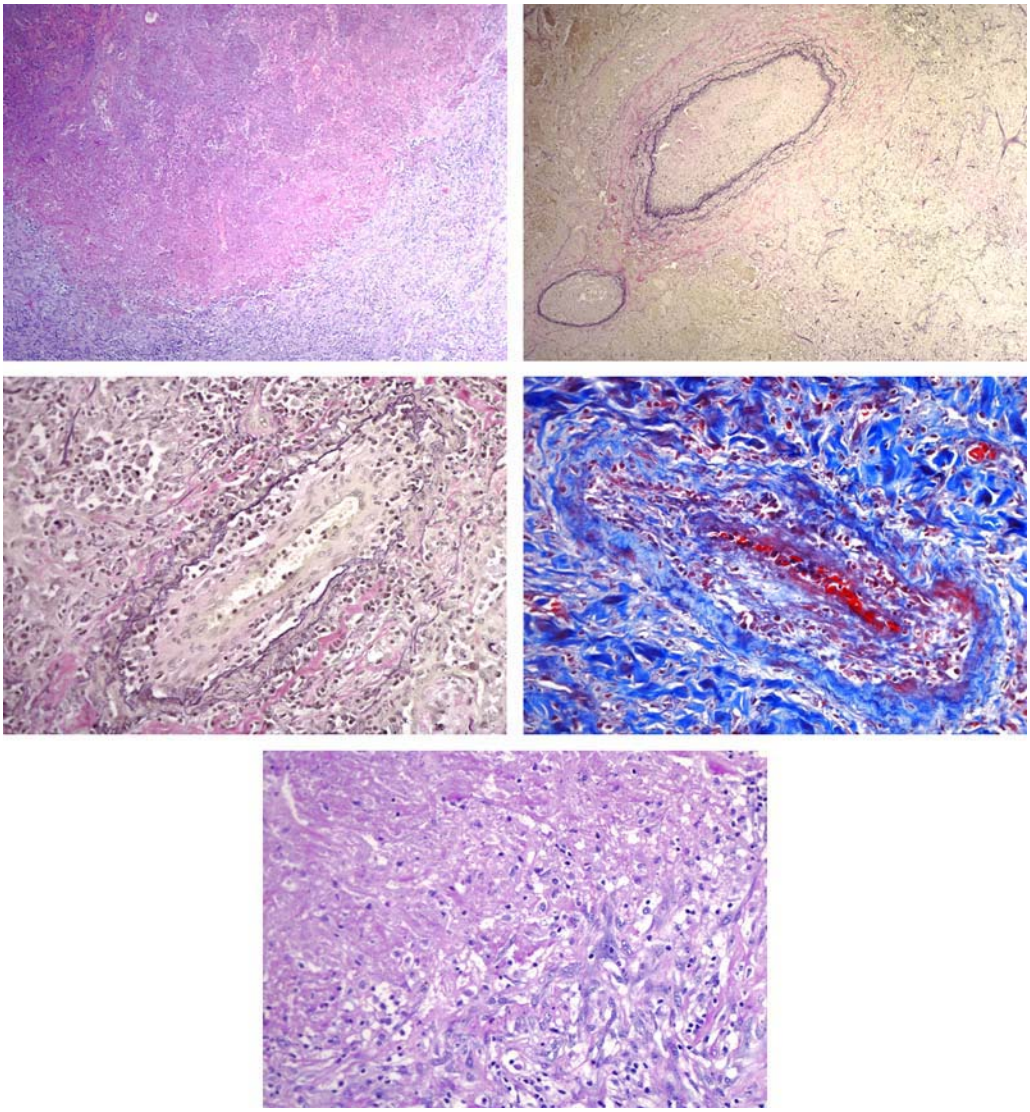
Diagnosis: Lung, open biopsy: Necrobiotic nodule, cause undetermined, ? rheumatoid nodule.

The necrobiosis with preserved elastica on special stains and palisading histiocytes (PAS stain) in at least a portion of the perimeter of the nodule makes me consider rheumatoid nodule as the best classical diagnosis for this lesion. Our special stains for organisms are negative. I cannot discount the reported history of drug abuse, which might predispose a person to embolic disease, but I could find no report in the literature of necrobiotic nodules associated with illicit drug abuse, nor have I seen such a case. I would expect a septic embolus to be more purulent.

On your section and on our special stains is a marked intimal proliferation of vessels (trichrome stain) in and near the necrobiotic nodule. I believe this intimal sclerosis is a secondary phenomenon and do not favor a primary vascular disease, although I cannot exclude that possibility. I considered WG or other vasculitis, but I do not favor this interpretation. Occasionally rheumatoid nodules may be the initial sign in patients who subsequently develop rheumatoid disease.

Thank you very much for sharing this case with us. All of the fellows on the service in pulmonary pathology enjoyed reviewing the case. I hope this finds you and your family well and prosperous. With best wishes for the new year,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6834 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6874

Diagnosis: Lung, open biopsies:

1. **Calcified intra-arterial nodule (wedge A).**
2. **Intraparenchymal lymph node (wedge B).**

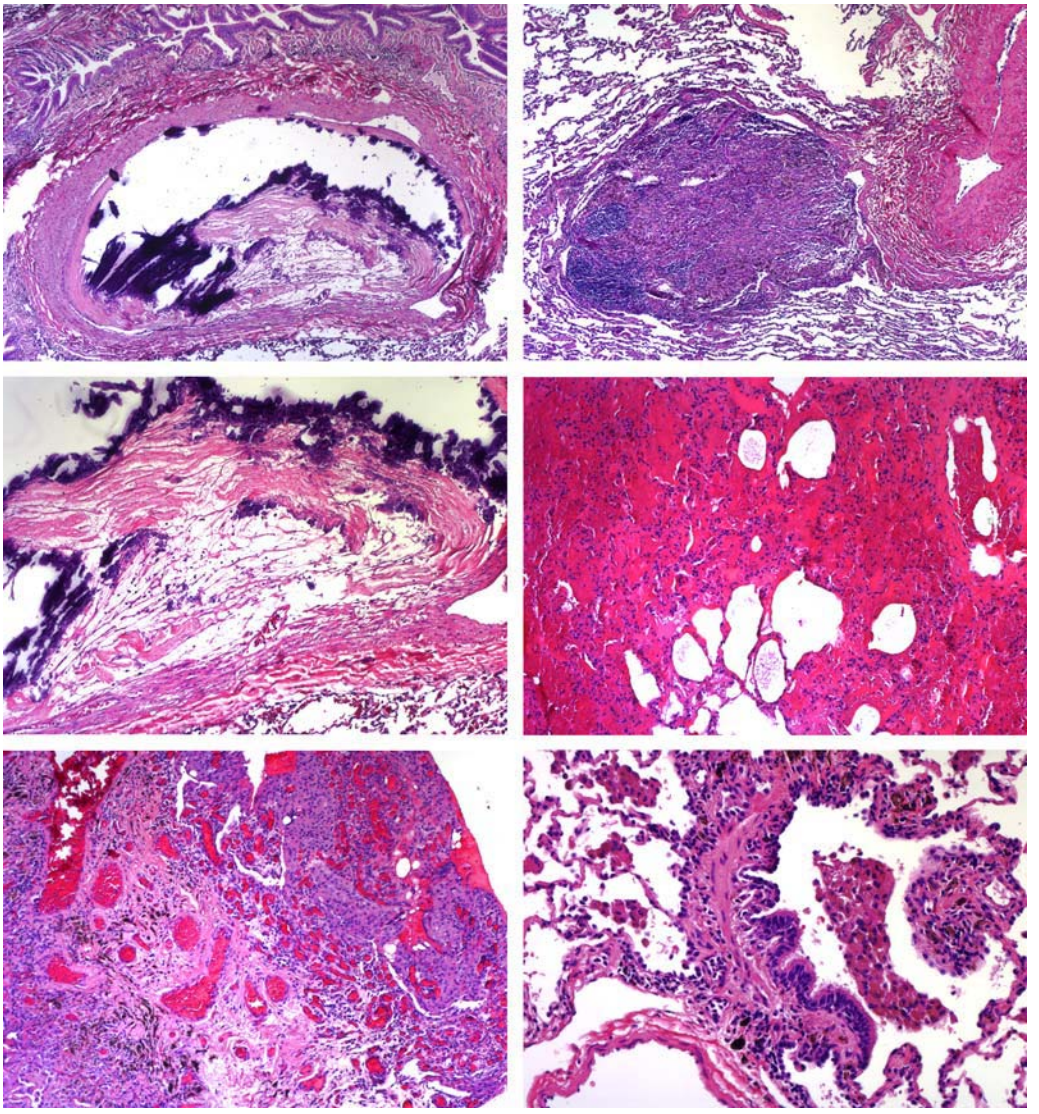
In wedge A is an unusual calcified nodule in the media of a pulmonary artery with eccentric protrusion into the lumen. The change could represent a calcified thromboembolus or a calcified intramural hematoma. In either case, the process is months or years old, without activity. The lumen of the vessel seems to remain patent. The lesion on the slide is about 3 mm in greatest diameter, so I am uncertain whether or not this accounts for a radiographic finding, but I could conceive of it as having been palpable at surgery or visualized on a computerized tomogram because it is calcified. In wedge B is a small intrapulmonary lymph node measuring about 2 mm in diameter. Again, I do not know whether this is the cause of a radiographic nodule, but in my experience intraparenchymal lymph nodes are one of the more common causes of "disappearing tumors of the lung." It is possible that our section has not passed through the main diameter of the nodule and that it could have been larger.

Apart from these two lesions is multifocal blood in the lung. I suspect that this is operative for the following reasons: 1) absence of hemosiderin suggests that it has not been present for more than 48 h; 2) the alveoli are compressed rather than expanded by blood, whereas bleeding into alveoli tends to expand them; 3) no capillaritis or vasculitis is present; 4) the lung in some areas of blood is atelectatic suggesting mechanical effect. The lung otherwise has pigment-laden histiocytes around bronchioles, a few alveolar histiocytes, and pleural adhesions.

In the differential diagnosis of disappearing tumors in the lung, I also considered in this case shrinking pleuritis with rounded atelectasis and arteriovenous malformation. However there is no evidence for these conditions on the slides, and the wedge resections have been thoroughly examined by your technique.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. All of your slides are returned under separate cover. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6874 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6926

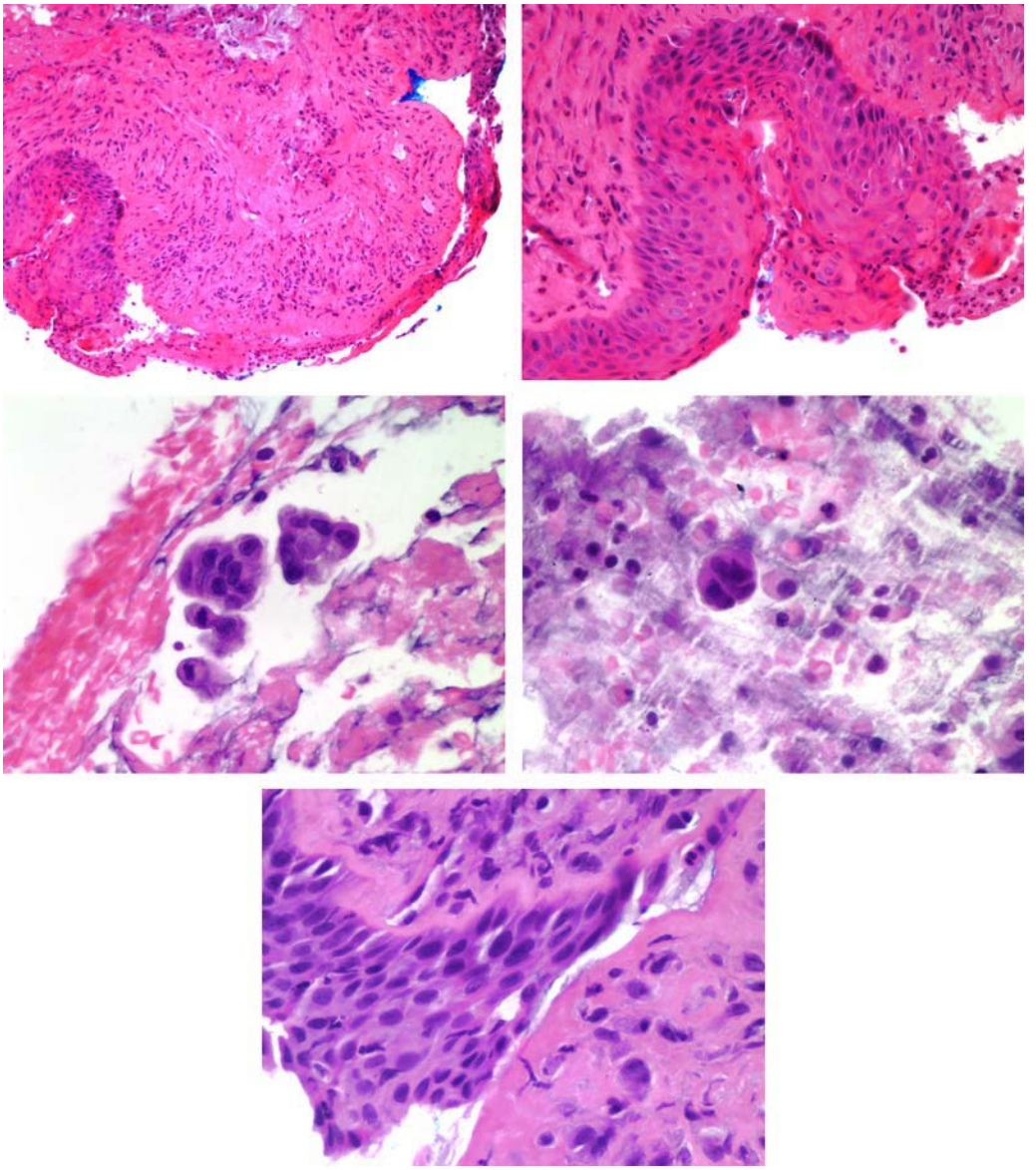
Patient: 69-yr-old male, who had a spontaneous gastric perforation following arthroscopic knee surgery. He was on ventilator support for 6–8 wk. His ARDS cleared, now leaving atelectasis and a left pleural effusion. A CT scan showed no mass.

Diagnosis: Bronchus, bronchoscopic biopsy and washings: Focal ulceration, with atypical squamous metaplasia, including highly atypical reactive epithelial cells.

The cytological preparations show squamous epithelial cells and clumps of atypical epithelial cells with enlarged nuclei. Multiple and enlarged nucleoli in some of the nuclei make one seriously consider carcinoma. However, the highly atypical cells are few in number when considering the totality of the case, and the nuclei preserve a relative regularity in size. The biopsy shows a focal ulceration which has been present for many days because there is fibrosis and capillary proliferation beneath it. Adjacent to this ulceration is squamous metaplasia with regeneration and highly atypical nuclei. The cytological features in the bronchial epithelium resemble those in the cytological preparation. Although I do not know that this particular site is the source of the highly atypical cells seen on the cytological preparations, the atypical cells in the washings are consistent with reactive epithelial cells such as might occur with ulceration. In any case, I do not believe the cytological preparations are diagnostic of malignancy.

Thank you for referring this case in consultation. Please keep me informed of any follow-up.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6926 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6603

Diagnosis: Lung, open biopsy:

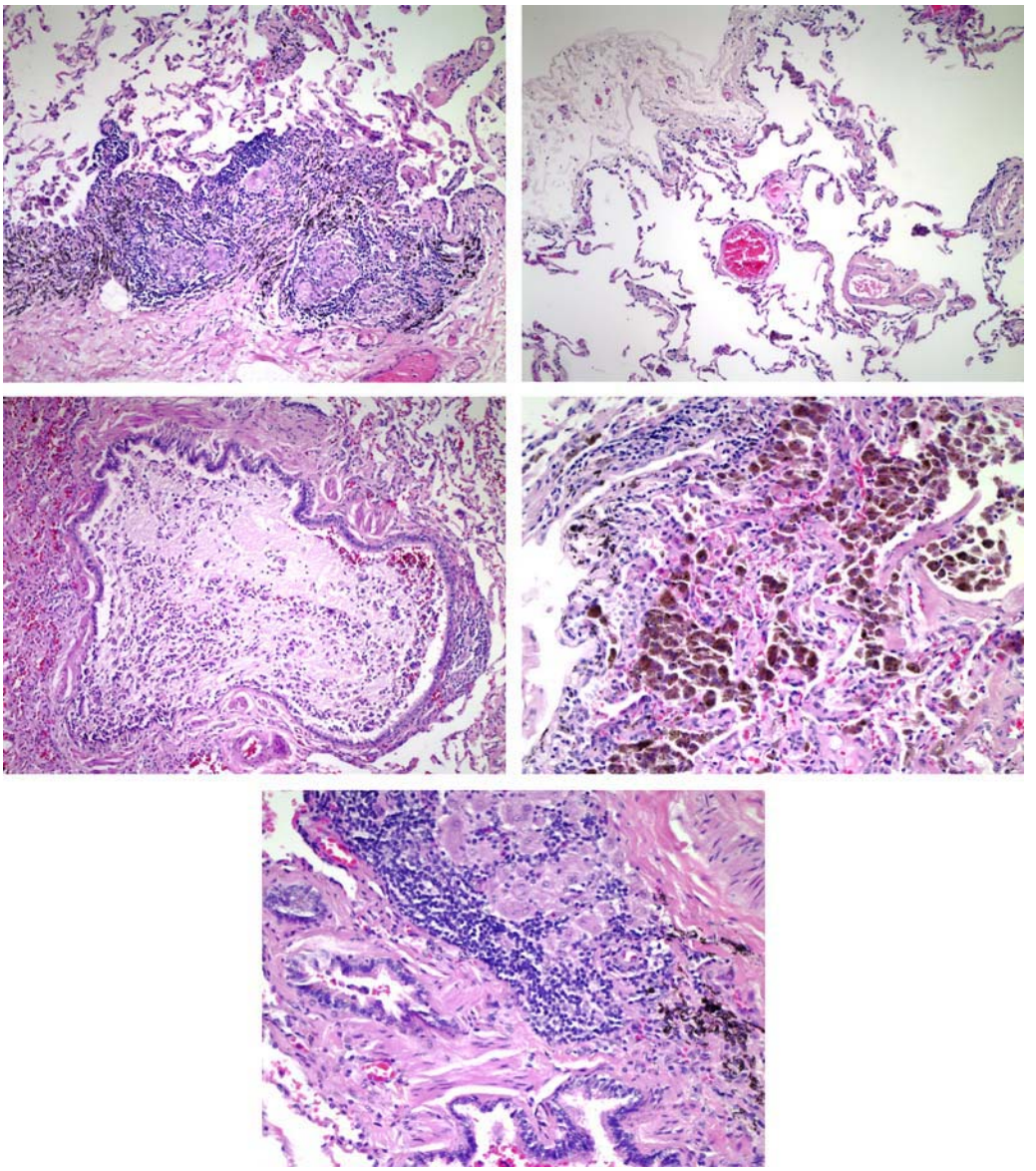
1. **Compact granulomas, few, scattered.**
2. **Mucus plugs and pigmented histiocytes in alveolar ducts, ? respiratory bronchiolitis (RB).**
3. **Emphysema, subpleural.**
4. **Hemosiderin.**

The most specific findings are the scattered interstitial granulomas, as you indicate. These raise a possibility of hypersensitivity reaction, but the bronchiolitis commonly seen with hypersensitivity reaction is not present. There is emphysema with free-floating fragments of alveolar walls near the pleura, mucus plugging of terminal bronchioles, and pigment-laden histiocytes in alveolar ducts. These are all sequelae of the smoking of cigarettes. Finally, there is the presence of hemosiderin indicative of prior focal hemorrhage, the cause of which is uncertain.

I cannot determine which of these processes is the most important disease clinically. I cannot exclude sarcoidosis, but I doubt it. RB can produce small nodules, but the degree of filling of alveolar ducts by pigmented histiocytes is not sufficient for a morphologic diagnosis of RB. I cannot be sure whether or not a nodule has been sampled. I am generally reluctant to involve emphysema as a cause of respiratory embarrassment based on open lung biopsy, but the emphysema and mucus plugs are quite prominent in this case.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6603 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6816

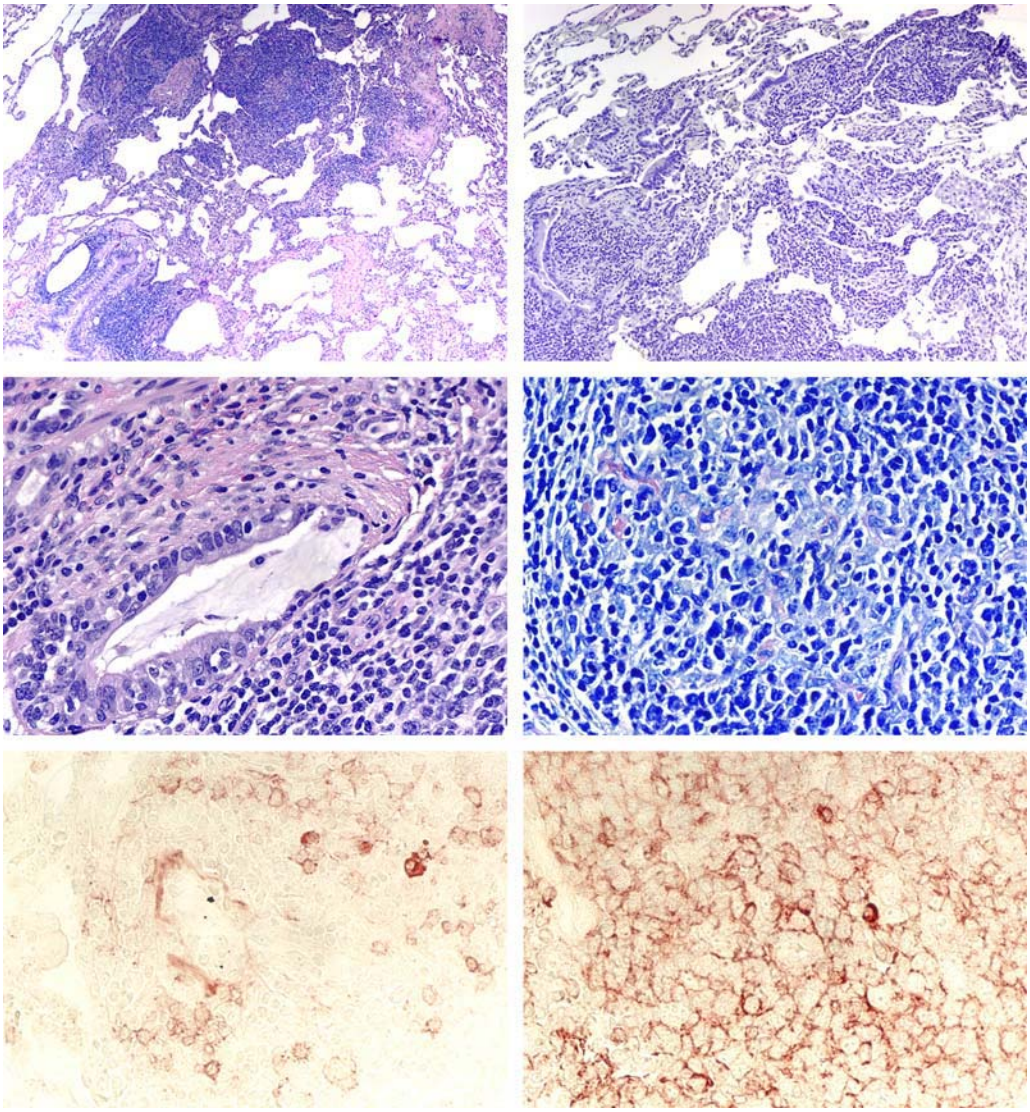
Diagnosis: Lung, open biopsy: Lymphoproliferative disorder, benign, with elements of follicular bronchiolitis and LIP.

Lymphoid proliferation includes reactive follicles with central vessels and a lymphocytic infiltrate which lies to some degree along lymphangitic pathways (peribronhiolar and septal). The follicular lymphoid hyperplasia oriented around bronchioles can be described as follicular bronchiolitis. The lymphocytic interstitial infiltrate extending into alveolar septa can be described as resembling LIP. Because some of the lymphoid proliferations form nodules with invasion by lymphocytes of connective tissue planes, we considered the possibility of a low grade malignant lymphoma such as a malignant lymphoma of mucosa-associated lymphoid tissue (MALToma). However, the infiltrate is not as extensive as generally seen with MALTomas, and the centroblast-like cells characteristic of that disease are not evident (Giemsa stain). We also considered lymphoplasmacytic lymphoma, but periodic acid-Schiff stain shows no intranuclear Dutcher bodies. We performed immunopathological evaluation for B cells and light chains to demonstrate restriction. The follicles contain both T cells and B cells. The B cells express both kappa and lamda light chains. Thus, this histology does not satisfy criteria for a malignant lymphoma. I performed additional stains (elastic tissue, trichrome, Giemsa) to further evaluate the slides. The connective tissue stains accentuate the vascular pattern of follicular centers and suggest that they are normal and not neoplastic

I understand that the patient has mediastinal lymphadenopathy, pleural effusion, densities on chest radiograph with air bronchograms, splenomegaly, shortness of breath, and fever. Although these clinical features raise the possibility of malignant lymphoma, the biopsy does not substantiate that impression. Collagen-vascular disease, Sjogren's syndrome, and immunosuppressed states are conditions that can produce lymphoproliferative reactions as are present here.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. Other pathologists in the department have reviewed the case and essentially concur with the above. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6816 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6618

Diagnosis: Lung, open biopsy: Lymphoid proliferation with sclerosis and obliterated bronchioles, consistent with Sjogren's syndrome.

A modest proliferation of lymphocytes is oriented around blood vessels and a few remaining terminal bronchioles. Like you, I considered low grade lymphoma of lymphomatoid granulomatosis type because of the combination of lymphocytes and sclerosis, but I agree that the quantity of the infiltrate and the absence of atypia indicate that this is not a malignant lymphoma. It is always possible that malignant lymphoma will later develop in a patient with Sjogren's syndrome. This degree of lymphoid proliferation may be seen in Sjogren's syndrome, which is the interpretation I prefer. Some of the scarring is focal. Focal scarring and inflamed arteries are in part unaccompanied by bronchioles. Therefore, I believe there has been an obliteration of bronchioles, probably of the constrictive rather than intraluminal obliterative type. This is an unusual manifestation of Sjogren's syndrome, but follicular bronchiolitis is common.

Thank you for referring this case in consultation. A member of our hematopathology section has reviewed the case and essentially concurs with the above. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.

References:

Deheinzelin D, Capelozzi VL, Kairalla RA, Barbas Filho JV, Saldiva PH, de Carvalho CR. Interstitial lung disease in primary Sjogren's syndrome. Clinical-pathological evaluation and response to treatment. Am J Respir Crit Care Med 1996;154:794–799.

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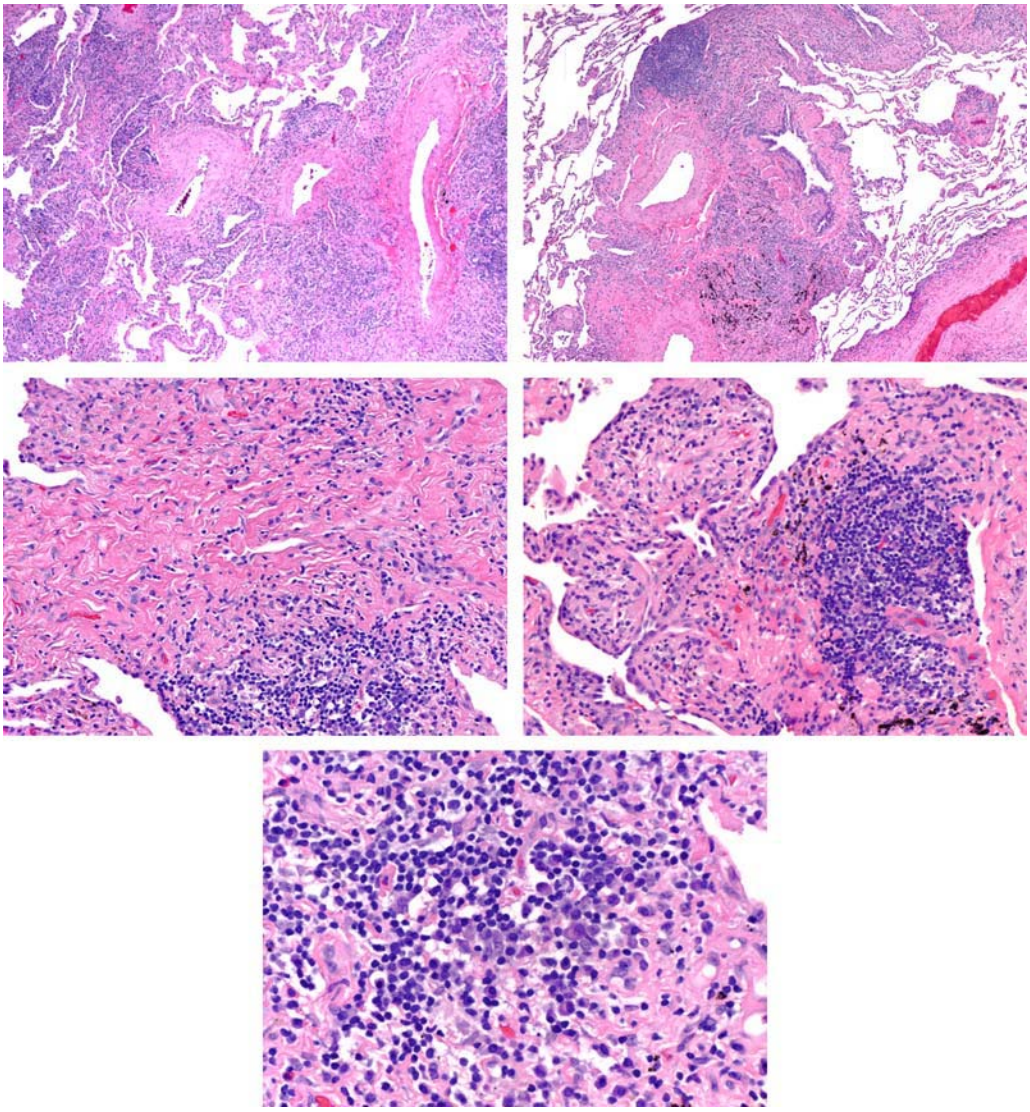
Hansen LA, Prakash UB, Colby TV. Pulmonary lymphoma in Sjogren's syndrome. Mayo Clin Proc 1989;64:920–931.

Tsokos M, Lazarou SA, Moutsopoulos HM. Vasculitis in primary Sjogren's syndrome. Histologic classification and clinical presentation. Am J Clin Pathol 1987;88:26–31.

Provost TT, Talal W, Harley JB, Reichlin M, Alexander E. The relationship between anti-Ro (SS-A) antibody-positive Sjogren's syndrome and anti-Ro (SS-A) antibody-positive lupus erythematosus. Arch Dermatol 1988;124:63–71.



Case 6618 (Chapter 7 – Miscellaneous Pulmonary Disease)

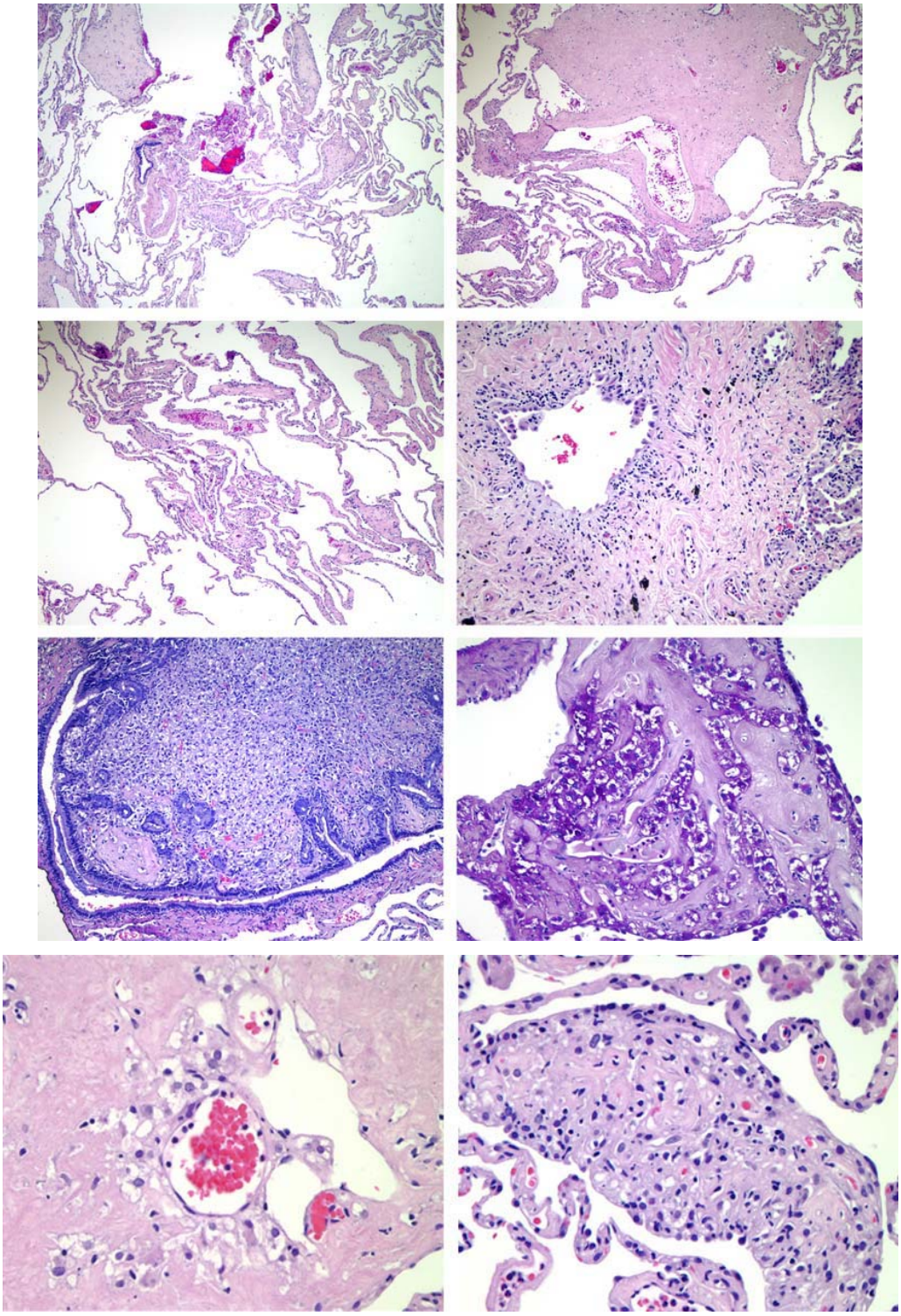
Case 7004

Diagnosis: Lung, open biopsy: Proliferation of clear epithelioid cells with marked PAS-positivity, type and significance uncertain, with focal sclerosis, ? unusual multifocal clear cell neuroendocrine proliferation, ? other.

I am not sure what this case represents. The epithelioid cells have clear cytoplasm and seem associated in part with vascular spaces. Our differential diagnosis is wide and includes lymphangioma, metastatic atrial myxoma, low grade intravascular sclerosing bronchoalveolar tumors, clear cell epithelioid leiomyomas or clear cell variant of lymphangioleiomyomatosis, and clear cell multifocal neuroendocrine proliferation. I would not make a diagnosis of malignancy in this case, firstly because I do not know what the lesion specifically is, secondly because there is no clinical evidence to support a malignant interpretation, and thirdly because there is no obvious treatment modality if this unusual process were called malignant. I considered an infectious etiology and, in particular, Whipple's disease and Mycobacterium avium/intracellulare. The acid-fast stain is negative. The PAS stain is markedly positive but without discernible organisms. This might support a diagnosis of a neuroendocrine cell proliferation with glycogen in a manner analagous to that which occurs in clear cell ("sugar") tumor. The biopsy also contains emphysema with small sclerotic and calcified scars.

Thank you for sharing this case with us. Please keep me informed of any follow-up. This is an elaboration of our telephone conversation.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7004 (Chapter 7 – Miscellaneous Pulmonary Disease)

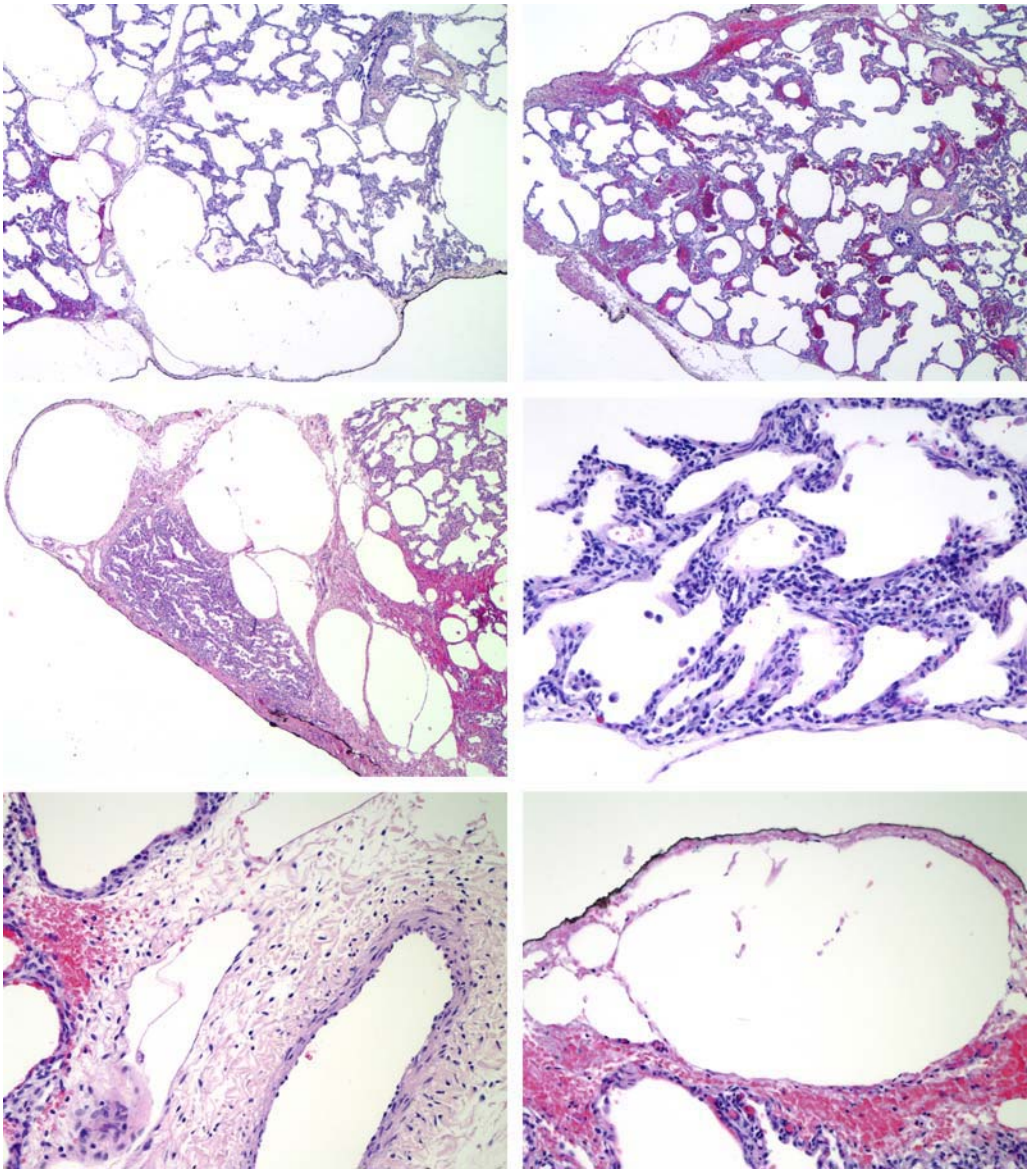
Case 6667

Diagnosis: Lung, open biopsy:

1. **Interstitial cystic spaces, consistent with congenital cystic lymphangiectasia.**
2. **Immature lung, regional, consistent with cellular interstitial pneumonitis.**

I have reviewed this case in conjunction with the clinical and radiographic features of the patient as presented by attending physicians and several other pulmonary pathologists at the Pediatric Pulmonary Rounds today. The above diagnoses best explain the patient's overall clinical course.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6667 (Chapter 7 – Miscellaneous Pulmonary Disease)

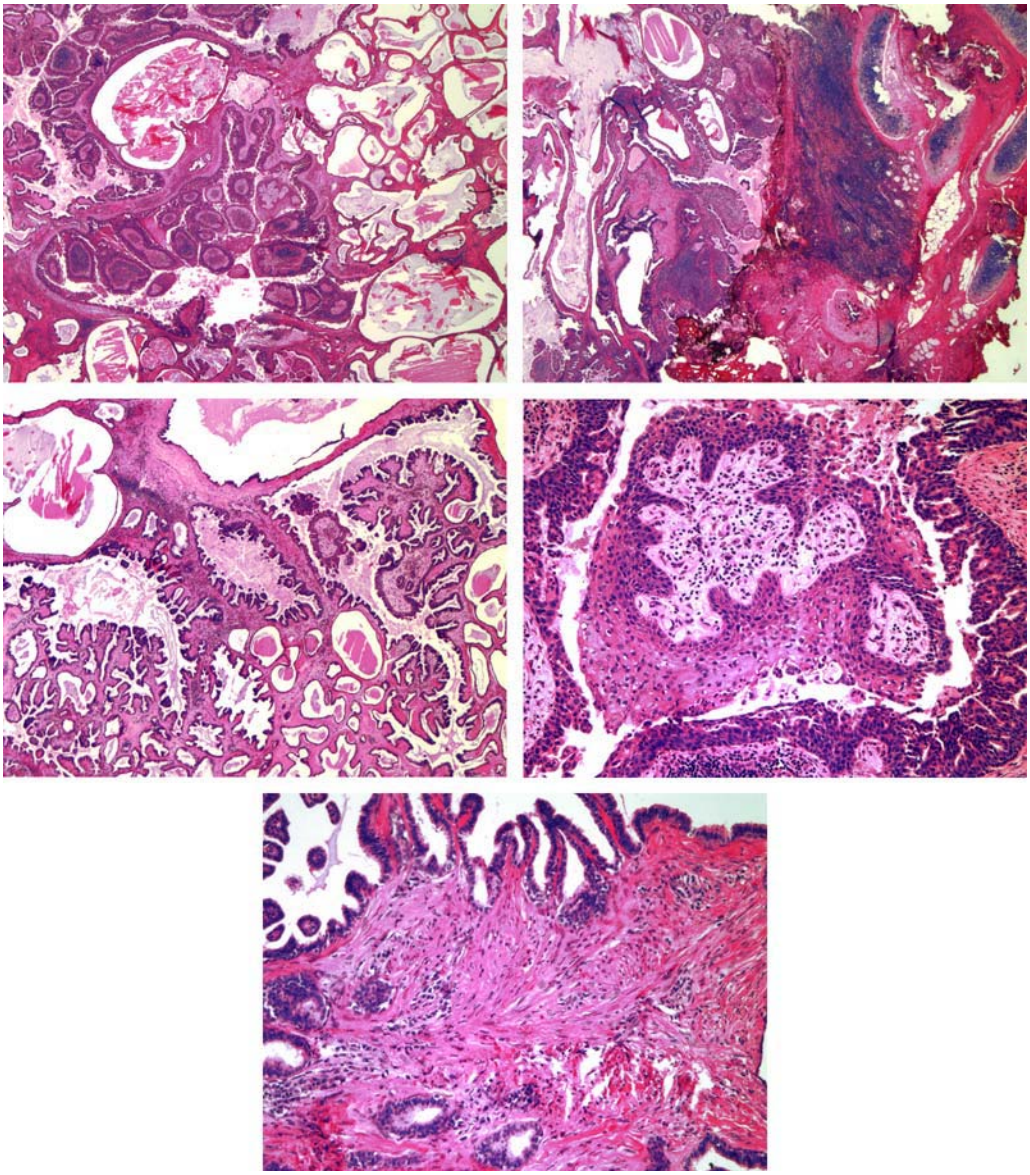
Case 6869

Diagnosis: Lung, wedge resection: Congenital cystic adenomatoid malformation, type II, with focal squamous metaplasia and hyperplasia, ? arising in a bronchial hamartoma.

This highly unusual lesion has both epithelial and mesenchymal elements. The epithelial elements include prominent papillarity, and the cells include both ciliated and nonciliated columnar epithelial cells. The mesenchyme is spindled and possibly smooth muscle in areas. The multifaceted low power appearance with cysts of varying size and a corrugated epithelium in regions indicates a congenital cystic adenomatoid malformation. The focal squamous metaplasia and hyperplasia are unusual. Occasionally cystic adenomatoid malformations arise in sequestrations. Rarely malignancies arise in cystic adenomatoid malformation, but there is no malignancy in this specimen. The outline of the nodule is like that of a bronchial hamartoma, and possibly this one has arisen in a hamartoma, which would be a new concept but not unlike that of origin in a sequestration. Papillary adenomas have a more monotonous and uniform appearance at low power magnification.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6869 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 6809

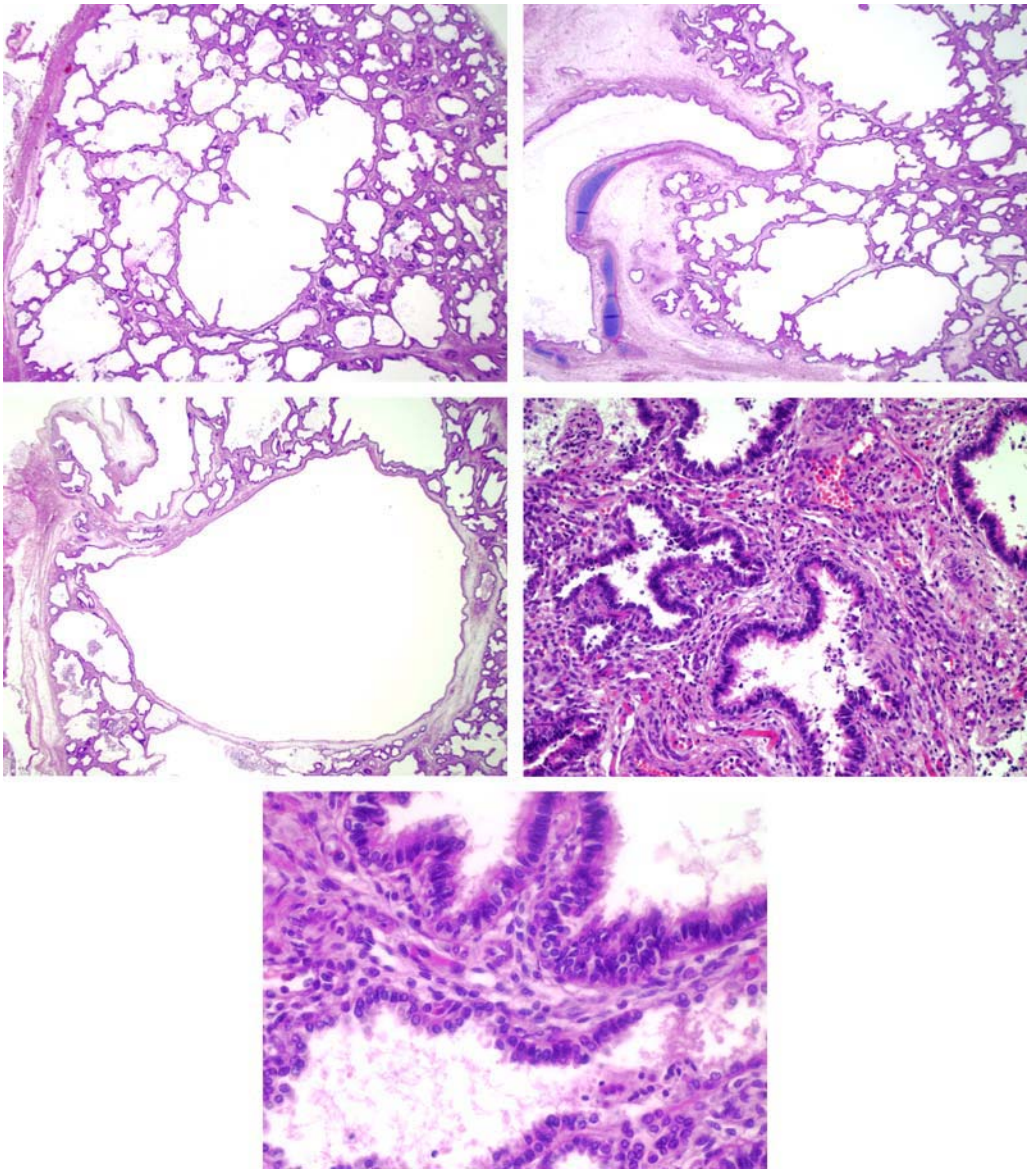
Patient: 13-d-old male

Diagnosis: Mass (periadrenal): Extralobar sequestration of the lung with congenital cystic adenomatoid malformation.

Histologically one sees relatively uniform bronchiolar structures lined by ciliated columnar epithelium associated with a primitive mesenchymal stroma and some more distal airspaces lined by flattened epithelium corresponding to alveolar ducts. The well structured composition is not what one expects in an extralobar sequestration, but it is in keeping with congenital cystic adenomatoid malformation. On the other hand, a congenital cystic adenomatoid malformation of the lung generally is not completely separated from the lung; nor does it lie beneath the diaphragm. So, a diagnosis of extralobar sequestration is appropriate as well. The large and relatively well-formed bronchus simulating a hilus is what one expects with sequestration and is very similar to the recent Case Records of the Massachusetts General Hospital. This is all very much in keeping with your interpretation. This is a very beautiful case. Thank you for sharing it with us.

I hope you have fond memories of your brief stay at the Massachusetts General Hospital. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6809 (Chapter 7 – Miscellaneous Pulmonary Disease)

Case 4408

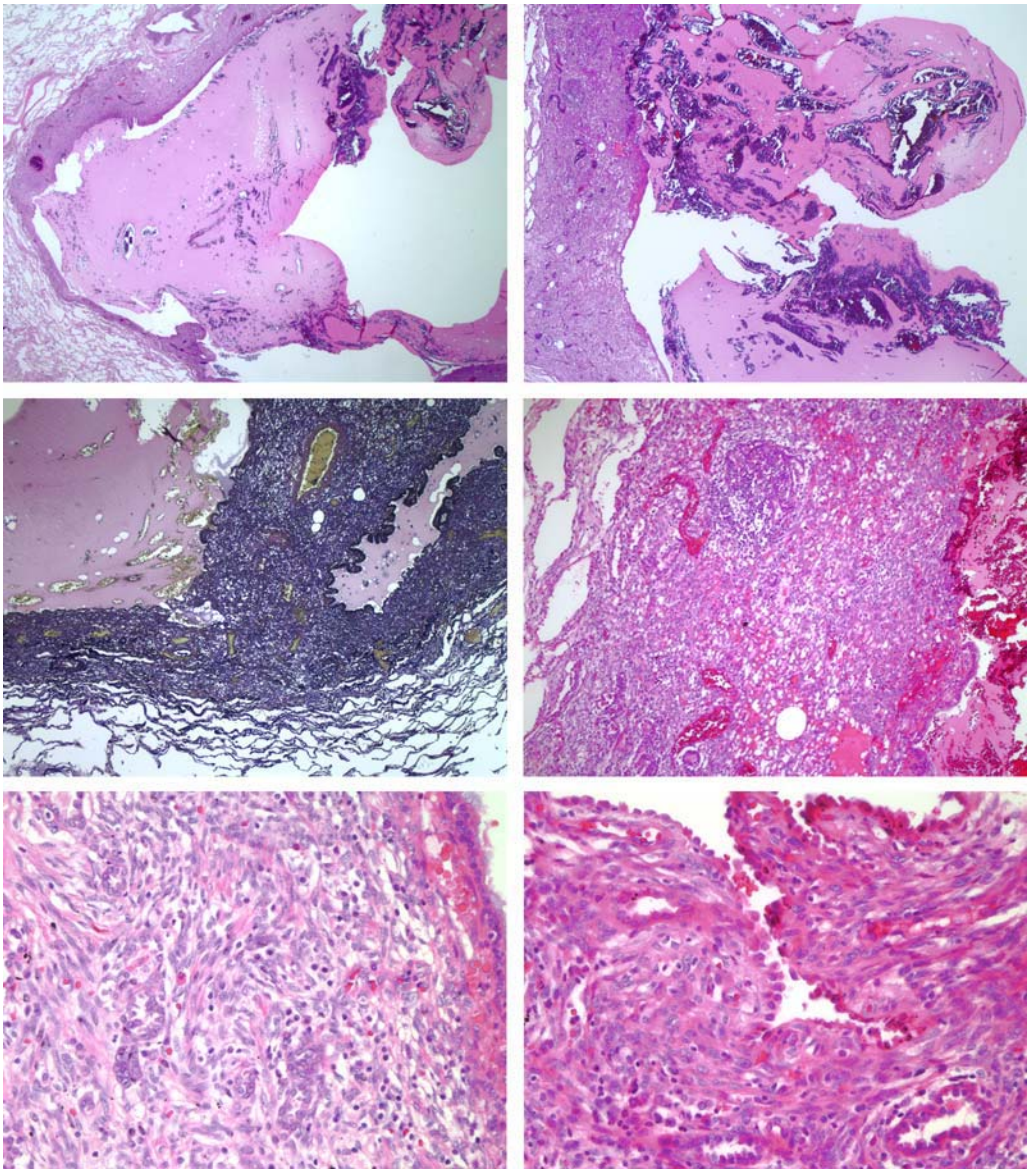
Patient: 34-yr-old female

Diagnosis: Lung, wedge resection: Cystic mesenchymal lesion, ? cystic mesenchymal hamartoma.

The low power configuration of a cyst lined by benign columnar epithelium and surrounded by a thin layer of proliferating spindle cells is consistent with a cystic mesenchymal hamartoma. However, the myxoid and vascular areas in the mesenchyme raise the possibility of a low-grade sarcoma, particularly a metastatic sarcoma from the uterus such as a low-grade leiomyosarcoma or stromal sarcoma. I cannot distinguish these two lesions histopathologically in this particular case.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 4408 (Chapter 7 – Miscellaneous Pulmonary Disease)

8 Non-Neoplastic Pleural Disease

CONTENTS

INTRODUCTION

The pathology of the pleura revolves largely around the diagnosis of diffuse malignant mesothelioma (DMM). The most important clinical distinction is drawing the line between various forms of reactive mesothelial hyperplasia and DMM. The diagnosis of DMM and distinguishing DMM from other pleural neoplasms will be discussed in Chapter 10.

Atypical mesothelial hyperplasia may include very bizarre nuclei. When compared with DMM, atypical mesothelial hyperplasia in the classical case will have fibrin on the serosal surface, ingrowth of the mesothelial cells into or beneath the fibrin, more edema, and a richer proliferation of capillaries. Invasion will not occur by definition, but entrapment of benign proliferating mesothelial cells in newly formed collagen may be confusing. Atypical mesothelial hyperplasia may involve the visceral pleural surface over a bronchogenic carcinoma.

Another common challenge is trying to decipher the etiology of a reactive pleuritis to the extent that histopathology allows. Histological forms of pleuritis that have diagnostic usefulness include the following:

- Purulent pleuritis
- Organizing fibrinous pleuritis
- Fibrinous pleuritis with mesothelial giant cells and cytoplasmic inclusions
- Rheumatoid pleuritis with palisading histiocytes and intrapleural rheumatoid nodule
- Fibrosing pleuritis with granulomas (e.g., tuberculosis)
- Reactive eosinophilic pleuritis

Purulent pleuritis suggests a parapneumonic effusion, an infected effusion, or empyema. Organizing fibrinous pleuritis **(6659)** is the common finding associated with congestive heart failure, pulmonary infarction, drug reactions, and collagen-vascular disease. Effusions resulting from rheumatoid disease may have histiocytic or mesothelial giant cells **(6866)** with cytoplasmic inclusions. Granulomas suggest tuberculosis until proven otherwise. Reactive eosinophilic pleuritis occurs after a pneumothorax.

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

The following list includes other peculiar pleural conditions:

- Mesothelial folds, nodules, and excrescences
- Mesothelial inclusion cyst **(6853)**
- Mesothelial cells in lymph nodes
- Shrinking pleuritis with rounded atelectasis **(6553)**
- Pleural fibrosis and metaplastic cells after pneumothorax

Mesothelial folds in a thoracoscopic specimen may appear as unaccounted for epithelioid cells in the middle of lung parenchyma. Mesothelial excrescences appear as microscopic nodules in cell blocks of pleural fluid or applied to lymph nodes removed at mediastinoscopy. Benign mesothelial cells may migrate through lymphatics from the pleural space into local lymph nodes. Rounded atelectasis disappears when the surgeon or pathologist incises the pleural scar responsible for the atelectasis, but histologically one may still detect bronchovascular bundles and alveolar walls stretched toward the thickened and enfolded visceral pleura. Cleft-like spaces lined by multinucleated histiocytes develop after pneumothorax. Columnar cells with large vacuoles line the pleural space after pneumothorax in patients with cystic fibrosis.

Finally, there are certain non-neoplastic pleural diseases that are associatied with exposure to asbestos:

- Pleural hyaline plaque **(6866)**
- Gross: bilateral, basal, calcified, visceral, or parietal
- Micro: bundles of acellular collagen in a basket-weave pattern
- Recurrent effusions with atypical mesothelial hyperplasia **(6560)**
- Premalignant potential controversial; difficult cytological diagnosis
- Pleuritis en cuirrasse **(7180)**; benign entrapment by proliferative pleural fibrosis
- Blesovsky's syndrome **(6557)**; rounded atelectasis resulting from localized and shrinking pleural fibrosis which tethers and contracts subjacent lung

SUGGESTED READINGS

Atypical Mesothelial Hyperplasia

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LETTERS

Case 6866

Diagnosis: Parietal pleura, open biopsy:

1. **Organizing fibrinous and fibrosing pleuritis.**
2. **Pleural hyaline plaque.**

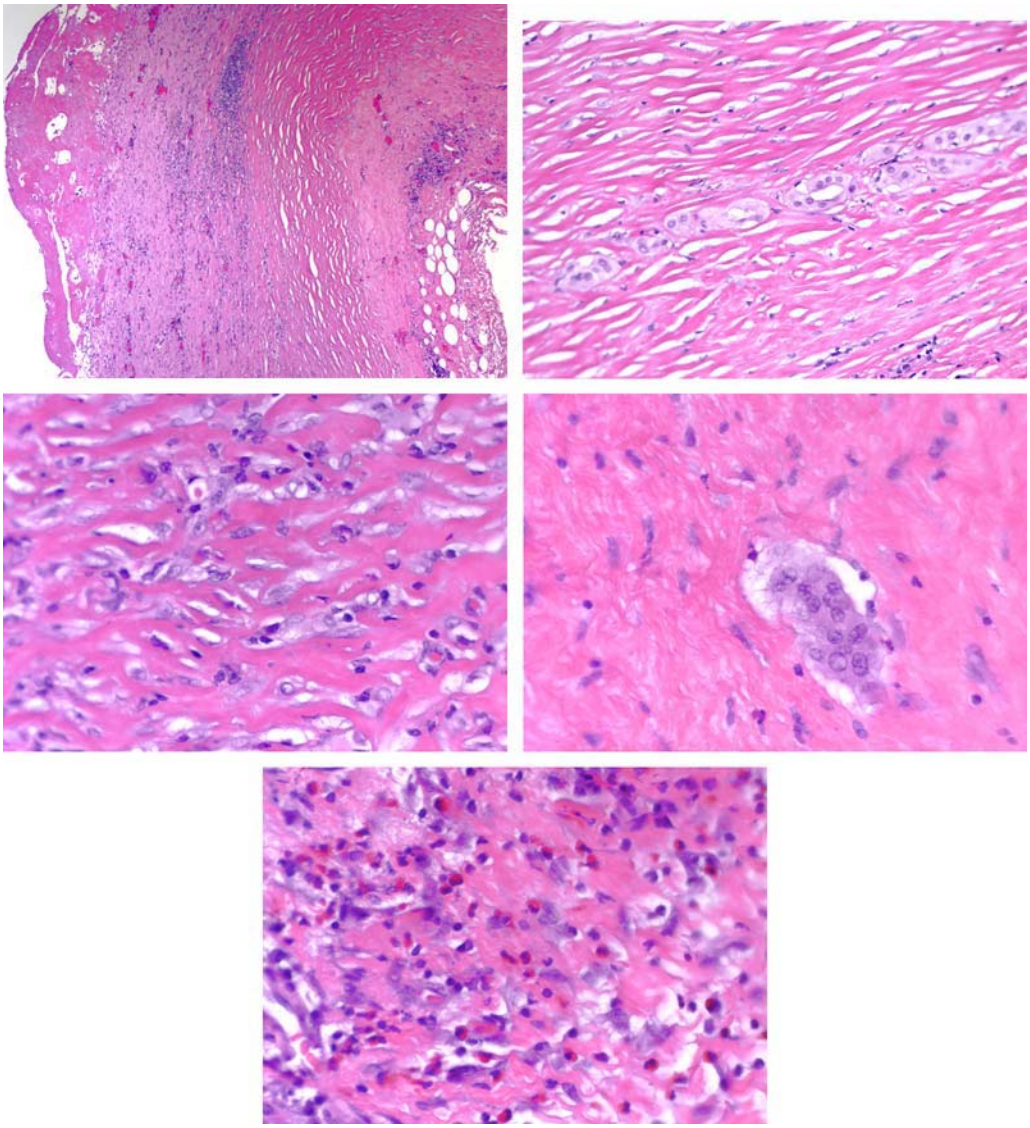
This case is difficult because between the areas of organizing fibrinous pleuritis and pleural hyaline plaque are other areas with spindled nuclei separated by collagen in a manner that simulates DMM of desmoplastic subtype. I cannot absolutely exclude that diagnosis. However, I do not favor it. There is no necrosis, no invasion, and no storiform pattern. I have seen this form of spindle cell proliferation previously in cases of organizing fibrinous pleuritis. I believe that this organized pattern may occur when an effusion is resorbed gradually.

There are entrapped nests of epithelioid cells in a few regions. These cells stain negatively for carcinoembryonic antigen. These nests are unusual, but I agree with your interpretation that these probably are entrapped mesothelial cells.

In some slides the pleuritis is associated with numerous eosinophils as well as multinucleated mesothelial cells or histiocytes. These findings raise the possibility that a pleural effusion may have been due to a drug reaction or to rheumatoid disease.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6866 (Chapter 8 – Non-Neoplastic Pleural Disease)

Case 6853

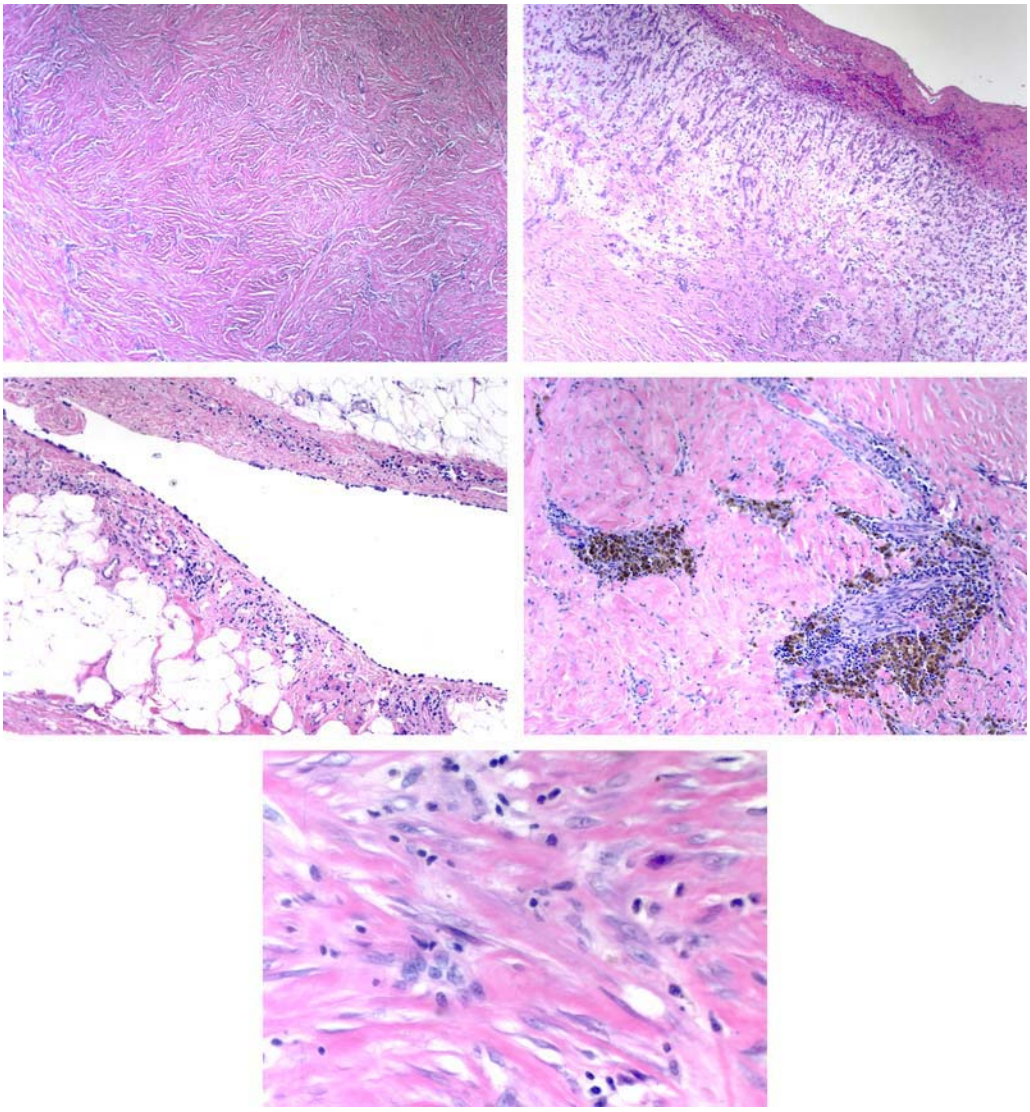
Diagnosis: Parietal pleura and chest wall, stripping: Organizing fibrinous pleuritis, fibrosing pleuritis, fibroblastic proliferation, and mesothelial inclusion cyst.

This case has its straight forward and its complicated aspects. The majority of the biopsy shows reactive organizing fibrinous pleuritis with new blood vessels arranged perpendicular to the pleural space, indicative of a reactive process. Old fibrotic scar with new vessels and extensive hemosiderin also indicates a reactive process. More complicated is hypercellular fibroblastic proliferation which produces a storiform pattern. We generally acknowledge that the storiform pattern is one attribute of desmoplastic DMM, but it is not by itself a criterion for malignancy. This case lacks all other criteria, that is, there is no invasion of fibroadipose tissue of chest wall, no necrosis, and no nuclear atypia. Finally, are the mesothelial-lined inclusion cysts in the fibroadipose tissue. I suspect these represent a phenomenon of entrapment.

I cannot absolutely exclude the subsequent develop of a DMM of desmoplastic subtype based on the regions of cellular proliferation with storiform pattern, but I doubt that possibility. The cells lining the inclusion cysts are hyperplastic mesothelial cells, but the absence of papillary proliferation makes me believe that this portion of the process is benign as well.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6853 (Chapter 8 – Non-Neoplastic Pleural Disease)

Case 6560

Diagnosis: Lung and pleura, open biopsies:

1. **Organizing fibrinous pleuritis.**
2. **Mesothelial proliferation with dense fibrosis, signficance uncertain.**
3. **Pleural hyaline plaque with calicification.**

This case is difficult. Regions of hypercellular spindle cell proliferation form a nodule and a cambium-like layer next to less cellular regions. One hypercellular nodule has some nuclear pleomorphism and many mitoses. A vague storiform pattern appears in other areas. These appearances raise the possibility of a DMM of desmoplastic subtype. Also in the differential diagnosis is desmoid tumor of the pleura. A diagnosis of malignancy cannot be made on this specimen because of the absence of necrosis and absence of lung tissue. Much of the specimen is an organizing fibrinous pleuritis with granulation tissue and ingrowth of capillaries into blood clot, and one could accept the worrisome areas as part of that pleuritis. Pleural hyaline plaque with calcification and ossification is also present.

I believe the focal staining for epithelial membrane antigen represents mesothelial cells. I believe there is weak staining for keratin as well in some of these cells.

The reported radiographic appearance of the chest CT scans raises the possibility of DMM, but if this had been malignant in 1997, I would expect (almost 2 yr later) that the patient now would have chest pain, weight loss, or other clinical stigmata of malignancy. On balance, I favor a reactive process in 1997. The challenge with the case suggests continued clinical follow-up. Rebiopsy might be considered depending on clinical circumstances, but rush to diagnosis is generally not indicated because of the very limited success of treatment.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

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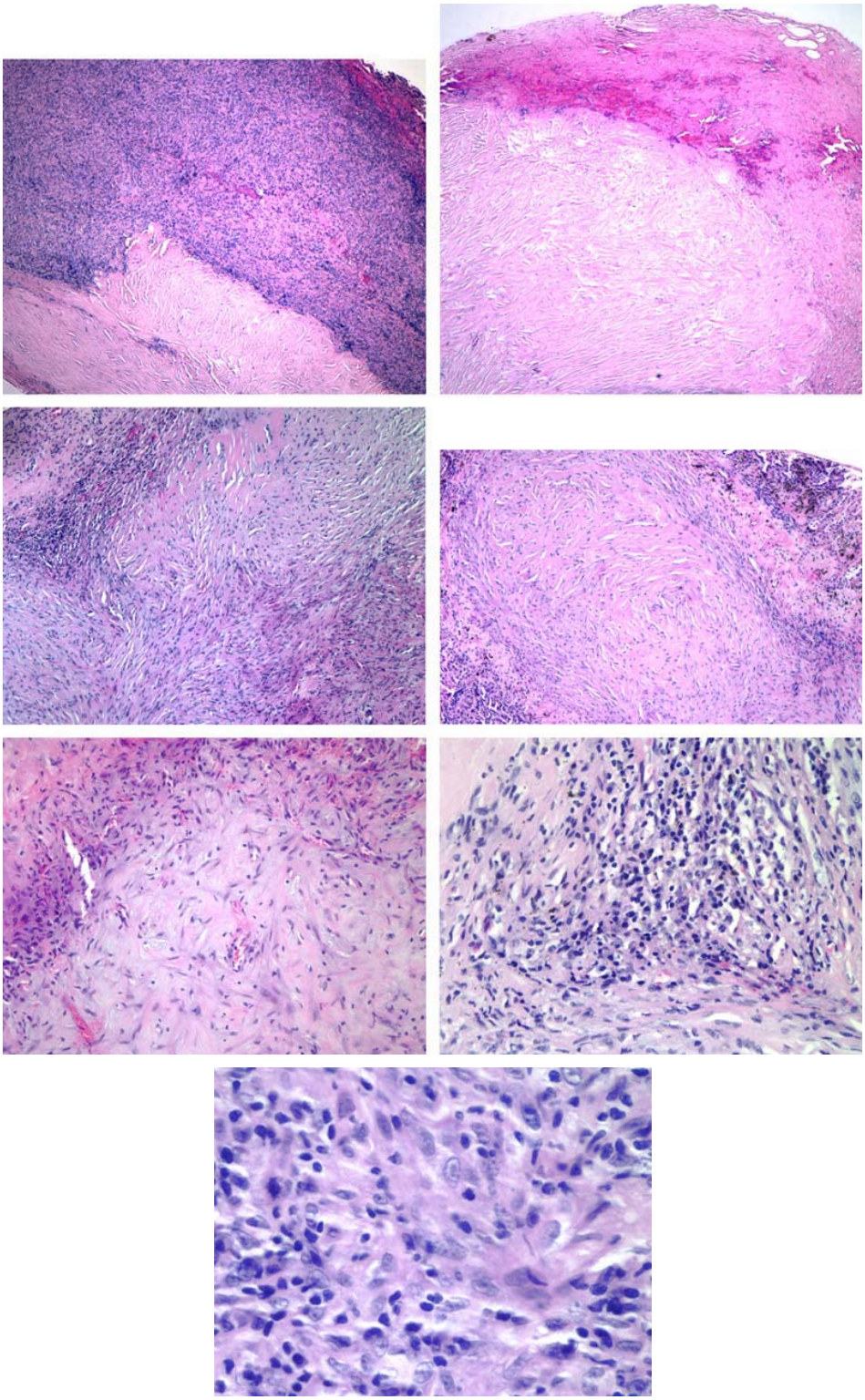


Case 6560 (Chapter 8 – Non-Neoplastic Pleural Disease)

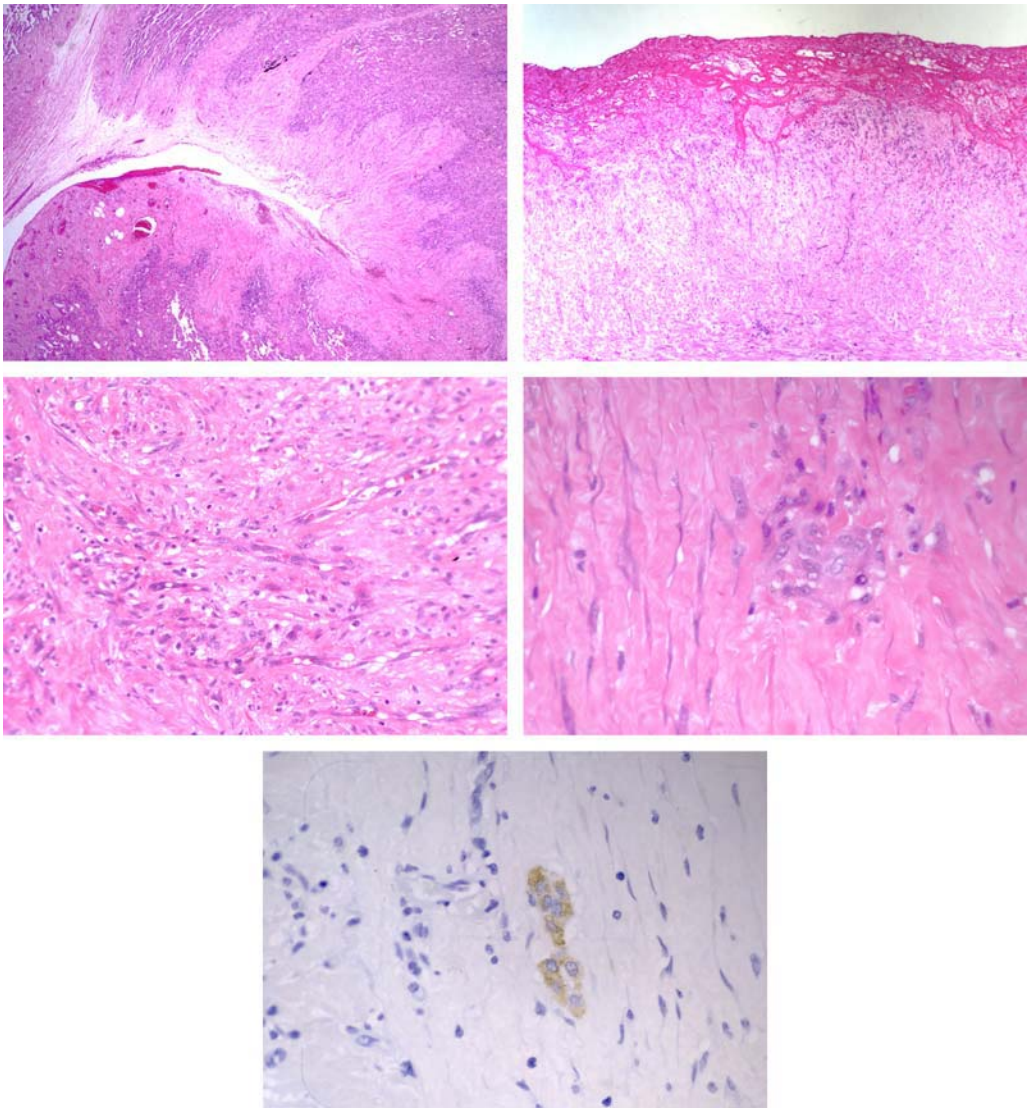
Case 6768

Diagnosis: Pleura and lung, pleural stripping: Organizing hemothorax, with organizing fibrinous pleuritis, marked endothelial proliferation, and entrapped mesothelial cells.

The great majority of the pleura has well established organizing hematoma, whereby the proliferating capillaries and endothelial cells are oriented perpendicular to the blood clot. The proliferative fibrosis in deeper regions with absence of storiform pattern is against DMM. One slide shows shrinking pleuritis with a 1 cm nodule of rounded atelectasis of the sort that typifies Blesovsky's syndrome, although in this case rounded atelectasis is apparently not a clinical consideration. Of concern about the case are the few nests of epithelioid cells which stain positively for keratin within the fibrous tissue. I considered pleural carcinomatosis, but I do not believe these cells have cytological features of malignancy in the slides stained with hematoxylin and eosin. I believe that they represent entrapped mesothelial cells. Thus, in summary, I believe we are dealing with a reactive process and not a malignancy. Considerations include hemothorax associated with operative procedure or Dressler's syndrome.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. I was very happy to hear from you again. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6768 (Chapter 8 – Non-Neoplastic Pleural Disease)

Case 6659

Diagnosis: Lung, open biopsy:

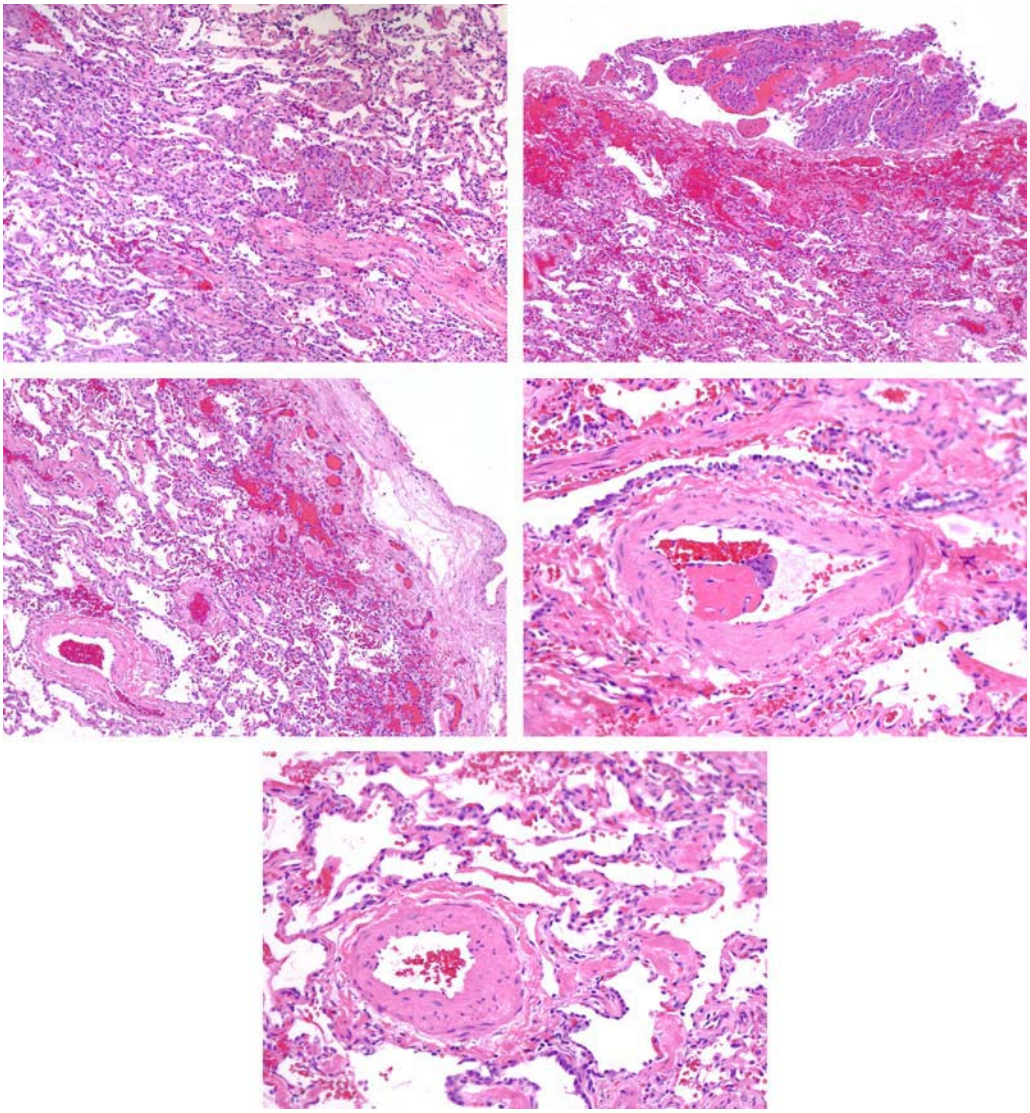
1. **Organizing fibrinous pleuritis, with scant alveolar fibrin and interstitial fibrosis in subpleural lung zone, nondiagnostic.**
2. **Microscopic thormboembolus, recent, one nonocclusive fragment.**

The most definite pathology is the organizing fibrinous pleuritis, which has been ongoing for several days to several weeks because there is edematous thickening of the visceral pleura as well as mesothelial hyperplasia. A small amount of fibrin in subpleural alveoli probably is part of the pleuritis. Apart from this change, the pathological findings are slight. There is interstitial fibrosis of a few alveolar walls, pigmented histiocytes in some alveolar ducts, and slight intimal and medial thickening of pulmonary arteries. The interstitial fibrosis is not sufficient for a diagnosis of interstitial pneumonitis, such as usual interstitial pneumonitis. The pigmented histiocytes are not sufficient for a diagnosis of respiratory bronchiolitis. The intimal and medial changes are not sufficient for a diagnosis of pulmonary arterial hypertension.

The morphological expression of pulmonary hypertension in the lung can be surprisingly focal. One truism is that plexogenic lesions, as seen in severe pulmonary hypertension, can be present in only every fifth or every tenth block of tissue. No plexogenic lesions, no hemosiderosis, and no vasculitis are apparent in these specimens. However, there is a nonocclusive piece of a single microscopic thromboembolus in one slide. In some other biopsies, I might not raise this diagnosis, but because of the patient's clinical history, the thromboembolus may be significant. The pleuritis could be related to thromboembolic disease. I cannot explain the reportedly severe respiratory difficulties in this patient. The above observations are essentially in agreement with your interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Casee 6659 (Chapter 8 – Non-Neoplastic Pleural Disease)

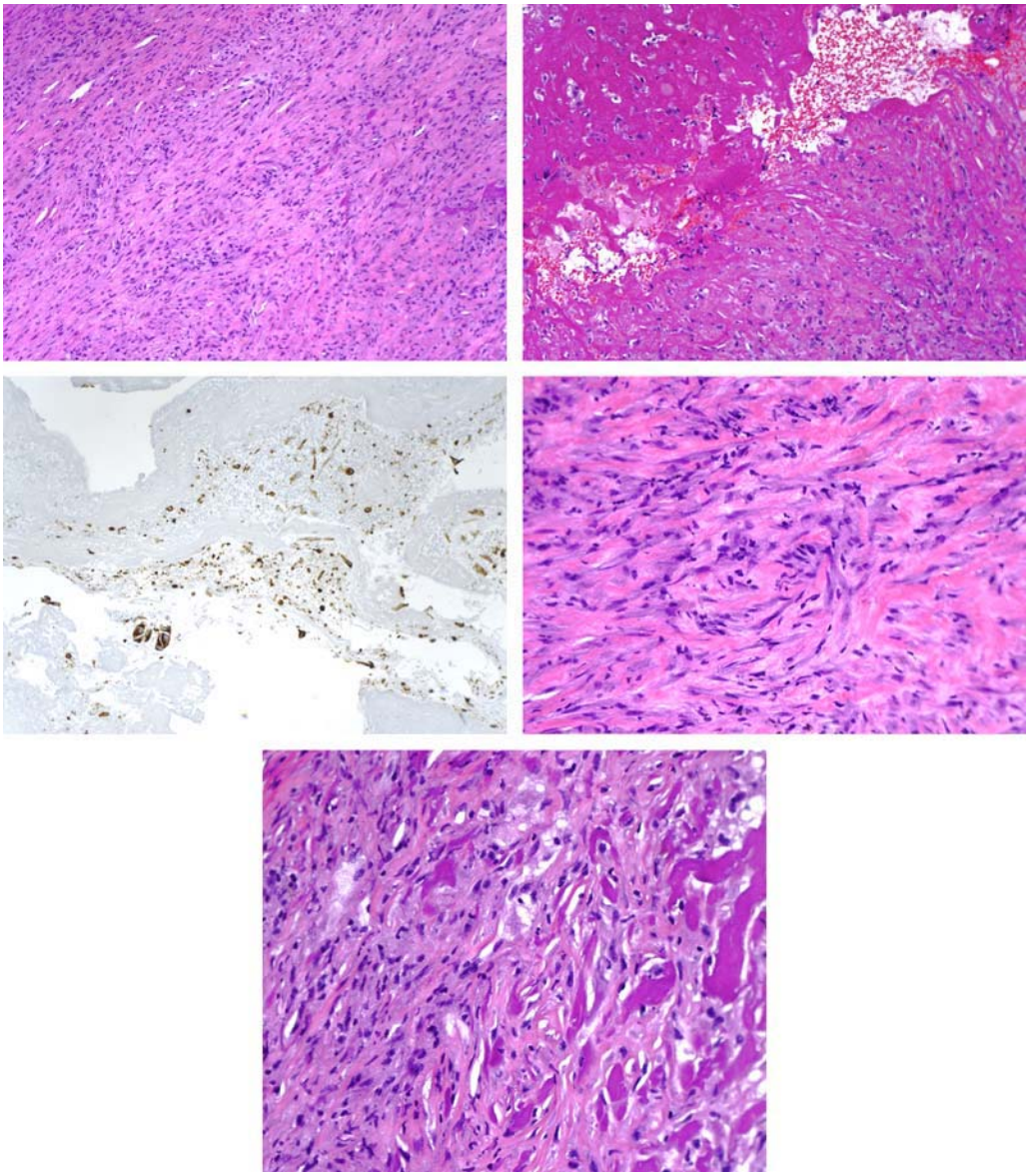
Case 6915

Diagnosis: Pleura, stripping: Organizing fibrinous and fibrosing pleuritis with cellular atypia.

The challenge in this case is that there are regions of benign reactive mesothelial proliferation with cells growing into hematoma and fibrin clot as well as other areas with hypercellular spindle cell proliferation separated by dense collagen. The latter raises DMM of desmoplastic subtype into the differential diagnosis. However, I have seen such cellularity and nuclear atypia in slowly resolving pleural and pericardial effusions including hematomas and therefore do not believe these regions are diagnostic of DMM. When I see a biopsy which has clearly reactive portions, I am particularly conservative in making a second diagnosis of malignancy. Vascularity throughout the specimen supports a reactive process. No invasion of tissue by the mesothelial cells is present, although proliferating spindled cells entrap columns of fibrin which simulate skeletal muscle. Your cytokeratin stains show positive staining for mesothelial cells. I find the relatively uniformly dispersed cells in large regions on the keratin stains more in keeping with a reactive process rather than with a malignancy. I detect only minimal storiform patterns on either the routine stains or the keratin stains to support a diagnosis of DMM. Although I am not absolutely sure that all of this specimen is benign and reactive, I believe it all is, and I definitely cannot make a diagnosis of malignancy on this specimen. Repeat biopsy may be indicated if symptoms persist, and this decision will depend on clinical circumstances.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6915 (Chapter 8 – Non-Neoplastic Pleural Disease)

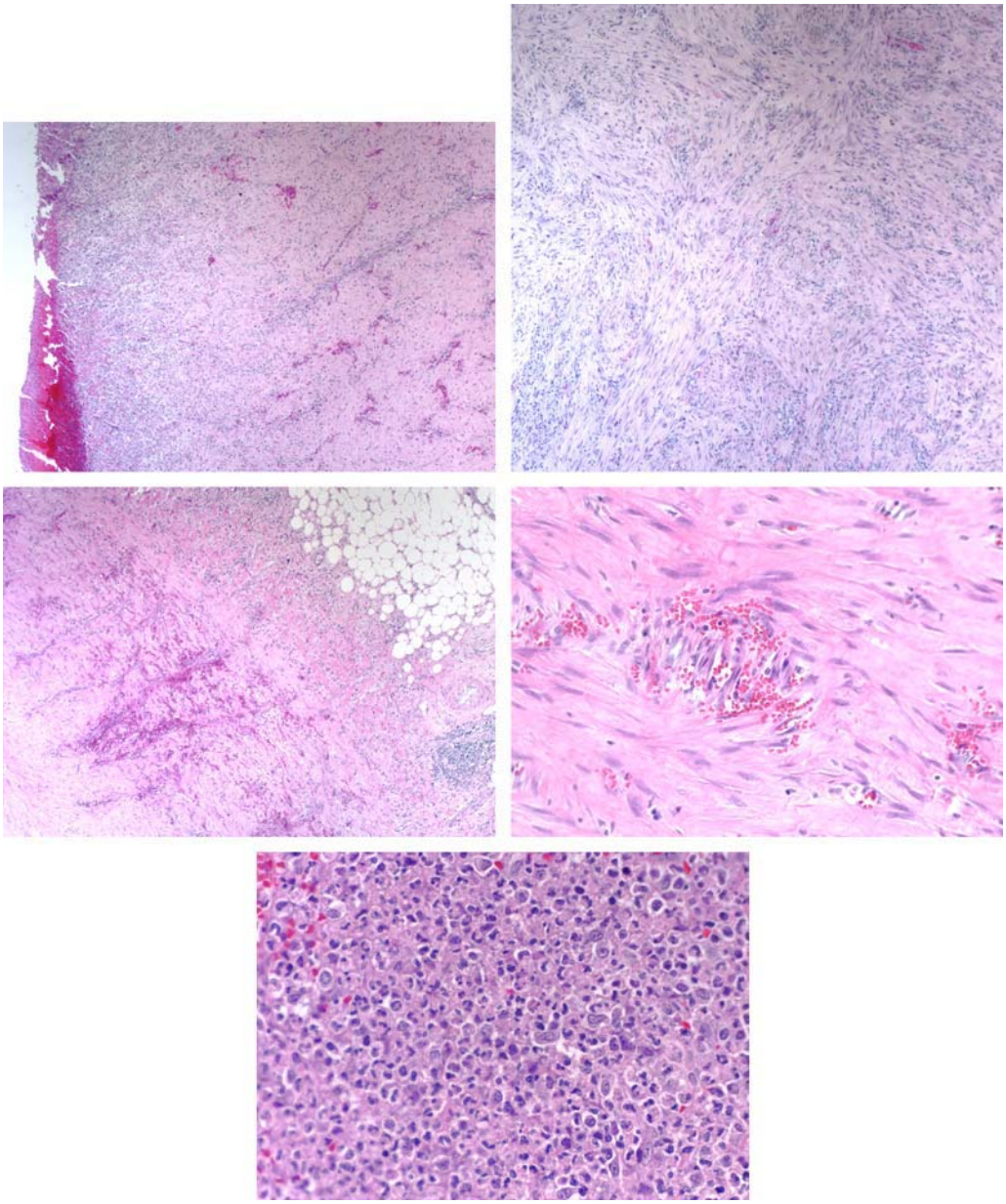
Case 6778

Diagnosis: Parietal pleura, stripping: Empyema, with mesothelial hyperplasia and fibrosing pleuritis.

When mesothelial hyperplasia is associated with empyema or hemothorax (in this case the former), my first inclination is to attribute the pleuritis to the empyema or hemothorax, and I believe that is the situation in this case. The perpendicular orientation of the mesothelial cells to the serosal surface, the rich admixture of lymphocytes and histiocytes, and the vascularity of the process all favor a reactive condition. The dense fibrosis, with broad bands of collagen deeper in the pleura, certainly raises desmoplastic DMM into the differential diagnosis. A storiform pattern is often helpful in diagnosing DMM, and a storiform pattern is established here. Nevertheless, I do not favor a malignant interpretation and must use this case as an example that there is no one feature short of tissue invasion or metastases to prove the malignancy of diffuse pleural neoplasia. My suspicion for DMM is low, and I do not believe it is the correct diagnosis here.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6778 (Chapter 8 – Non-Neoplastic Pleural Disease)

Case 7180

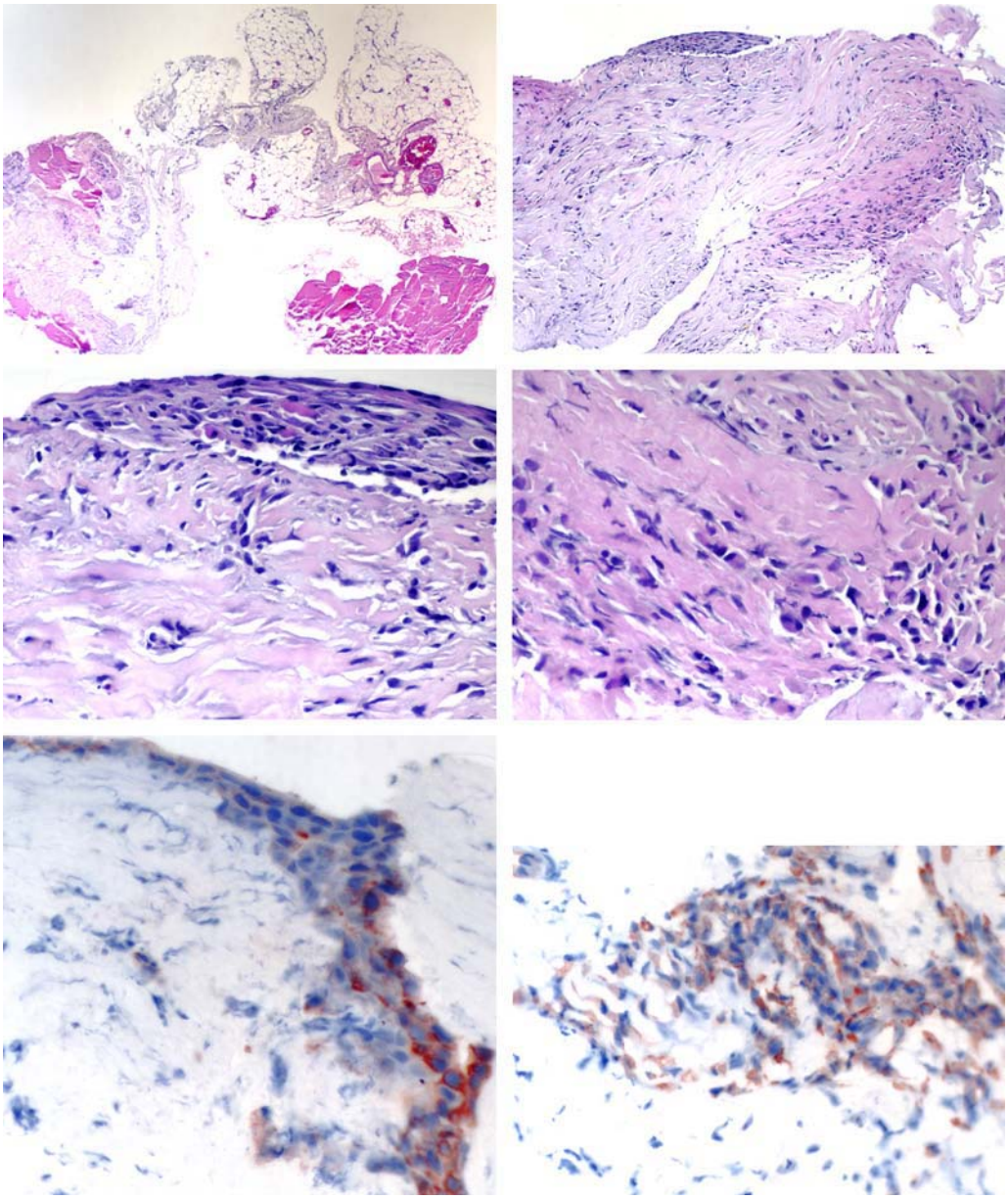
Diagnosis: Parietal pleura, needle biopsy: Mesothelial proliferation and fibrosis, nature uncertain, consistent with reactive mesothelial hyperplasia.

A pleural biopsy is 3 mm in greatest diameter on the slides. There is dense laminar fibrosis, and between broad bundles of collagen are angular and spindled hyperchromatic nuclei. The distribution of the cells within the collagen and their similarity to a single layer of hyperchromatic mesothelial cells on the surface makes me believe these are hyperplastic and reactive mesothelial cells that have been entrapped in scar, and makes me believe that this process represents an organizing fibrosis. Features useful in the definite diagnosis of DMM (storiform pattern, necrosis, invasion) are not present in this small specimen.

In the differential diagnosis, we also considered DMM and metastatic adenocarcinoma. To further study the case, we performed the following stains: mucicarmine, AE1-3 keratin, carcinoembryonic antigen, calretinin and carcinoembryonic antigen. A portion of spindled cells within collagen stained for keratin. The mesothelial cells on the surface also stain for keratin. Cells within collagen do not stain for carcinoembryonic antigen, calretinin, prostate specific antigen or mucicarmine for mucin. There are fewer cells in these recuts than in your original sections. These results are not in themselves decisive but do not support a diagnosis of either DMM or metastatic adenocarcinoma.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. Additional tissue is necessary for more precise morphological diagnosis. Whether a more precise diagnosis is necessary depends upon clinical circumstances. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7180 (Chapter 8 – Non-Neoplastic Pleural Disease)

Case 6821

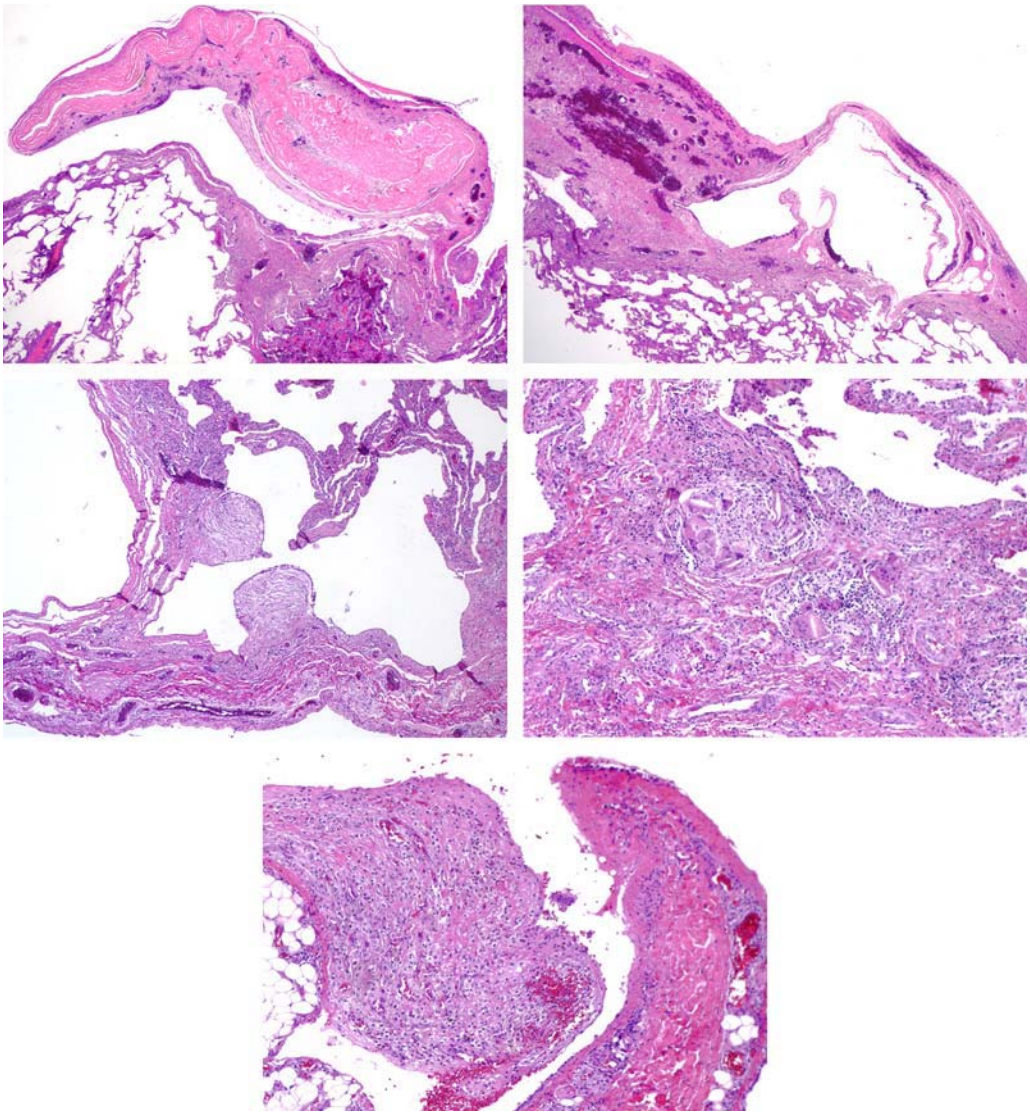
Diagnosis: Lung and pleura, open biopsy:

1. **Pneumothorax.**
2. **Organizing and old pleuritis with pleural adhesions, mesothelial hyperplasia, subpleural bullae, blebs, and subpleural histiocytic giant cell reaction.**

The pleural bullae and an intrapleural bud with associated adhesions are what one usually encounters with spontaneous penumothorax of unknown cause. The histiocytic giant cell reaction could be due to prior instrumentation or to a reaction to nitrogen, which can sometimes elicit such a reaction when loculated beneath the pleura. Intrapleural blebs (by definition, a bleb is not connected to alveoli) are not commonly observed but are prominent in this case. The varying age of the adhesions suggests repeated episodes of pneumothorax. I searched for three discernible causes of pneumothorax in young persons: 1) eosinophilic granuloma; 2) lymphangioleiomyomatosis; 3) pneumocystis infection with cysts. I find none. Reactive eosinophilic pleuritis, as seen in some cases of pneumothorax, is not present. In my experience, young individuals with spontaneous pneumothorax usually have no discernible etiology. Many young men with spontaneous pneumothorax have a tall and thin habitus.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6821 (Chapter 8 – Non-Neoplastic Pleural Disease)

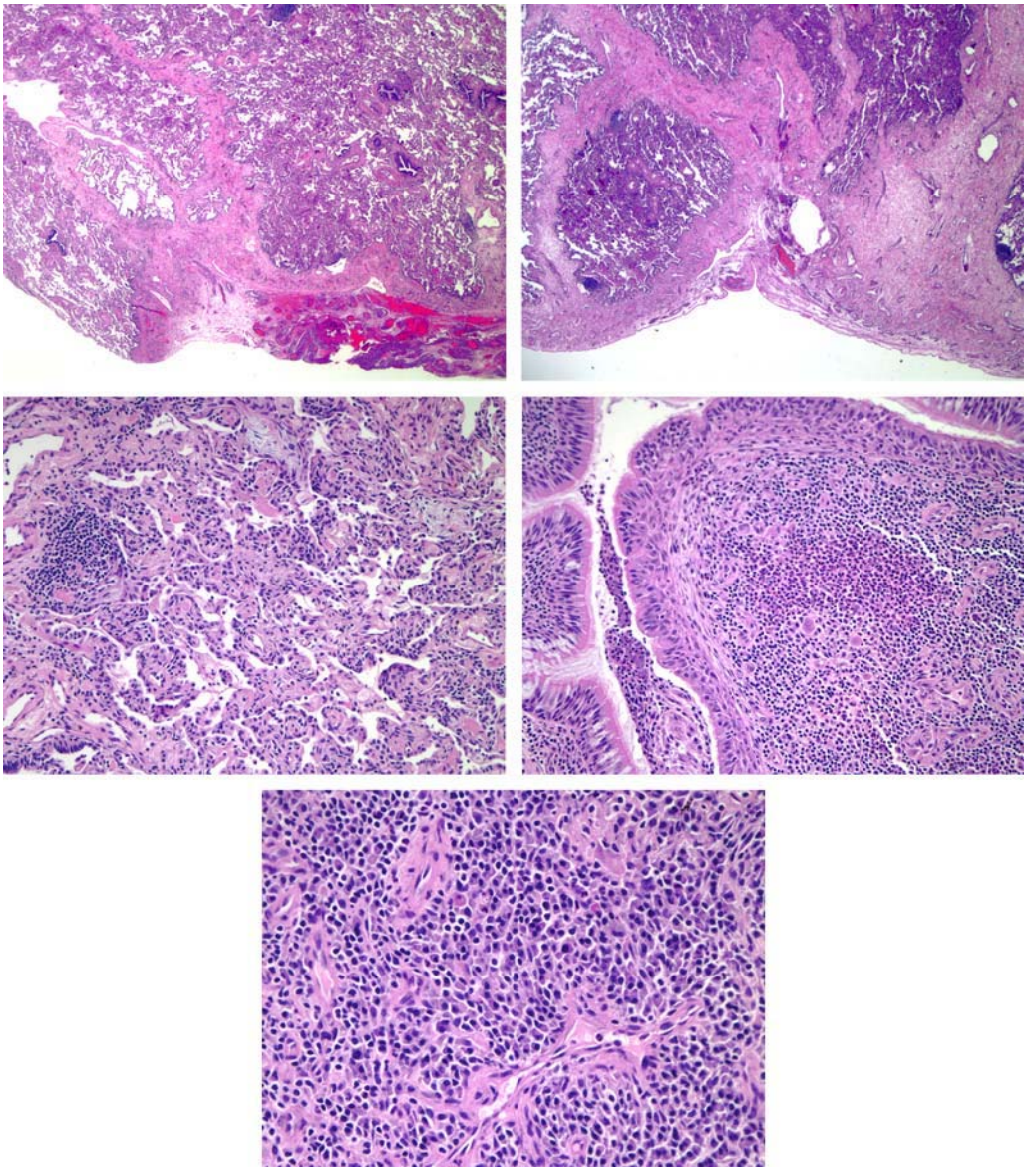
Case 6553

Diagnosis: Lung, wedge resection: Shrinking pleuritis with rounded atelectasis.

The high-power histology is that of purulent bronchiolitis surrounded by a small amount of organizing pneumonia (OP) but more atelectasis with fibrosis. The low-power histology of many indented and expanded lobular septae associated with a fibrotic pleura which has caused puckering and invagination of the septa constitutes shrinking pleuritis with rounded atelectasis, also known as Blesovsky's syndrome or pleuroma. It is one of the causes of so-called disappearing tumor in the lung. The pleural adhesion in this case includes sheets of plasma cells as well as pus. In other cases of Blesovsky's syndrome, the pleuritis consists of asbestos-associated pleural fibrosis. No malignancy is present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6553 (Chapter 8 – Non-Neoplastic Pleural Disease)

Case 6557

Diagnosis: Lung, wedge resection:

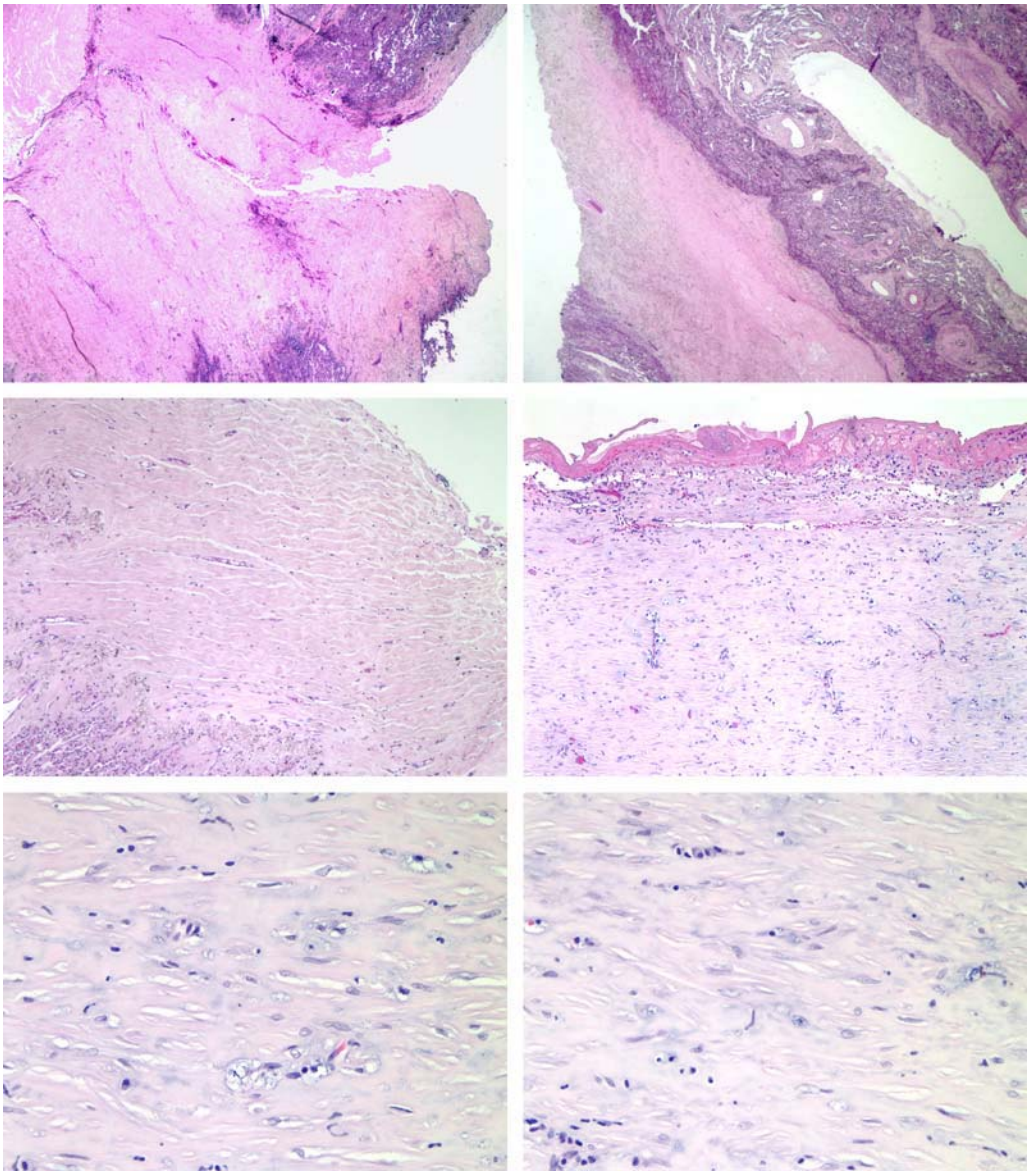
1. **Shrinking pleuritis with rounded atelectasis.**
2. **Atypical mesothelial proliferation.**

The markedly thickened pleura due to old collagenous fibrosis with lobulation of the pleural thickening into lung, retraction of thickened lobular septa continuous with the pleura, and adjacent atelectasis constitute shrinking pleuritis with rounded atelectasis. This is also known as Blesovsky's syndrome and pleuroma. This is in agreement with your interpretation.

On the surface of the pleura is a spindle cell proliferation with keloidal type collagen. This proliferation is consistent with a reactive process, but I cannot absolutely exclude an early desmoplastic form of DMM. Against DMM are lack of cellular atypicality, lack of storiform pattern, and absence of necrosis. Special studies would not decide the issue of reaction vs malignancy. Intraoperative observation of presence or absence of other deposits of abnormal tissue on the pleura might be helpful. Follow-up of the patient might be considered.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6557 (Chapter 8 –Non-Neoplastic Pleural Disease)

Case 6811

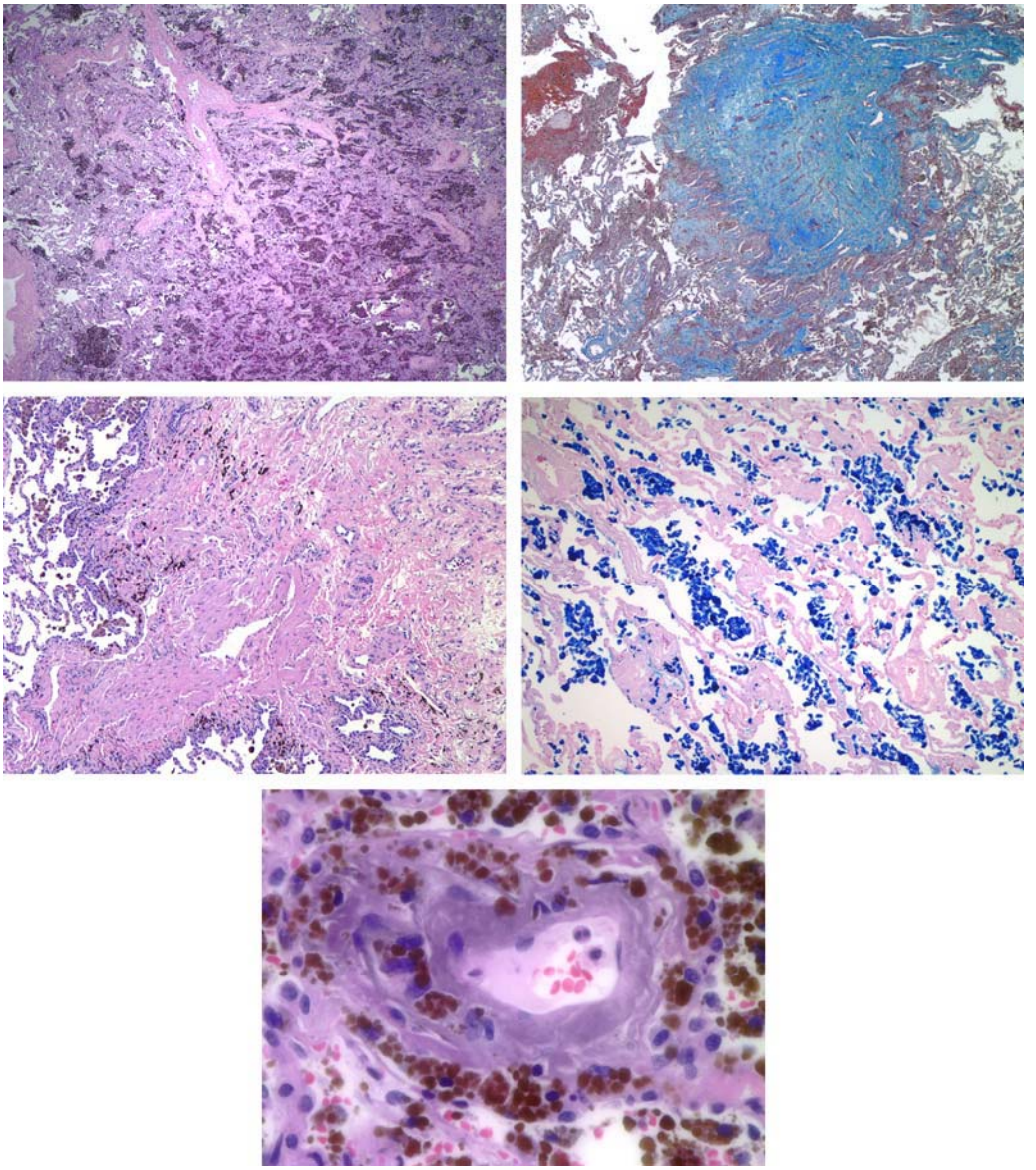
Diagnosis: Lung, open biopsy: Proliferative pleural fibrosis, subpleural OP, and extensive hemosiderosis, cause undetermined.

There is marked alveolar filling by histiocytes which contain abundant hemosiderin (iron stain). In the descriptive sense, this is hemosiderosis. The case is unusual, however, because of extensive pleural fibrosis with adhesions with pleural fibrin. There is also sclerosis and narrowing of small veins with early basophilic deposition, possibly representing calcium. I have reviewed the chest radiographs and obtained several special histochemical stains.

I am not able to precisely connect the pleural fibrosis and the hemosiderosis. There is fibrosis invaginated into the lung (trichrome stain), and I considered shrinking pleuritis with atelectasis (Blesovsky's syndrome), but this condition is usually not associated with hemosiderosis. I considered multiple pulmonary infarctions, but I can find no definite thromboembolic disease nor infarcts. I considered bronchiolitis obliterans organizing pneumonia (BOOP) with hemorrhage, wherein patients with BOOP present with hemoptysis, but the radiograph and the extensive pleural fibrosis are not typical for that condition. Wegener's granulomatosis and Goodpasture's syndrome can be excluded by serologic studies, but the radiographic findings observed here would seem improbable. I considered trauma with subsequent hemothorax and underlying hemosiderosis. I considered old hemothorax of some other cause (such as old viral pleuritis) with resultant fibrous adhesions as well as pulmonary hemorrhage, but there is little hemosiderin in the pleura. Finally, I considered a pleural neoplasm, and a few areas in the thickened pleura have a cellular proliferation of spindle cells, but diagnostic features of a malignant mesothelioma are not present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6811 (Chapter 8 – Non-Neoplastic Pleural Disease)

II Neoplastic Pulmonary and Pleural Disease

INTRODUCTION

This section will focus on neoplastic disease of the lung and pleura. A few benign lesions have presented diagnostic problems and are included in this section. The majority of cases shown here are malignant, however, and illustrate a broad spectrum of tumors, both across and within subclasses of neoplasms. The importance of distinguishing between primary and metastatic lesions involving lung and pleura is demonstrated.

In Chapter 9, the four major types of carcinoma of the lung are illustrated by multiple cases of each type in order to reinforce the reader's recognition of variant histological features of each type. Other epithelial tumors of major airways are also included. In addition, focus is placed on diagnostic challenges characteristic of lymphomas and malignant mesenchymal tumors involving the lung. The diagnostic problem of sarcomatoid carcinoma is also addressed.

Finally, the goal of Chapter 10 is to help the pathologist distinguish between reactive and neoplastic lesions of the pleura. Having determined that a pleural lesion is neoplastic, the pathologist must then determine if the lesion is benign or malignant, a critical issue in the case of mesothelioma. The next step in this diagnostic "gauntlet" is to determine if a sarcomatoid pleural tumor is a malignant mesothelioma or sarcoma. Furthermore, is a malignant epitheloid lesion a mesothelioma or carcinomatosis? In other words, is the lesion primary or metastatic to the pleura? Multiple cases are included in this chapter to help the reader traverse this gauntlet.

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

9 Lung Tumors

CONTENTS

INTRODUCTION

The vast majority of cases in this chapter illustrate pertinent histological features of malignant tumors of the lung. There are, however, peculiar pulmonary neoplasms which may be confused with common bronchogenic carcinomas. Below is a list of these neoplasms, some of which are illustrated.

- Alveolar adenoma
  - Grossly soft to the touch and difficult to see
  - Cystic spaces filled with fluid, resembling lymphangioma
  - Small cuboidal pneumocytes lining cystic spaces
- Sclerosing hemangioma **(6942)**
  - Proliferating small oval cells of dubious origin
  - Papillary fibroepithelial structures
  - Sclerosis, hemosiderin, xanthoma cells
- Intravascular sclerosing tumor (epithelioid hemangioendothelioma)
  - Perimeter of tufts of epithelioid endothelial cells protruding into alveoli
  - Center of hyaline sclerosis with entrapped alveoli
  - Factor VIII positivity
- Pulmonary blastoma
  - Epithelial elements resembling endometrium
  - Squamous morules
  - Mesenchyme variable from benign to malignant
- Inflammatory pseudotumor (IPT)
  - Organizing pneumonia with fibrin and necrosis
  - Plasma cell granuloma with sheets of plasma cells
  - Fibrous proliferation with storiform pattern
  - Occasionally resembles low-grade malignant fibrous histiocytoma

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

• Malignant lymphoma of lymphomatoid granulomatosis-type
  – Nodules of large pleomorphic cells (high-grade lesion)
  – Invasion and destruction of vessels and bronchi
  – Centrally cellular and surrounded by organizing fibrin

CARCINOMA OF THE LUNG

There are four major types of carcinoma of the lung: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma. There are three other malignant neoplasms of the major bronchi: carcinoid tumor, adenoid cystic carcinoma, and mucoepidermoid carcinoma. The small size of bronchoscopic and needle biopsies is the root of many of the problems in lung tumor diagnosis. The smaller the sample, the greater is the inherent error in sampling and the more the cells will be squeezed.

Adenocarcinoma

Adenocarcinoma is subtyped into three major growth patterns: acinar, papillary, and bronchioloalveolar. The three commonly coexist **(6773)** and merge one into another. Most solid solitary peripheral nodules of adenocarcinoma will be predominantly acinar with sclerosis but exhibit growth of carcinoma cells along alveolar walls at their periphery for a distance of one or two alveoli. Such examples are best classified as adenocarcinoma of acinar type with peripheral bronchioloalveolar spread. The salient feature of bronchioloalveolar cell carcinoma, which gives it an intrinsic difference biologically and radiologically, is not its cell of origin but its growth through the air spaces.

Adenocarcinoma of Acinar Subtype: Attributes

- Most common subtype
- Glandular spaces
- Desmoplastic fibrosis

Adenocarcinoma of Papilary Subtype: Attributes

- Papillary piling up of cells, often in air spaces
- Generally well or moderately differentiated
- Least common of three subtypes

Adenocarcinoma of Bronchiolalveolar Subtype

The defining attributes of bronchioalveolar adenocarcinoma are as follows:

- Lepidic (butterfly-like spread) along intact alveolar walls **(6467)**
- Spread as ringlets of cells in the airspace
- Pneumonic consolidation or multifocal

Three possible cells of origin of bronchioalveolar adenocarcinoma are:

- Clara cell
- Mucinous cell **(6619)**
- Pneumocyte

Dysplastic pneumocytes develop around scars, in reaction to drugs and radiation, in diffuse alveolar damage, and in response to viral infection. Transbronchial lung biopsies from immunosuppressed patients often contain atypical pneumocytes. Dysplastic pneumocytes generally taper in degree of atypia down to normal over the space of many alveoli, whereas the leading cell of an advancing bronchioloalveolar carcinoma abruptly meets a normal pneumocyte.

Atypical Adenomatous Hyperplasia (Bronchioloalveolar Proliferation of Uncertain Malignant Potential): Attributes

- Common incidental findings in lungs resected for adenocarcinoma or squamous cell carcinoma
- Macroscopic: Firm white nodules 1–5 mm in diameter
- Focal stellate scar
- Hyperchromatic enlarged cuboidal pneumocytes
- Sharp demarcation from surrounding lung
- No desquamation of neoplastic cells
- Probable precursor lesion for malignancy

Pulmonary Mucinous Cystic Tumor of Borderline Malignancy: Attributes

- Solitary mucus-filled cyst
- Cyst wall is fibrous and lined by tall columnar mucinous cells, resembling mucocele of appendix
- Mucinous cells escape into lung, resembling bronchioloalveolar carcinoma, through defects in fibrous wall

Colloid variant of bronchioloalveolar carcinoma **(6619)** is a malignant, airspace-filling disease in which the predominant alveolar content is mucus rather than malignant cells. In distinction from mucinous cystic tumor, the lesion has no fibrous edge. The cells are tall and columnar with copious mucus. The leading edge typically is devoid of recognizable malignant cells and may be misinterpreted as mucus impaction with mucinous pneumonia or as alveolar proteinosis. Metastatic colloid carcinoma of the colon enters the differential diagnosis.

Squamous Cell Carcinoma

The defining attributes of squamous cell carcinoma in the lung are keratin pearls or intercellular bridges on light microscopy. The sequence of basal cell hyperplasia, squamous metaplasia, dysplasia, and squamous cell carcinoma *in situ* develops over approx 20 yr prior to invasive squamous cell in most (but not all) patients. Dysplasia and squamous cell carcinoma *in situ* can appear in honeycomb fibrosis, but the diffuse fibrotic lung disease generally determines prognosis more than the squamous change in such patients.

Squamous cell carcinoma *in situ* exists, but its duration and reversibility are uncertain. In a given patient, its extent and probable multifocality will not be known until after resection. Surgical management of squamous cell carcinoma *in situ* is not uniform. The diagnosis of squamous cell carcinoma in situ should be avoided if possible. Repeat biopsy is often a better approach.

Regenerative squamous atypia occurs around inflammatory ulcers in the bronchial mucosa and particularly at the site of recent biopsies. Granulation tissue around the atypia may be misinterpreted as desmoplastic reaction in response to invasion.

Squamous cell papillomatosis is a multifocal proliferation of well differentiated squamous cells. The tracheobronchial tree becomes carpeted by polyps. In children, the disease may be a result of human papilloma virus. The disease may spread slowly into the parenchyma and cause death by hypoxia.

Solitary squamous papilloma may arise in the trachea or major bronchi of adults. The tumor generally lacks anaplasia. There is a spectrum of noninvasive, minimally invasive, and locally invasive forms. Metastasis is uncommon.

Basaloid carcinoma is a variant which has basaloid differentiation **(6815)** as seen in skin and salivary gland tumors. The diagnosis requires that a majority of the tumor show basaloid features, because small components are quite common in squamous cell carcinoma of the lung.

Small Cell Carcinoma

Small cell carcinoma is defined as a tumor composed of epithelial cells which lack squamous or glandular differentiation and whose nuclei measure 25 μm or less in diameter on average in slides of paraffin-embedded tissue

Small Cell Carcinoma: Attributes

- Oval or fusiform nuclei so densely chromatic that nucleoli are obscure
- Solid tumor with extensive necrosis
- Cells arrayed in ribbons and rosettes
- Diffuse permeation of mucosa or lymph node
- Encrustation of walls of blood vessels by hematoxylinophilic nuclear material released from disintegrating tumor cells
- Neurosecretory granules in most cases, tonofilaments common, mucus vacuoles uncommon on ultrastructural examination

Small Cell Carcinomas: Subtypes

- Oat cell (classic form)
- Intermediate cell
- Mixed with other forms of pulmonary malignancy, particularly mixed with large cell carcinoma

Mixed Small Cell–Large Cell Carcinoma

- Diagnosis of major cell subtype
- Prognosis of large cell carcinoma
- Not the same as large cell neuroendocrine carcinoma or large cell carcinoma with neuroendocrine differentiation

Most studies have shown little or no difference between oat cell and intermediate cell subtypes in response to therapy and prognosis. Mixed small cell–large cell carcinomas **(6571)** respond less well to chemotherapy than do pure small cell carcinomas.

Small Cell Carcinoma: Histological Effects of Therapy

- Conversion to squamous cell carcinoma, adenocarcinoma, or large cell carcinoma

- Total necrosis or sclerosis or both
- Granulomatous inflammation in response to necrotic tumor

Ways to Change the Size of Cells of an Undifferentiated Carcinoma

- Cells appear larger
  - Frozen section
  - Zenker's or mercuric fixative
- Cells appear smaller
  - Crush (small biopsy)
  - Dehydration (small biopsy)
  - Pyknosis in vivo
  - Necrosis resulting from therapy

Carcinoid Tumor

Localized lesions of small cell carcinoma must be distinguished from atypical carcinoid tumors. Typical carcinoid tumors are also called well-differentiated neuroendocrine carcinomas, atypical carcinoid tumors are also called moderately differentiated neuroendocrine carcinomas, and small cell carcinomas are also called poorly differentiated neuroendocrine carcinomas.

Atypical Bronchial Carcinoid: Defining Features

- Increased cellularity
- Disorganized architecture
- Pleomorphism
- Mitoses
- Necrosis

Atypical carcinoid tumors classically have been graded as slightly (grade 1), moderately (grade 2), or markedly (grade 3) atypical. Most cases are at one of the two poles; few fall into the moderately atypical category. Slightly atypical carcinoids have a prognosis little worse than common carcinoids, but even carcinoid tumors without atypical features may metastasize and cannot be called benign. Markedly atypical carcinoids metastasize in more than one-half of patients. Distinction of atypical carcinoid tumor from small cell carcinoma cannot be made reliably on a needle biopsy of a peripheral mass and should be left for the resected specimen.

Large Cell Carcinoma

Large cell carcinoma designates a carcinoma with large cells and no identifiable squamous or glandular or neuroendocrine differentiation on light microscopic examination. The more sections one examines, the more chance of finding some differentiation and the less will be the incidence of this diagnosis. Non-small cell carcinoma is a working clinical diagnosis or a cytological diagnosis but not a precise histological diagnosis if adequate tissue is available.

Large cell neuroendocrine carcinoma **(6752)** is a large cell carcinoma that exhibits organoid patterns and expresses neuroendocrine markers. Large cell carcinoma with neuroendocrine differentiation **(6985)** lacks organoid patterns but expresses neuroendocrine differentiation immunopathologically or ultrastructurally.

PECULIAR FEATURES OF ANY FORM OF CARCINOMA

Spindle-cell elements may appear in any form of carcinoma but are most common with squamous cell carcinoma. If the spindle cell elements predominate or obscure epithelial elements, the tumor can be designated as a sarcomatoid carcinoma (**6531**). The inflammatory variant of sarcomatoid carcinoma is particularly difficult to recognize when the malignant cells form less than 10% of the area on the slides and are assumed to be atypical entrapped epithelial cells.

Clear cells appear in 20–50% of squamous cell carcinomas and adenocarcinomas (**4406**). Rarely is a tumor entirely clear cell, and it is this sort that must be distinguished from metastatic renal cell carcinoma.

Ectatic blood vessels appear in squamous cell carcinomas, adenocarcinomas, and diffuse malignant mesothelioma (DMM). Angiosarcoma enters the differential diagnosis when hemorrhage obscures the underlying malignancy.

Mixtures of squamous cell carcinoma, adenocarcinoma, and small cell carcinoma appear in direct proportion to the extent of sampling. Diagnosis of the dominant cell type is the practical choice when small foci of a second tumor type are found. If approximately one-fourth or more of the tumor is a second type, a diagnosis of a mixed carcinoma is made, but the biological implications of a mixed carcinoma are largely unknown.

Other uncomon but distinctive features include rhabdoid cells, giant cells resembling trophoblast, osteoclast-like giant cells, marked lymphoid infiltrate, and marked eosinophilic reaction.

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LETTERS

Case 6840

Diagnosis: Lung, open biopsy:

1. **Crystal-storing histiocytic tumor.**
2. **Lymphoplasmacytic proliferation.**

This case is relatively unique. The preeminent pathology consists of massed histiocytes with densely eosinophilic cytoplasm. In some areas the eosinophilia is globular or crystalline. This is associated with plasma cells containing similar crystals. There is also a background of lymphocytes and fibroblasts in the histiocytic tumefaction. Two of the many slides of lung show a proliferation of small lymphocytes with lymphoid follicles.

Crystal-storing histiocytic tumors have been described in bone marrow and soft tissue, and the pathology in those cases is similar to this. Those patients often have plasma cell dyscrasia, multiple myeloma or gammopathies. Crystal-storing histiocytic tumors have rarely been described in the lung. We have seen another case in the last year in a patient with Evan's syndrome.

To further evaluate the lymphocytes, I prepared some immunopathological studies. The lymphoid cells are a mixture of T and B lymphocytes, and there is no monoclonality demonstrable by staining for kappa and lambda light chains. Analysis of light chains is not necessarily dependable when using formalin fixed tissue. One could investigate the patient by serum protein electrophoresis, as we discussed earlier.

Necrosis as observed here is not commonly seen in crystal-storing histiocytic tumors. For this reason, I performed silver, acid fast, periodic acid-Schiff, and Brown-Hopps stains for organisms. None is present. I do not favor infection. Because the necrosis is bounded by palisading histiocytes in some regions, I considered Wegener's granulomatosis, which could be further evaluated by serologic test for antineutrophil cytoplasmic antibody, but I do not favor this diagnosis. A recent case of crystal-storing histiocytic tumor was associated with Clofazimine treatment for leprosy.

The infiltrative pattern of spindled cells in some areas and the necrosis raised sarcoma into the differential diagnosis, but I do not believe that this is a malignant tumor.

Thank you for referring this case in consultation. This is an elaboration of my telephone call. Please call if you have questions. The case has been reviewed by other members of the department, and this letter includes some of their observations. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

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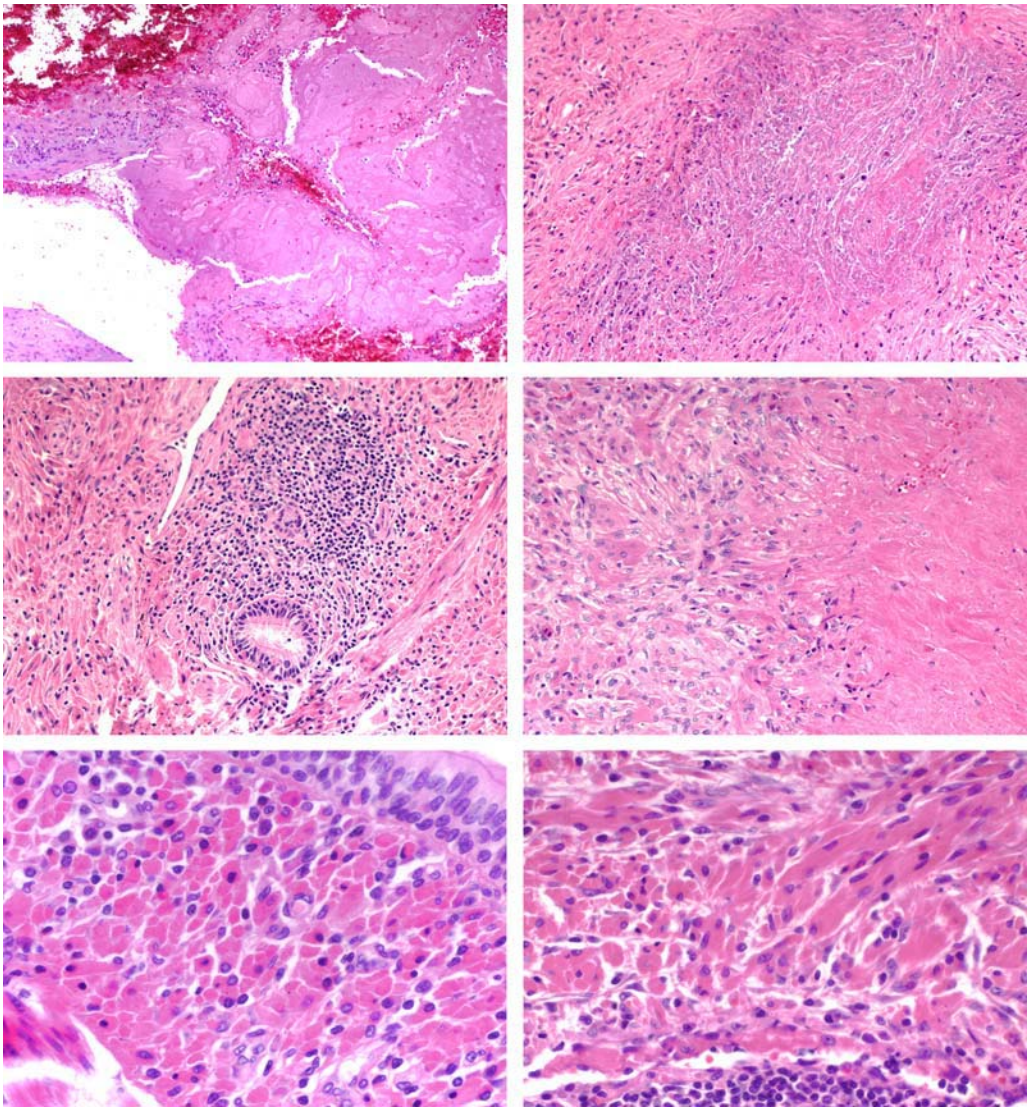


Case 6840 (Chapter 9 – Lung Tumors)

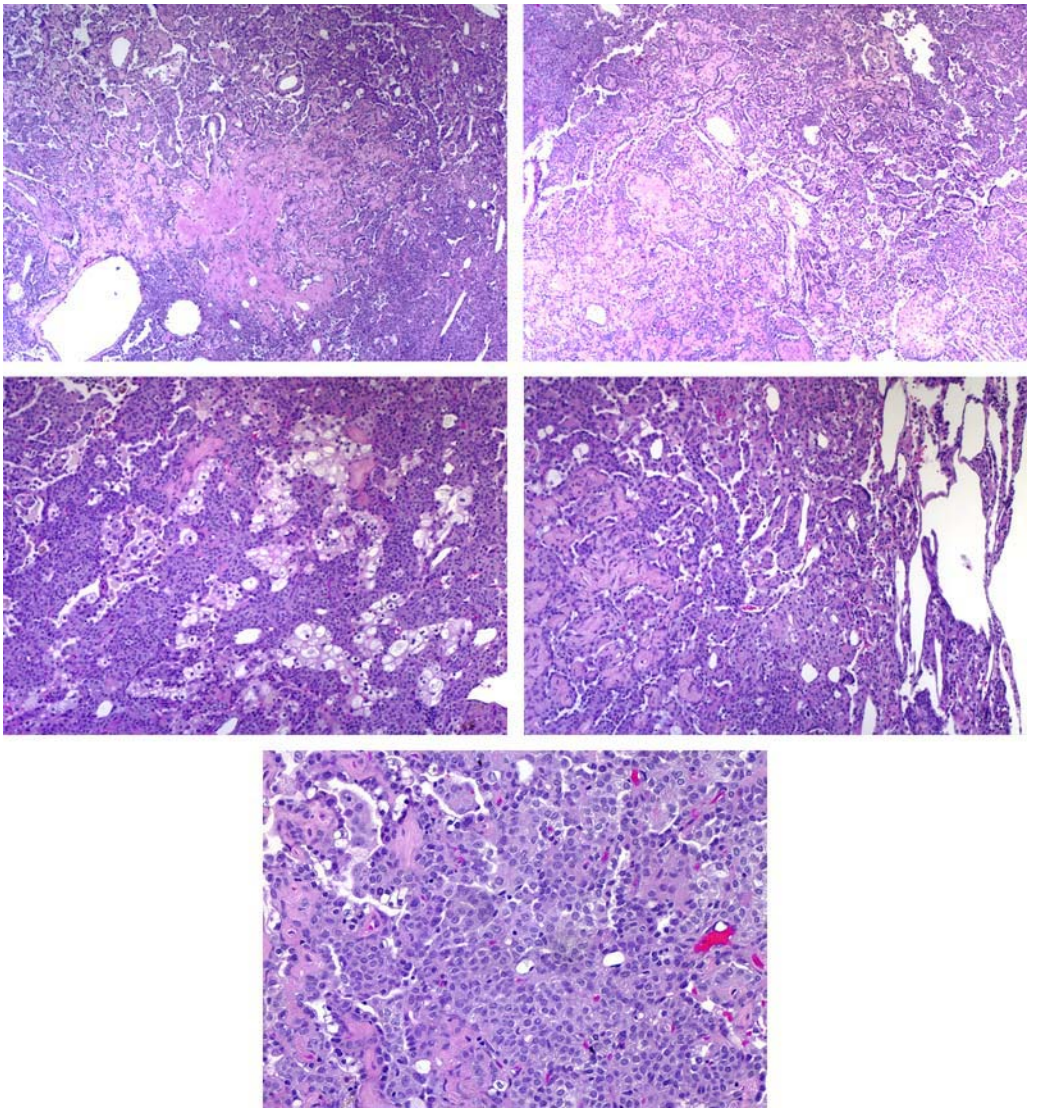
Case 6942

Diagnosis: Lung, wedge resection: Sclerosing hemangioma.

This nodule is composed of sheets of cuboidal cells with bland oval nuclei whose cytological features suggest sclerosing hemangioma, which I believe is the correct interpretation. There is interstitial sclerosis in the center of the lesion and a small amount of xanthomatous change, which are also found in sclerosing hemangioma. The differential diagnosis includes principally bronchoalveolar sclerosing tumor (epithelioid hemangioendothelioma, IVSBAT), as you indicate, but the relative circumscription of the lesion, the absence of alveolar filling by the cells at the periphery of the lesion, and the character of the cells themselves favor sclerosing hemangioma. The immunopathological findings are also consistent with that interpretation. Epithelial membrane antigen is often positive in sclerosing hemangioma when keratin stains are equivocal and might be further investigated but is not necessary for diagnosis in this case in my opinion. I suspect that the cells with microvilli in the electron micrographs are entrapped bronchioloalveolar cells. In fact, in one of the micrographs these cells line an alveolus occupied by a vacuolated histiocyte, and I believe this is good evidence to support that interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6942 (Chapter 9 – Lung Tumors)

Case 6838

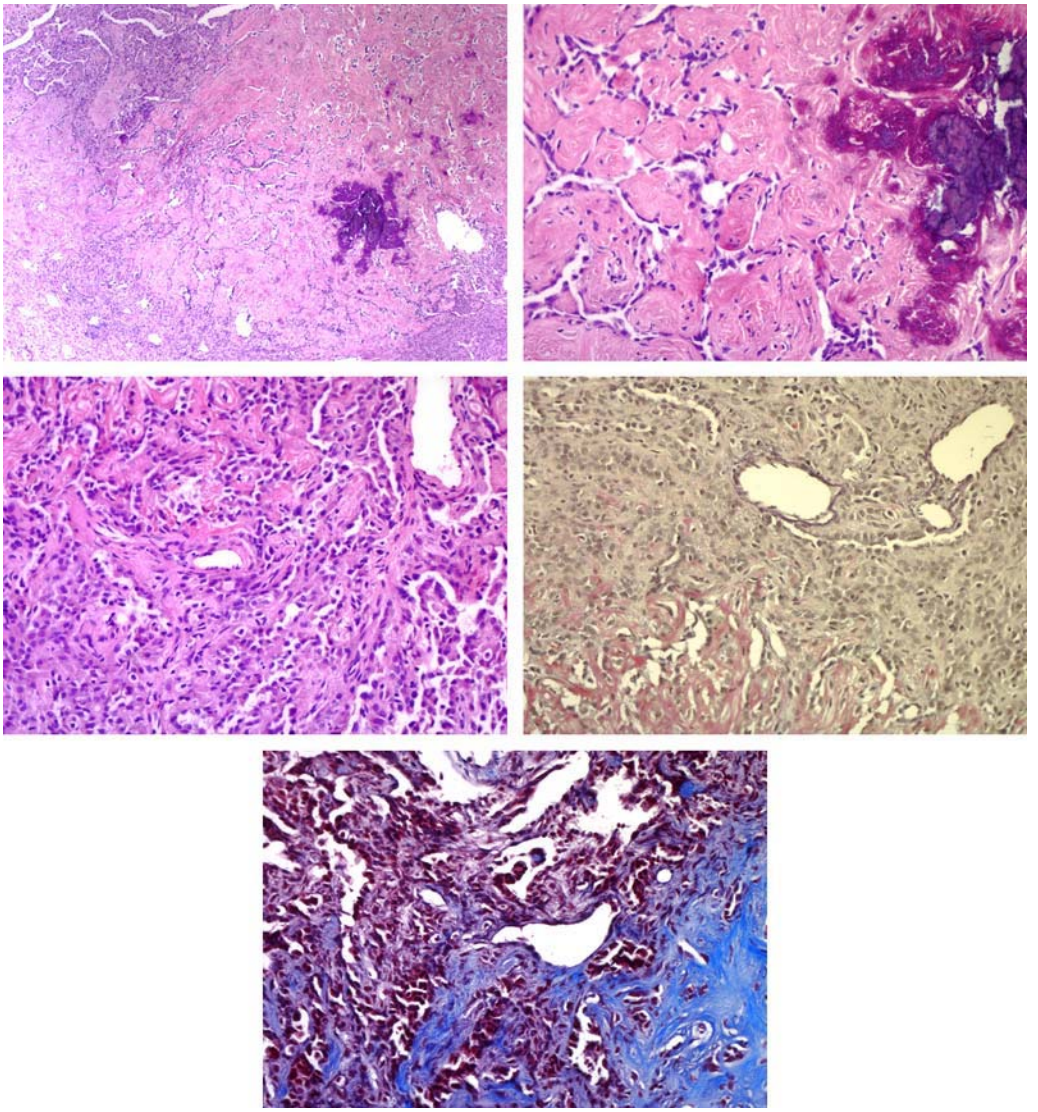
Diagnosis: Lung, wedge resection: Sclerosing hemangioma.

This discrete nodule is composed of bland oval epithelial cells with abundant amphophilic cytoplasm. The banality of the nuclei, the associated sclerosis and calcification, and the entrapment of respiratory epithelium characterize a sclerosing hemangioma. The immunopathological markers performed at Boston University are consistent with that interpretation in that the cells stain for epithelial membrane antigen, stain weakly for keratin, and do not stain for endothelial or neuroendocrine markers. There are many entrapped capillaries (trichrome stain) in the lesion, and they stain for endothelial markers.

Sclerosing hemangioma is considered a benign neoplasm of pneumocytes with a peculiar component of sclerosis (elastic stain). When the lesion was initially described, observers were impressed by vascularity and hemorrhage and hence considered it a hemangioma, but it has become apparent that these are not vascular tumors. This stands in distinction to epithelioid hemangioendothelioma (intravascular sclerosing bronchoalveolar tumor), which is a neoplasm of endothelial cells and is malignant. To my knowledge there has been only one case of sclerosing hemangioma which has metastasized, and that was to regional lymph nodes only. In this case nuclear features are not those of malignancy, no mitoses are present, and no necrosis is present. Sclerosing hemangioma of the lung occasionally may be multiple.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have further questions. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6838 (Chapter 9 – Lung Tumors)

Case 7007

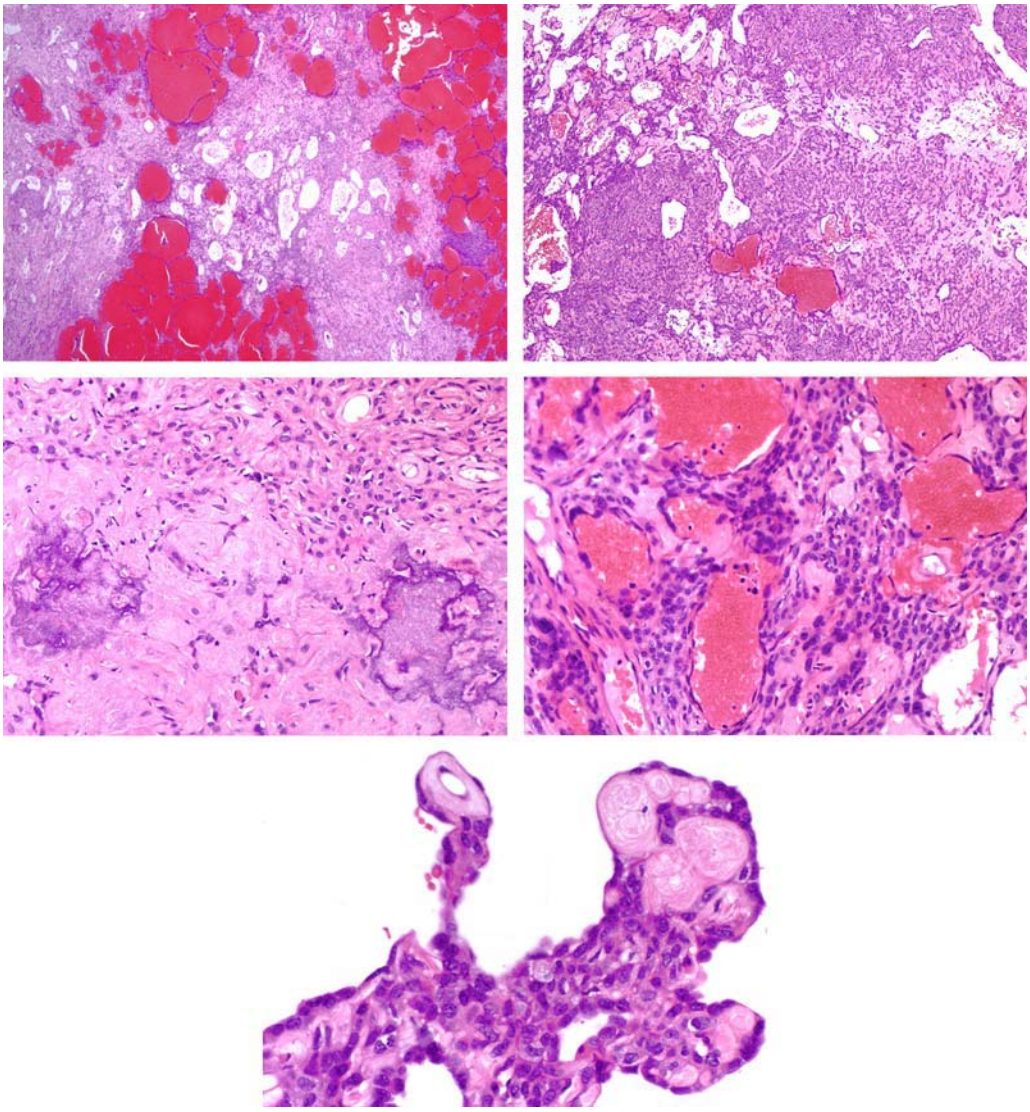
Patient: 69-yr-old female

Diagnosis: Lung, lobectomy: Sclerosing hemangioma.

The variegated patterns in this tumor are good for sclerosing hemangioma. They include ectatic blood vessels, extensive sclerosis with hyalinization, and focal calcification. Most definitive are the regions of solid cellular tumor, the individual nuclei of which are relatively regular and the cellular contours of which are relatively cuboidal. The blood vessels are particularly prominent in this case. Your immunopathological results are consistent with sclerosing hemangioma. In the differential diagnosis, we considered and then excluded fibrous tumor with unusually prominent blood vessels.

Thank you for sharing this case with us. It is such a nice example of a vascular lesion that you could consider someone showing this as part of the IAP pulmonary disease panel, even though it is not a vascular neoplasm.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7007 Chapter 9 – Lung Tumors)

Case 4430

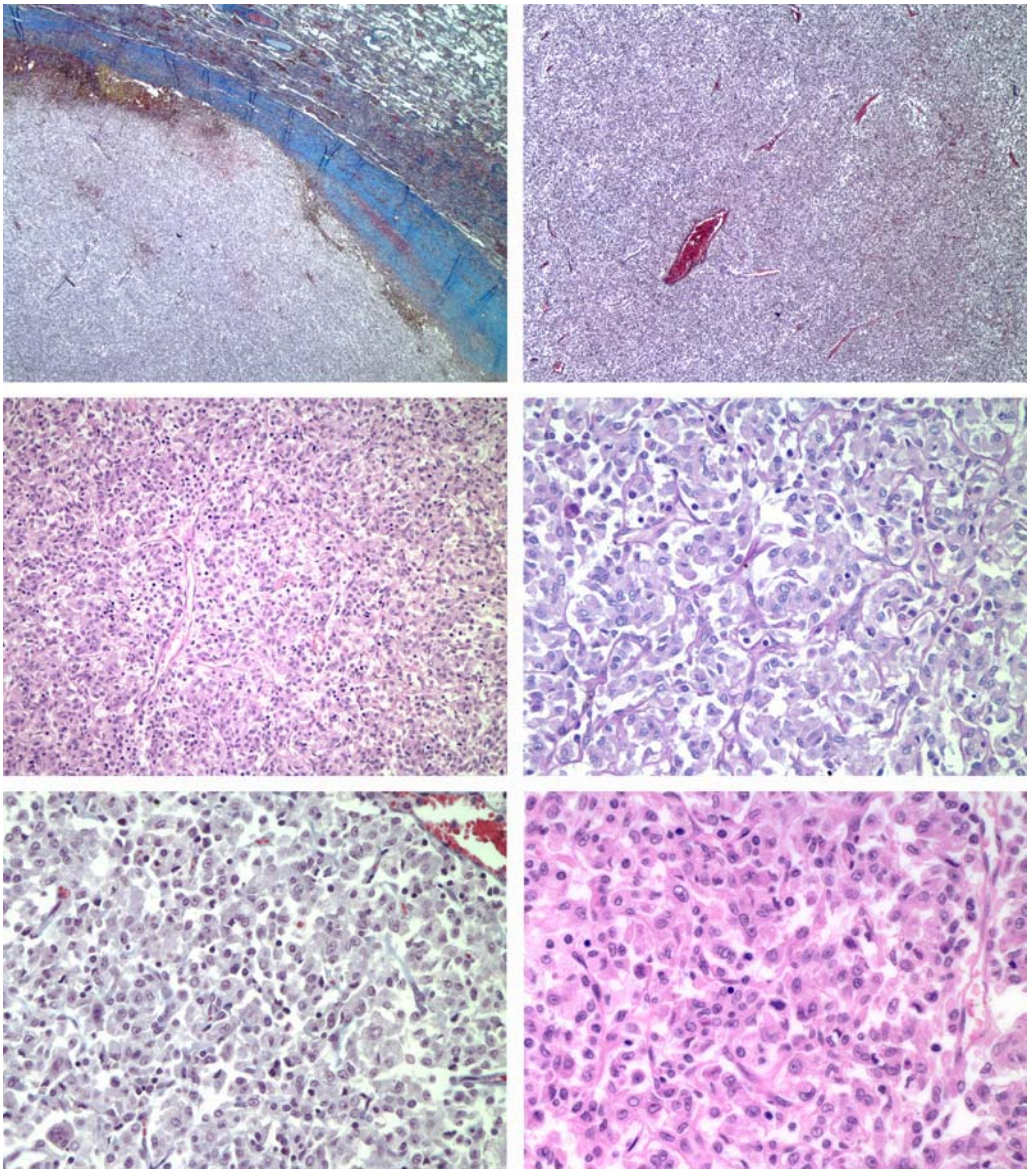
Patient: 26-yr-old male

Diagnosis: Lung, lobectomy: Benign mesenchymal tumor.

This large discrete tumor (trichrome stain) is composed of cells with small oval bland nuclei and abundant vacuolated cytoplasm. I cannot make a specific diagnosis. A nested appearance (PAS stain) limits the differential diagnosis. I favor a paraganglioma or meningioma. Sclerosing hemangioma is possible on the H&E section, but the negative immuochemical stains are against this diagnosis. I do not favor a carcinoid tumor, clear cell sugar tumor, or plasma cell granuloma.

Thank you for referring this case in consultation. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 4430 (Chapter 9 – Lung Tumors)

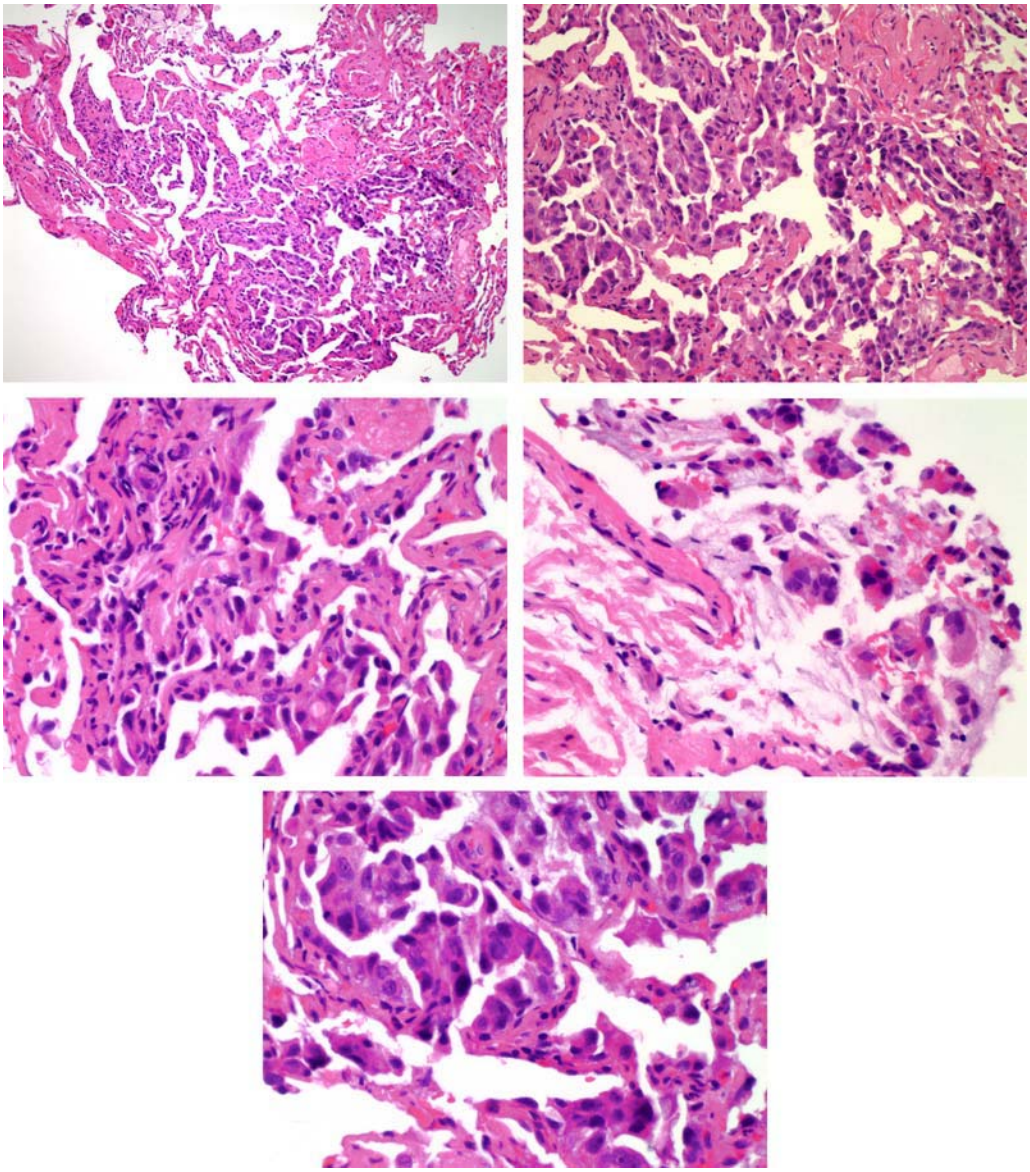
Case 6773

Diagnosis: Lung, bronchoscopic biopsy: Adenocarcinoma.

One biopsy contains small bits of an adenocarcinoma. The tumor is represented by a maximum of approx 50 cells on the largest cross sectional area. The adenocarcinoma is cytologically of a moderate degree of differentiation, but the specimen is too small to further subcategorize the adenocarcinoma. Small strips of carcinoma cells line a portion of an alveolar wall, so that there is an element of bronchioloalveolar pattern. Glands and micropapillae are present as well; the adenocarcinoma thus has mixed patterns. The other specimens contain no definite malignant cells. This is essentially in agreement with your interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. I have retained one slide for our permanent teaching collection and hereby return the remainder.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6773 (Chapter 9 – Lung Tumors)

Case 6780

Patient: 72-yr-old male

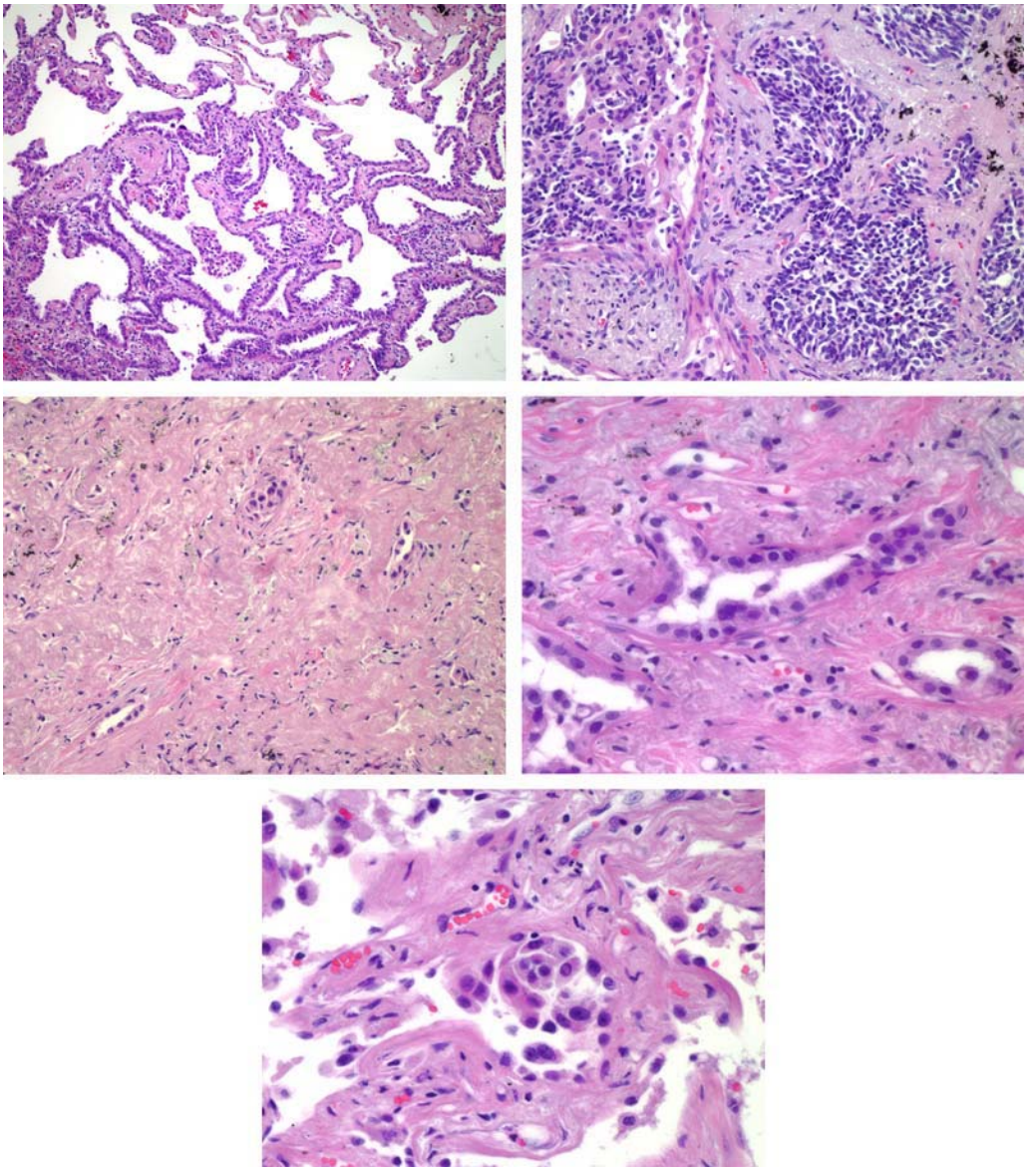
Diagnosis: Lung, wedge resection: Adenocarcinoma, well differentiated, subpleural, associated with a scar and with a tumorlet of carcinoid type. Lung, wedge resection:

1. **Adenocarcinoma, few nests of cells.**
2. **Highly atypical proliferation, diffuse, associated with interstitial fibrosis.**

The largest nodule consists of a well-differentiated adenocarcinoma of a type that, to some degree, resembles fibroadenoma. There is a component of bronchioloalveolar spread at the edge of the tumor. Many of the neoplastic cells have intranuclear inclusions indicative of pneumocytic differentiation. The second specimen is more complicated. The most convincing evidence of malignancy are a few ringlets of the same cells of bronchioloalveolar subtype of adenocarcinoma with intranuclear inclusions. Also present in the same slide is another scar with entrapped atypical pneumocytes that probably represents carcinoma, but the cells are too few in number to permit a diagnosis of a second primary carcinoma in its own right if this were the only tissue I had. The second specimen also contains extensive interstitial fibrosis with diffuse atypicality of pneumocytes. The atypicality is marked in some regions and probably represents a premalignant condition.

Thank you for sending this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6780 (Chapter 9 – Lung Tumors)

Case 6711

Diagnosis: Lung, wedge resection: Adenocarcinoma, poorly differentiated with signet-ring cells, associated with a scar.

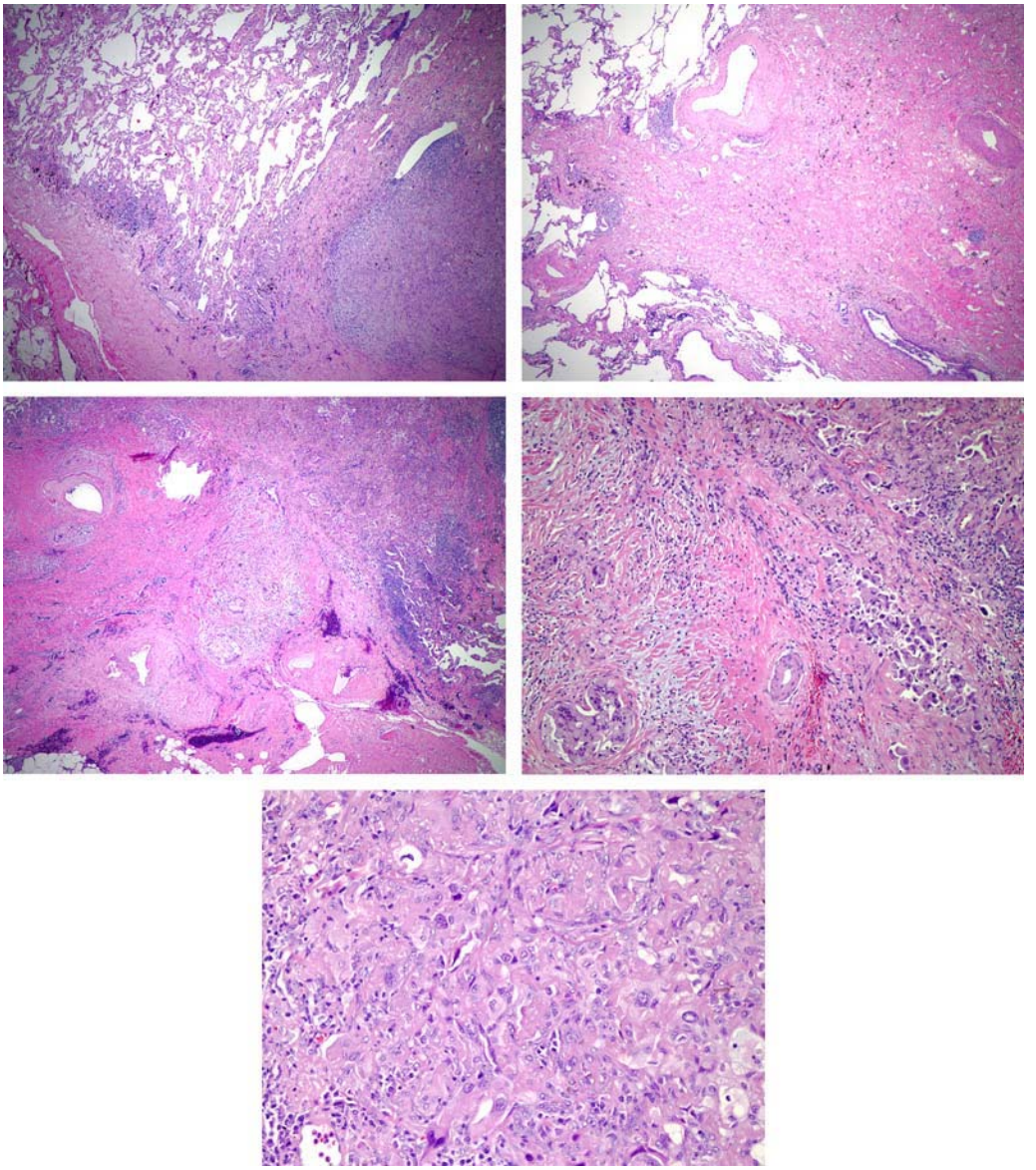
A nodule has two components: 1) a triangular-shaped scar with elastosis and which may represent an old infarct and 2) nests and glandular structures lined by pleomorphic cells. The nuclear changes suffice for a diagnosis of malignancy, and the glandular structure and signet ring cells indicate an adenocarcinoma of a poor degree of differentiation. Although atypical epithelial cells often develop in association with infarct scars, in this case the proliferation is a carcinoma. Signet-ring cell carcinoma is an uncommon form of adenocarcinoma arising in the lung but does occur (*see* reference below). I cannot exclude a metastasis from gastrointestinal tract, adrenal gland, or other site. However, the association with the scar makes me favor a primary carcinoma in the lung. The carcinoma is subpleural and has invaded through the visceral pleura and through an adhesion into fibroadipose tissue of chest wall. The lung also has pleural fibrosis away from the carcinoma and emphysema.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Hayashi H, Kitamura H, Nakatani Y, Inayama Y, Ito T, Kitamura H. Primary signet-ring cell carcinoma of the lung: histochemical and immunohistochemical characterization. Hum Pathol 1999;30:378–383.



Case 6711 (Chapter 9 – Lung Tumors)

Case 7137

Diagnosis: Lung, wedge resection (blocks A): Adenocarcinoma, well-differentiated.

Lung, re-excision specimen (blocks B): Atypical adenomatous hyperplasia, multiple foci.

This case is difficult. A nodule 7 mm in greatest diameter on the slide has glands which are abnormal in contour and lined by cells with atypical and hyperchromatic nuclei. The degree of nuclear pleomorphism and the desmoplasia associated with the glands suffices for a diagnosis of adenocarcinoma in my opinion and in the opinion of other pathologists in the department who have reviewed the case.

The specimen representing re-excision has multiple foci of atypical adenomatous hyperplasia in the three slides of B blocks (B1, B4, B6) that I have available for review and in a recut slide I have made from one B block (B4). These foci have atypical and in areas highly atypical epithelial cells. One scar has a small amount of desmoplastic fibrosis, and the other sites have fibrosis and inflammation. These lesions are only a few millimeters in diameter and do not suffice for a diagnosis of adenocarcinoma. Atypical adenomatous hyperplasia is now generally thought to be a precursor of adenocarcinomas at least by molecular studies but not clearly in a clinically significant manner. Some patients with atypical adenomatous hyperplasia have multiple small nodules distributed through all lobes on CT scans, and because there are several in this small piece of tissue, I suspect that many more are present in the patient's lungs. Such patients can be followed radiographically, depending on clinical circumstances. It is difficult to know more precisely what to recommend, because the natural history of these microscopic lesions is not well established. If the patient smoked cigarettes, it would be particularly advisable to stop smoking cigarettes.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

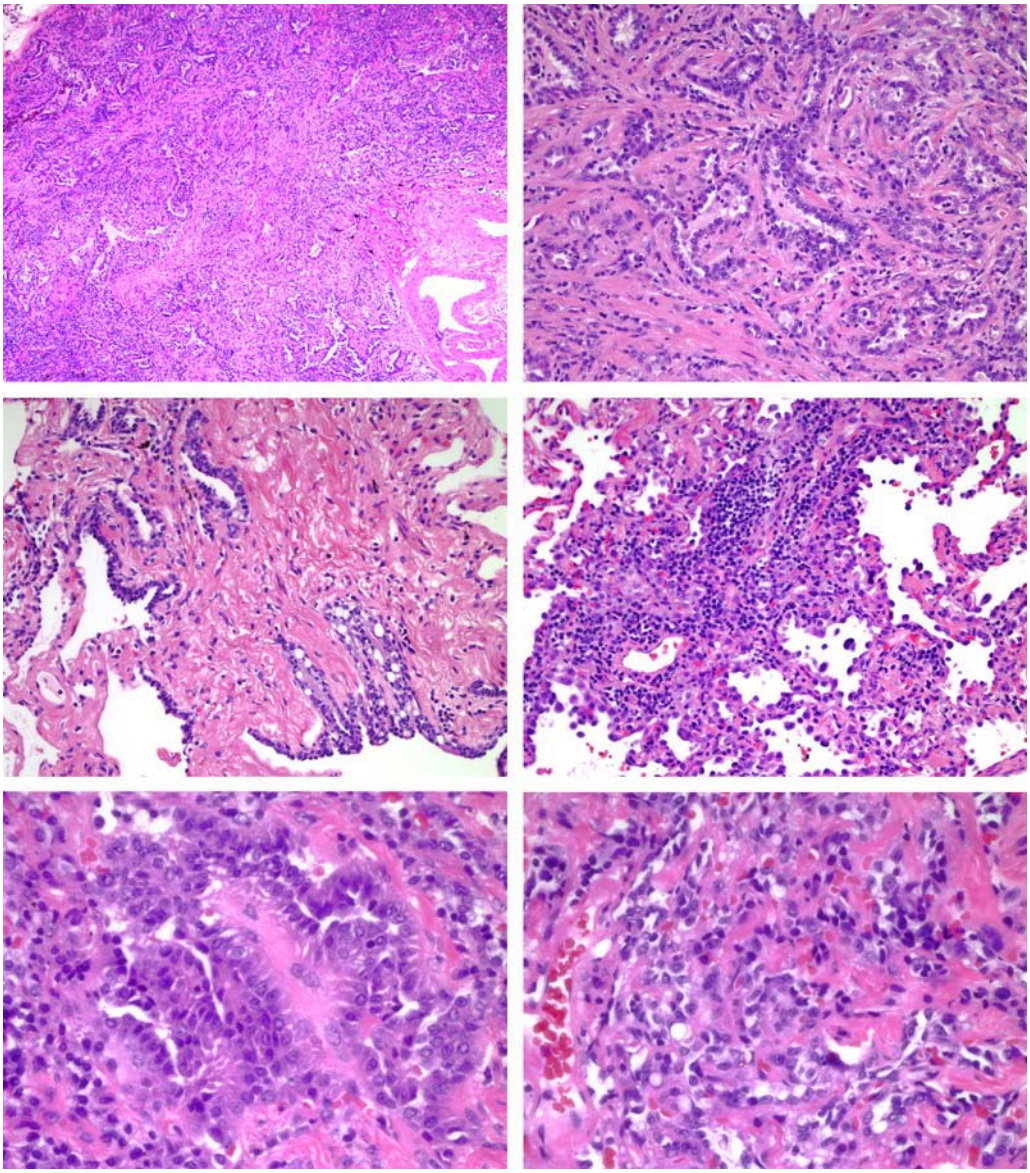
Sincerely yours,
Eugene J. Mark, M.D.

References:

Sterner DJ, Masuko M, Roggli VL, Fraire AE. Prevalence of pulmonary atypical alveolar cell hyperplasia in an autopsy population: a study of 100 cases. Mod Pathol 1997;10:469–473.

Yokozaki M, Kodama T, Yokose T, et al. Differentiation of atypical adenomatous hyperplasia and adenocarcinoma of the lung by use of DNA ploidy and morphometirc analysis. Mod Pathol 1996;9:1156–1164.

Kitamura H, Kameda Y, Ito K, Hayashi H. Atypical adenomatous hyperplasia of the lung. Implications for the pathogenesis of peripheral lung adenocarcinoma. Am J Clin Pathol 1999;111:610–622.



Case 7137 (Chapter 9 – Lung Tumors)

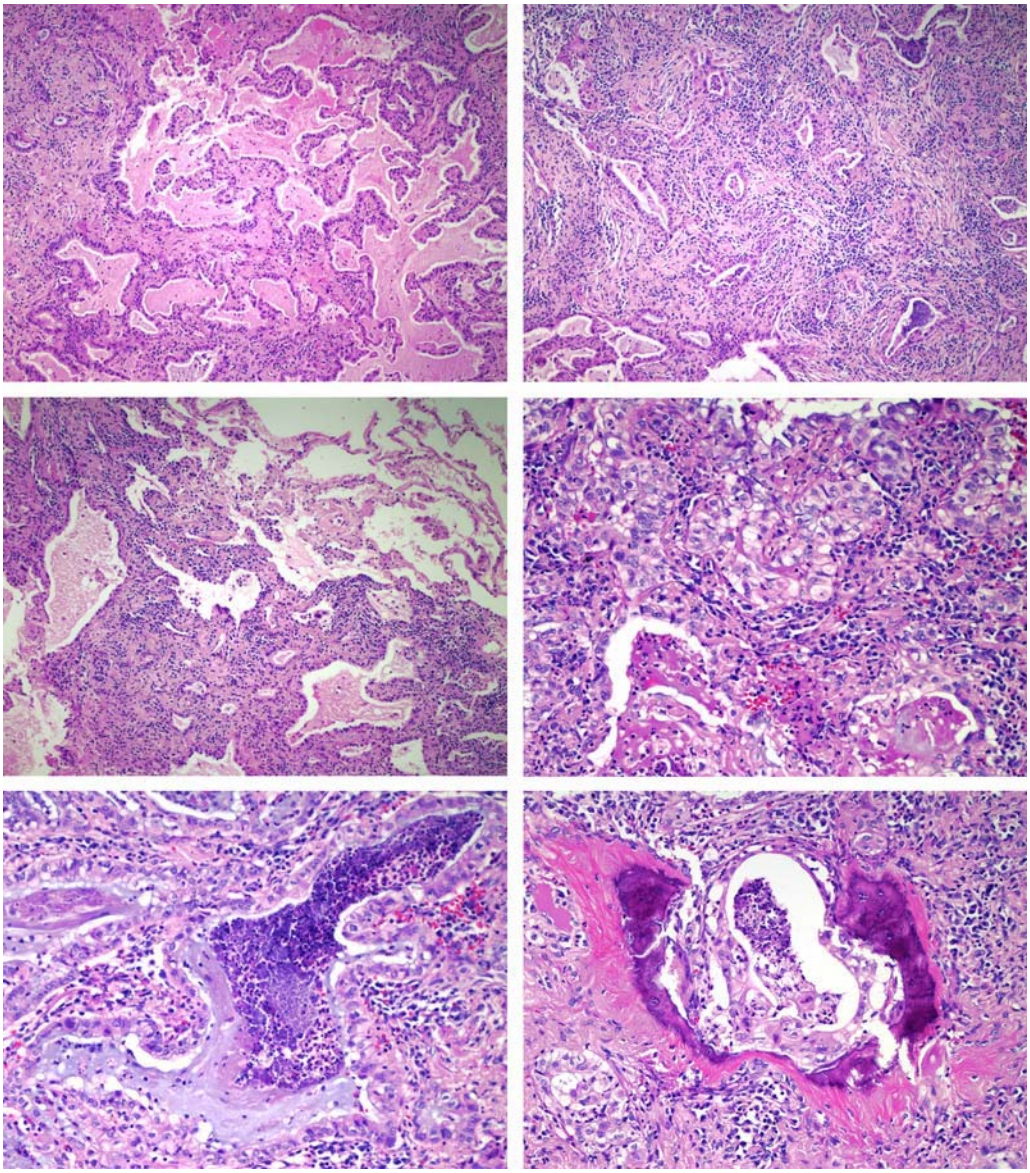
Case 6601

Diagnosis: Lung, wedge resection: Adenocarcinoma, poorly differentiated, with inspissated mucus simulating bronchocentric granulomatosis (BCG) and with focal ossification.

This unusual carcinoma has regions with pleomorphic nuclei having large nucleoli and other areas with smaller and more regular cells whose nuclear features nevertheless are malignant. There is abundant thick eosinophilic secretion in glandular spaces, and this mucus has attracted a neutrophilic exudate with disintegration of the nuclei simulating BCG. Regions of clear cell change are present. Focal ossification is present. I suspect that this is a bronchogenic carcinoma because there is one focus of atypical adenomatous hyperplasia, because of the marked desmoplastic reaction, and because of the bronchioloalveolar type spread at the periphery of the lesion.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6601 (Chapter 9 – Lung Tumors)

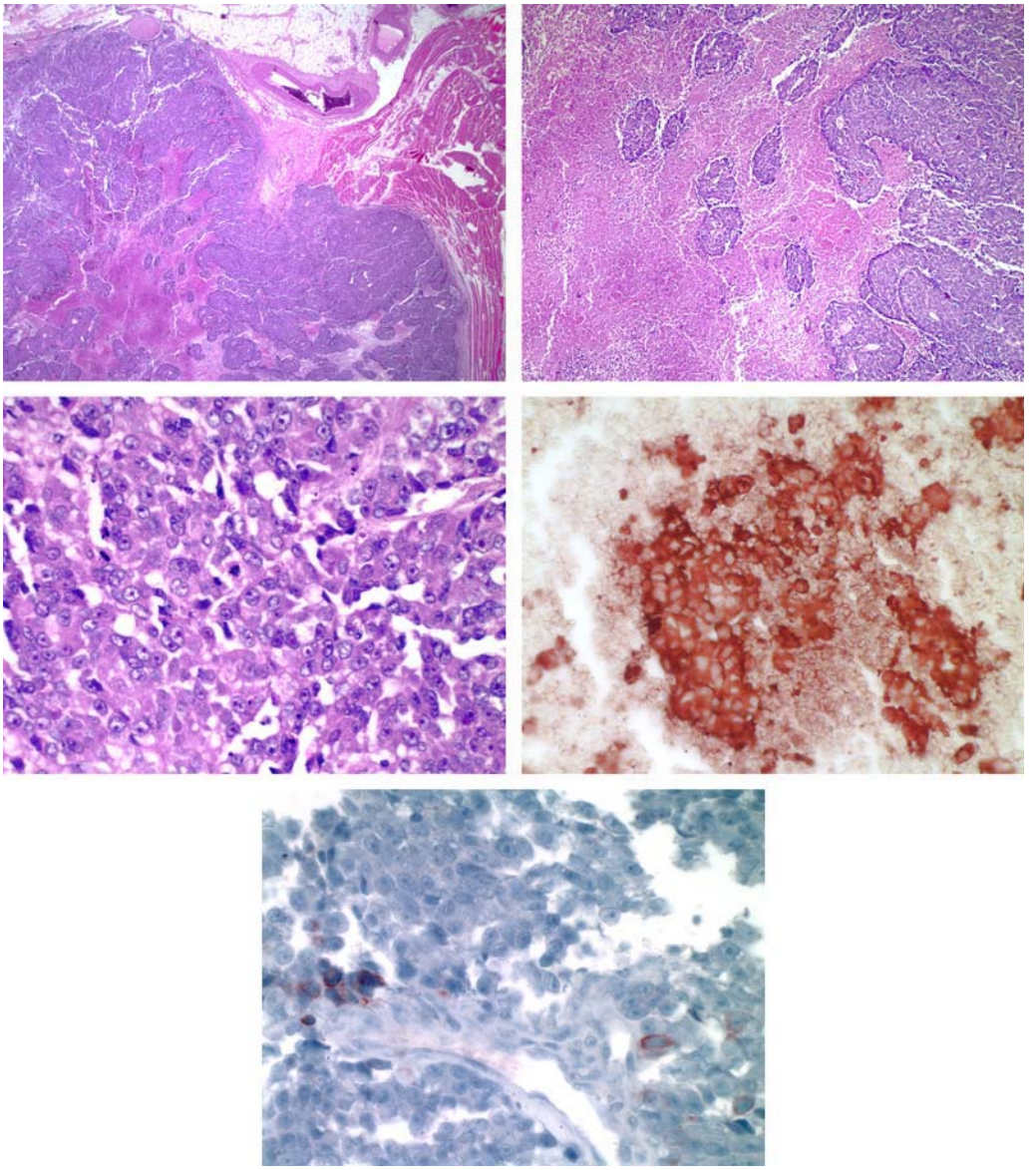
Case 4429

Diagnosis: Mediastinum, needle aspiration biopsy: Carcinoma, probably adenocarcinoma.

Small nests of epithelioid cells have hyperchromatic nuclei and cannibalism sufficient for a diagnosis of malignancy. I do not know the significance of your positive staining for chromogranin. If this had ever been a neuroendocrine lesion, it is now a malignant one. In an attempt to further define the lesion, I performed a variety of histochemical and immunmochemical stains. The malignant cells do not stain for mucin with alcian blue or mucicarmine stains. The malignant cells stain positively for keratin and for carcinoembryonic antigen. Some of the cells stain positively for LeuM1 antigen and B72.3 antigen. There is positive staining of large epithelial cells for neuron-specific enolase with high background. More specific stains for neuroendocrine differentiation are negative, specifically, chromogranin, serotonin, and gastrin. Overall, the results indicate that this is a carcinoma. I also performed stains for estrogen and progesterone receptors. These stains are negative. I do not know the origin of this carcinoma.

Thank you for referring this case in consultation. Your slides and our negative chromogranin stain are enclosed. Additional tissue will be necessary for more precise moprhological diagnosis. This is a confirmation of my earlier telephone call with a physician attending the patient. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 4429 (Chapter 9 – Lung Tumors)

Case 4406

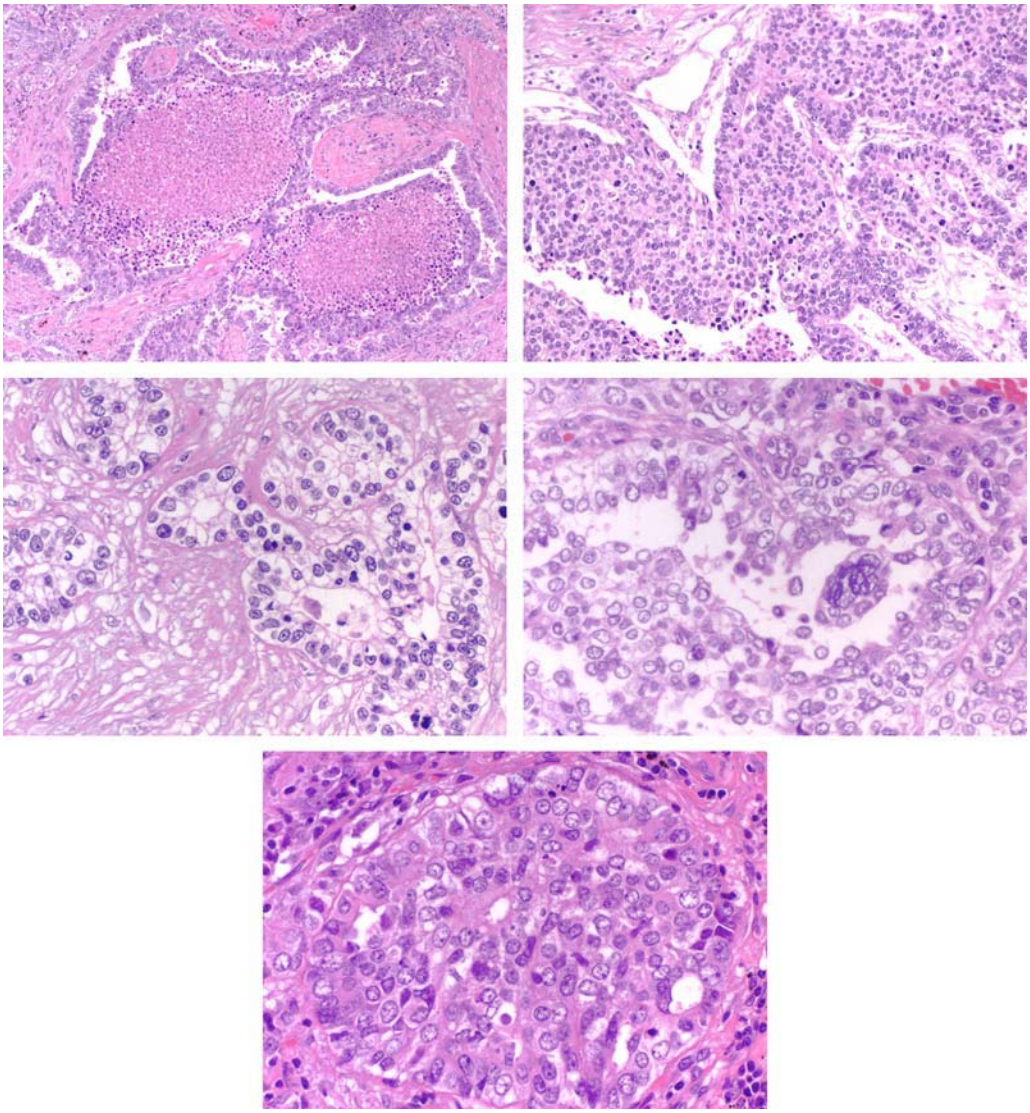
Patient: 65-yr-old male
Diagnosis: Lung, lobectomy:

1. **Adenocarcinoma of fetal lung type, poorly differentiated.**
2. **Subpleural honeycomb fibrosis.**

The complex glandular and papillary structure, the sheets of cells with clear cytoplasm including subnuclear vacuoles, and palisading of cells suffice for a diagnosis of adenocarcinoma of fetal lung type, as you indicate. The nuclear pleomorphism, giant nucleoli and necrosis indicate that this is a poorly differentiated or high-grade tumor. The clear cell change seems greater than in any other cases that we have encountered. There is a prominent brush-border around the luminal surface of some of the glands very much like the adenocarcinoma of the stomach which you include. Large ill-defined morules similar to those seen in pulmonary endodermal tumor have intercellular bridges. Subpleural honeycomb fibrosis is older and separate from desmoplasia in reaction to the tumor.

Thank you for sharing this case with me and permitting me to add it to our permanent teaching collection. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 4406 (Chapter – Lung Tumors)

Case 6954

Diagnosis: Lung, transbronchial biopsy:

1. **Compact granulomas, extensive, in part in lymphangitic distribution.**
2. **Metastatic carcinoma, in part within lymphatics.**

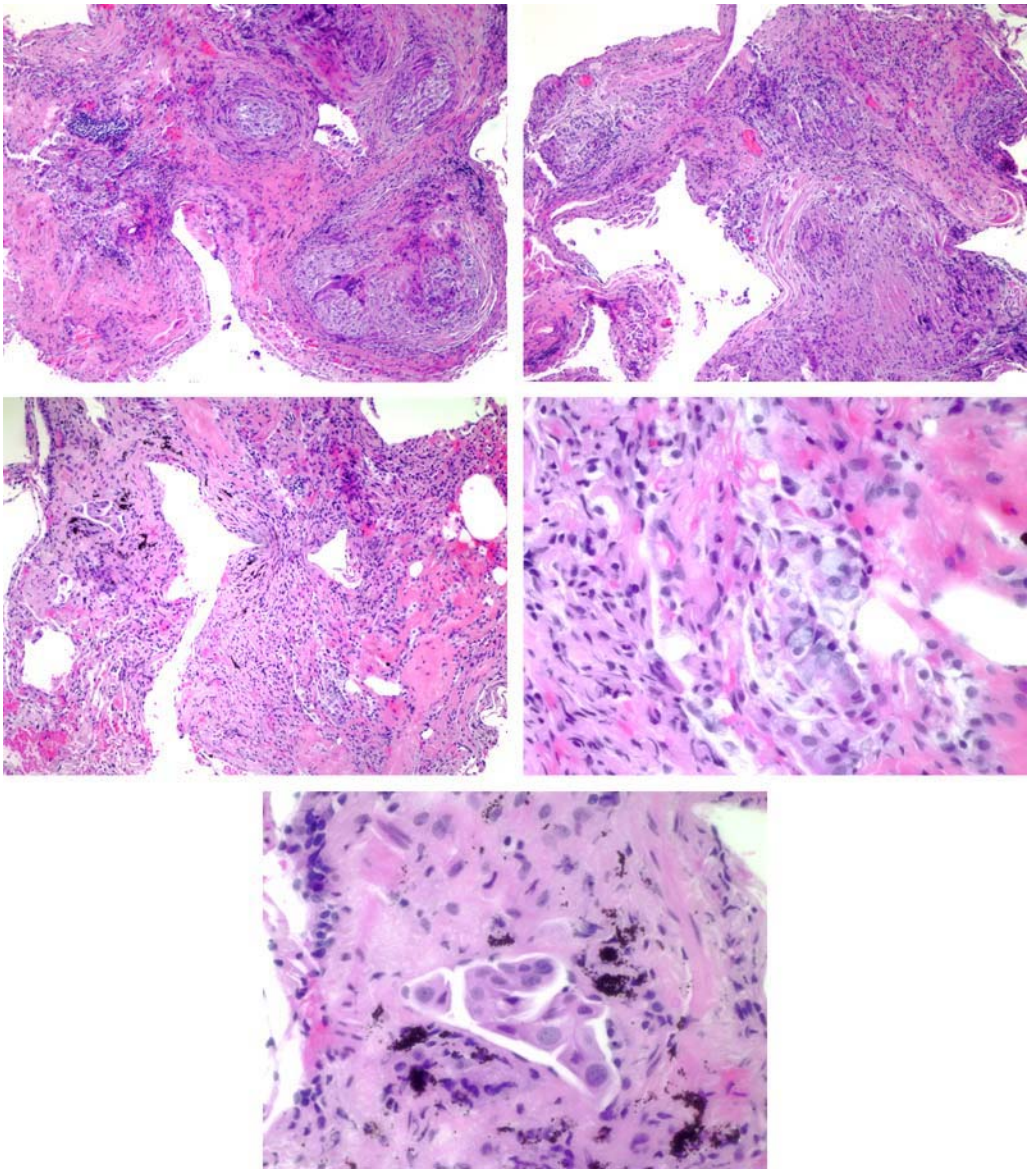
This case is complicated because of two different and probably independent processes. The first process is the numerous compact noncaseating granulomas, which are extensive and conglomerate and in part lie around bronchovascular bundles. The character of the granulomas and their location are consistent with sarcoidosis. I cannot exclude an infectious etiology. I understand that your stains for mycobacteria and fungi are negative.

The second process is occasional small clumps of highly atypical cells, some of which are in distended lymphatics beneath bronchiolar mucosa. I believe these cells represent carcinoma because of their nuclear characteristics and location. They do not appear on every cut of tissue. I cannot determine the origin of this carcinoma. The histology is consistent with a breast primary or, less likely, a pulmonary primary. I understand that staining for estrogen and progesterone receptors was attempted but unsuccessful because of loss of the atypical cells on the recut sections. Poorly formed granulomas or more diffuse granulomatous reaction sometimes occurs as a response to tumor, but these granulomas are so discrete that I suspect that they are not a reaction to tumor.

I do not know whether the granulomas or the carcinoma or both are causing the radiographic and clinical findings. The granulomas are much more extensive than the malignancy on the biopsy specimen and have resulted in scarring.

The above observations are essentially in agreement with your own. Thank you for referring this case in consultation. This is a confirmation of our earlier discussion. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6954 (Chapter 9 – Lung Tumors)

Case 6467

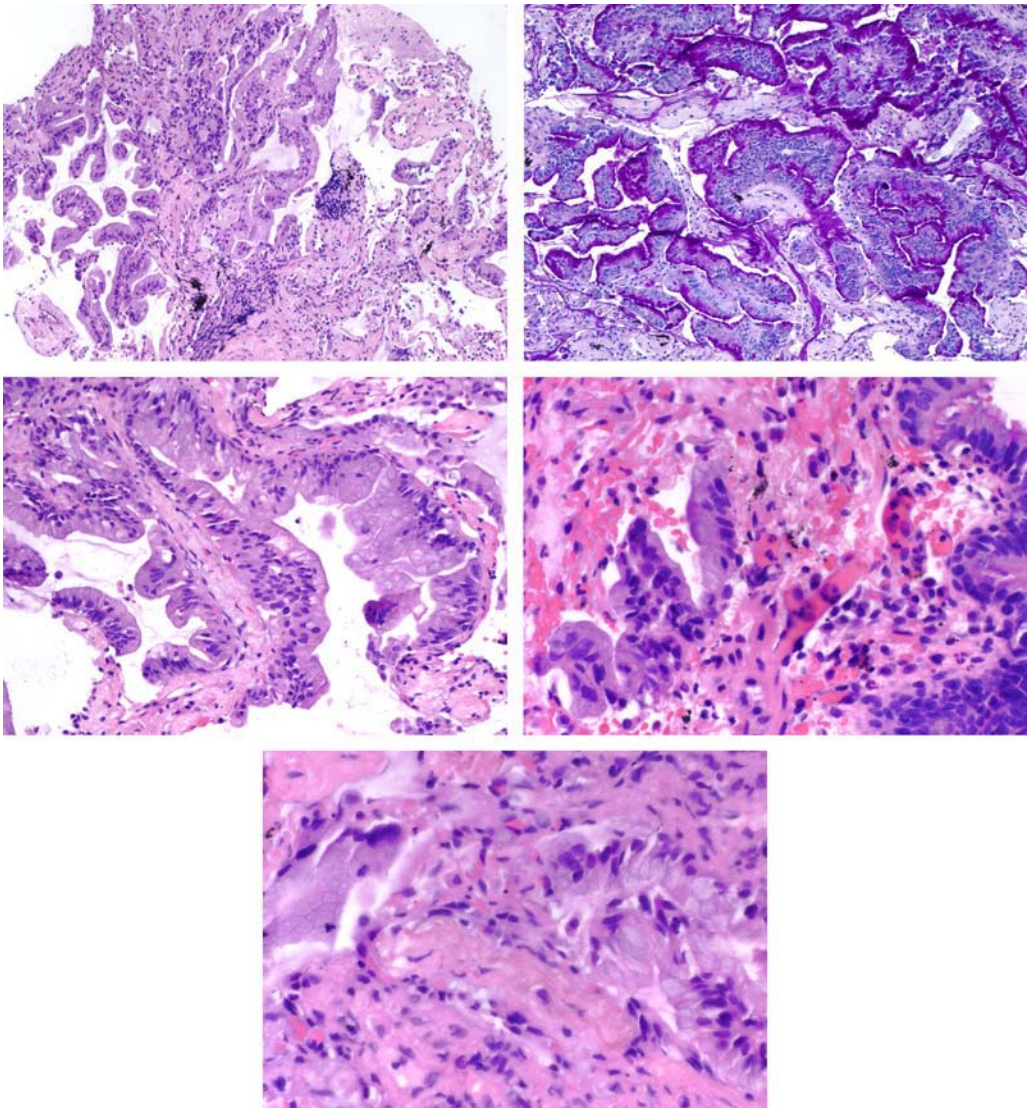
Patient: 68-yr-old female with left upper lobe pneumonia.

Diagnosis: Lung, bronchoscopic biopsy: Adenocarcinoma, bronchioloalveolar subtype.

The nuclear features of the cells define malignancy, the mucinous differentiation in the abnormal columnar cells (PAS stain) defines an adenocarcinoma, and the growth of the carcinoma cells along the walls of alveoli in a lepidic fashion characterizes bronchioloalveolar carcinoma. We categorize adenocarcinoma of the lung into acinar, papillary, and bronchioloalveolar subtypes by the standards of the World Health Organization. Many cases have mixed subtypes, but this specimen shows all of the adenocarcinoma to be bronchioloalveolar. The clinical history of pneumonic consolidation on the X-ray is the most distinctive radiographic presentation of bronchioloalveolar carcinoma. Metastases to the lung sometimes can simulate primary bronchioloalveolar carcinoma histologically, but usually the resemblance is superficial. This case appears to be primary rather than metastatic.

Thank you for referring this case in consultation. This letter is a confirmation of our telephone conversation. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6467 (Chapter 9 – Lung Tumors)

Case 6619

Diagnosis: Lung, lobectomy: Adenocarcinoma, bronchioloalveolar subtype, largely mucinous.

An adenocarcinoma has tall columnar mucinous cells growing along alveolar walls in a manner characteristic of bronchioloalveolar carcinoma. In addition to the intracellular mucin, there is voluminous extracellular mucin which fills alveoli apart from carcinoma or contains isolated carcinoma cells. Patients with this colloid form of bronchioloalveolar carcinoma may have clinical problems with bronchorrhea. There is a subpleural bulla lined by neoplastic cells, and it is possible that carcinoma has arisen in a bulla. I do not believe it has arisen from a mucinous tumor of borderline malignancy. The tumor is multicentric. There is probable lymphatic invasion, but the lymph nodes available for review are free of tumor. Although the nuclear features are relatively well differentiated, the multicentricity and colloid production are bad prognostic signs in my opinion.

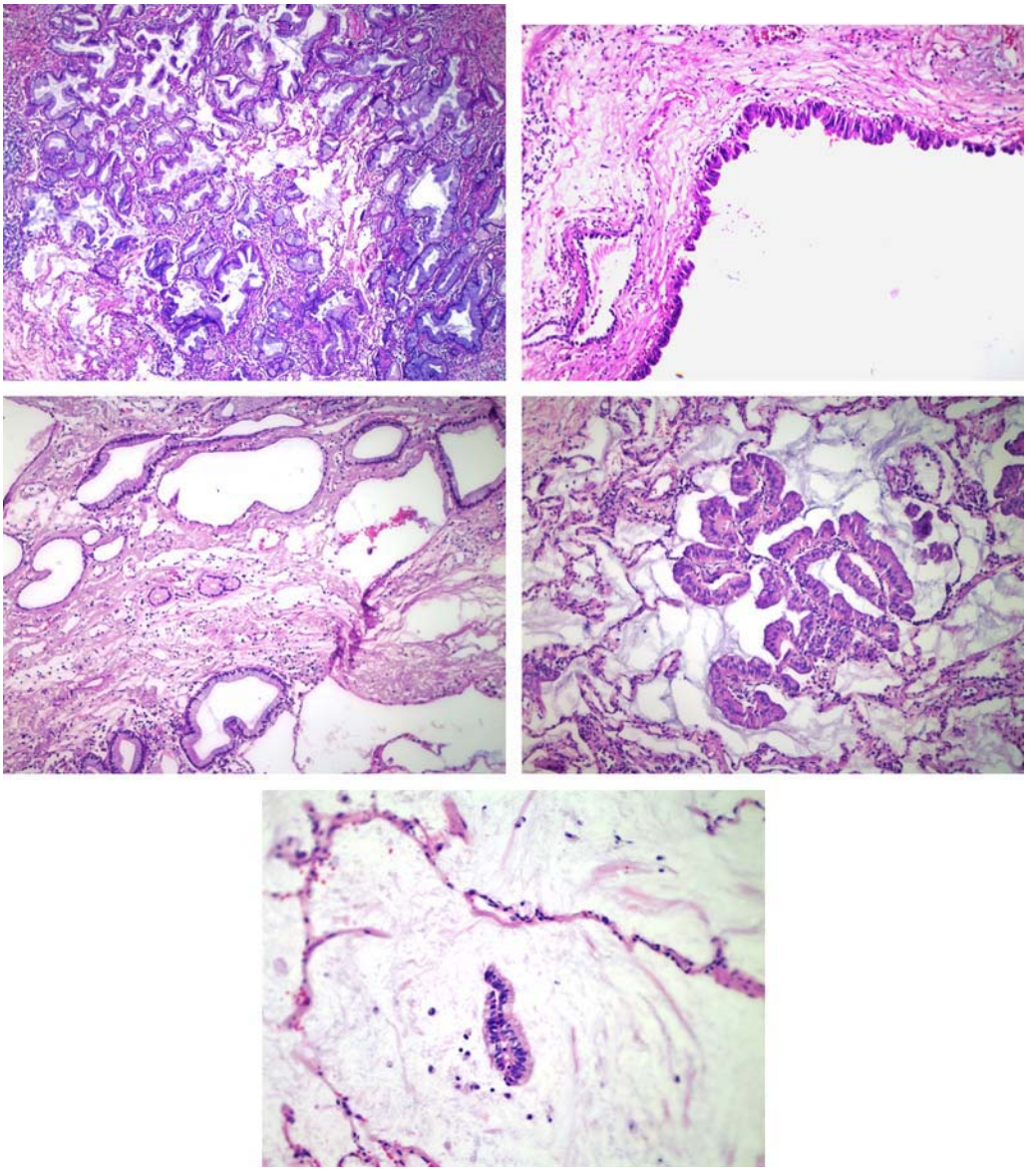
Thank you for referring this case in consultation. Please keep me informed of any follow-up and all if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

Spiro SG, Lopez-Vidriero M-T, Charman J, Das I, Reid L. Bronchorrhoea in a case of alveolar cell carcinoma. J Clin Pathol 1975;28:60–65.

Scannel JG. "Bleb" carcinoma of the lung. J Thorac Cardiovasc Surg 1980;80:904–908.



Case 6619 (Chapter 9 – Lung Tumors)

Case 7174

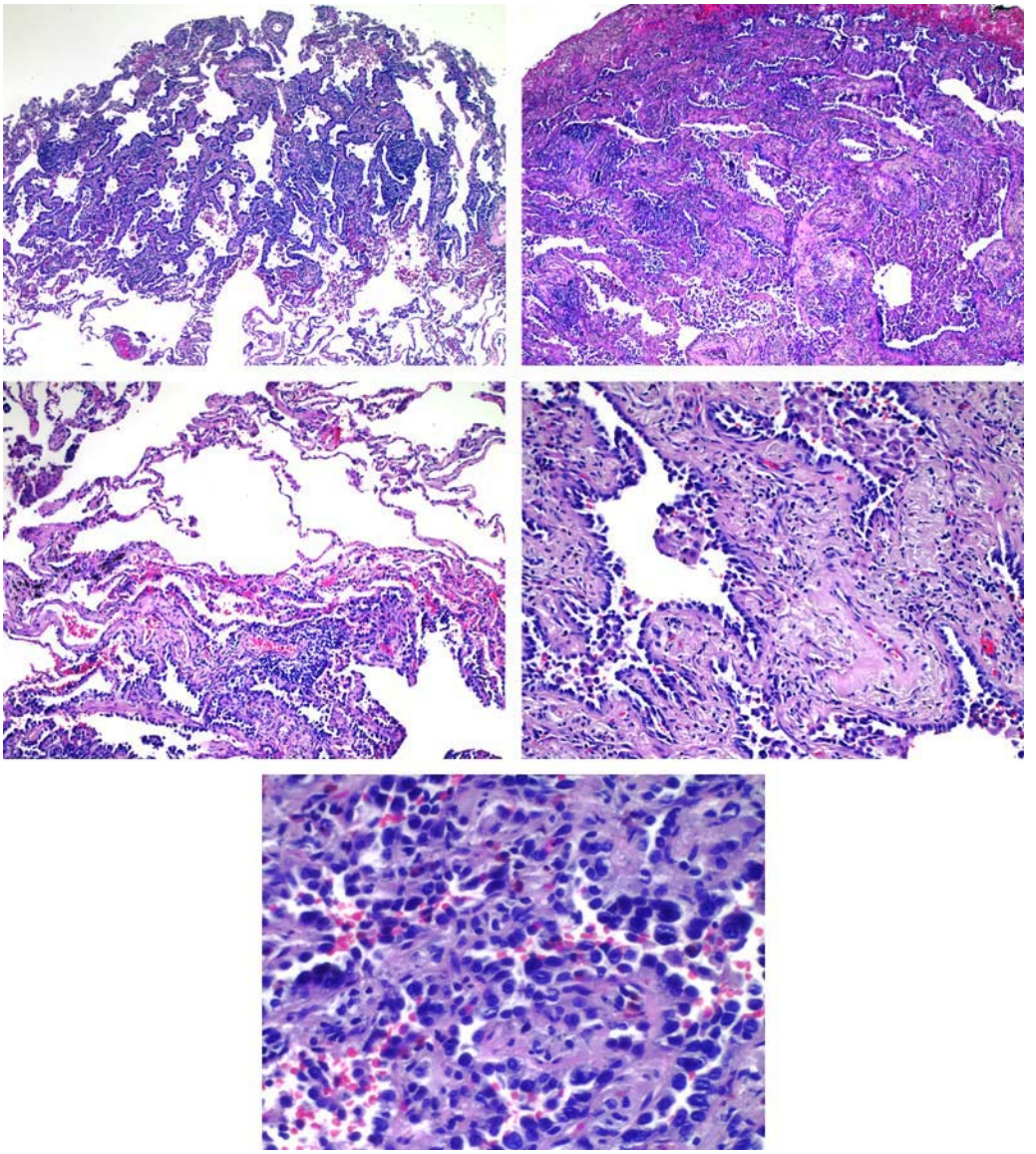
Diagnosis: Lung, wedge resection: Adenocarcinoma, bronchioloalveolar subtype.

The degree of nuclear hyperchromatism and pleomorpism, the abrupt demarcation between proliferating cells and normal alveoli, and the desmoplastic reaction indicate an adenocarcinoma of bronchioloalveolar subtype in my opinion and in the opinion of other pathologists in our department who have reviewed the case. The principal differential diagnosis is atypical adenomatous hyperplasia (AAH). I use that diagnosis generally for lesions 5 mm or less in diameter. This lesion is larger than that. Although interstitial fibrosis may be present to a modest degree in AAH, the extensive desmoplastic fibrosis and inflammation here is not seen in AAH. We do not routinely use p53 and MIB1 in evaluation of such lesions, and I do not have sufficient experience to comment on their meaning in this case.

The prognosis in this subpleural lesion, which seems to be stage I, is relatively favorable if unifocal. Nevertheless, I believe this lesion has the capacity to metastasize. There are two foci of tumor in two of the sections, and I do not know whether this represents sectioning effect or multifocality.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7174 (Chapter 9 – Lung Tumors)

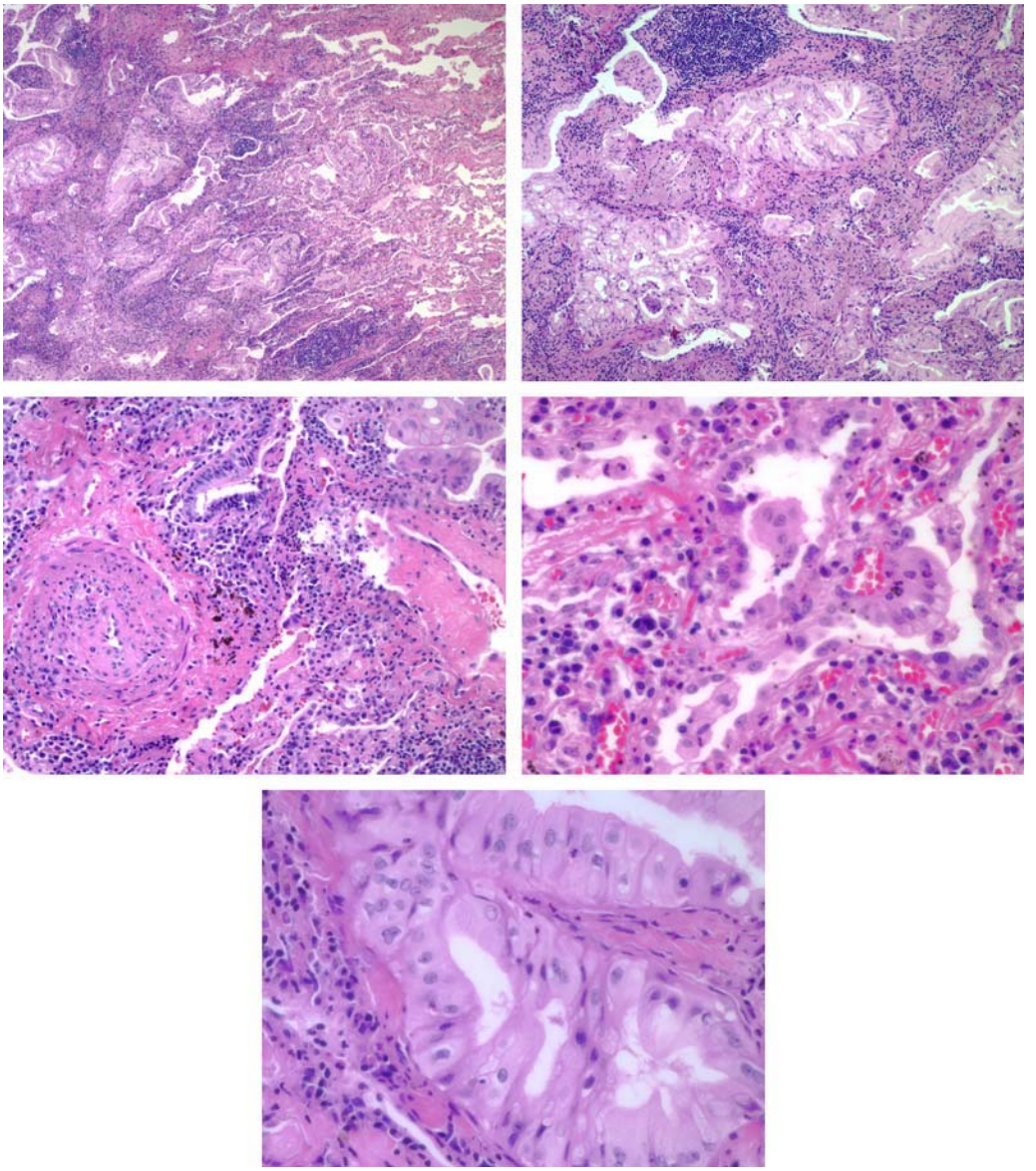
Case 6688

Diagnosis: Lung, open biopsy: Adenocarcinoma, bronchioloalveolar subtype.

Malignant columnar cells line alveolar airspaces and proliferate with pseudopalisading and micropapillae. The pattern is that of a bronchioloalveolar carcinoma. I believe this has likely originated in the lung for the following reasons: 1) there is a brush border on some of the neoplastic cells; 2) two cell types are present amidst the neoplastic cells, mucinous and nonmucinous; 3) sclerosis and lymphoid hyperplasia are associated with areas of tumor and not with areas free of tumor, a phenomenon occasionally seen in bronchioloalveolar carcinoma. I see old thrombosed and sclerosed blood vessels with a few atypical nuclei within the blood vessels, but I do not believe there is vascular invasion or embolic tumor. No carcinomatous arteriopathy (proliferative intimal hyperplasia associated with embolic carcinomatosis) is present.

Thank you for referring this case. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6688 (Chapter 9 – Lung Tumors)

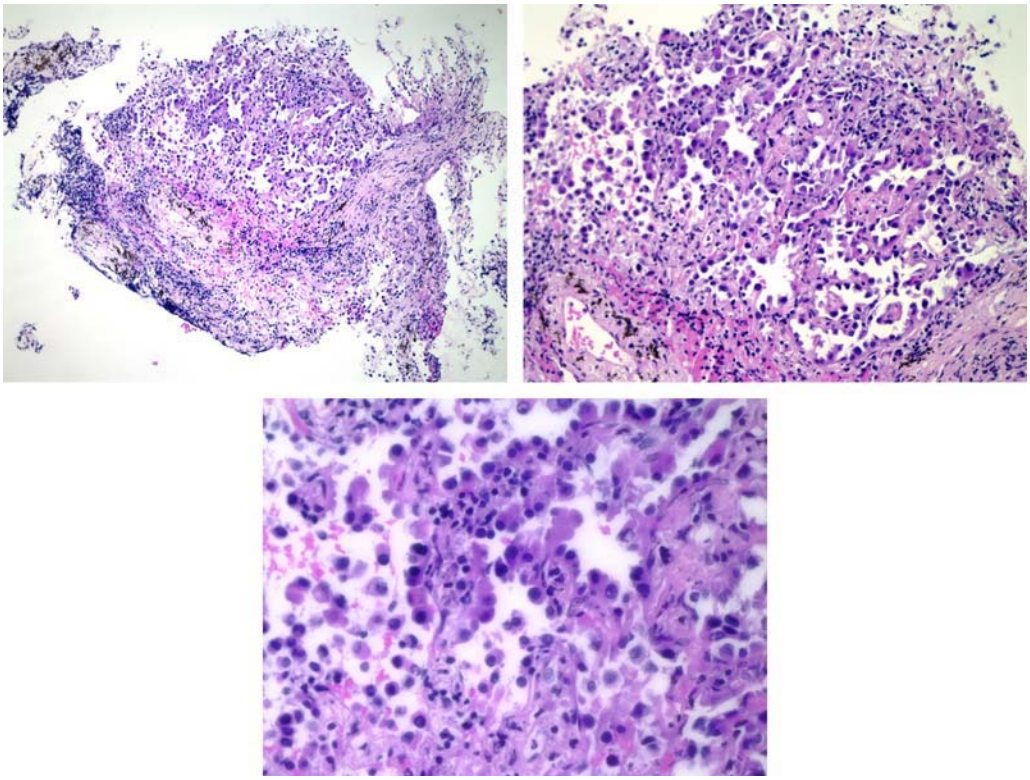
Case 6810

Diagnosis: Lung, bronchoscopic biopsy and brushings: Adenocarcinoma, bronchioloalveolar subtype.

The bronchial brushings have marked cytologic atypia of glandular cells with marked three dimensional change. In retrospect, the cytologic findings are highly suspicious of adenocarcinoma. The bronchoscopic biopsy shows sufficient nuclear atypia to confirm a diagnosis of adenocarcinoma, and the manner of spread of the cells is in keeping with an adenocarcinoma of bronchioloalveolar subtype. I believe the tumor is primary because of the hobnail appearance of the cells and the intranuclear inclusions suggestive of pneumocytic origin. On the biopsy alone, one might consider AHH, but this entity should not produce positive cytological findings nor a mass on the X-ray, and the nuclear changes would be in excess of what I expect for AAH.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. I have retained one histologic section and hereby return the remainder including all of the cytological preparations. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6810 (Chapter 9 – Lung Tumors)

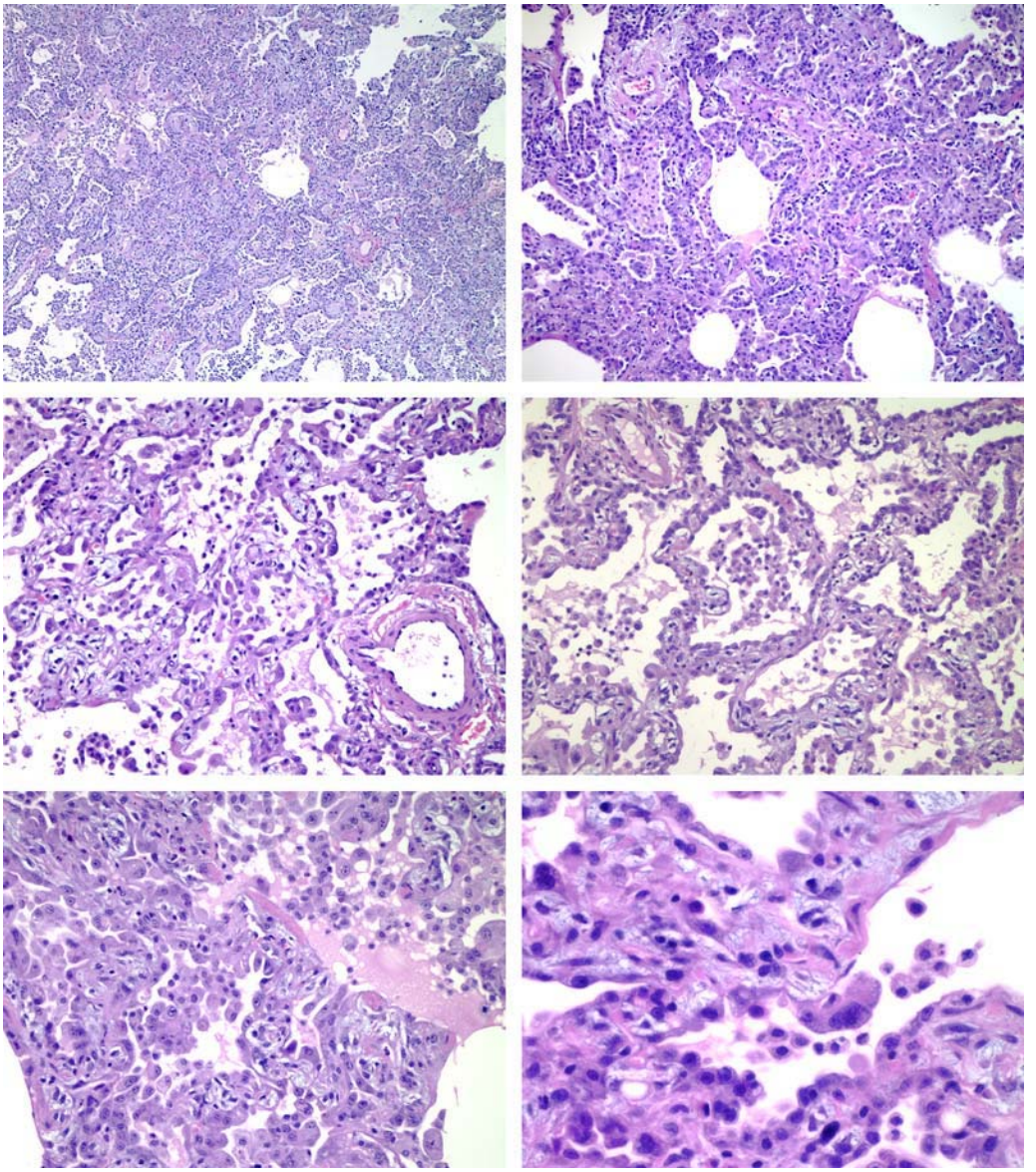
Case 6504

Diagnosis: Lung, open biopsy: Highly atypical cells in alveolar airspaces and lining alveolar walls, ? bronchioloalveolar carcinoma of the dishesive type.

This case is difficult. Some regions have desquamative histiocytes with admixed lymphocytes and pigmented histiocytes indicative of a desquamative intersitital pneumonitis-like reaction. Other regions, however, have alveolar filling by cells with nuclear features highly suggestive of malignancy. I suspect that this represents the dishesive form of bronchioloalveolar carcinoma. With this in mind, I have performed several additional studies.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6504 (Chapter 9 – Lung Tumors)

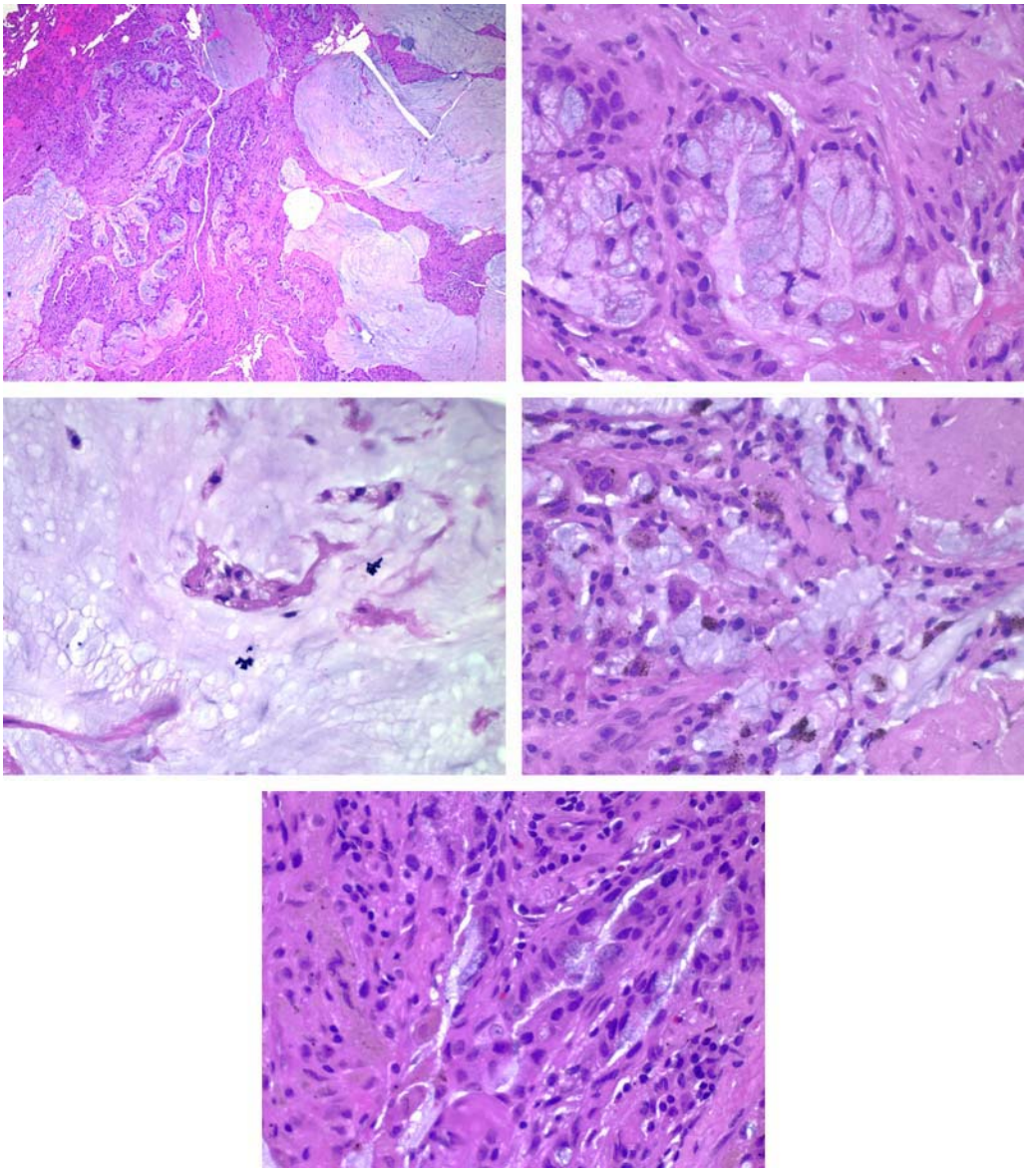
Case 6850

Diagnosis: Lung, wedge resection: Adenocarcinoma, colloid type.

This case is difficult because the lesion is composed principally of pools of thick basophilic mucus, amidst which are small nests and single cells with abundant mucinous cytoplasm and pleomorphic nuclei with enlarged nucleoli. In one area, these highly atypical cells form complex glands. I believe the histology is that of an adenocarcinoma with extensive mucin production, that is, the equivalent of colloid carcinoma of the colon or breast. Although one can sometimes distinguish primary and metastatic colloid carcinoma in the lung, that situation arises when there are more malignant cells to evaluate than are present here. In this case with relatively few malignant cells, I do not know whether this is primary or metastatic. However, on a statistical basis, this is more likely to be primary if there is not an apparent carcinoma elsewhere at the time the patient presents with a lung nodule. I do not appreciate a cyst or remnant of a cyst, so I would not call this a cystadenocarcinoma.

Thank you for referring this case on consultation. Please keep me informed of any follow-up and call if you have questions. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6850 (Chapter 9 – Lung Tumors)

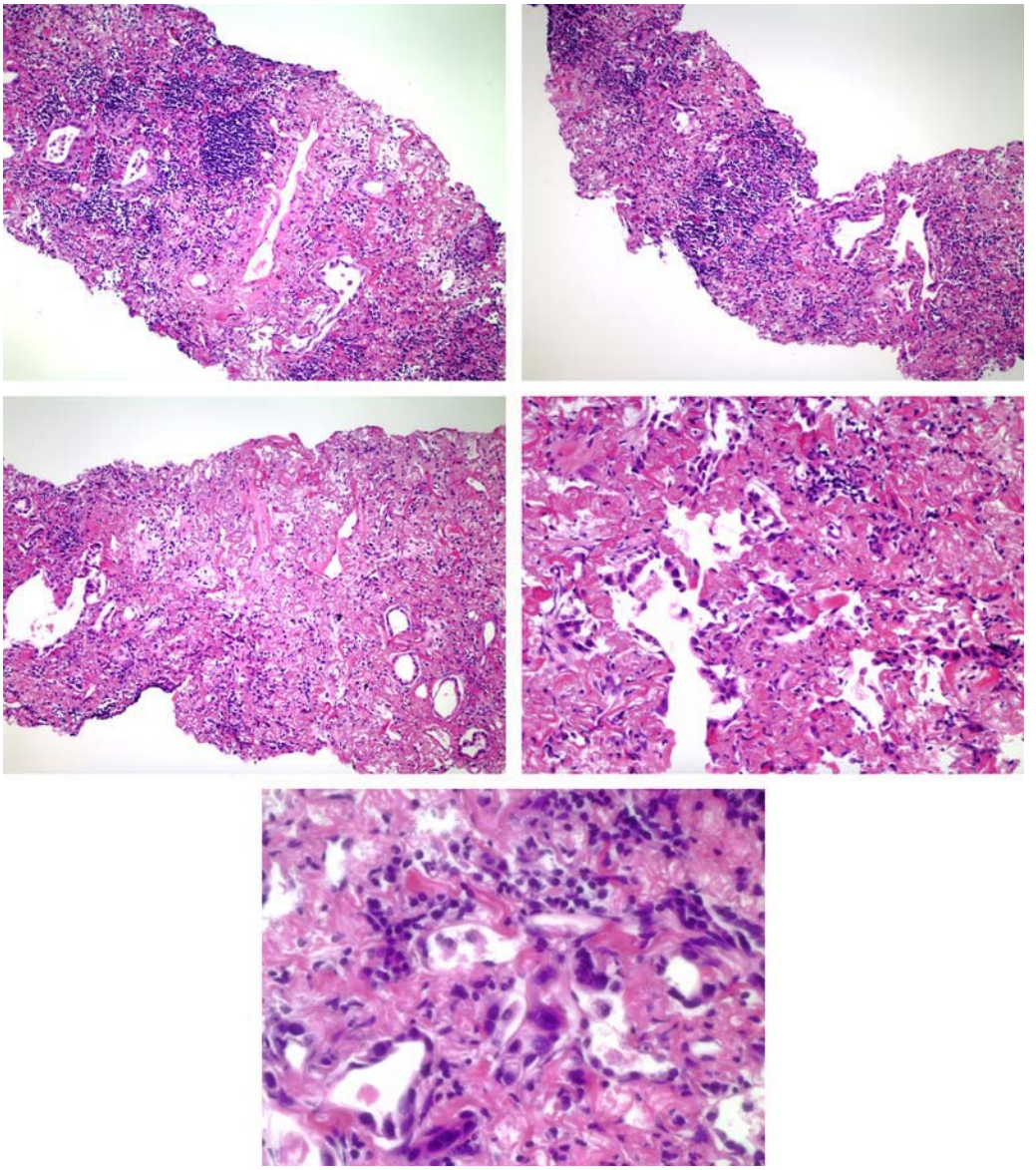
Case 6830

Diagnosis: Lung, needle biopsy: Adenocarcinoma, well differentiated, with extensive desmoplastic fibrosis and elastotic scarring.

This case is very difficult because we are faced with a specimen which is principally elastotic and fibrous scar with glandular spaces lined by highly atypical epithelial cells. The differential diagnosis is that of a scar with marked atypia or adenocarcinoma that is well differentiated. I believe the nuclear changes, the small nests of cells surrounded by desmoplastic inflammation indicative of invasion, and foci of mucinous cells which are not a form of reaction suffice for a diagnosis of an adenocarcinoma. Some airspaces are lined by benign but reactive epithelial cells, and the juxtaposition of reactive and malignant cells further complicates the interpretation. In some regions of the biopsy, I cannot be certain whether the epithelial cells are benign or malignant, but I believe the biopsy in total is sufficient for a diagnosis of adenocarcinoma. Because of the complexity of the findings, I have shown the case to several other members in the department. Some believe the findings are equivocal. Two attending pathologists, in addition to myself, believe the changes are diagnostic of malignancy.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6830 (Chapter 9 – Lung Tumors)

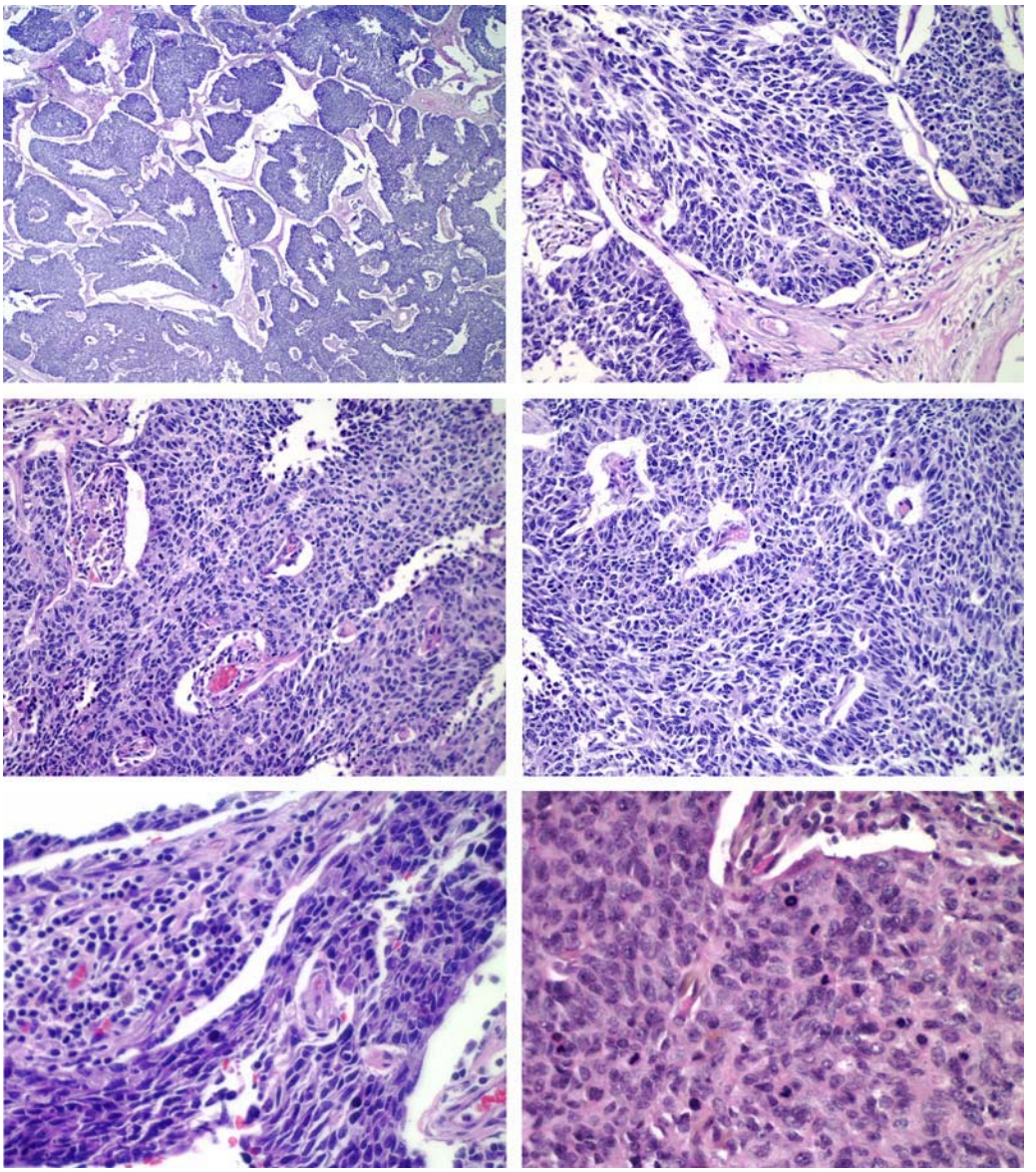
Case 6815

Diagnosis: Lung, lobectomy: Squamous cell carcinoma, poorly differentiated with small cells and basaloid differentiation.

The differential diagnosis in this case includes principally squamous cell carcinoma with regions of small cells and basaloid features vs large cell neuroendocrine carcinoma. This is essentially the question which you pose. There is definite keratinization by virtue of intercellular bridges, dyskeratotic cells and maturation of keratinocytes with flattened cells having eosinophilic cytoplasm in some areas. The low-power pattern made me consider large cell neuroendocrine carcinoma, for which reason we did immunologic studies for neuroendocrine markers. The carcinoma cells stain positively for keratin (Kreyburg stain) with extensive staining in some areas. There is no staining for synaptophysin or for chromogranin. Thus, this case does not qualify for large cell neuroendocrine carcinoma despite an organoid appearance, which I believe is due to the basaloid differentiation. Some cases of squamous cell carcinoma prove problematic when there are regions with small cells, and that would be the case here if a biopsy sampled regions with small cells or regions with the basaloid differentiation. Unusual are rosettes within the sheets of carcinoma cells. Rosettes can occur in small cell carcinoma, but I do not believe this is a small cell carcinoma. One focus of tumor is present in the lung distant from tumor. The significance of this is uncertain.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6815 (Chapter 9 – Lung Tumors)

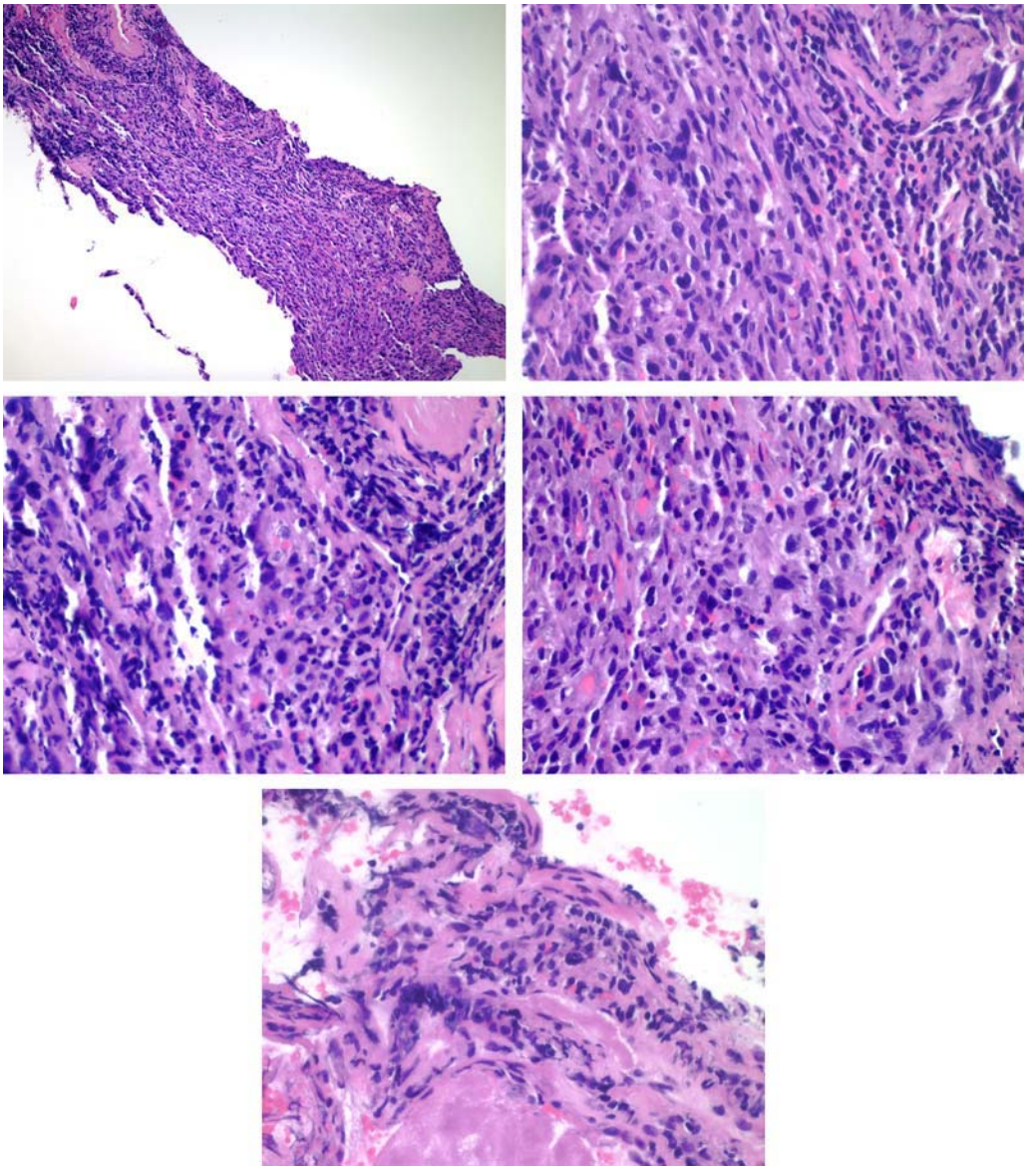
Case 6884

Diagnosis: Bronchus, bronchoscopic biopsy: Poorly differentiated carcinoma, consistent with poorly differentiated adenocarcinoma.

I believe the histology is that of a carcinoma because of the cohesion of the cells and the ample eosinophilic cytoplasm. Although the nuclei are relatively small, I do not believe this is a small cell carcinoma, because in some areas the tumor forms large nests, and in some areas the nuclei are open with visible nucleoli. I cannot determine whether this is intrinsically adenocarcinoma, squamous cell carcinoma, or a combination of the two. There is no clinical difference among these phenotypes. I favor adenocarcinoma because of vacuolar change with basophilic granules in some of the cells. Cases of either adenocarcinoma or squamous cell carcinoma with relatively small nuclei, such as this case, pose recurrent problems in differentiation from small cell carcinoma.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6884 (Chapter 9 – Lung Tumors)

Case 7069

Diagnosis: Kidney: Transitional cell carcinoma, grade 2/3. Lung, wedge resection:

1. **Squamous cell carcinoma, moderately differentiated,? arising in a bulla.**
2. **Emphysema, marked.**

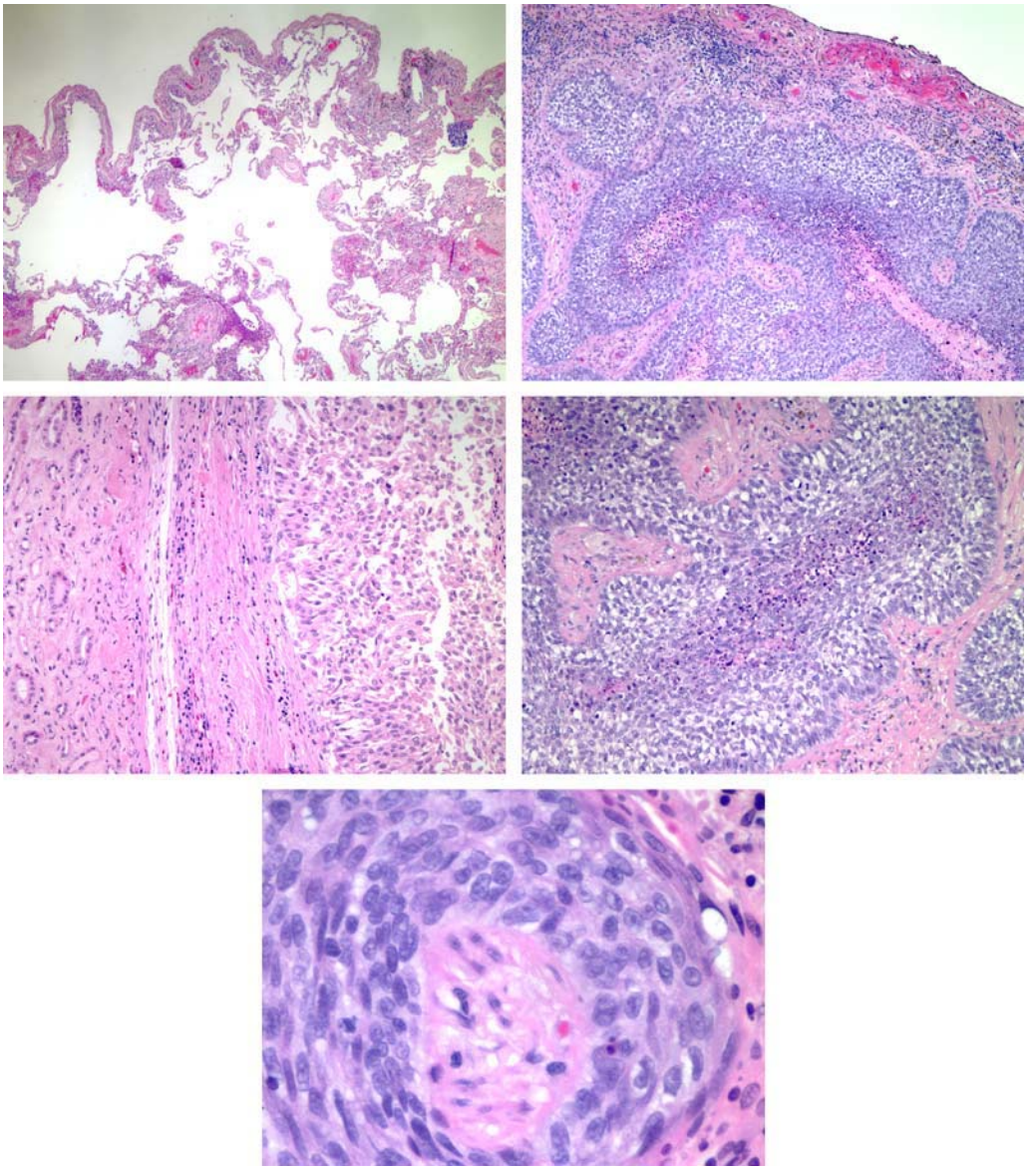
The squamous cell carcinoma in the lung appears to me like a primary by virtue of its configuration and the patterns of necrosis and sclerosis. There is extension of carcinoma along walls of alveolar septa, a feature I associate with squamous cell carcinomas of the lung. Large ectatic airspaces might have represented a bulla. Since this carcinoma is subpleural, it may have arisen in a bulla and represent the entity of carcinoma arising in a bulla. I believe the appearance of the transitional cell carcinoma in the kidney is sufficiently dissimilar to make it very unlikely that the squamous cell carcinoma in the lung is a metastasis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Zulueta JJ, Bloom SM, Rozansky MI, White AC. Lung cancer in patients with bullous disease. Am J Respir Crit Care Med 1996;154:519–522.



Case 7069 (Chapter 9 – Lung Tumors)

Case 6828

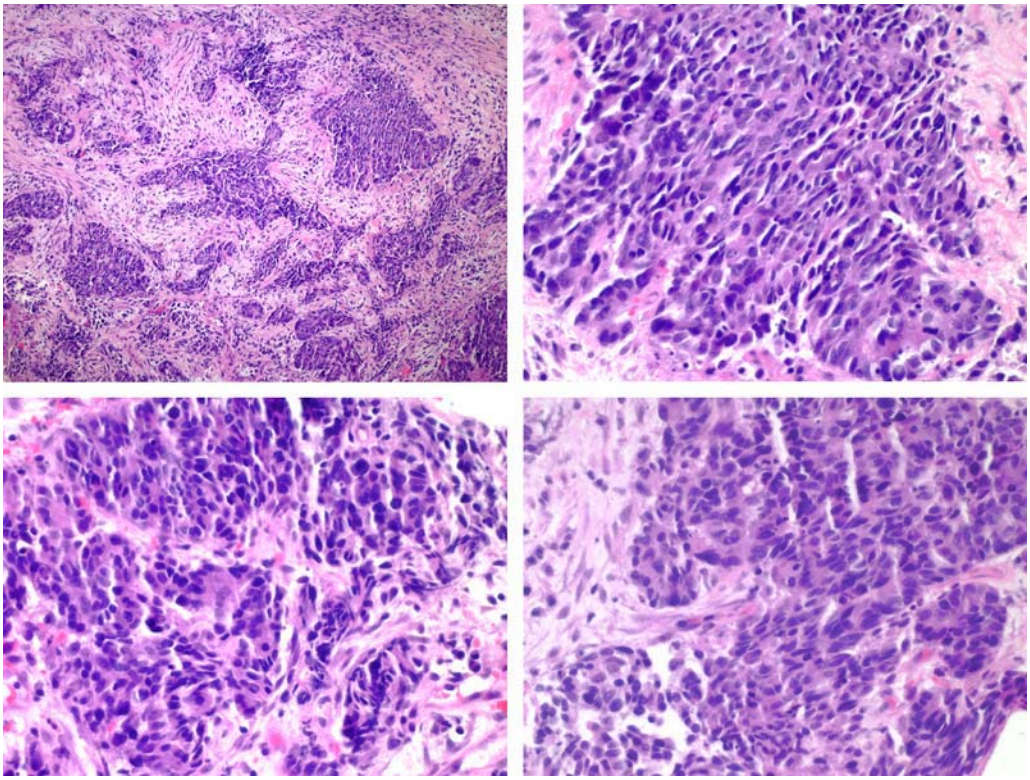
Diagnosis: Bronchus, bronchoscopic biopsy: Poorly differentiated carcinoma, consistent with poorly differentiated squamous cell carcinoma with small cells.

Larynx, biopsy: Squamous cell carcinoma, moderately differentiated, keratinizing.

The two tumors are different. The laryngeal carcinoma is a squamous cell carcinoma which is moderately differentiated with extensive keratinization and quite different from the bronchoscopic tumor. I believe these are two independent primaries. The interpretation of the bronchial tumor poses problems. Initial examination of the cytologic preparations shows clumps of small cells and raises the differential diagnosis of small cell carcinoma. However, nuclear details are better discerned than usual for small cell carcinoma. The same finding applies in the tissue, that is, the nuclei have distinct chromatin and visible nucleoli. Cytoplasm is ample with probable intercellular bridges in some areas, but no keratinization comparable to that in the laryngeal tumor is present. I believe the best diagnosis on the slide stained with hematoxylin-eosin is a non-small cell carcinoma consistent with a poorly differentiated squamous cell carcinoma with small cells. I am more impressed with nesting than basaloid features, and I do not know whether the remainder of the tumor would have basaloid features or not. In any case, basaloid squamous cell carcinoma has a natural history similar to other squamous cell carcinomas of the bronchus. I am not relying on the immunopathological findings in total to make the diagnosis, but to the degree that there is no neuroendocrine staining, they support a diagnosis of poorly differentiated squamous cell carcinoma.

Thank you for referring this case in consultation. Our senior cytopathologist has also reviewed some slides of the case and essentially concurs with the above. The case is difficult. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6828 (Chapter 9 – Lung Tumors)

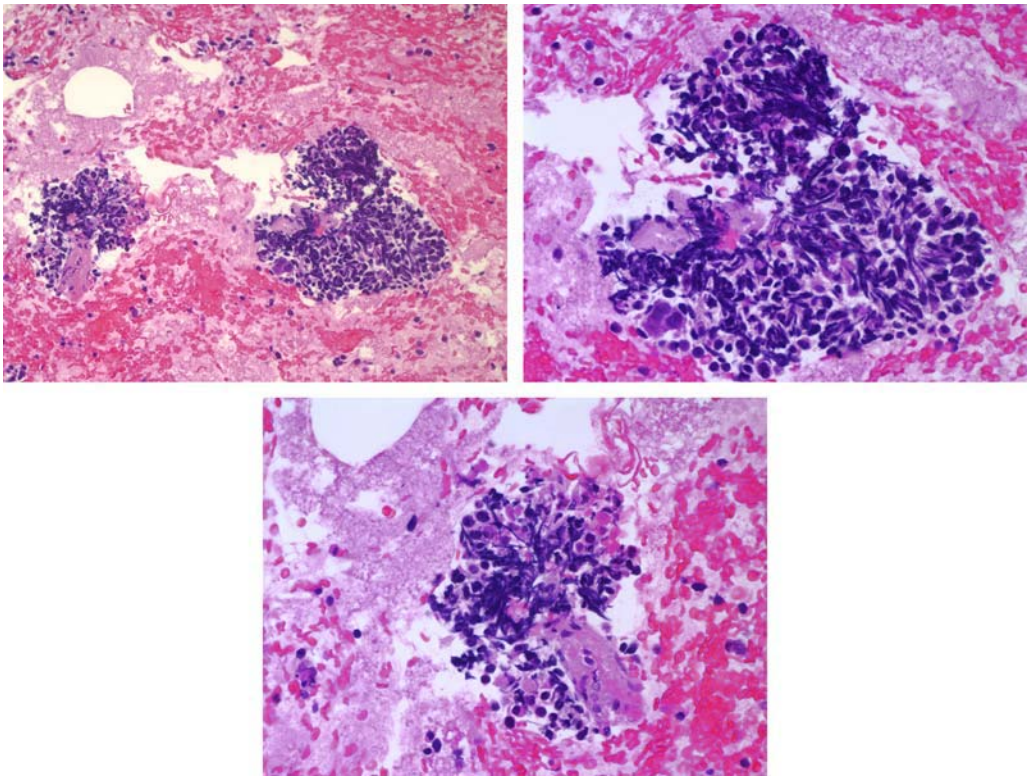
Case 6592

Diagnosis: Lung, needle aspiration: Small cell carcinoma.

The diagnosis rests on a few small cohesive clumps of cells with very dark and opaque nuclei, no visible nucleoli, and scant cytoplasm. Spindled nuclei and crushed cells are present along with oval nuclei. On the cell block stained with hematoxylin and eosin, the primary diagnosis is small cell carcinoma, and your special studies are consistent with this diagnosis, in that the cells stain positively for cytokeratin with punctate staining and stain positively for chromogranin. The accompanying smear has scant material, and I am not able to make a diagnosis on that smear other than degenerate malignant cells. This is essentially in agreement with your interpretation. The only item in the differential diagnosis theoretically is a highly atypical carcinoid tumor, but the largest nest of cells has no organoid differentiation, and a clinical impression of a Pancoast tumor would not correlate well with a highly atypical carcinoid tumor.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. I have retained one slide for our permanent teaching collection in pulmonary pathology and hereby return all of the remainder, including all of your special studies and all of your cytological preparations.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6592 (Chapter 9 – Lung Tumors)

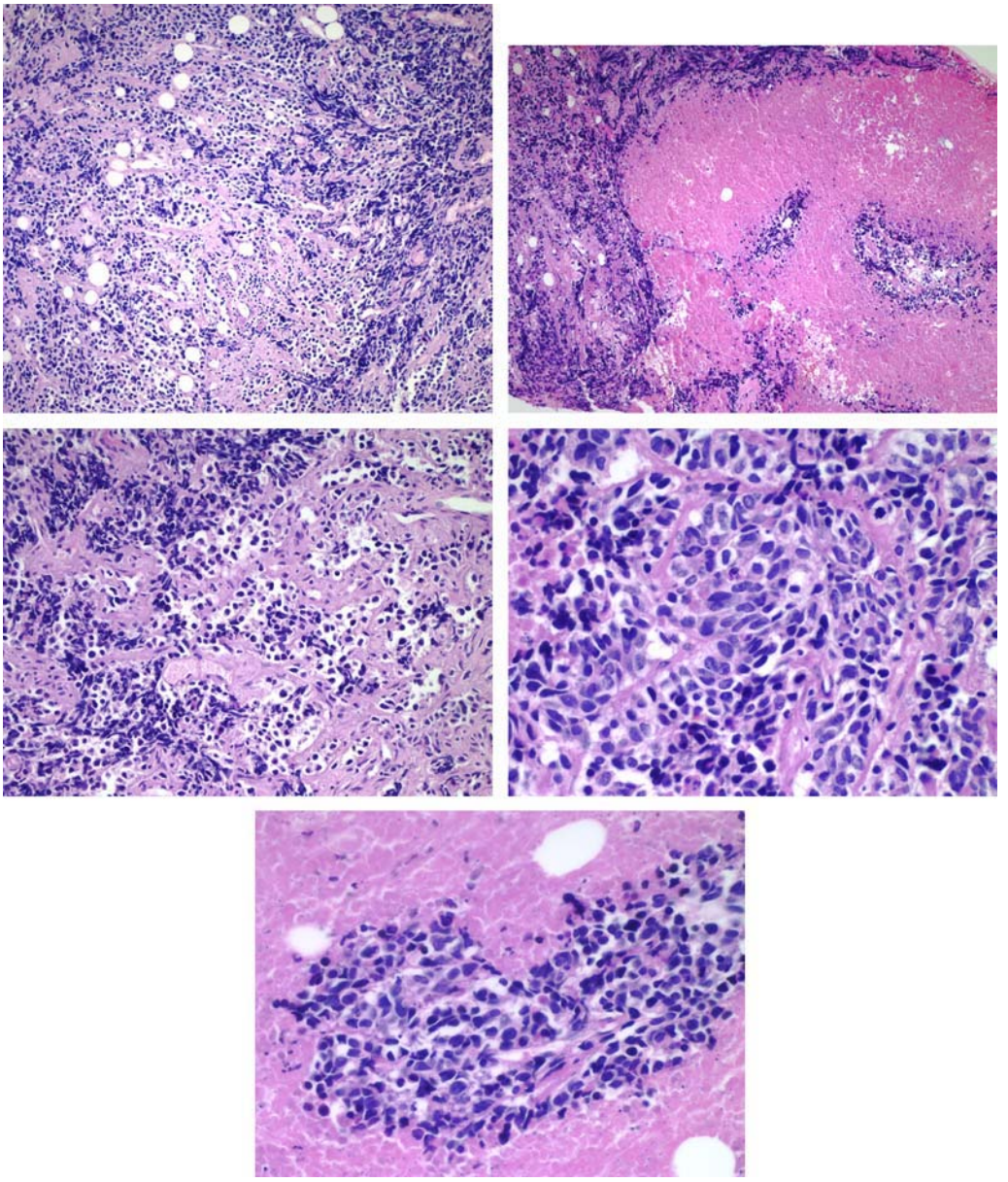
Case 7133

Diagnosis: Mediastinum, biopsy: Small cell carcinoma.

Fibroadipose tissue is suffused by nests of cohesive small hyperchromatic nuclei which form nests and infiltrate as indian files. This is a small cell carcinoma by virtue of the size of the nuclei (slightly larger than lymphoid cells that are present in the biopsy), hyperchromaticity and smudged character of the nuclei with indistinct nucleoli, and scant cytoplasm. Your immunopathological studies corroborate the diagnosis by virtue of showing punctate staining for keratin. They also show the neuroendocrine derivation by virtue of focal positive granular staining for synaptophysin and chromogranin. The cells do not stain for common leukocyte antigen. Although occasional cells are somewhat larger than the principal population of small cells, the overall appearance, including the necrosis, the nuclear characteristics of even the larger cells, and the reported clinical history are all in keeping with a small cell carcinoma of neuroendocrine origin.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. Your special studies are hereby returned. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7133 (Chapter 9 – Lung Tumors)

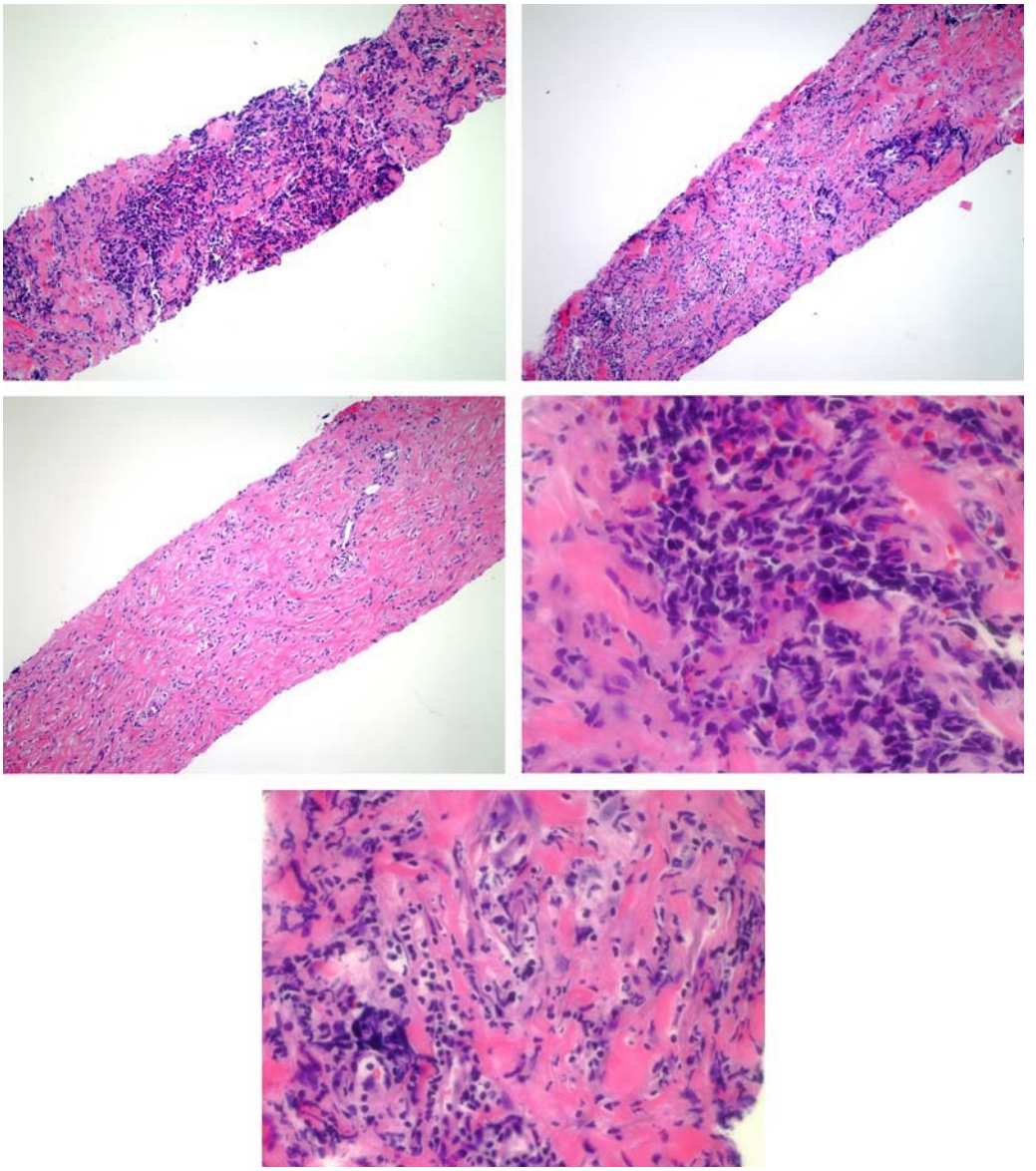
Case 6767

Diagnosis: Bronchus, brushings and biopsy: Small cell malignant tumor, consistent with small cell carcinoma.

This tumor is malignant by virtue of the hyperchromatic nuclei with nests and sheets of small malignant cells. The lack of appreciable cytoplasm and the size of the nuclei make me favor small cell carcinoma over large cell neuroendocrine carcinoma, and I believe the characteristic molding of small cell carcinoma is present on the smears of the tumor. Because of the prominent sclerosis in the biopsy, possibly tissue from the mediastinum, I also considered desmoplastic DMM and sclerosing thymoma, but I do not believe other features of the case are consistent with that interpretation. Much of the tumor in smears and sections is necrotic. Other pathologists in the department have reviewed the case and essentially concur with the above. Insufficient tissue remains in the block for further analysis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6767 (Chapter 9 – Lung Tumors)

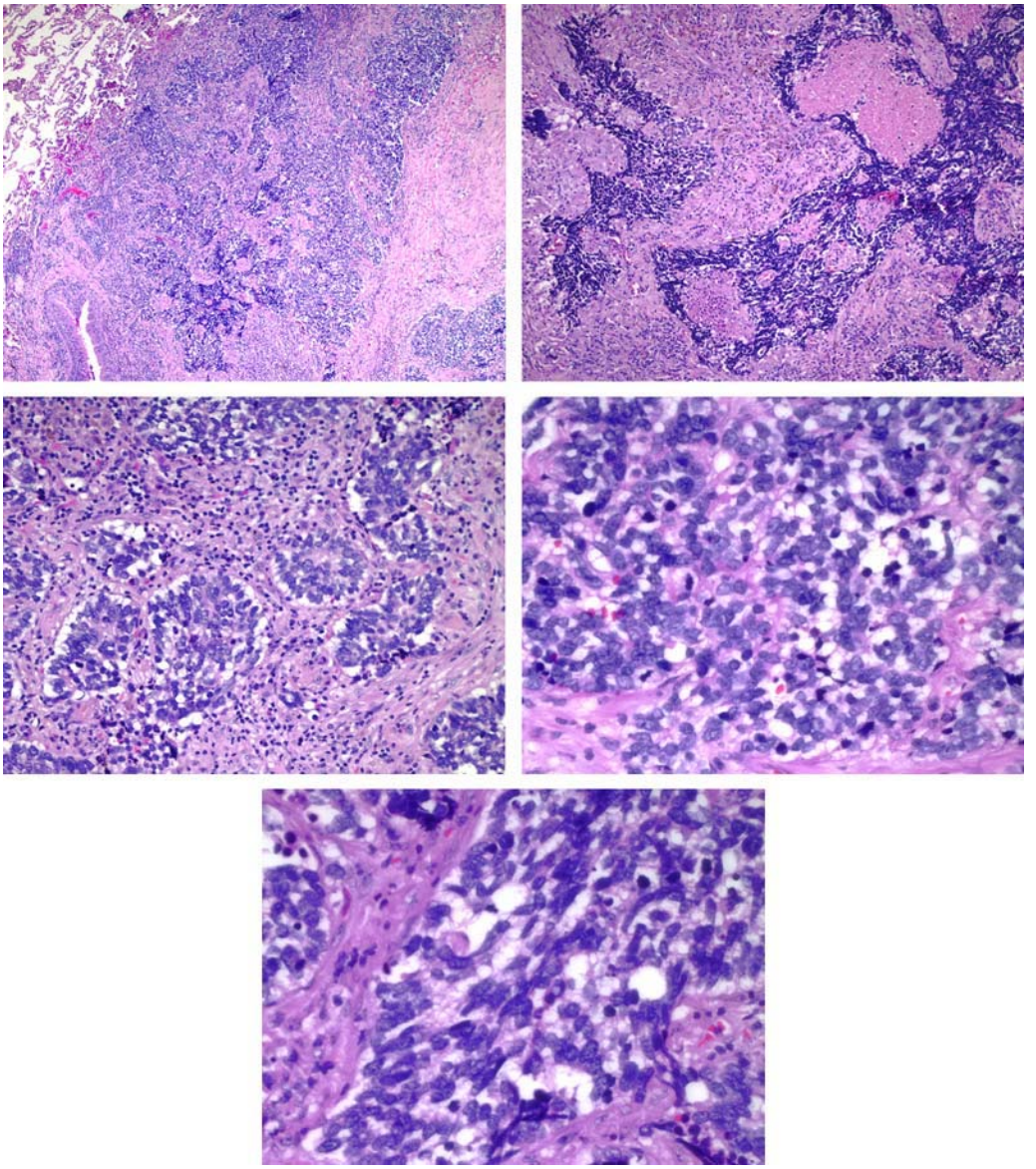
Case 7145

Diagnosis: Lung, segmental resection and lobectomy: Small cell carcinoma, with extensive desmoplastic inflammation and fibrosis.

The differential diagnosis of this case includes markedly atypical carcinoid tumor, small cell carcinoma, and large cell neuroendocrine carcinoma. I believe that the degree of necrosis and mitotic activity as well as the relatively solid growth pattern in some areas is in excess of what one would accept for atypical carcinoid tumor of any degree of atypicality, and that a diagnosis of carcinoma is appropriate. The differential diagnosis then comes between small cell carcinoma and large cell neuroendocrine carcinoma. Yet another consideration might be basaloid squamous cell carcinoma, but your positive neuroendocrine markers (neuron-specific enolase, synaptophysin) and the character of the cells are consistent with basaloid squamous cell carcinoma. I agree with you that the cells by size are small and within the range of small cell carcinoma. The open nucleoplasm with prominent nucleoli typical of large cell carcinoma is not present. Rosettes are present in some regions. Fusiform cells are present in some regions. These features all combine for a diagnosis of small cell carcinoma. The lesion seems to be stage I by virtue of apparent size and location, so the prognosis of this lesion is better than that of the usual small cell carcinoma. The role of additional therapy for stage I small cell carcinoma is not clearly defined.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7145 (Chapter 9 – Lung Tumors)

Case 4433

Diagnosis: Lung, right upper lobe: Small cell carcinoma, with focal glandular differentiation.

Lung, right lower lobe (completion pneumonectomy): Squamous cell carcinoma, moderately differentiated.

The two carcinomas are of histologically different types and therefore, by the common definition, represent independent primaries. The small cell carcinoma has hyperchromatic nuclei and scant cytoplasm characteristic of this neoplasm. The focus of glandular differentiation does not change the diagnosis, as it comprises such a small proportion of the tumor. The positive staining for neuron-specific enolase corroborates the diagnosis. There is spread of carcinoma cells into air spaces for a few millimeters in the region of the main mass.

The second carcinoma is a squamous cell carcinoma of a moderate degree of differentiation. Keratin pearls are present. The tumor abuts but does not invade the pleura. There is invasion of lymphatics in the vicinity of the tumor. A moderate degree of centriacinar emphysema is present.

Synchronous carcinomas of the lung constitute about 1% of all bronchogenic carcinomas. The combination of small cell carcinoma and squamous cell carcinoma is the most common, constituting approximately one-half of all cases of double primaries. A recent review (Ferguson) suggests that the overall prognosis of such patients is worse than the stage of either tumor, with an overall survival of 20%; this author wondered whether synchronous cancers of different cell types might nevertheless represent metastasis. Triple synchronous malignant lung tumors have been reported, and we have seen some of these.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

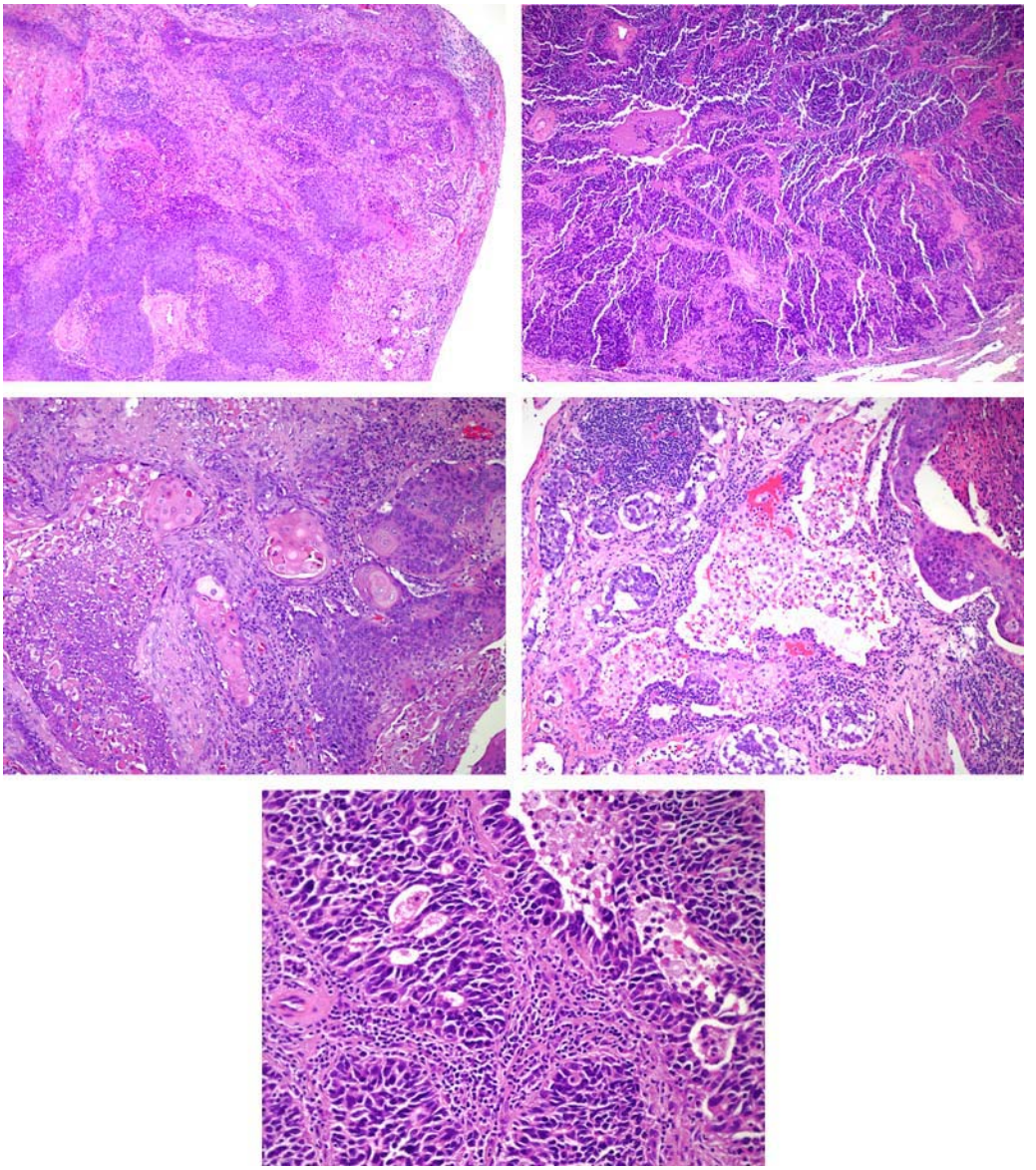
Ferguson MK. Synchronous primary lung cancers. Chest 1993; 103:398S–400S.

Rohwedder JJ, Weatherbee L. Multiple primary bronchogenic carcinoma with a review of the literature. Am Rev Respir Dis 1974;109:435–445.

Chaudhuri MR. Independent bilateral primary bronchial carcinomas. Thorax 1971;26:476–480.

Wu SC, Lin ZQ, Xu CW. Multiple primary lung cancers. Chest 1987;92:892–896.

ung-Legg Y, McGowan SE, Sweeney KG. Synchronous triple malignant tumors of the lung. A case report of bronchial carcinoid, small cell carcinoma, and adenocarcinoma of the right lung. Am J Clin Pathol 1986;85:96–101.



Case 4433 (Chapter 9 – Lung Tumors)

Case 6571

Patient: 69-yr-old male

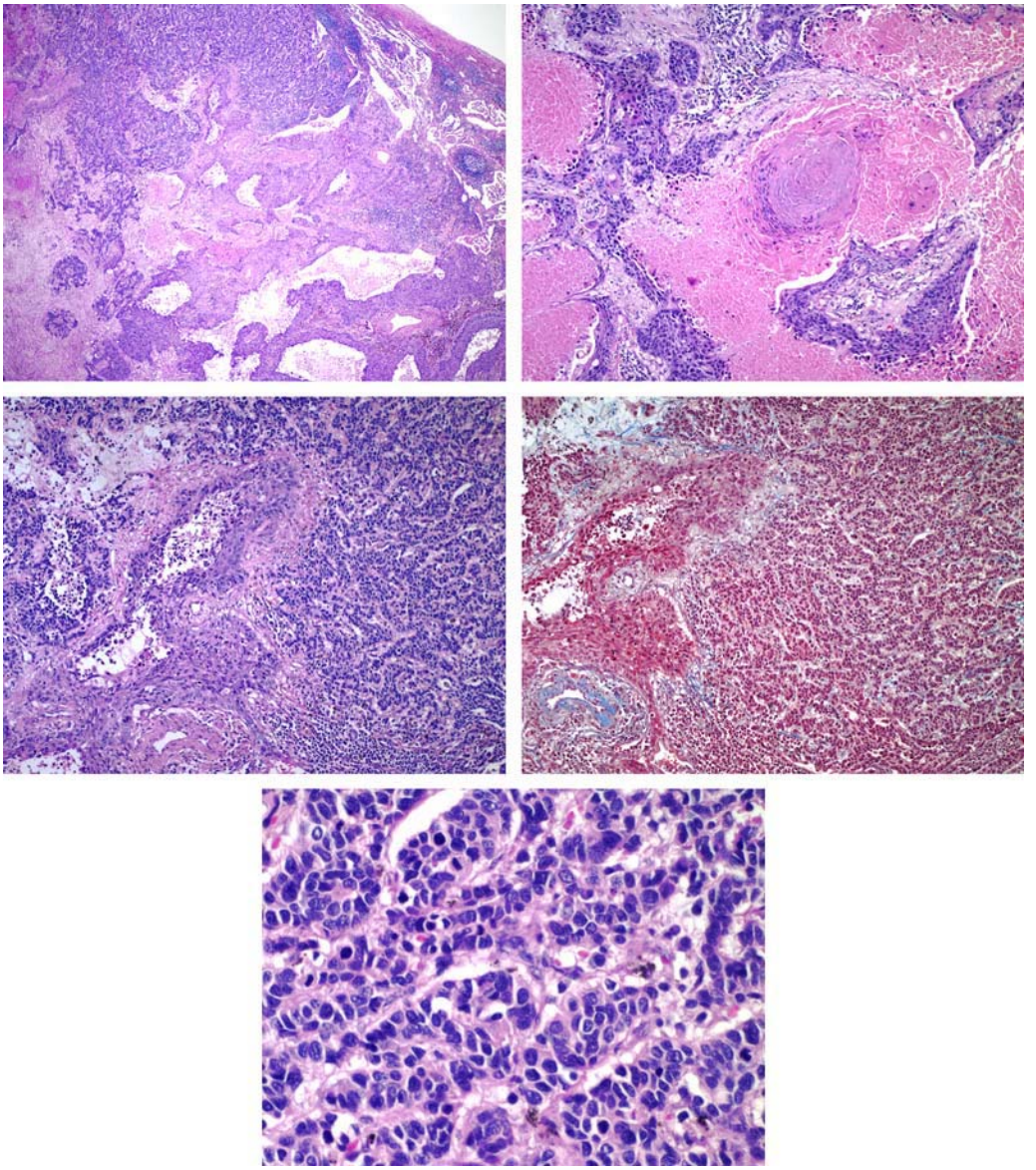
Diagnosis: Lung, wedge excision: Mixed small cell-squamous cell carcinoma.

This nodule has large areas which, by themselves, characterize small cell carcinoma and other areas which, by themselves, characterize squamous cell carcinoma. I make a diagnosis in general of a mixed carcinoma when I do not have to search more than a few seconds for the two components of the mixture (trichrome stain), and this case satisfies that criteria. I make a diagnosis of squamous cell carcinoma with focal neuroendocrine differentiation, as an example, when someone has already screened the case and has to point the minor focus out to me.

Criteria of the World Health Organization are morphologic categories, and do not necessarily take into account expected prognosis or treatment. In the area of mixed tumors with a component of small cell carcinoma, very little is known about the biologic behavior. It has been my experience that oncologists feel more at ease in handling small cell carcinomas than other forms of carcinoma because the standards in chemotherapy are better defined. They tend to default toward the small cell carcinoma when there is a mixture. On the other hand, stage is important in small cell carcinoma as in other carcinomas, and there is evidence that a stage I small cell carcinoma that has been resected does not necessarily need chemotherapy. The area is a confusing one from a clinical standpoint.

Thank you for referring this case in consultation. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6571 (Chapter 9 – Lung Tumors)

Case 7115

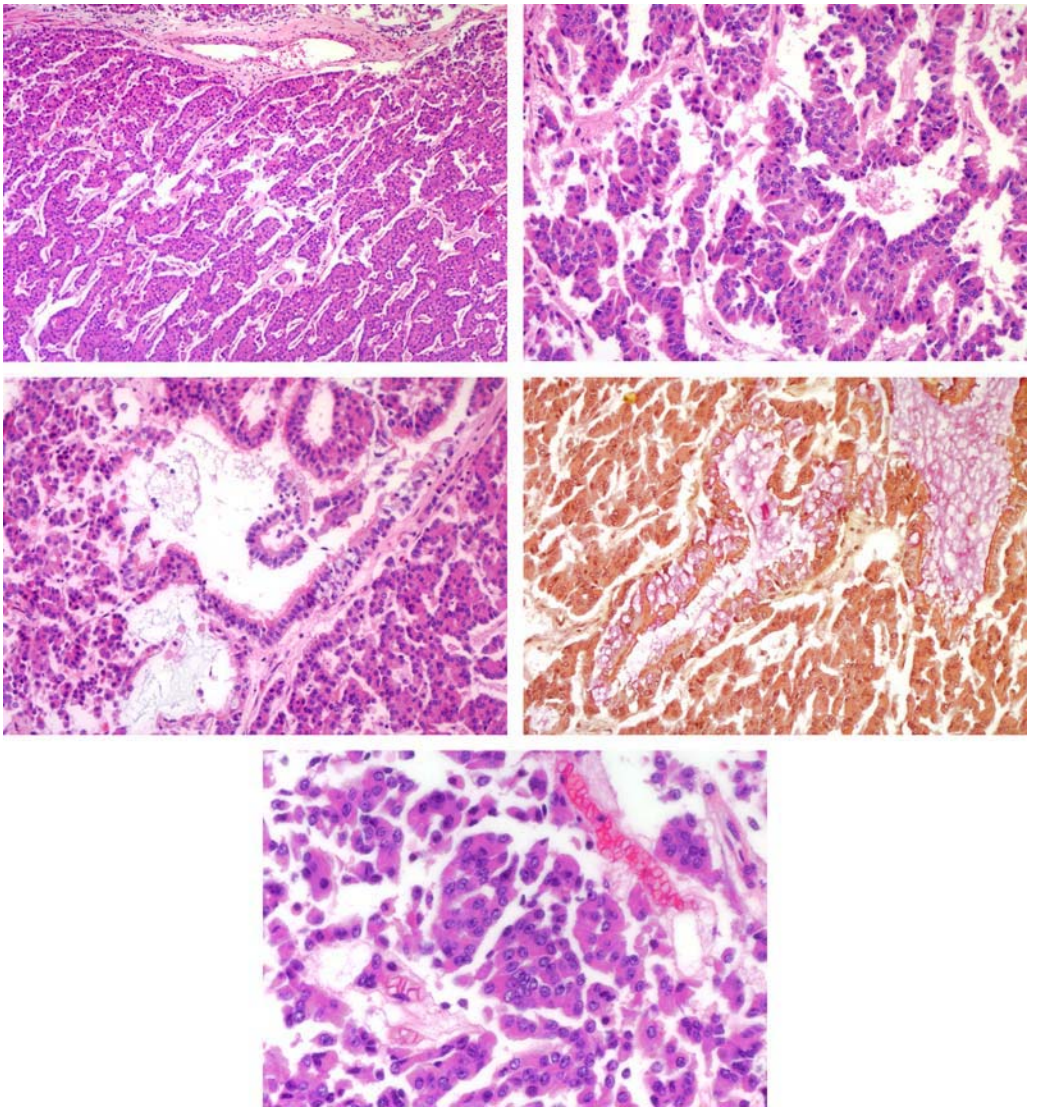
Diagnosis: Bronchial tumor, expectorated: Carcinoid tumor.

Cells of the neoplasm have relatively regular nuclei with salt-and-pepper chromatin and abundant granular eosinophilic cytoplasm. The tumor cells grow in trabeculae and form a few rosettes. A rich vascular network is present within the tumor, and this is commonly observed in carcinoid tumors. Features of atypicality (mitosis, necrosis, nuclear pleomorphism) are absent. Ciliated and mucinous (mucicarmine stain) epithelial cells are entrapped within the tumor.

Occasionally carcinoid tumors in the bronchus grow on long stalks, or more commonly, they form endobronchial masses. I have encountered other types of expectorated tumors but not previously an expectorated piece of a carcinoid tumor.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7115 (Chapter 9 – Lung Tumors)

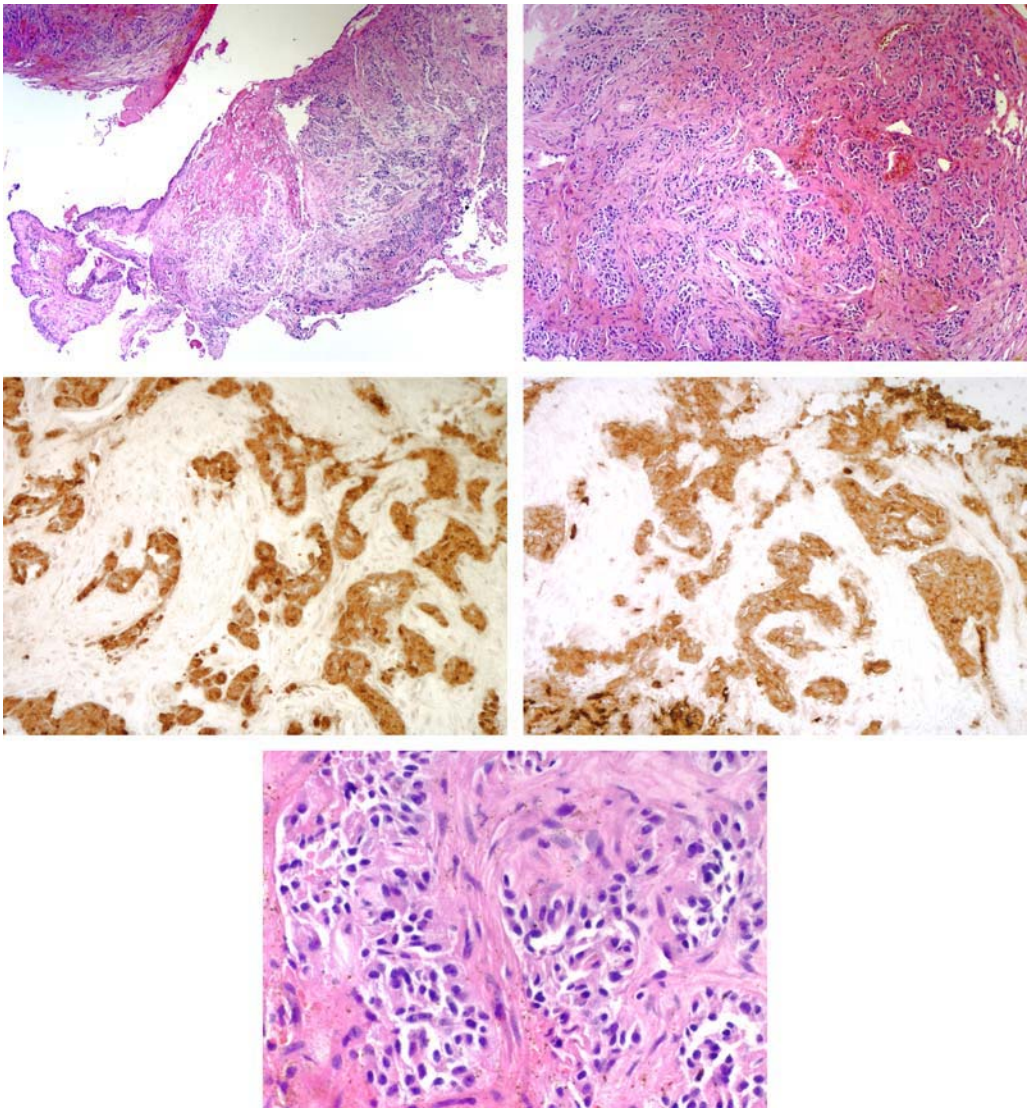
Case 6673

Diagnosis: Bronchus, biopsy: Carcinoid tumor.

Nests of small irregular epithelial cells have clear or granular cytoplasm. There is prominent vascular proliferation associated with the proliferating epithelial cells. My differential diagnosis on the routinely stained slide is carcinoid tumor vs metastatic well differentiated adenocarcinoma. I obtained several special studies. Intracellular mucin is not present on alcian blue or mucicarmine stains. The malignant cells stain for keratin, neuron-specific enolase, and synaptophysin. The malignant cells also stain for carcinoembryonic antigen. The malignant cells do not stain for prostatic acid phosphatase or prostate specific antigen. These results indicate a neuroendocrine tumor and corroborate the diagnosis of carcinoid tumors. Features of atypicality in carcinoid tumor (necrosis, mitoses, nuclear pleomorphism) are not present in this small specimen.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6673 (Chapter 9 – Lung Tumors)

Case 6652

Diagnosis: Lung, wedge resection: Carcinoid tumor, with melanin-containing cells.

Overall this carcinoid tumor has typical features, including organoid appearance and regular nuclei with finely dispersed chromatin. Criteria for atypicality are not present. The tumor cells stain distinctively for chromogranin on your slides. There is more diffuse staining for S-100 antigen. Some of the staining probably represents high-background, but some of the cells contain distinct granules, and a few cells are packed with granules. This correlates with the presence of rare melanin-containing cells, which I find best in block D. I reviewed the literature on melanin-containing carcinoid tumors and find that such tumors may stain positively for S-100 antigen. Some of these S-100 positive cells are felt to be sustenatacular cells and therefore of neural derivation. In other cases, oncocytic cells contain the melanin, and I believe your case better fits into this category. At their most dense accumulation, melanin-stuffed cells here comprise only about one cell in a thousand, but I suspect that a larger number contain melanosomes ultrastructurally. The biologic behavior of melanin-containing carcinoid tumors in the lung is no different from other pulmonary carcinoid tumors.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. Your immunopathological studies are hereby returned. If you would like me to send along the dotted melanin-containing cells, please let me know.

Sincerely yours,
Eugene J. Mark, M.D.

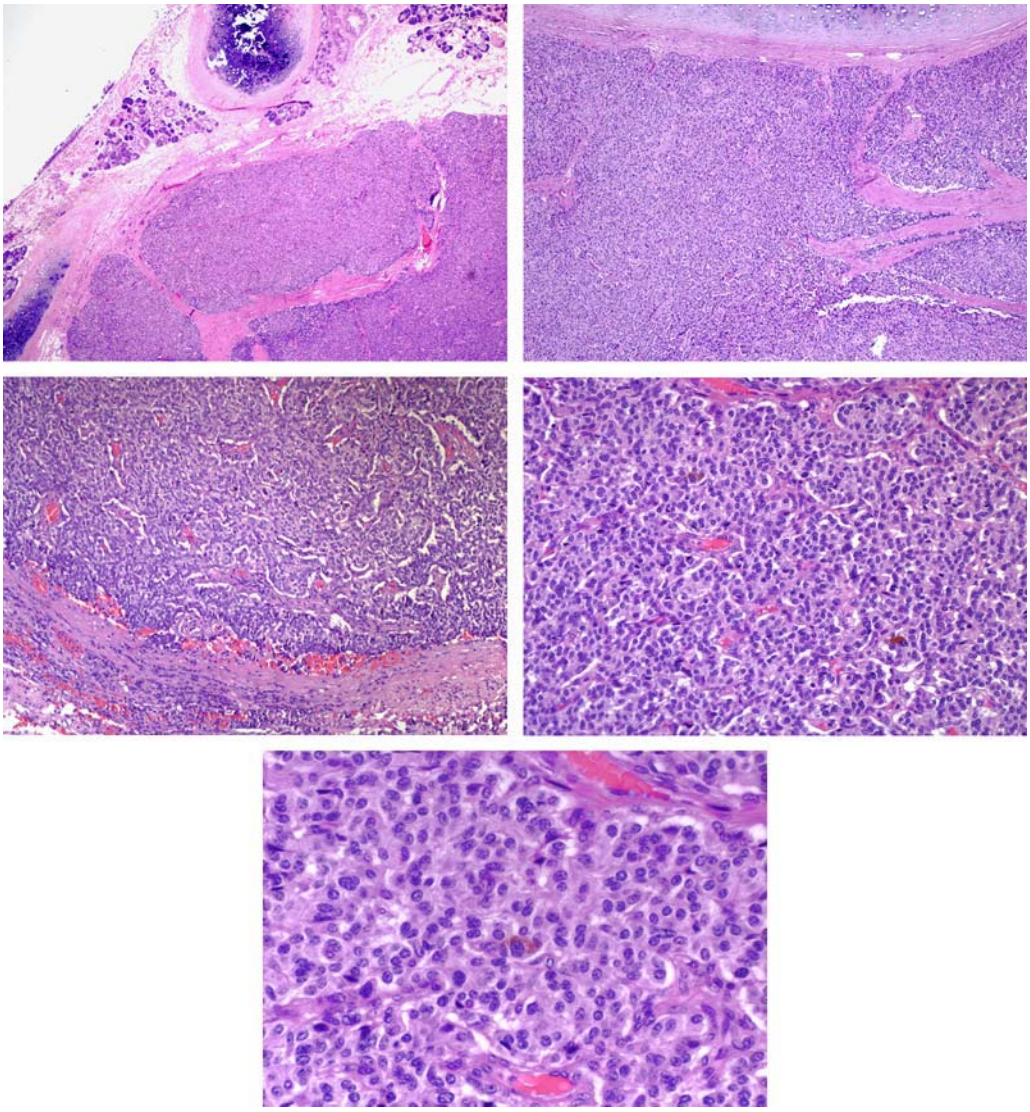
References:

Gal AA, Koss MN, Hochholzer L, DeRose PE, Cohen C. Pigmented pulmonary carcinoid tumor. An immunohistochemical and ultrastructural study. Arch Pathol Lab Med 1993;117:832–836.

Fukuda T, Kobayashi H, Kamishima T et al. Case Report. Peripheral carcinoid tumor of the lung with focal melanin production. Pathol Internat 1994;44:309–316.

Barbareschi M, Frigo B, Mosca L, et al. Bronchial carcinoids with S-100 positive sustenatacular cells. Pathol Res Pract 1990;186:212–217.

Capella C, Gabrielli M, Polak JM, et al. Ultrastructural and histological study of 11 bronchial carcinoids. Virchows Arch Pathol (A) 1979;381:313–329.



Case 6652 (Chapter 9 – Lung Tumors)

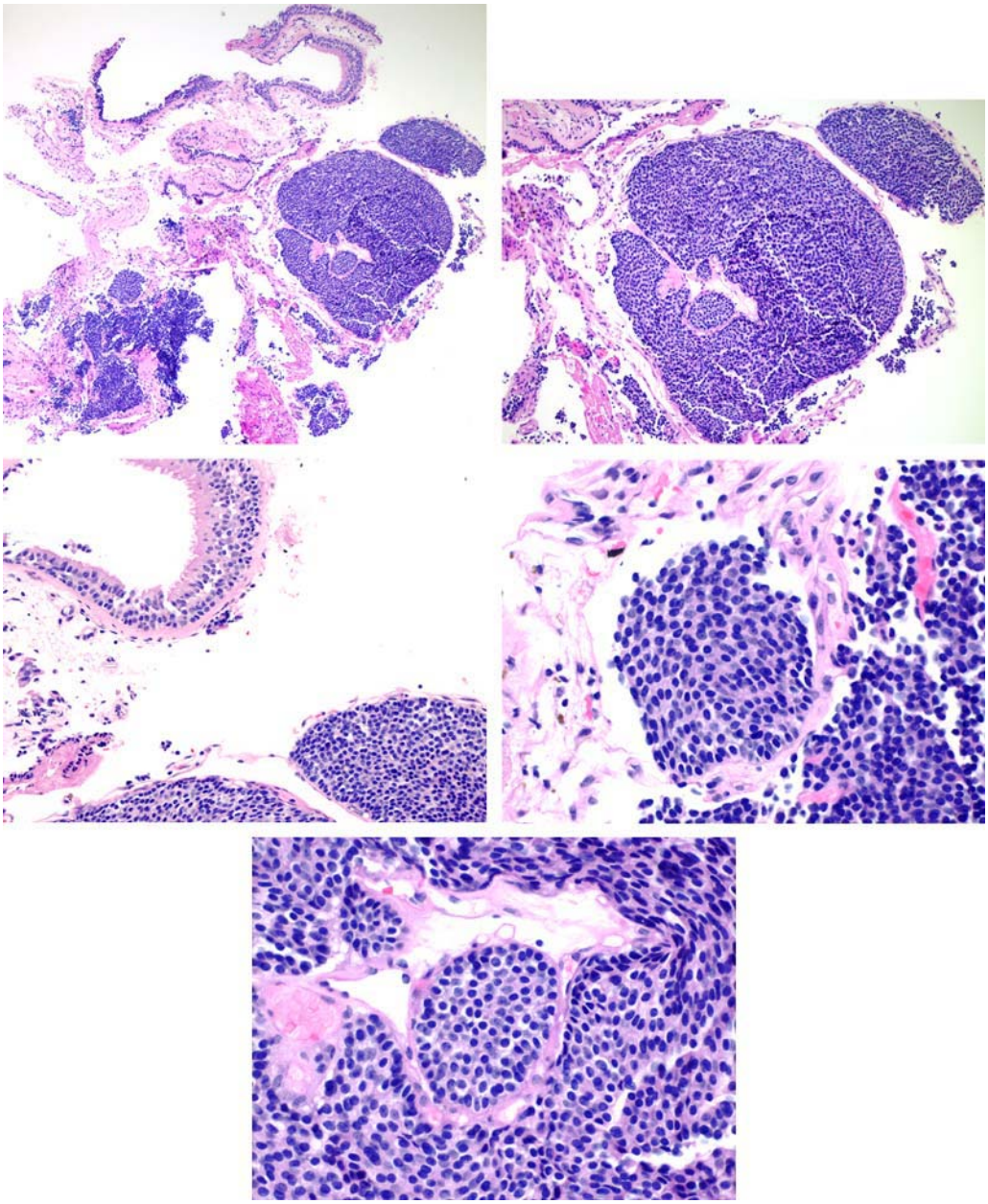
Case 7172

Diagnosis: Bronchus, bronchoscopic biopsy: Cellular epithelial tumor, ? carcinoid tumor.

Nodules of tumor are composed of cells with regular oval nuclei and syncytial eosinophilic cytoplasm. The nuclei have a salt-and-pepper chromatin pattern as often occurs in carcinoid tumor. This and your positive stains for neuron-specific enolase make me favor this interpretation. However, the staining for other neuroendocrine markers (chromogranin, synaptophysin) is negative, and the staining with neuron-specific enolase is uneven and not sufficient in itself to convince me that this is a neuroendocrine lesion. In the differential diagnosis, we considered a monomorphous adenoma and a metastasis. The marked positivity on staining for keratin is somewhat unusual for carcinoid tumor and means that we cannot absolutely exclude a monomorphic adenoma. I doubt metastasis because there is no cytological evidence of malignancy, but we cannot rule out this possibility.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7172 (Chapter 9 – Lung Tumors)

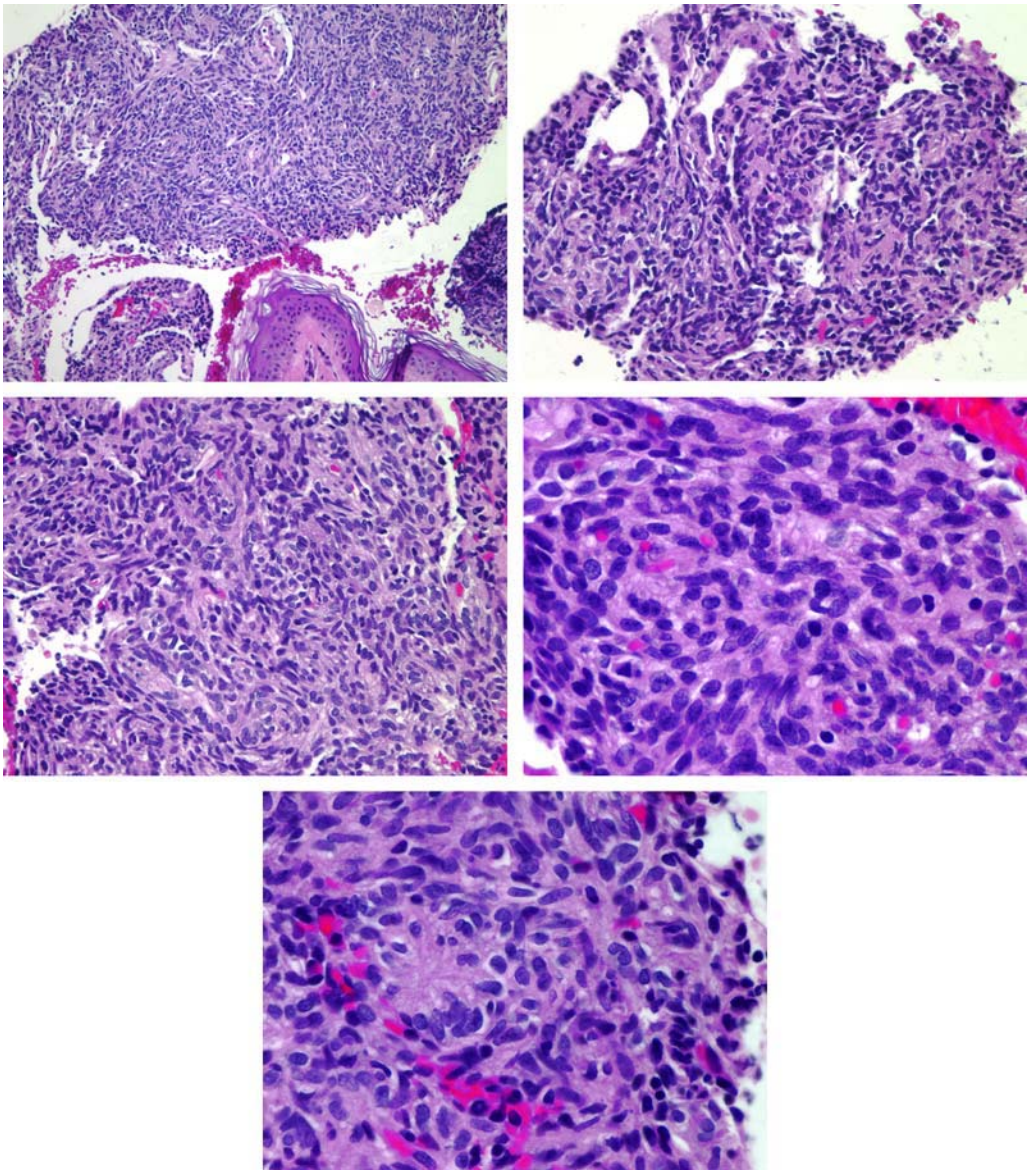
Case 6648

Diagnosis: Lung, needle biopsy: Spindled and epithelioid neoplasm, type undetermined, ? carcinoid tumor, ? metastasis, ? other.

This case is difficult because the immunopathological studies do not confirm what I would have expected as the most probable diagnosis. I favor a carcinoid tumor of a spindle cell type because of a nested appearance and the nuclear features, but the chromogranin stain is negative. The weak keratin staining would fit with carcinoid tumor. Like you, I also thought this could represent a fibrous tumor of the pleura, but the CD34 stain is negative. When I see a tumor in the lung that is not readily explainable, I wonder about metastasis, and in this case, I might consider a uterine stromal sarcoma. Pulmonary thymoma and pulmonary meningioma are other possibilities. I do not favor a synovial sarcoma or pulmonary blastoma, although I cannot exclude these possibilities. If this is a sarcoma, it is low grade.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. I have retained one slide for our permanent teaching collection in pulmonary pathology and hereby return all of the remainder. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6648 (Chapter 9 – Lung Tumors)

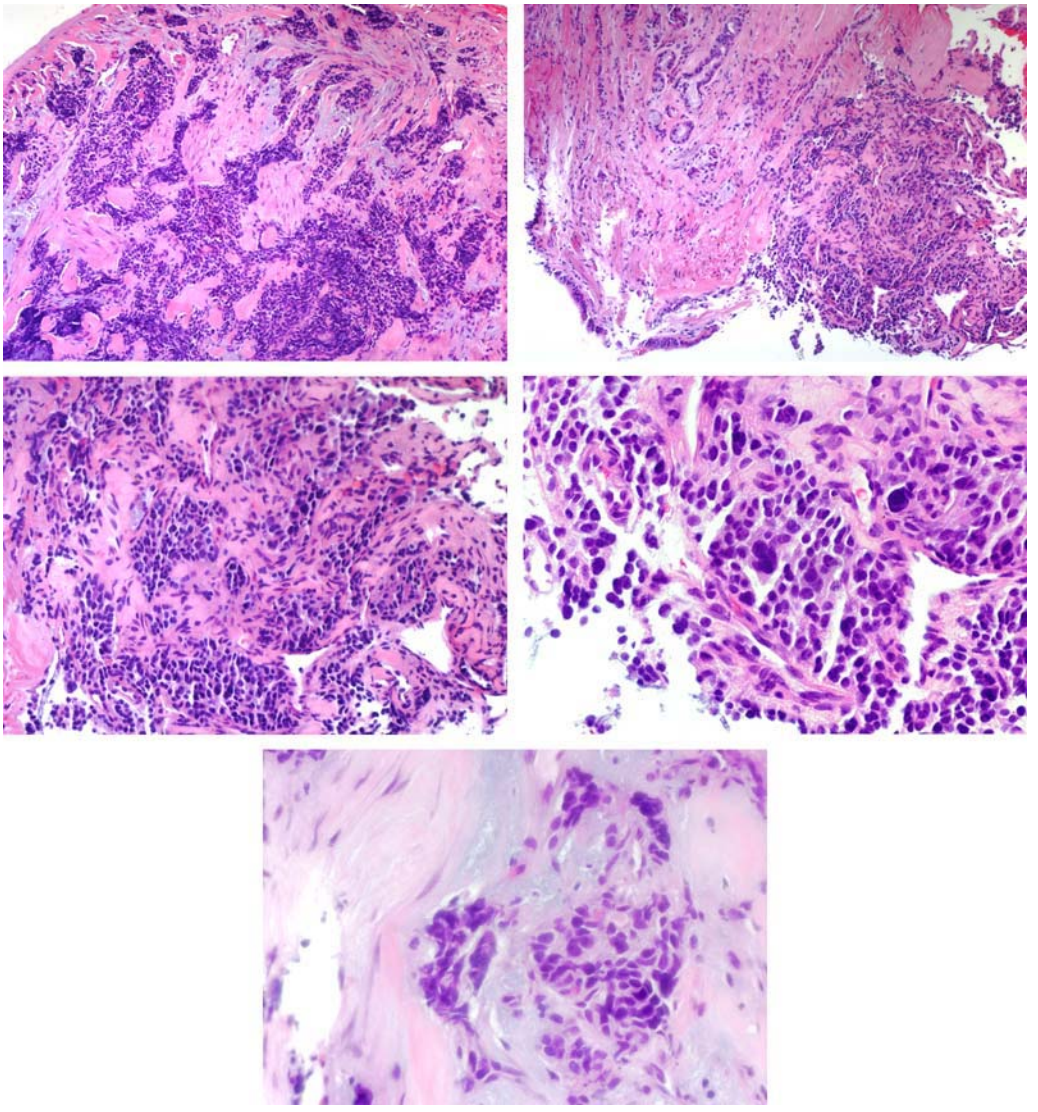
Case 6454

Diagnosis: Bronchus, bronchoscopic biopsy: Neuroendocrine neoplasm, probably carcinoid tumor.

An infiltrative neoplasm of small irregular cells has an organoid pattern as well as infiltration by small groups of cells in the lamina propria. Fibrosis and crush-effect make interpretation difficult. However, I believe the organoid appearance in the absence of necrosis and mitoses is against a small cell carcinoma and more in keeping with a carcinoid tumor. The intense positivity for chromogranin is also in favor of carcinoid tumor and would not be expected in small cell carcinoma in my experience. I do not appreciate mitoses or sufficient nuclear pleomorphism to make me diagnose atypical carcinoid tumor, although I cannot exclude that possibility. However, I favor a carcinoid tumor of the usual type.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6454 (Chapter 9 – Lung Tumors)

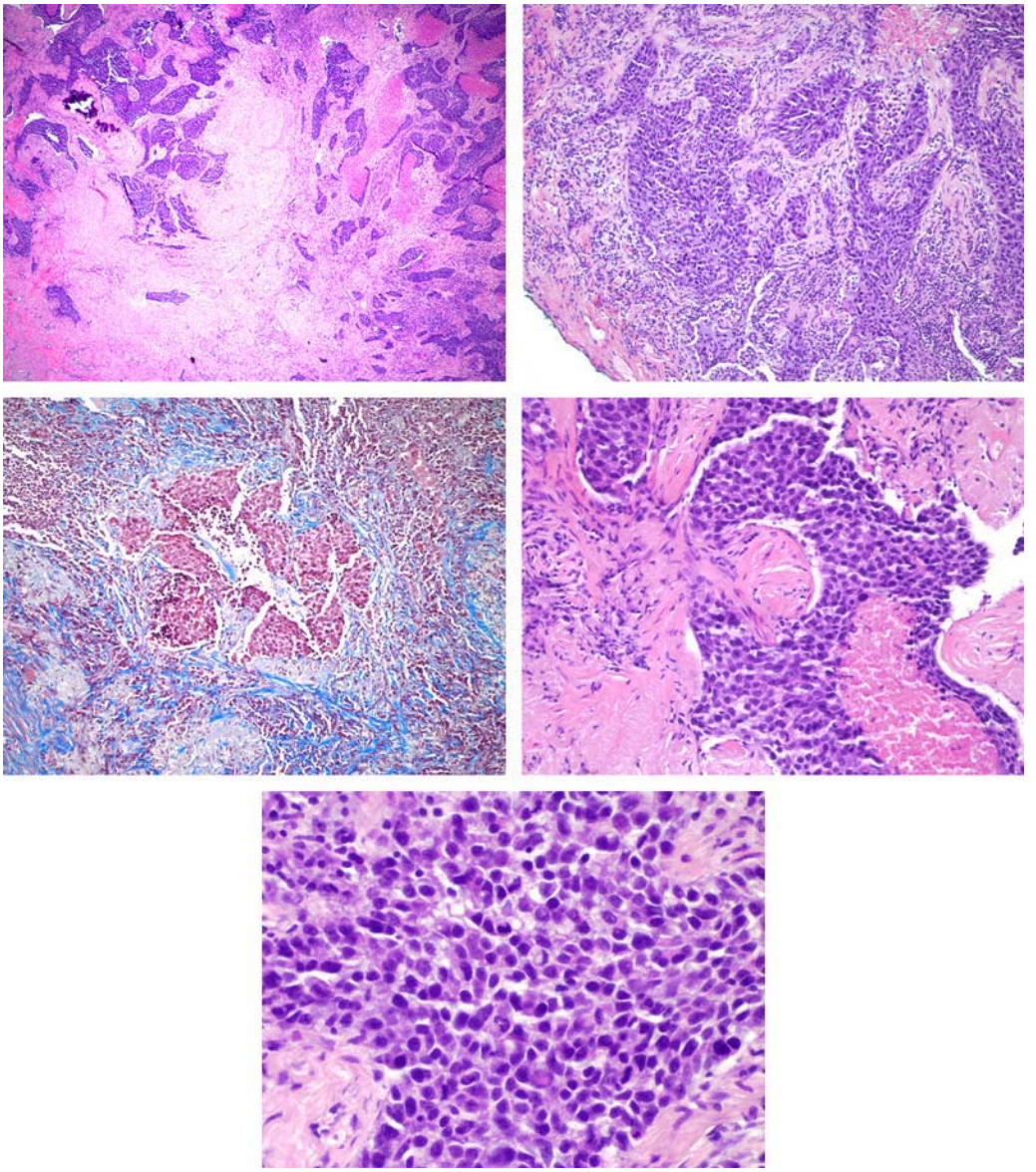
Case 6752

Diagnosis: Lung, wedge resection: Large cell neuroendocrine carcinoma.

This case is difficult because the differential diagnosis includes three entities with disputed boundaries in the literature: 1) markedly atypical carcinoid tumor; 2) small cell carcinoma with mixed population of large cells; 3) large cell neuroendocrine carcinoma. By current standards, the large numbers of mitoses in this case take it out of the category of atypical carcinoid tumor. When faced with the distinction of small cell carcinoma versus large cell neuroendocrine carcinoma, both of presumed neuroendocrine lineage, I favor large cell neuroendocrine carcinoma because of the absence of central necrosis and the presence of nests of tumor producing a mosaic pattern and eliciting desmoplastic fibrosis (trichrome stain). This patient's lesion, being peripheral and possibly completely resected and stage I, should have a sanguine prognosis when compared to that of most patients with large cell neuroendocrine carcinoma of the lung. The neuroendocrine differentiation does not affect prognosis by current standards, but the stage of tumor certainly does.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6752 (Chapter 9 – Lung Tumors)

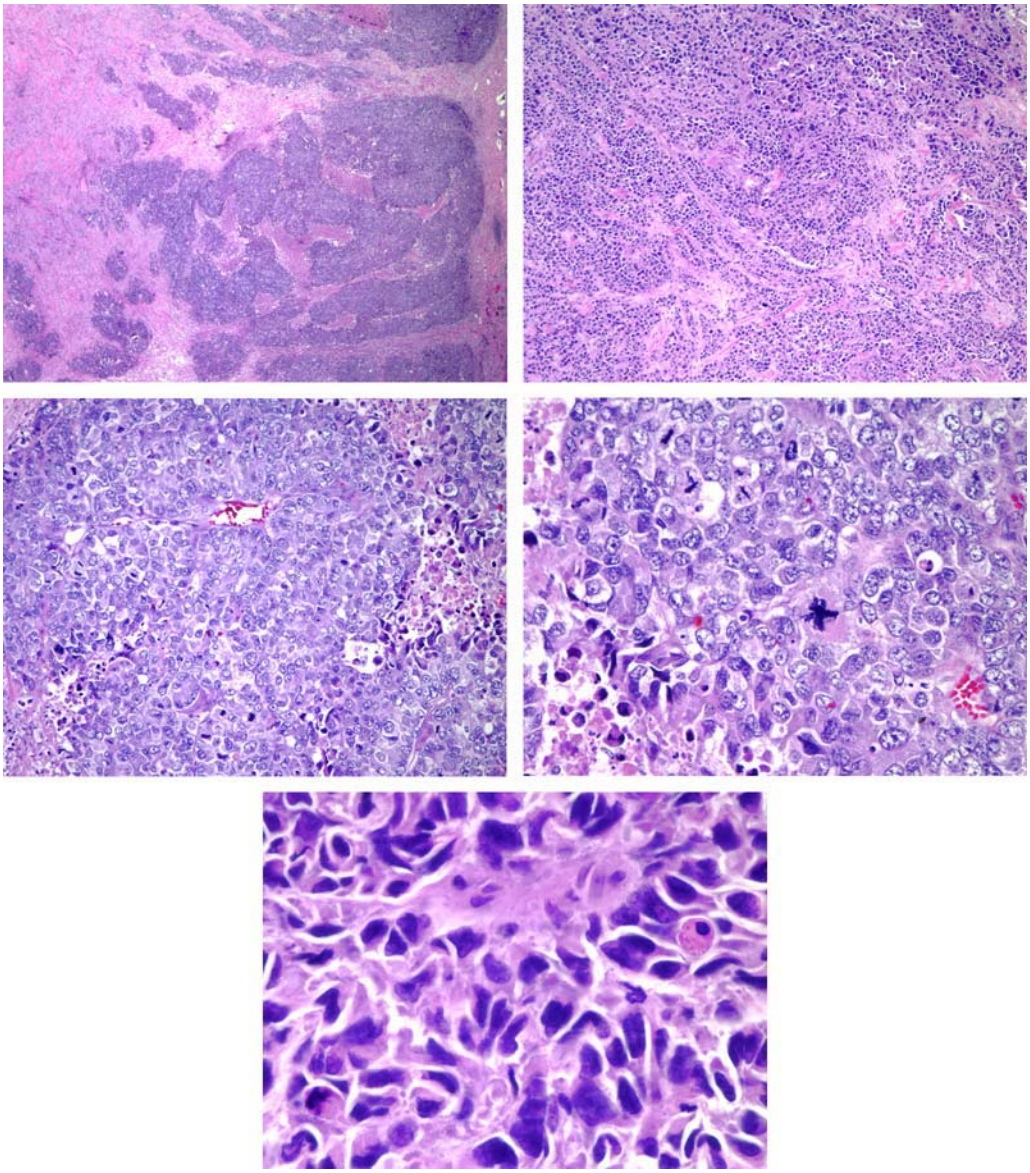
Case 6985

Diagnosis: Lung, lobectomy: Large cell carcinoma, with neuroendocrine differentiation.

This case is difficult because there is an apparent mosaic pattern in a few regions and focal staining for synaptophysin and chromogranin. The latter is consistent with either large cell neuroendocrine carcinoma or large cell carcinoma with neuroendocrine differentiation, as you indicate. Because most of the tumor cells are so anaplastic and because there is predominantly sheet-like growth in most areas, I would classify this as a large cell carcinoma rather than large cell neuroendocrine carcinoma.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6985 (Chapter 9 – Lung Tumors)

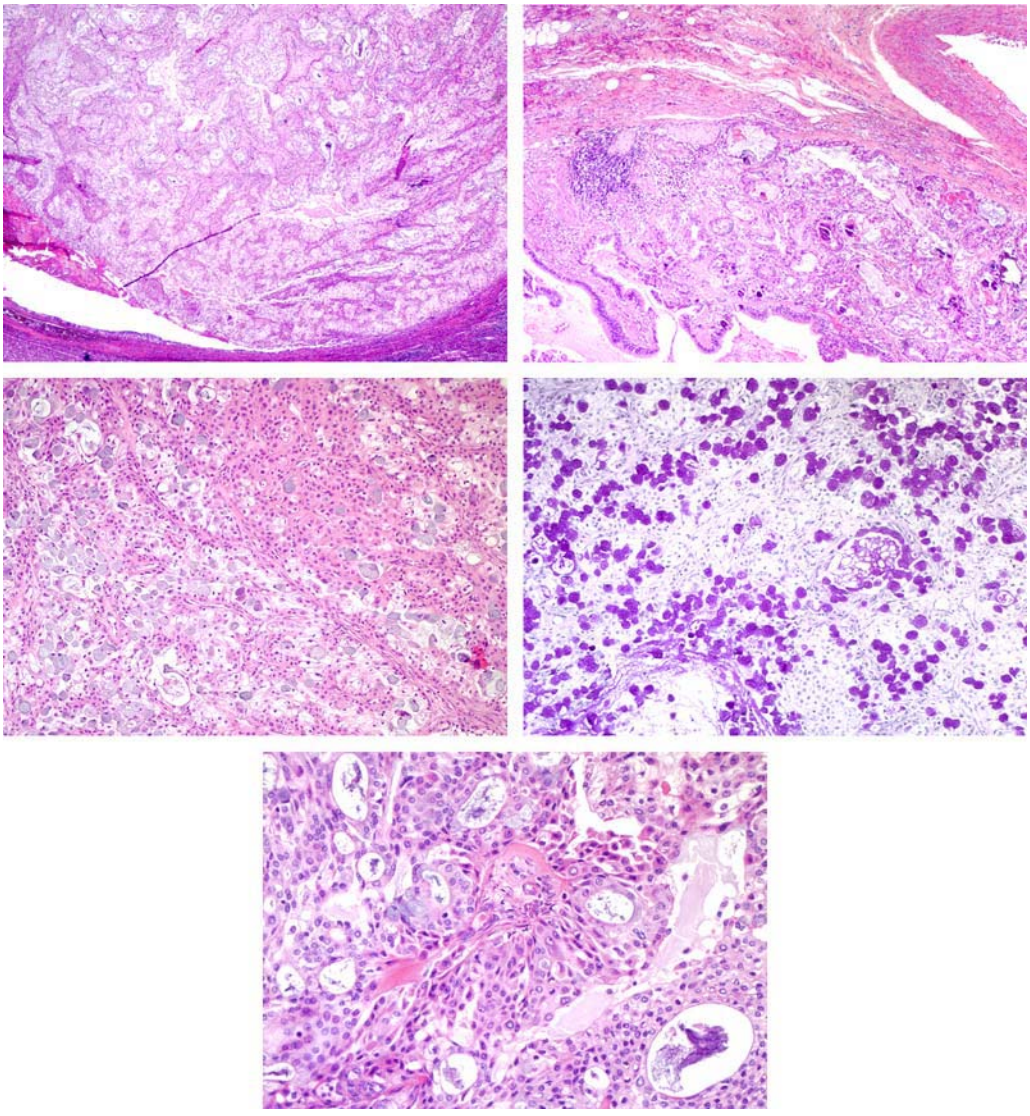
Case 6709

Diagnosis: Lung, wedge resection: Mucoepidermoid carcinoma, grade 2/3.

This intrabronchial tumor is a mucoepidermoid carcinoma by virtue of mucinous areas, squamoid areas, and sheets of transitional cells (cuboidal cells with amphophilic cytoplasm and no distinct keratinization). I would grade the tumor as moderately differentiated (grade 2/3) based on nuclear features of the cells and the sheets of transitional cells (PAS stain). The tumor invades from bronchus into adjacent lung and into fibroadipose tissue and lymphoid tissue near bronchi, where tumor abuts blood vessels and nerves. If there is no definite evidence of tumor at the resection margin, surgeons would not necessarily perform a complete lobectomy and rather follow the patient closely. If there is a question of whether or not tumor is present at the resection margin, the surgeon and pathologist must get together with the specimen and slides and make that determination. There are many causes for seemingly positive resection margins which do not represent true resection margins because of tissue shrinkage or other artifacts. Decision for other modes of therapy must be based on the clinical circumstances with which I am not necessarily familiar in this case, but it is not clear that radiotherapy would be indicated at this time. I do not believe there is a role for chemotherapy at this time.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6709 (Chapter 9 – Lung Tumors)

Case 6531

Diagnosis: Lung, wedge resection:

1. **Sarcomatoid carcinoma.**
2. **Subpleural bulla with histiocytic lining.**
3. **Emphysema.**

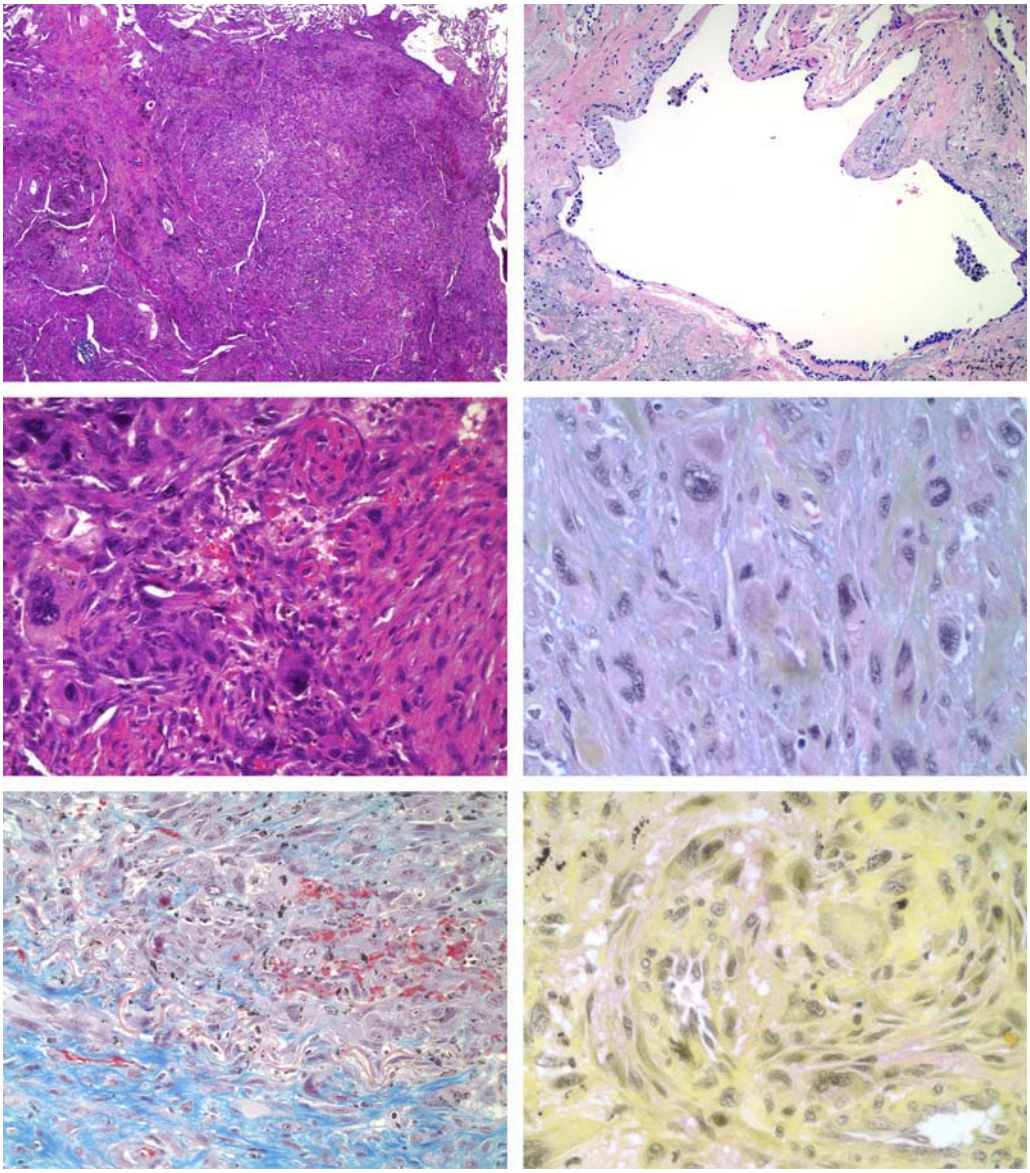
The nodule measuring approx 1 cm in greatest diameter on the slides has anaplastic and hyperchromatic nuclei which suffice for a diagnosis of malignancy. Regions of the tumor have abundant eosinophilic cytoplasm and cytoplasmic membrane sufficient for a diagnosis of large cell carcinoma. There may be intercellular bridges, and I suspect that this is a poorly differentiated squamous cell carcinoma. A Kreyberg stain shows some diffuse cytoplasmic staining for keratin. A mucicarmine stain shows some diffuse cytoplasmic staining for mucin. Regions of spindled cells (trichrome stain) make this a sarcomatoid carcinoma. There is also a bulla with histiocytes lining its wall. Carcinomas can arise in bullae. In this case, the carcinoma seems adjacent to but not within the bulla.

Thank you for referring this case in consultation. This is an elaboration of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Zulueta JJ, Bloom SM, Rozansky MI, White AC. Lung cancer in patients with bullous disease. Am J Respir Crit Care Med 1996;154:519–522.



Case 6531 (Chapter 9 – Lung Tumors)

Case 4407

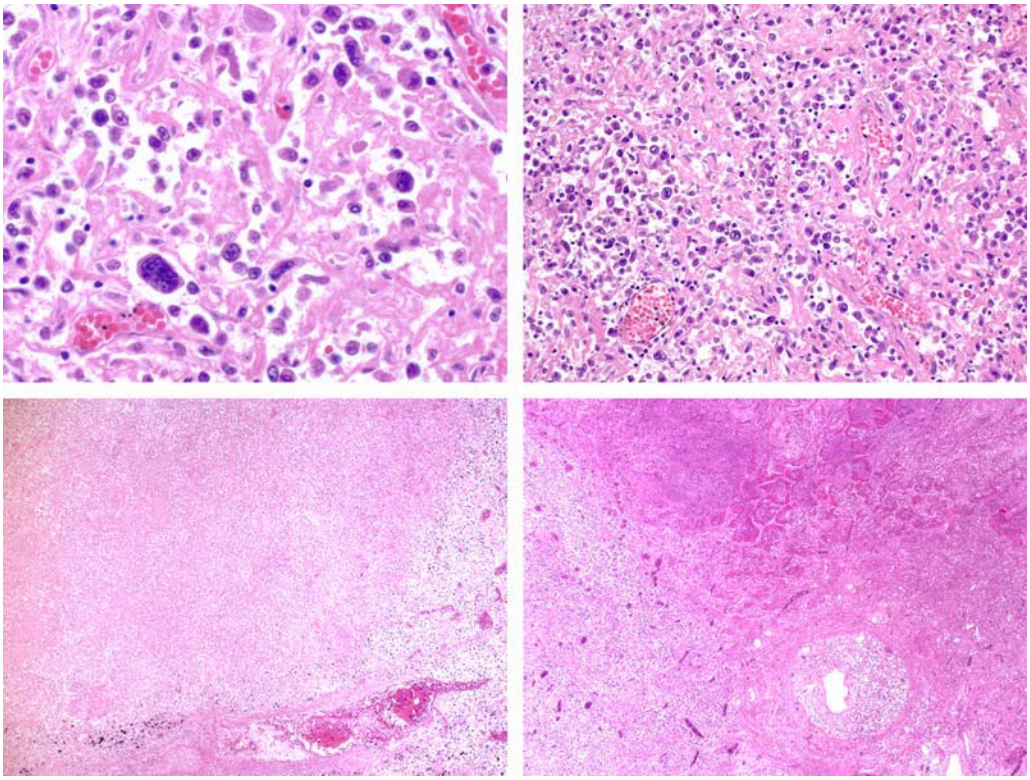
Patient: 70-yr-old male with AIDS and a tumor which is EB virus-positive on immunohistochemistry and *in situ* hybridization.

Diagnosis: Lung, autopsy: Large cell lymphoma (B-cell, associated with AIDS).

The large malignant cells are so pleomorphic that a diagnosis of malignant lymphoma is not intuitively obvious on the sections stained with hematoxylin and eosin. However, the dyshesiveness of the cells and the history of AIDS comport with a diagnosis of lymphoma. There is extensive necrosis, and I detect no organisms. Two recent papers at the International Academy of Pathology meeting in San Francisco describe the prevelance of Ebstein-Barr virus in malignant lymphomas of lymphomatoid granulomatosis type. I do not know the significance of the EBV in this case of AIDS. We have seen this form of large cell lymphoma particularly in the brain in patients dying with AIDS.

Thank you for sharing this case with me and allowing me to add it to our permanent teaching collection in pulmonary pathology. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 4407 (Chapter 9 – Lung Tumors)

Case 6640

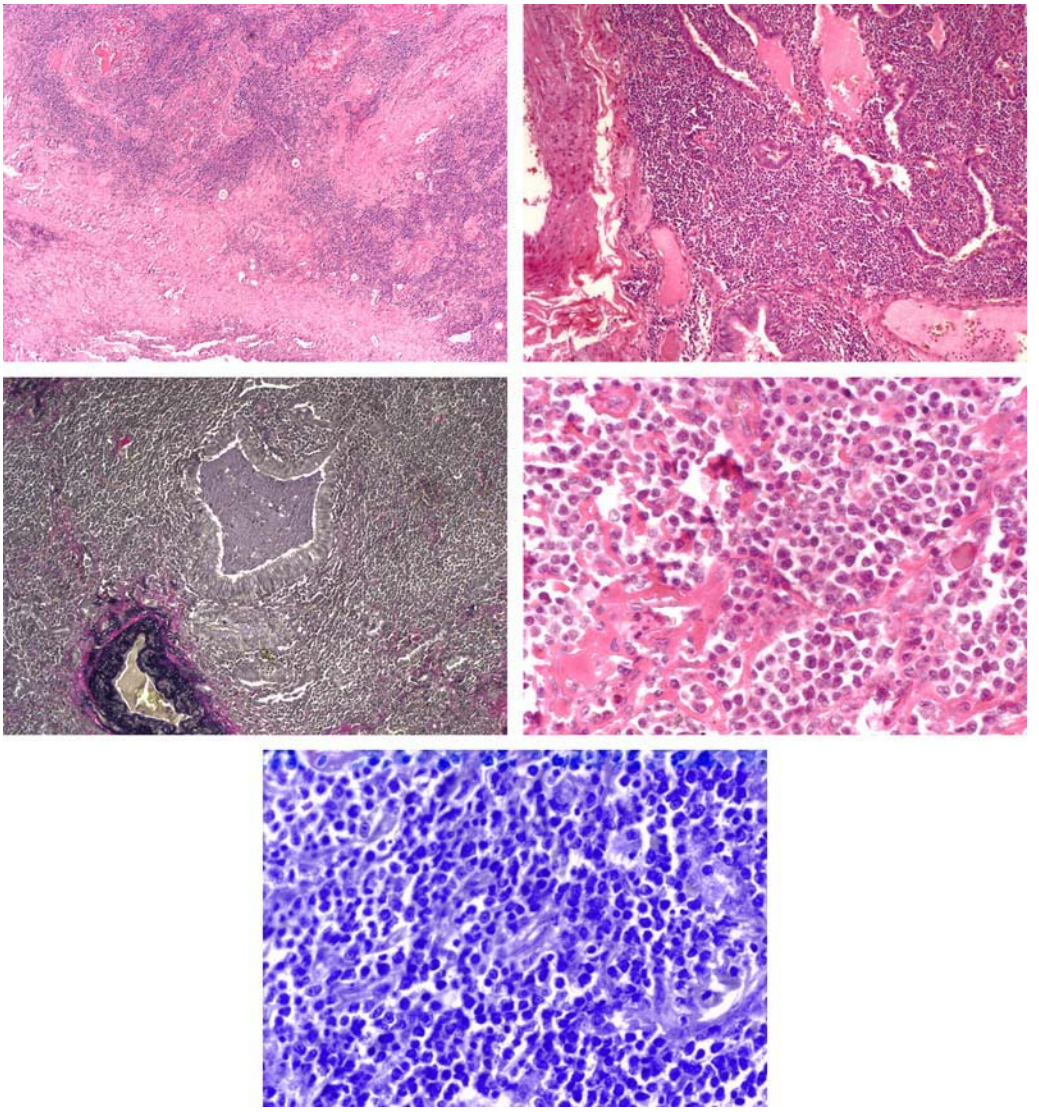
Diagnosis: Lung, open biopsy: Malignant lymphoma, B-cell, low-grade, lymphoplasmacytic type.

This lymphoid proliferation is malignant by virtue of quantity and disruption of dense connective tissue plains by the lymphoid cells. On the other hand, the process is low grade (Giemsa stain) by the slight degree of nuclear atypicality. There is a preponderance of plasma cells, many of which contain Dutcher bodies. The malignant lymphoma is of B-cell type based on this appearance as well as on the staining for B-cells (L26), although many T cells are also present on staining (CD3). Light chain restriction is difficult to demonstrate in tissue embedded in paraffin, but I interpret the lambda staining as positive and the kappa as negative despite background staining. The histology is also consistent with a malignant lymphoma of mucosa associated lymphoid tissue (MALToma), which is a low grade B-cell lymphoma. A diagnosis of lymphoplasmacytic lymphoma implies systemic disease with involvement of bone marrow and serum protein abnormalities, whereas a MALToma tends to be confined to the site of origin, which in this case would be the lung.

This malignant lymphoma is not lymphomatoid granulomatosis because it is not angiocentric or bronchiolocentric (elastic stain); nor does it have the varied population of cells, including at least a few large atypical cells.

Thank you for referring this case in consultation. This case has also been reviewed by a member of our hematopathology section, and she essentially concurs with the above. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6640 (Chapter 9 – Lung Tumors)

Case 4425

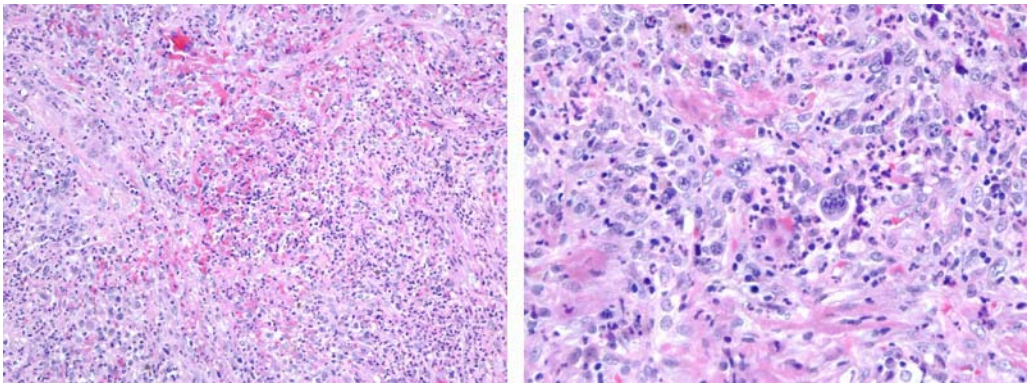
Diagnosis: Lung, open biopsy: Large cell lymphoma, high grade, T-cell subtype.

The cellular tumor is composed of mononuclear cells with pleomorphic nuclei admixed with neutrophils and fibroblasts. The neoplasm is multifocal. Necrosis is present. Cohesive nests characteristic of carcinoma are not evident. Occasional multinucleated cells appear. The histology on the H&E sections indicates a large cell lymphoma of a high grade of malignancy.

I performed immunopathological studies on the tissue in paraffin which you provided. The malignant lymphoid cells stain positive for a T-cell marker (CD45 RO) and negative for a general lymphoid marker (LCA), epithelial cells (keratin), B-cell marker (L26, CD45 RA), histiocytes (CD68), and myeloid cells (LeuM1). This confirms your impression that this is a T-cell lymphoma.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 4425 (Chapter 9 – Lung Tumors)

Case 6530

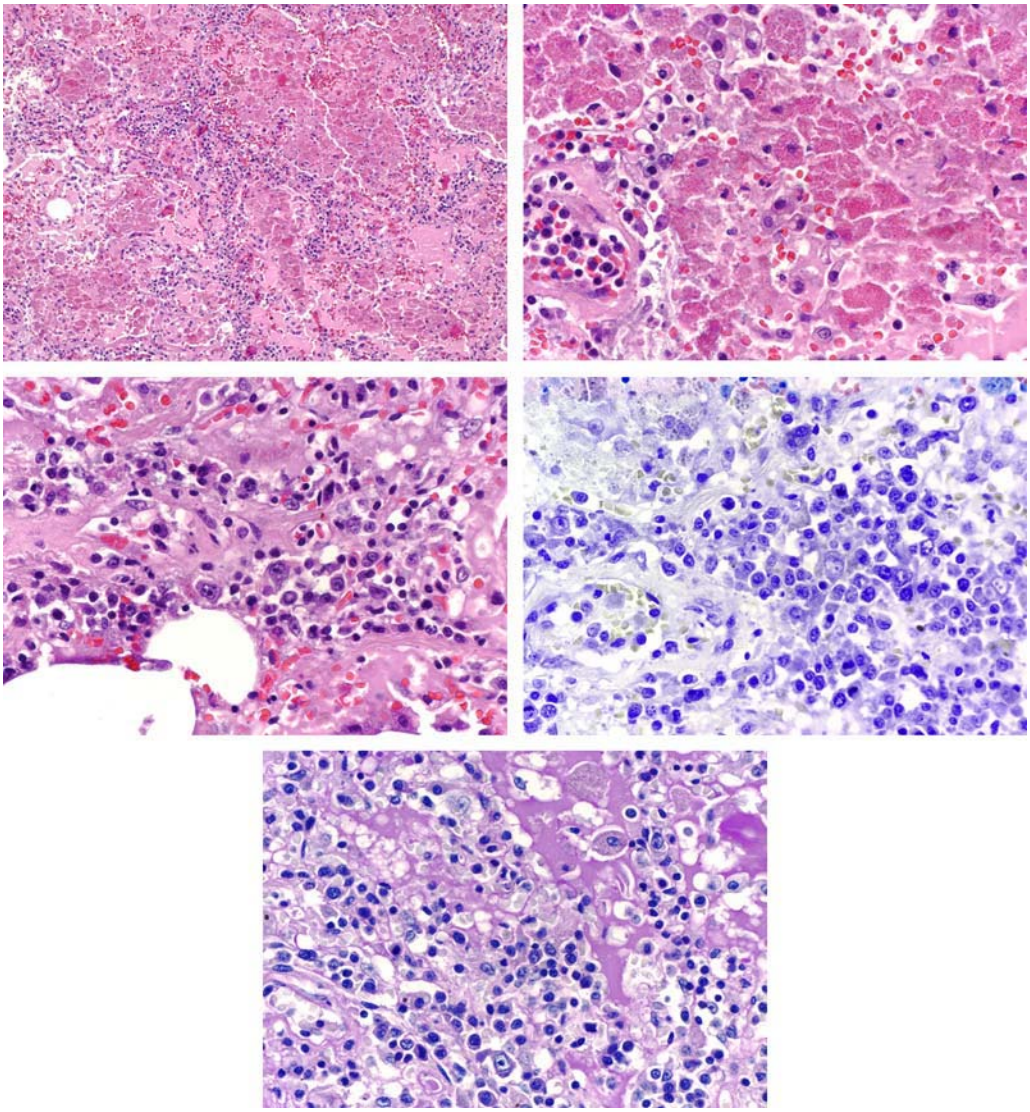
Diagnosis: Lung, autopsy:

1. **Lymphoplasmacytic lymphoma, with extensive intravascular (Giemsa stain) and interstitial lymphoma.**
2. **Organizing fibrin and protein, consistent with immunoglobulins in alveoli.**

The character of the flocculent and granular eosinophilic material in the alveoli is unusual. Some of the material appears to be flocculent fibrin. There probably are immunoglobulins as well, as you suggest. The material does not have the characteristic glassy appearance of pulmonary alveolar proteinosis, and I do not favor that diagnosis. The eosinophilic material is associated in some areas with edema (PAS stain) and is not associated with lipid crystals, other reasons against a diagnosis of lipoproteinosis. The material has characteristics that I associate with macroglobulins as seen in vessels in the kidneys or skin. The changes are distinctive. Globules of the presumed immunoglobulins lie in cytoplasm of histiocytes as well as in alveolar spaces. Ultrastructural analysis could also be performed to exclude lipoproteinosis. I would anticipate an absence of whorled myelin figures. I stained slides for organisms and find none.

Thank you for referring this case in consultation. It will be instructive for our teaching program. Please send along additional cases as you desire. I hope to meet you at a meeting sometime in the future. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6530 (Chapter 9 – Lung Tumors)

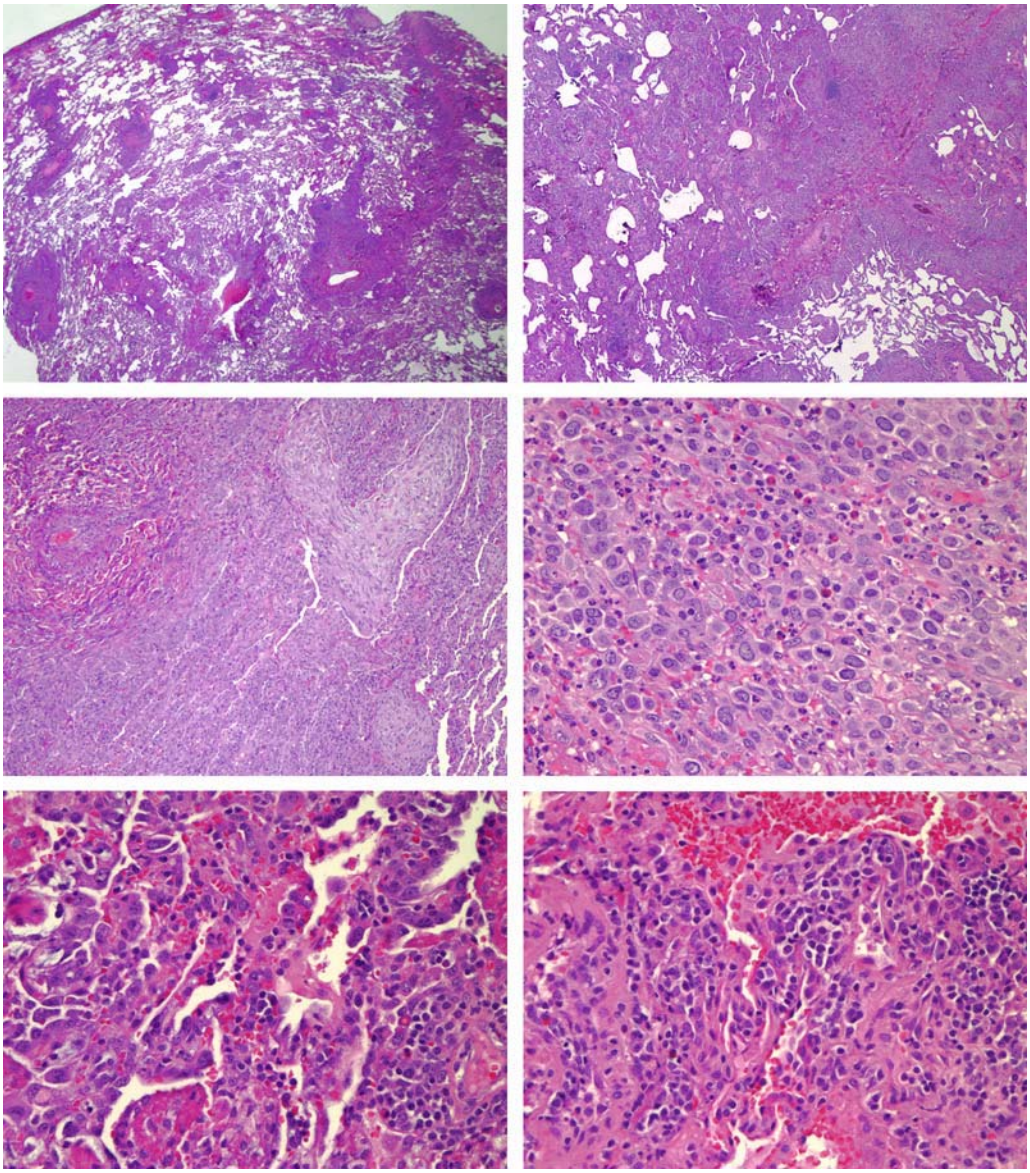
Case 6469

Diagnosis: Lung, open biopsy: Malignant tumor with eosinophils, ? malignant lymphoma, ? undifferentiated carcinoma.

This case is difficult and has been reviewed by other members of our department. The history of prior Hodgkin's disease and the eosinophils raised the possibility of Hodgkin's disease or high-grade non-Hodgkin's lymphoma. We have subsequently reviewed the prior lymph node biopsy and concur with the diagnosis of Hodgkin's lymphoma. I feel that the disease in the lung is similar to that in the lymph node. Our chief hematopathologist feels the processes are different and is concerned about an epithelioid malignancy. Your special studies do not settle the issue. I performed many additional immunopathological studies on the block which you provided, but the remaining tissue in the block proves to have only scattered tumor cells, which are insufficient for interpretation. I favor a malignant lymphoma but cannot make a definite diagnosis beyond malignancy. Electron microscopy would be the most direct route to establishing the nature of the malignancy in this case.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6469 (Chapter 9 – Lung Tumors)

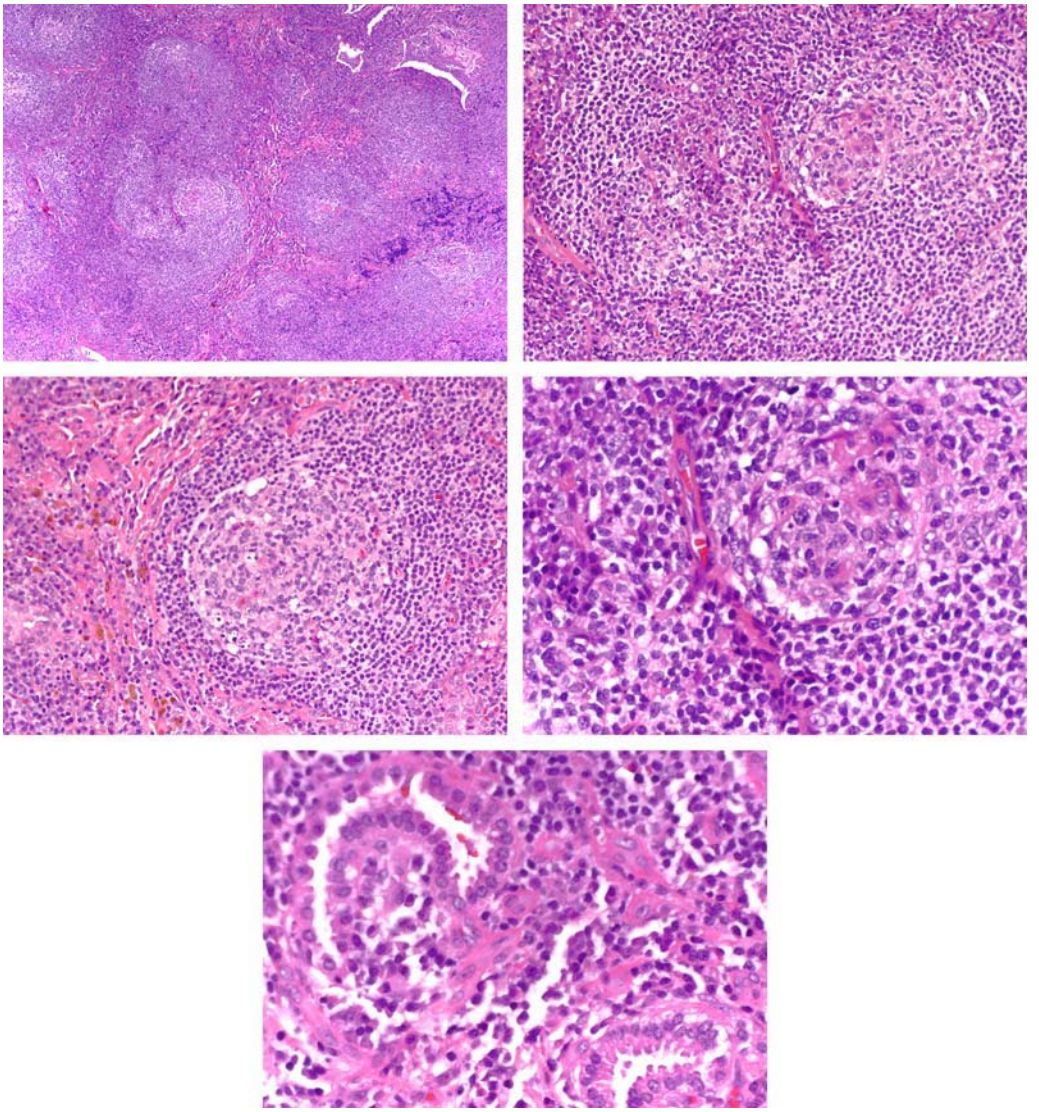
Case 6645

Diagnosis: Lung, wedge resection: Lymphoproliferative disorder, ? low-grade malignant lymphoma of mucosa-associated lymphoid tissue, with follicular hyperplasia.

This nodule consists of a lymphoid proliferation with prominent follicular architecture. The magnitude of the infiltrate and the cellularity with a relatively small component of sclerosis make me believe this is a lymphoproliferative process rather than an inflammatory pseudotumor. Without the reported results, I probably would have diagnosed a MALToma. The marker studies do not show light chain restriction, but this restriction can only be reliably found in plasma cells in fixed tissue and generally requires frozen tissue for its demonstration in lymphocytes. The prominent follicles are not typical of a MALToma. On the other hand, there are regions with centroblast-like cells mimicking follicle centers. One can see florid follicular hyperplasia of this sort with Sjogren's syndrome and other autoimmune processes. Based on the magnitude of the infiltrate, I believe this will either eventuate into a MALToma or is a MALToma. If frozen tissue becomes available in the future, other marker studies could be performed.

Thank you for referring this case in consultation. Our hematopathology unit has also reviewed the case and essentially concurs with the above. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6645 (Chapter 9 – Lung Tumors)

Case 6649

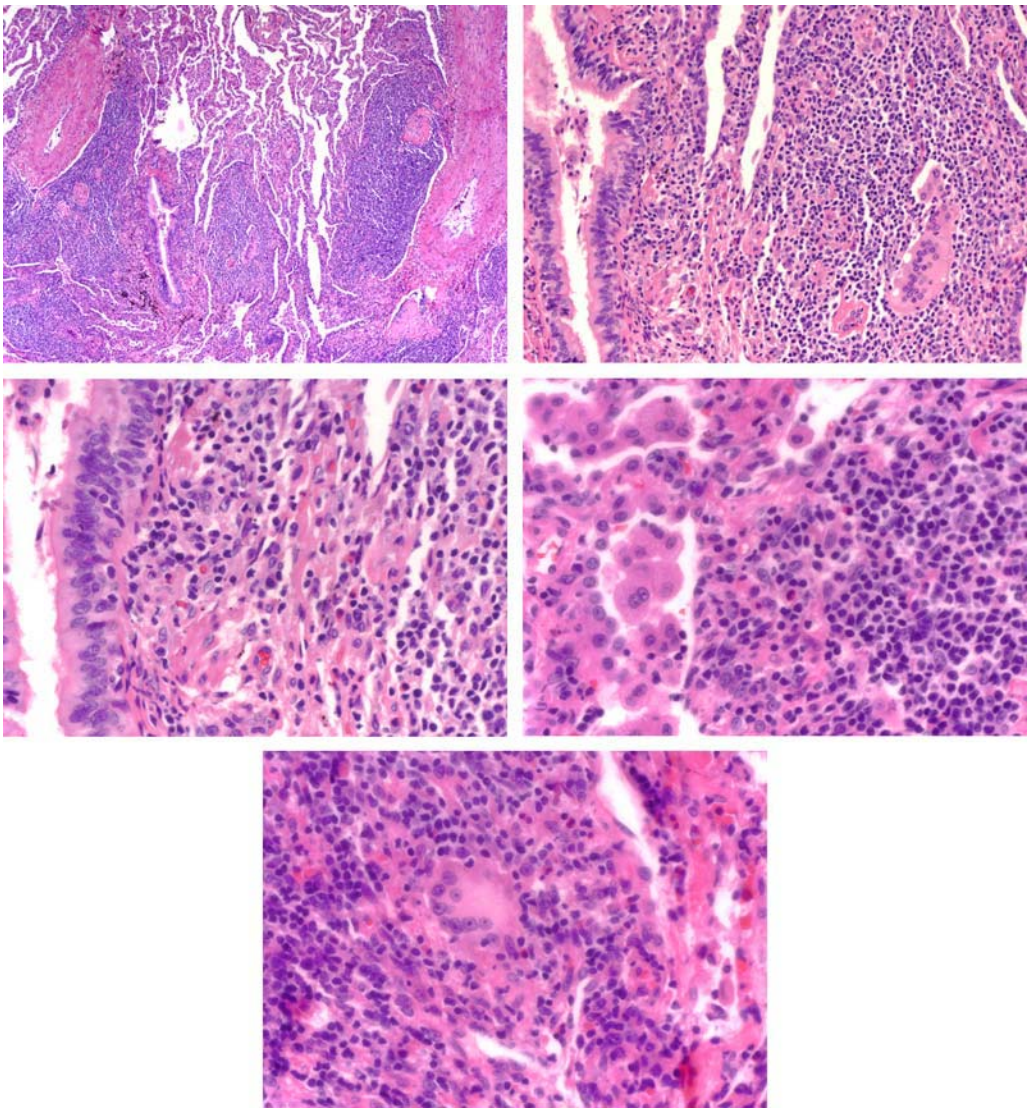
Diagnosis: Lung, open biopsy: Lymphoid proliferation, principally perivascular and peribronchiolar, nondiagnostic, ? low-grade malignant lymphoma, ? follicular bronchiolitis.

A lymphoid proliferation encircles small arteries and bronchioles. Cellular atypia is not present, and for this reason, as well as for the lack of angioinvasion, I do not believe this is a malignant lymphoma of lymphomatoid granulomatosis type, even of low grade. I am suspicious, however, that this is a malignant lymphoma of small B-lymphocytes of low grade. Restriction of light chains would not be expected to be demonstrable in this paraffin embedded tissue because the cells are principally lymphocytes rather than plasma cells. Light chain restriction could be performed if frozen tissue is or becomes available.

In a general sense, this does qualify as the older designation of lymphocytic interstitial pneumonitis, although in this case, the process is more peribronchiolar than diffuse and interstitial. The differential diagnosis principally would be that of follicular bronchiolitis. There is a small neutrophilic infiltrate and an organizing fibrinous pleuritis but no significant bronchiolectasia. I do not favor this interpretation, and I cannot exclude a reactive process, but I suspect that the patient will have slowly progressive disease.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6649 (Chapter 9 – Lung Tumors)

Case 6939

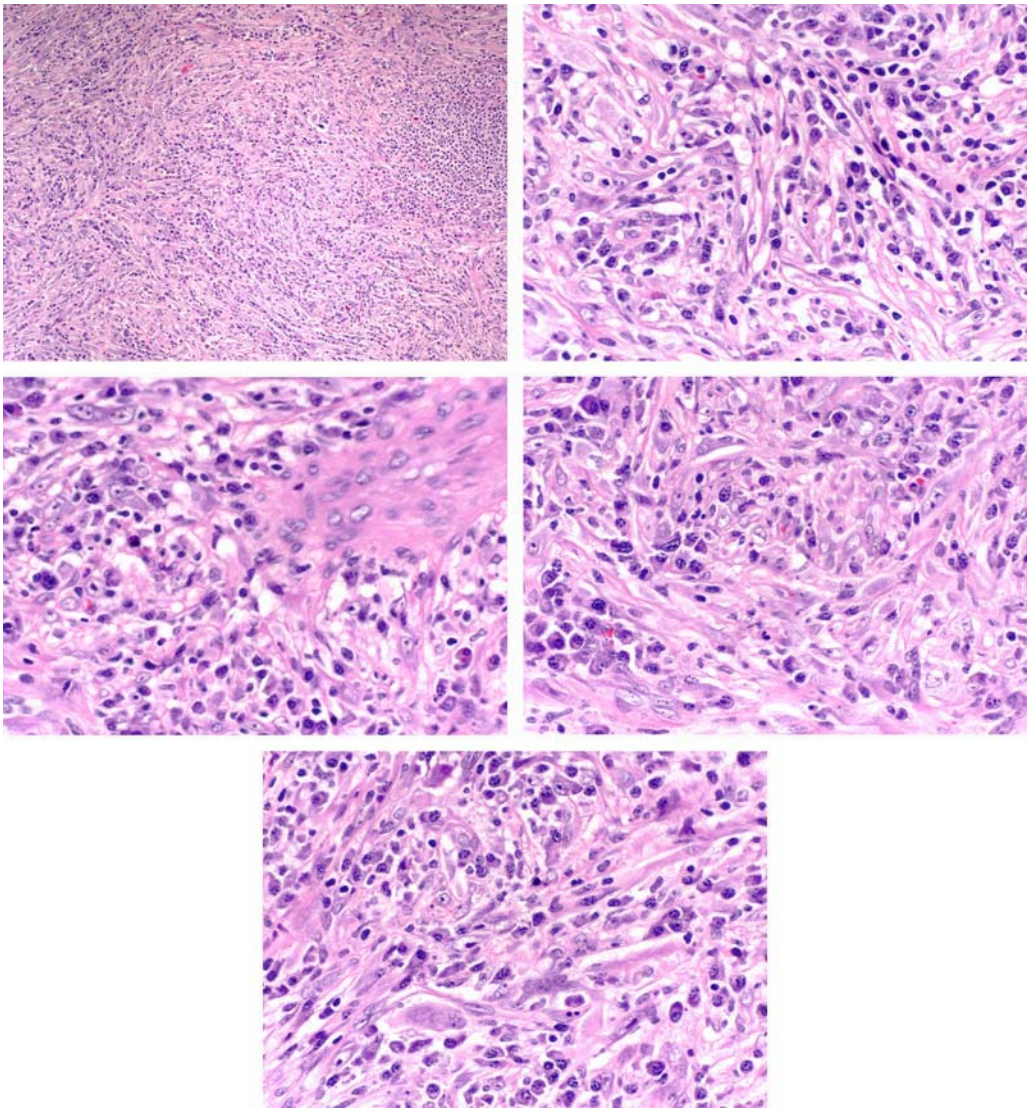
Diagnosis: Lung, wedge biopsy: Inflammatory myofibroblastic tumor with markedly atypical fibroblastic cells and prominent plasmacytic infiltrate, probably neoplastic.

The majority of this cellular tumor is composed of plasma cells and fibroblasts. The plasma cells include mature and immature forms and Mott cells. This aspect represents a lesion referred to in children as plasma cell granuloma. In adults, I consider plasma cell granuloma to be a form of inflammatory pseudotumor and reactive. In children, however, plasma cell granuloma may be a different condition, because some lesions invade and behave in an aggressive manner.

In this case, there is as well a spindle cell proliferation including markedly enlarged and elongated nuclei with contorted forms and enlarged nucleoli. These spindled cells form fascicles with resemblance of storiform pattern in a few areas. The appearance of these cells is neoplastic rather than reactive in my opinion and in the opinion of a senior member of our soft tissue section. In my opinion and experience, the most suitable diagnosis is a myofibroblastic tumor which is probably neoplastic and of a low-grade malignancy although difficult to prove because diagnostic features of malignancy are not apparent. I suspect that some pathologists would call this a low-grade sarcoma. I have seen cases similar to this, where the lesion invaded mediastinum and metastasized locally.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6939 (Chapter 9 – Lung Tumors)

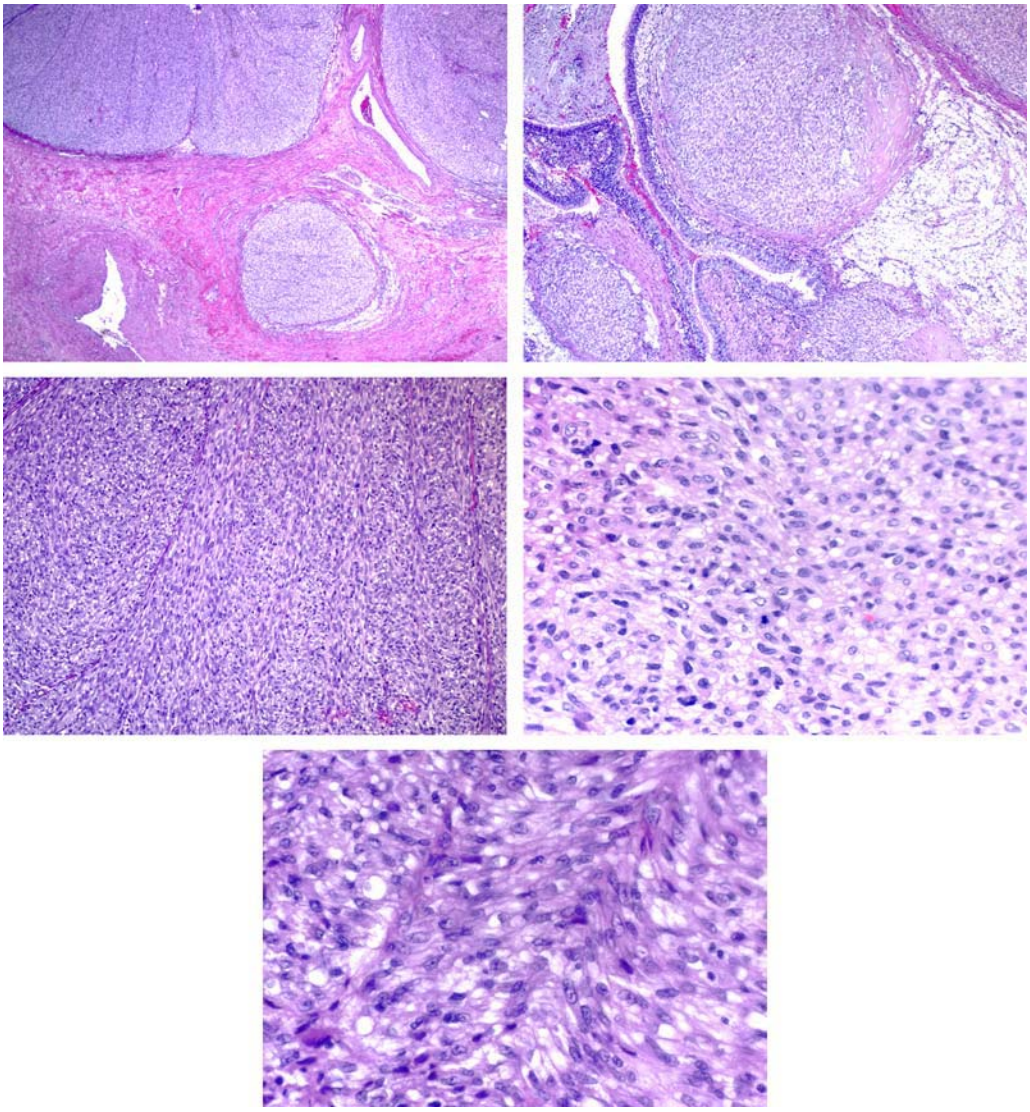
Case 7126

Diagnosis: Lung, lobectomy: Leiomyosarcoma, low-grade (grade 1/3).

Despite the paucity of mitoses, I believe this tumor is malignant by virtue of its aggressively pushing borders and extensive hypercellularity as well as nuclear pleomorphism. My concept of inflammatory myofibroblastic tumor is that of a lesion very difficult to distinguish from inflammatory pseudotumor, and I do not believe this case resembles the latter because there is so little inflammation and rather a monotonous population of proliferating cells. The fascicular growth of the lesion and the vacuolization of cytoplasm lead me to believe that this is of smooth muscle origin.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7126 (Chapter 9 – Lung Tumors)

Case 6634

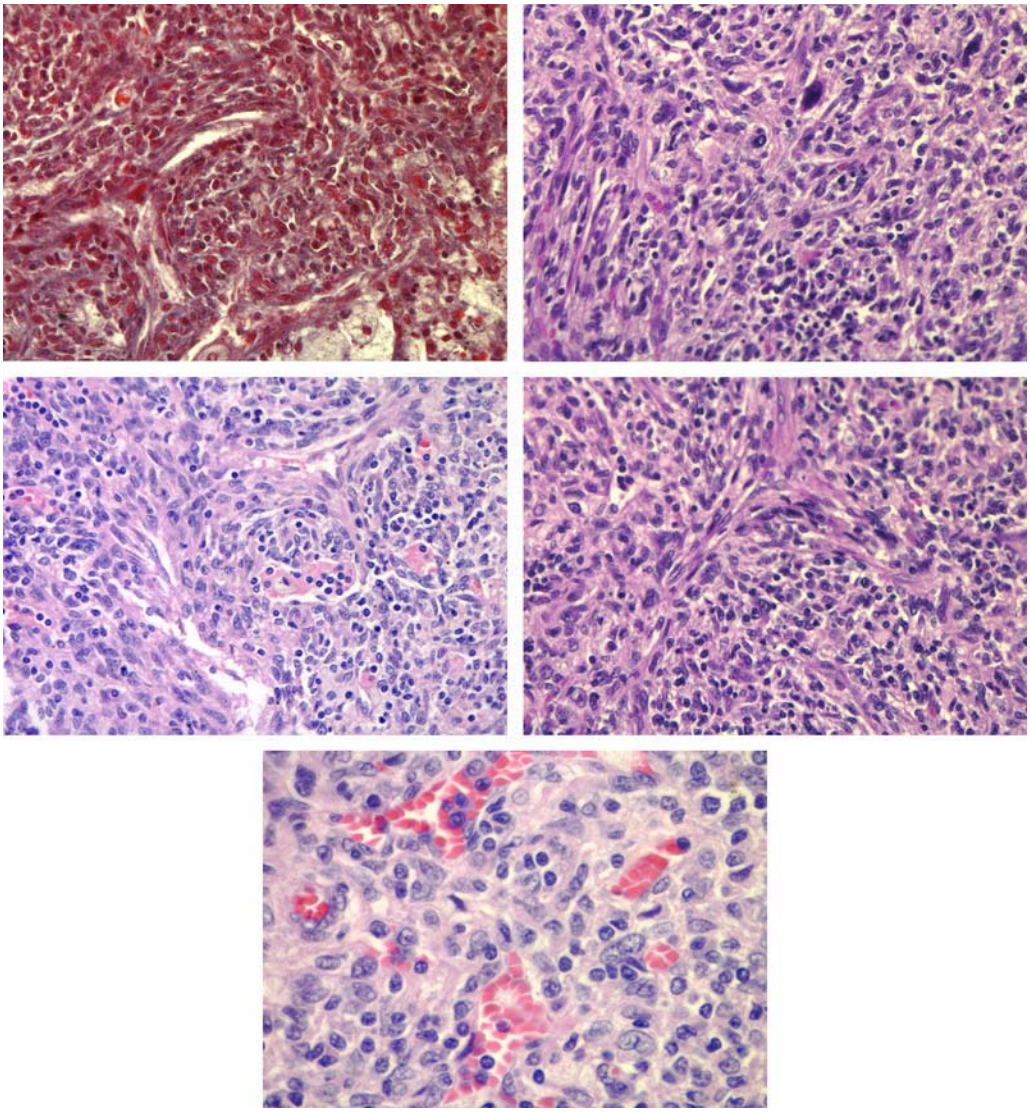
Patient: 56-yr-old male

Diagnosis: Lung, lobectomy: Malignant fibrous histiocytoma, low grade (grade 1/3).

This well circumscribed tumor has a polymorphic composition (trichrome stain) of fibroblasts, plasma cells, lymphocytes, and rare large bizarre cells. The differential diagnosis is a low grade sarcoma vs inflammatory pseudotumor in my opinion. The large bizarre cells and a rare mitosis make me believe this is neoplastic and a low grade sarcoma despite an absence of necrosis. The pleomorphism and a vague storiform pattern make me favor malignant fibrous histiocytoma. The lesion is low grade, and overall the prognosis is sanguine, although the lesion was sizable when resected. The uniform population of bland cuboidal cells characteristic of sclerosing hemangioma is not present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. Our soft-tissue pathologists in the department have reviewed the case and concur that the tumor is a low grade sarcoma. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6634 (Chapter 9 – Lung Tumors)

Case 7085

Diagnosis: Lung and pleura, resection: Fibrosarcoma, low grade, with sclerosing and epithelioid features.

This case is very unusual for a lung tumor, and I have not seen a case exactly like it. The case has been reviewed by many junior and senior pathologists in the department. There is not a uniformity of diagnoses. All observers feel it is either very worrisome for diagnostic of malignancy. The reluctance of some to make a diagnosis of malignancy is based on the rarity of mitoses. I favor a diagnosis of low grade sarcoma despite the rarity of mitoses, in large part because of the primitive and pleomorphic nature of the nuclei. Some nuclei have giant nucleoli. There is an aggressive pushing edge of the tumor in some areas (trichrome stain). In addition to the worrisome nuclei, there is also a component of the tumor with a more banal spindle cell proliferation simulating fibrous tumor of the pleura. The tumor abuts the inked margin at one point over a distance of a few millimeters, whereas the remainder of the margin in that slide and other slides has fibroadipose and lymphoid tissues.

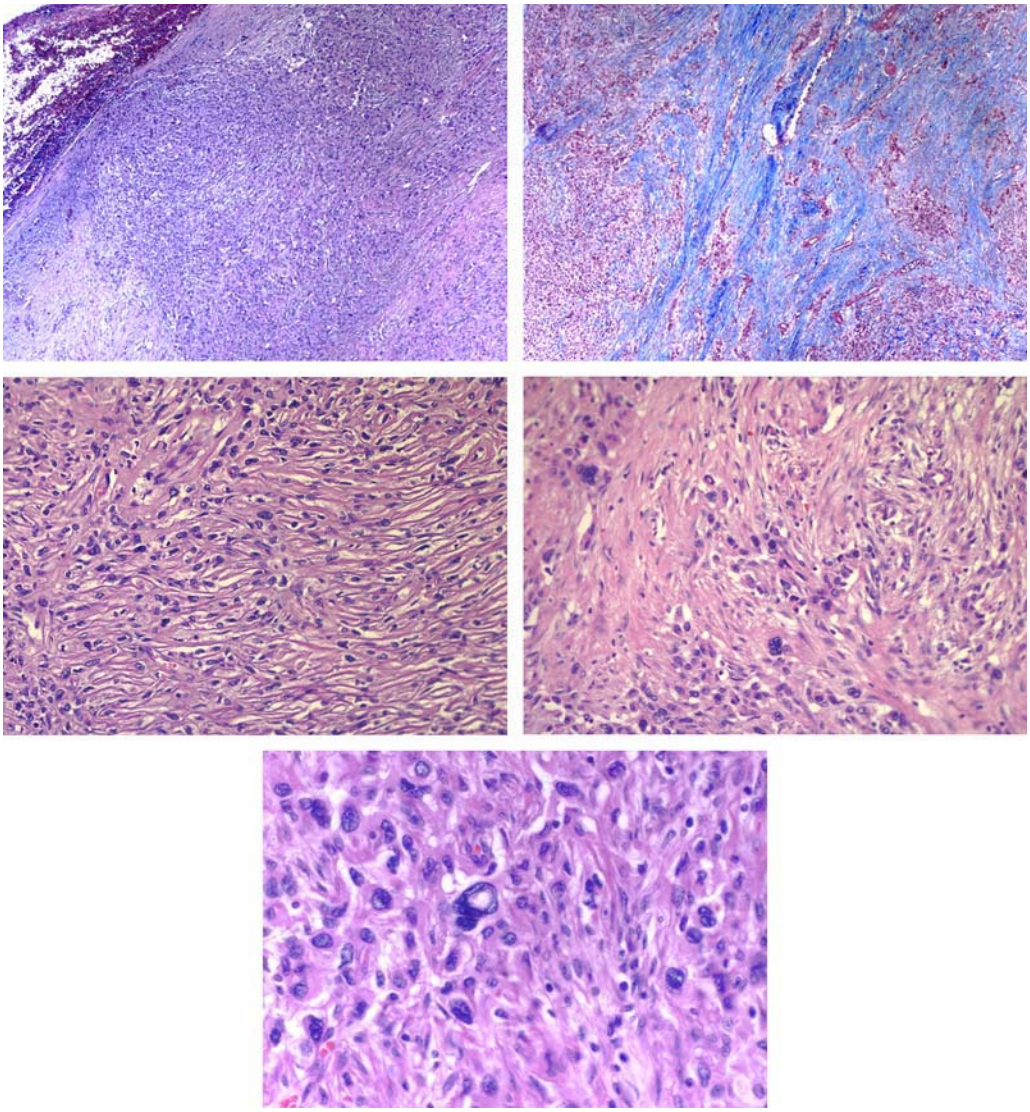
Our histochemical studies show an absence of mucus in the cells with mucicarmine and periodic acid-Schiff and Giemsa stains. Immunochemically, the malignant cells stain in regions for keratin and for epithelial membrane antigen as well as for vimentin. The proliferating cells do not stain for CD31, CD34, factor VIII, S-100 antigen, muscle actin, or lysozyme. Some cells scattered within the neoplasm stain for KP1. I believe the differential diagnosis is essentially that between a fibrosarcoma that has arisen from a fibrous tumor of the pleura (so-called malignant fibrous tumor of the pleura) or a sclerosing epithelioid fibrosarcoma. The immunochemical findings are against fibrous tumor of the pleura and consistent with a sclerosing epithelioid fibrosarcoma, which is the diagnosis that I prefer. Another possible diagnosis is malignant fibrous histiocytoma, but this case does not have the lymphohistiocytic component characteristic of malignant fibrous histiocytoma. Fibrosarcoma is now generally thought to be a facet of malignant fibrous histiocytoma. From a biologic point of view, there would be no difference between a low grade sarcoma of these various forms. In the differential diagnosis we also considered fibrous histiocytoma, synovioma, metastatic malignant melanoma, and other conditions but have done our best to exclude them.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. This is an elaboration of our earlier telephone conversations. The delay in diagnosis was caused by the sequential study and restudy of the immunochemical results. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Eyden BP, Manson C, Banerjee SS, Roberts IS, Harris M. Sclerosing epithelioid fibrosarcoma: A study of five cases emphasizing diagnostic criteria. Histopathology 1998; 33:354-360.



Case 7085 (Chapter 9 – Lung Tumors)

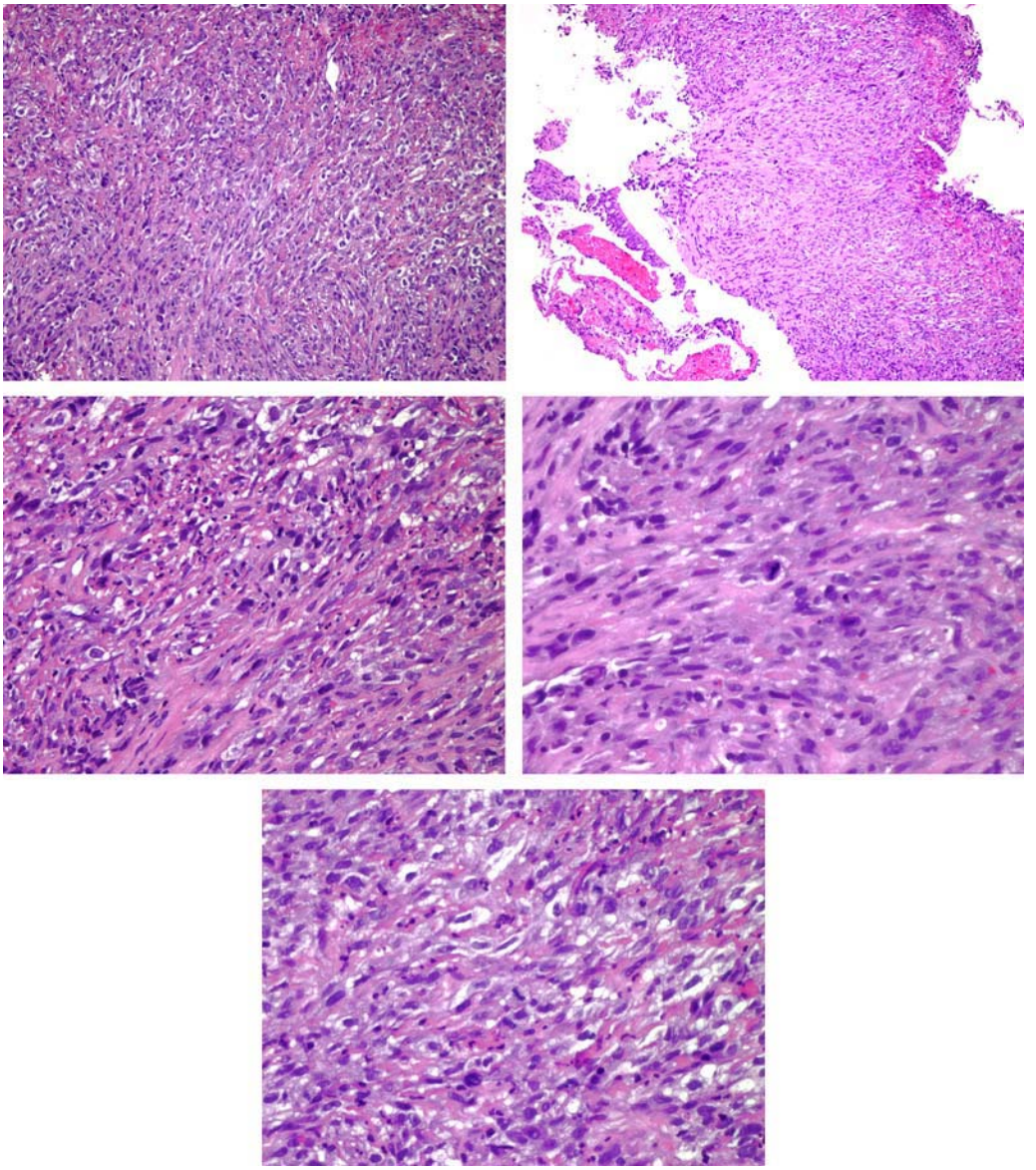
Case 6594

Diagnosis: Bronchus, bronchoscopic biopsy: Malignant spindle-cell neoplasm.

One piece among the biopsy samples consists of a malignant spindle-cell neoplasm with ulceration of the surface. There is necrosis of individual tumor cells and many mitoses, including atypical mitoses. An epithelioid appearance of some of the cells with amphophilic cytoplasm and possible intracytoplasmic vacuoles suggests a sarcomatoid carcinoma, which is the diagnosis I prefer and which I believe is essentially in agreement with your interpretation. I understand that your stains for keratin were not conclusive. I cannot exclude a sarcoma of high grade. The fascicular arrangement of the cells could be seen in either sarcomatoid carcinoma or malignant fibrous histiocytoma.

Thank you for referring this case in consultation. Ultrastructural examination or additional tissue would be advantageous to distinguish between sarcomatoid carcinoma and high grade sarcoma, but whether or not this distinction is indicated depends upon clinical circumstances, including stage of disease.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6594 (Chapter 9 – Lung Tumors)

Case 6582

Diagnosis: Lung, lobectomy: Malignant peripheral nerve sheath tumor origin, high-grade, with melanin-containing cells.

This case is intriguing because it has elements of both a sarcoma and a malignant melanoma. The fascicles of spindled cells could be seen in either condition. The storiform pattern with giant cells is in keeping with a malignant fibrous histiocytoma. The fascicles and giant nuclei with pseudoinclusions are in keeping with a malignant peripheral nerve sheath tumor. The epithelioid cells with finely granular brown melanin can be seen in malignant peripheral nerve sheath tumors. This pigment does not stain for iron, although there is more coarse brown hemosiderin in the tumor elsewhere. The lesion is high grade with many mitoses, including atypical mitoses. Prognosis is guarded, but I suspect that the tumor will behave as a sarcoma and not as a malignant melanoma.

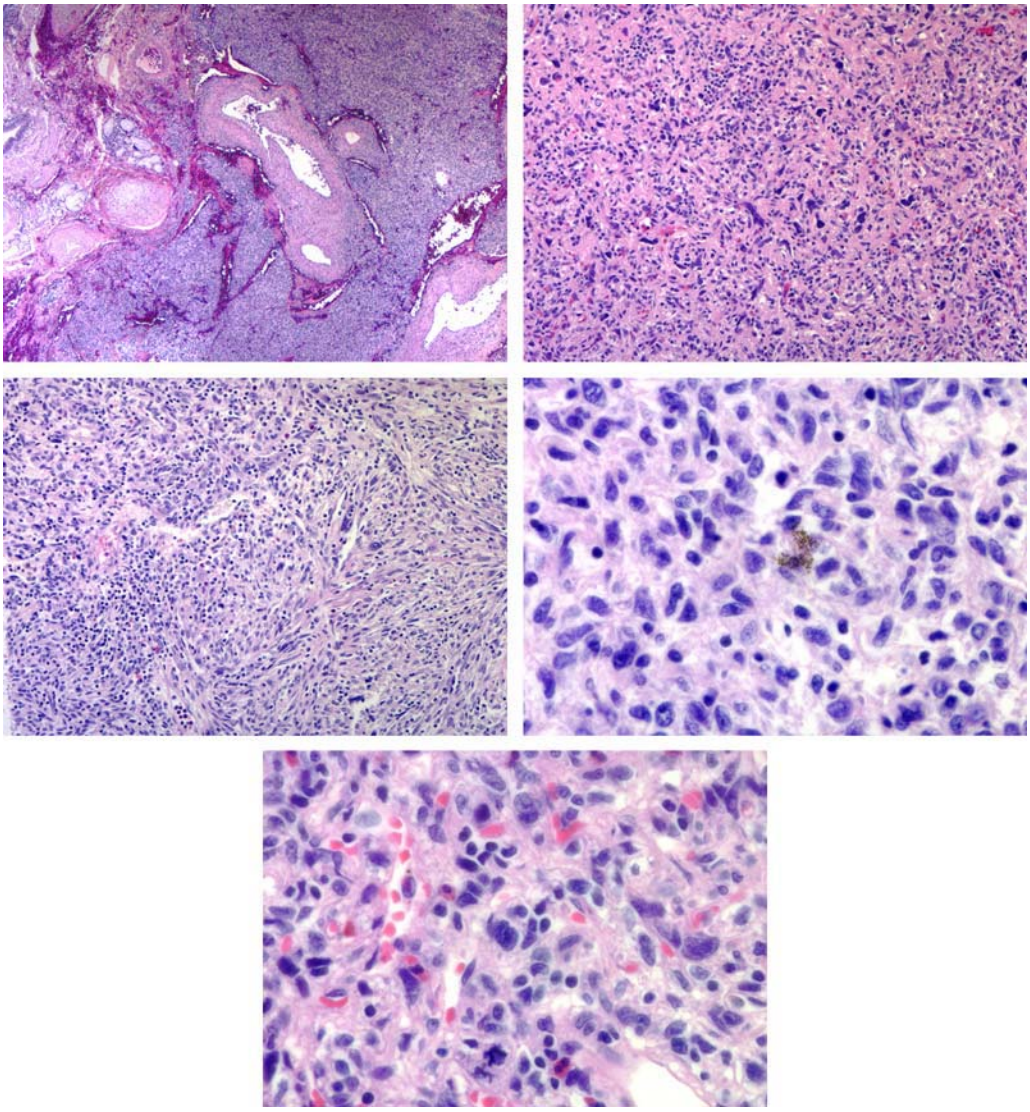
Thank you for the opportunity to review this case. A member of our soft tissue division has reviewed the case and concurs with the above. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

References:

Roviaro G, Montorsi M, Varoli F, et al. Primary pulmonary tumours of neurogenic origin. Thorax 1983;38:942–945.

Kitamura H, Kitamura H. Primary epithelioid malignant schwannoma of the lung. Path Intern 1994;44:317–324.



Case 6582 (Chapter 9 – Lung Tumors)

Case 6604

Diagnosis: Lung, mediastinal excision: Synovial sarcoma, grade 2/3.

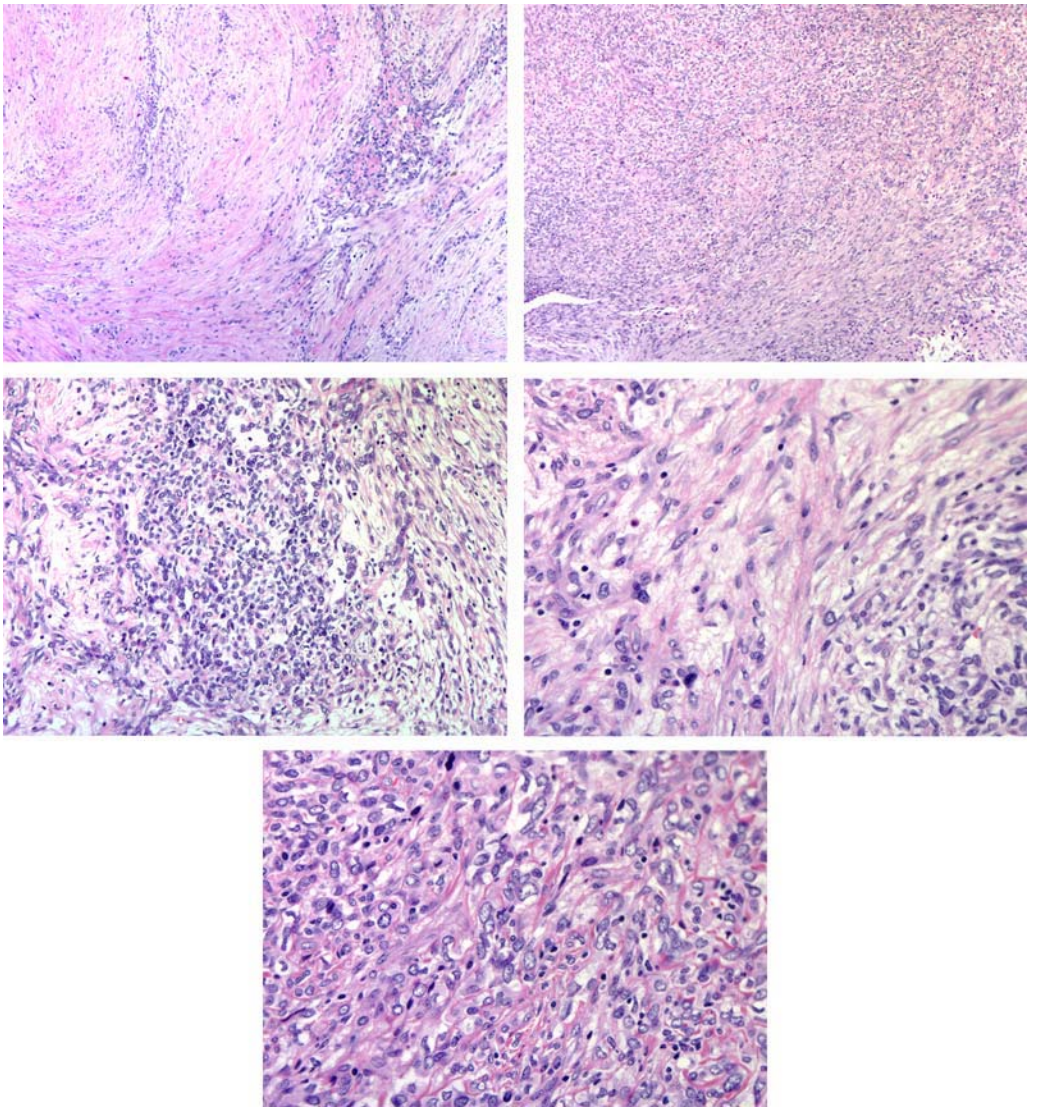
A malignant tumor is principally composed of oval and spindled cells with inconspicuous cytoplasm. The density of the oval cells and the fascicular growth pattern suggest synovioma. Occasional islands of epithelioid cells also support that diagnosis. The differential diagnosis includes nerve sheath tumor or a mixed mesenchymal tumor, but I do not favor these interpretations. I do not believe this is a carcinoma infiltrating mesenchyme, or a thymic carcinoma.

Our bone and soft tissue section has also reviewed the case and concurs. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.

Reference:

Witkin GB, Miettinen M, Rosai J. A biphasic tumor of the mediastinum with features of synovial sarcoma. A report of four cases. Am J Surg Pathol 1989;13:490–499.



Case 6604 (Chapter 9 – Lung Tumors)

Case 6551

Patient: 61-yr-old female

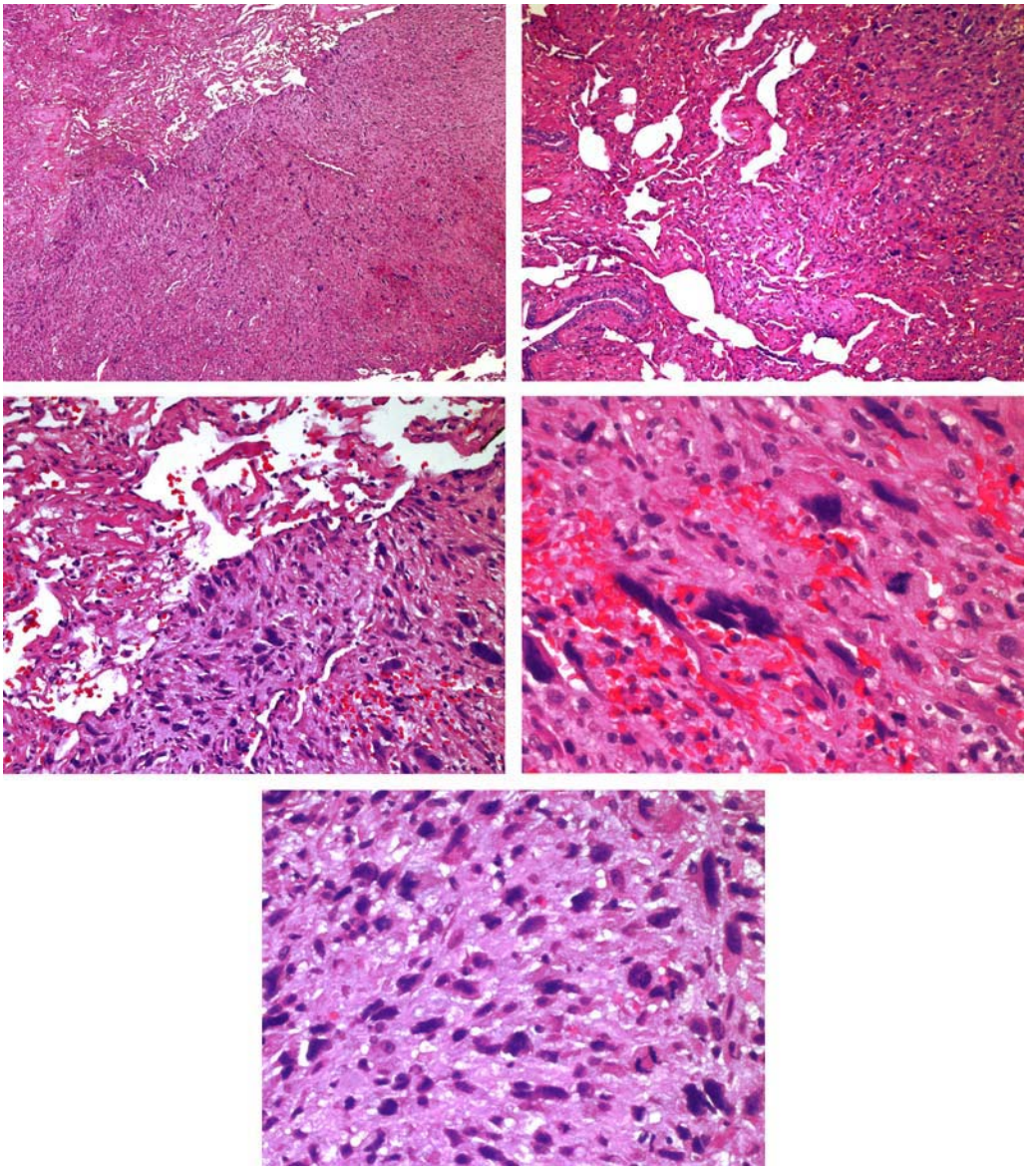
Clinical history: The patient had an amputation of a lower extremity 2 1/2 years previously. The primary reportedly was a malignant fibrous histiocytoma or some related neoplasm. She developed a subpleural nodule. This constitutes this specimen.

Diagnosis: Lung, wedge resection: Metastatic epithelioid leiomyosarcoma.

The nodule consists of a malignant tumor with biphasic morphology. The epithelioid aspects are more prominent, whereby there is abundant eosinophilic cytoplasm and cohesive aggregates of cells. Nuclei are pleomorphic, and some nuclei are markedly pleomorphic with giant nucleoli and atypical mitoses. A small portion of the tumor is mesenchymal, whereby the cells have elongated or spindled nuclei and grow in fascicles. The differential diagnosis of this malignant biphasic tumor in the lung and pleura includes DMM, synovial sarcoma, sarcomatoid carcinoma, and epithelioid leiomyosarcoma. The degree of nuclear pleomorphism is against malignant mesothelioma and synovial sarcoma. Sarcomatoid carcinoma cannot be excluded on the slides stained with hematoxylin and eosin, but your immunochemical stains are in keeping with a metastatic epithelioid leiomyosarcoma.

Note: Slides of the primary are not available for review. This tumor stains positively for vimentin, pan-actin, smooth muscle actin, and desmin. The tumor stains negatively for KP1 antigen, antichymotrypsin, and cytokeratin.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6551 (Chapter 9 – Lung Tumors)

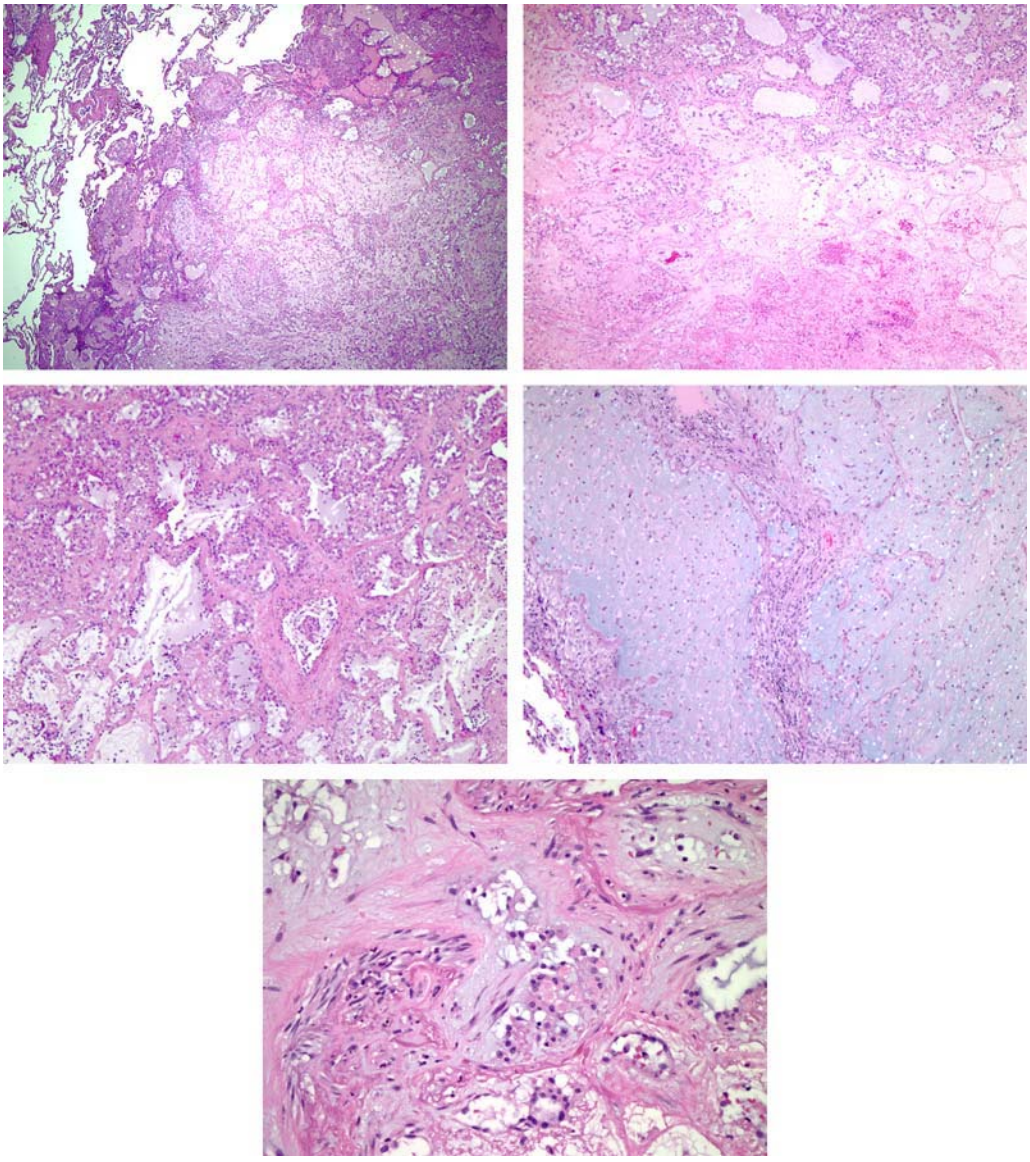
Case 6503

Diagnosis: Lung, excision of tumor: Chordoid chondrosarcoma.

This most unusual pulmonary process is malignant by virtue of nuclear pleomorphism, although such pleomorphism is only apparent in some regions. I believe the most specific histology is the chondroid appearance with rows of eosinophilic cells somewhat resembling the physyliferous cells of a chordoma. Focal necrosis is present. I suspect that this is a metastasis because I am not aware of chordoid chondrosarcoma arising in the lung. In the differential diagnosis, I considered intravascular sclerosing tumor (epithelioid hemangioendothelioma), but I do not favor this interpretation.

Thank you for the opportunity to review this case. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6503 (Chapter 9 – Lung Tumors)

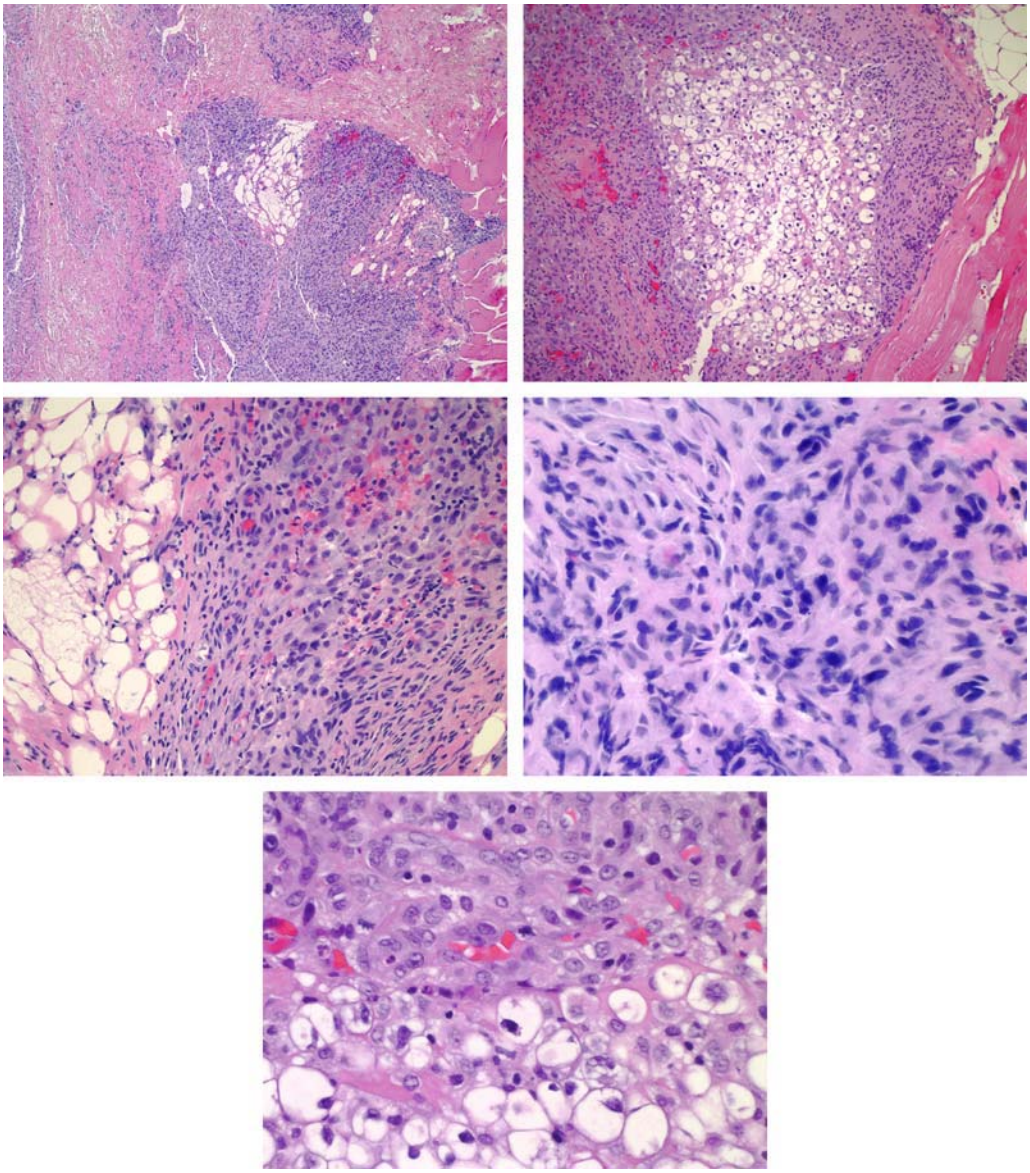
Case 6452

Diagnosis: Pleura, open biopsy: Malignant epithelioid tumors with clear cells, ? metastatic undifferentiated carcinoma, ? DMM.

An unusual epithelioid tumor with areas of elongated cells covers serosal surface and invades fibroadipose tissue. There is marked variability of the nuclei in some regions. Cytoplasm is abundant. A few foci of prominent clear cell change are present. The latter raise the possibility of metastatic renal cell carcinoma, which can produce diffuse pleural thickening. Other sources of metastases cannot be excluded. I understand that the patient has mediastinal adenopathy and an adnexal mass. One of my colleagues, who has reviewed the case, agrees that this is a malignant epithelioid neoplasm and cannot exclude metastatic undifferentiated carcinoma of the ovary. I cannot exclude DMM, but I favor metastatic carcinoma. Mucus is not demonstrable on your stains, nor do the immunopathological studies provide a specific source for the tumor. There is staining for cytokeratin in many cells and for calretinin in a few cells. I will obtain estrogen and progesterone markers as you requested.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. I have retained one slide stained with hematoxylin and eosin and hereby return the remainder. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6452 (Chapter 9 – Lung Tumors)

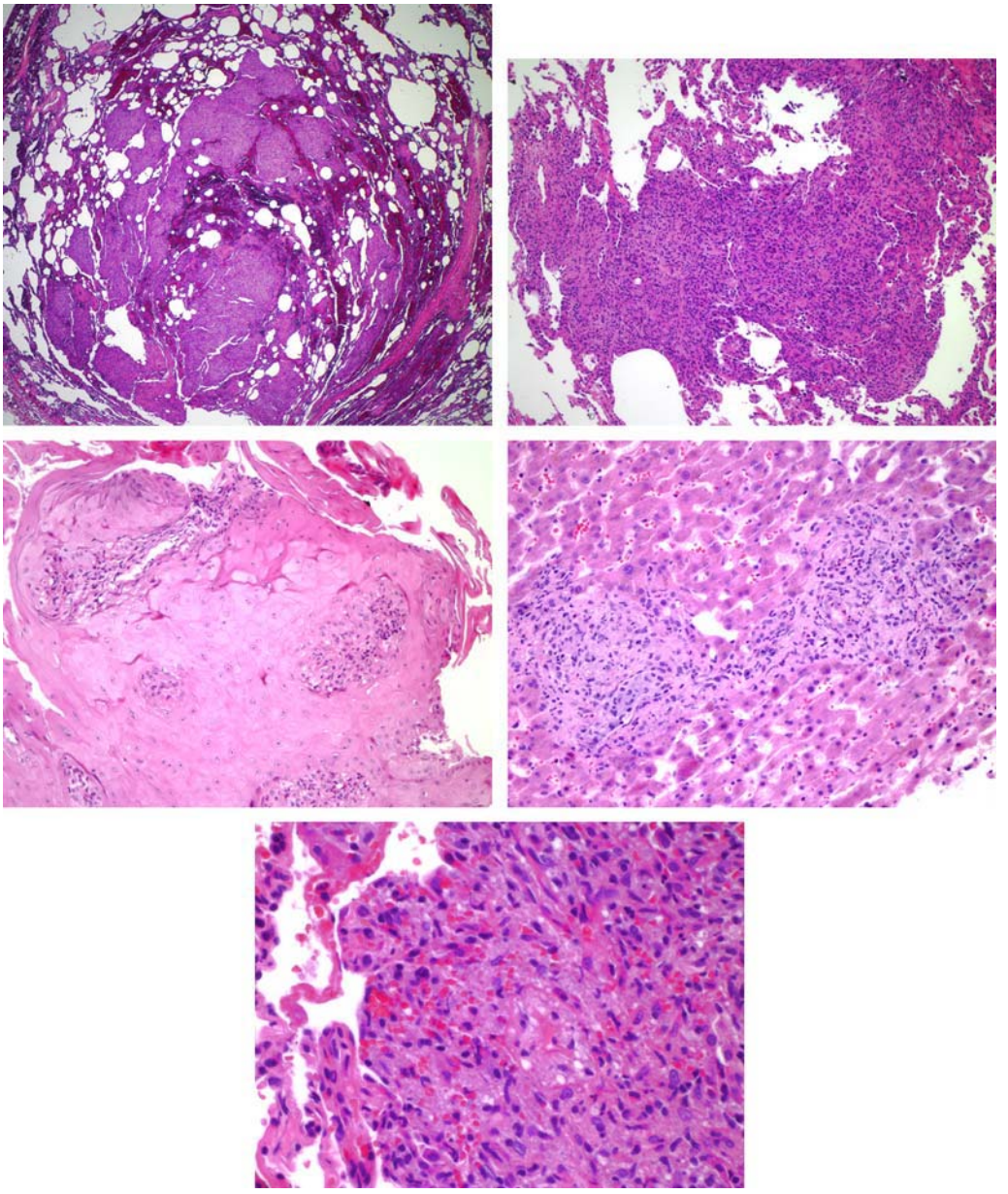
Case 6621

Diagnosis: Lung, open lung biopsy: Focal histiocytic infiltrate, consistent with disseminated histiocytosis X.

The nodular accumulation of the cells in the lung is unusual. The cells appear to be histiocytes, and your stains for S-100 suggest that they are Langerhans' cells. The pathology is not that of eosinophilic granuloma of the lung but does comport with disseminated histiocytosis X as seen in children. The infiltrations of the tip of papillae in the esophagus and in the portal tracts of the liver are consistent with that interpretation. In the differential diagnosis, I considered an infection and particularly mycobacterium intercellulare or Whipple's disease, since both of these diseases can give nodular collections of vacuolated histiocytes in the lung. However, my stains for mycobacteria (acid-fast) and Whipple's organism (periodic acid-Schiff) are negative. These two diagnoses are made somewhat less probable because of the changes in the esophagus. I believe the process is neoplastic, but I would not favor a diagnosis of malignant lymphoma because I believe we have explained the nature of the predominant cell, which is atypical.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6621 (Chapter 9 – Lung Tumors)

Case 6483

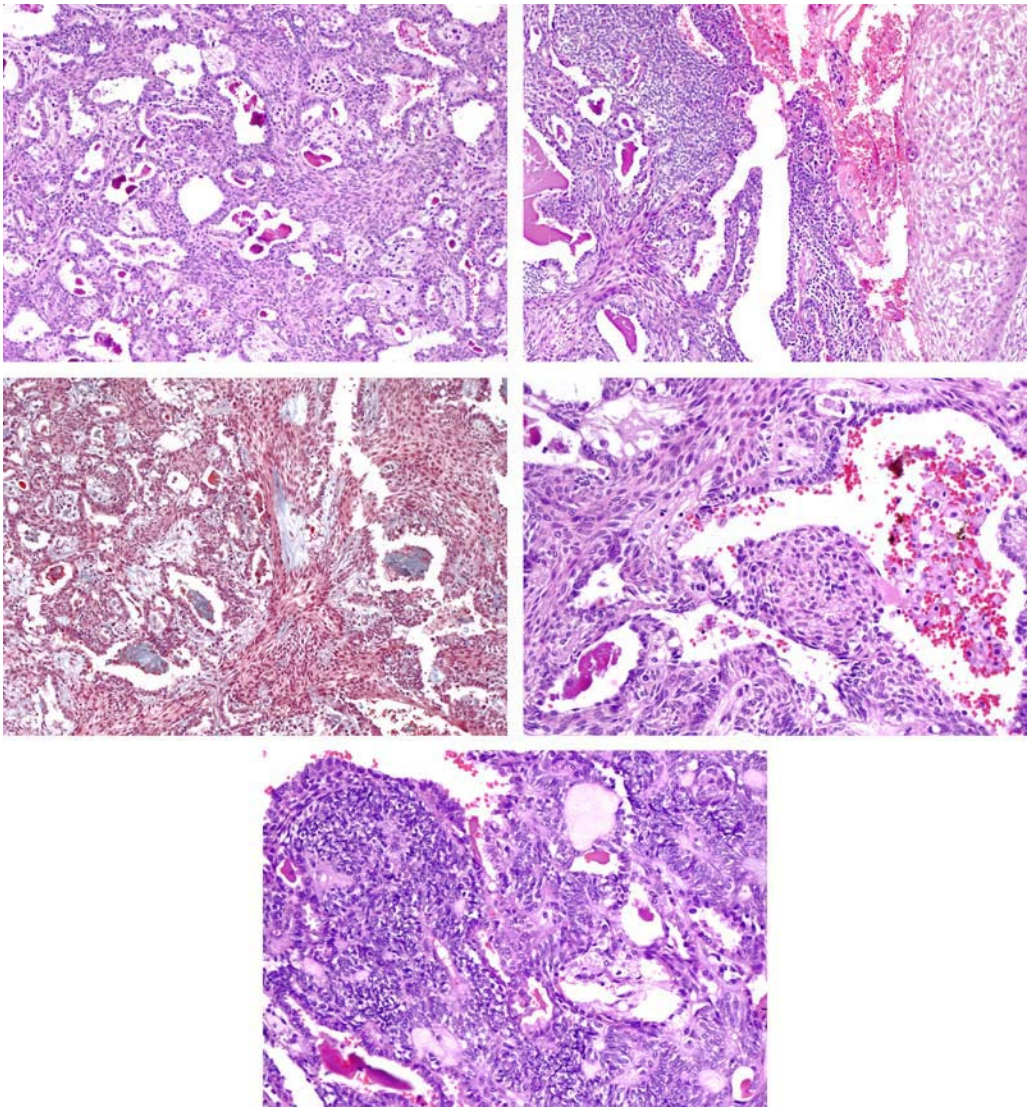
Patient: Elderly farmer, with a 25-yr smoking history and a subpleural mass which was white/gray, quite soft, and friable.

Diagnosis: Lung, open biopsy: Biphasic neoplasm, ? pulmonary blastoma, probably low-grade malignant.

This unusual neoplasm has a distinct glandular component as well as a spindle-cell component. I understand that the spindled cells stain for keratin, and there seem to be transitions between the epithelium and spindled cells, but I wonder whether there may be a mesenchymal component as well. I cannot precisely categorize this lesion, but I believe it most closely resembles a pulmonary blastoma. Because of the variety of the appearances of blastoma and because the resemblance of this case to low-grade endometrial adenoacanthoma, I favor that possibility. The squamous change could represent the morules that occur in blastoma. I had considered a low-grade mucoepidermoid carcinoma, but I do not favor this diagnosis. A few regions of the tumor have a Wilms' tumor-like appearance, which is another reported variety of blastoma. I suspect that this is a low-grade malignancy that has been probably cured by resection.

Thank you for the opportunity to review this case. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6483 (Chapter 9 – Lung Tumors)

Case 6835

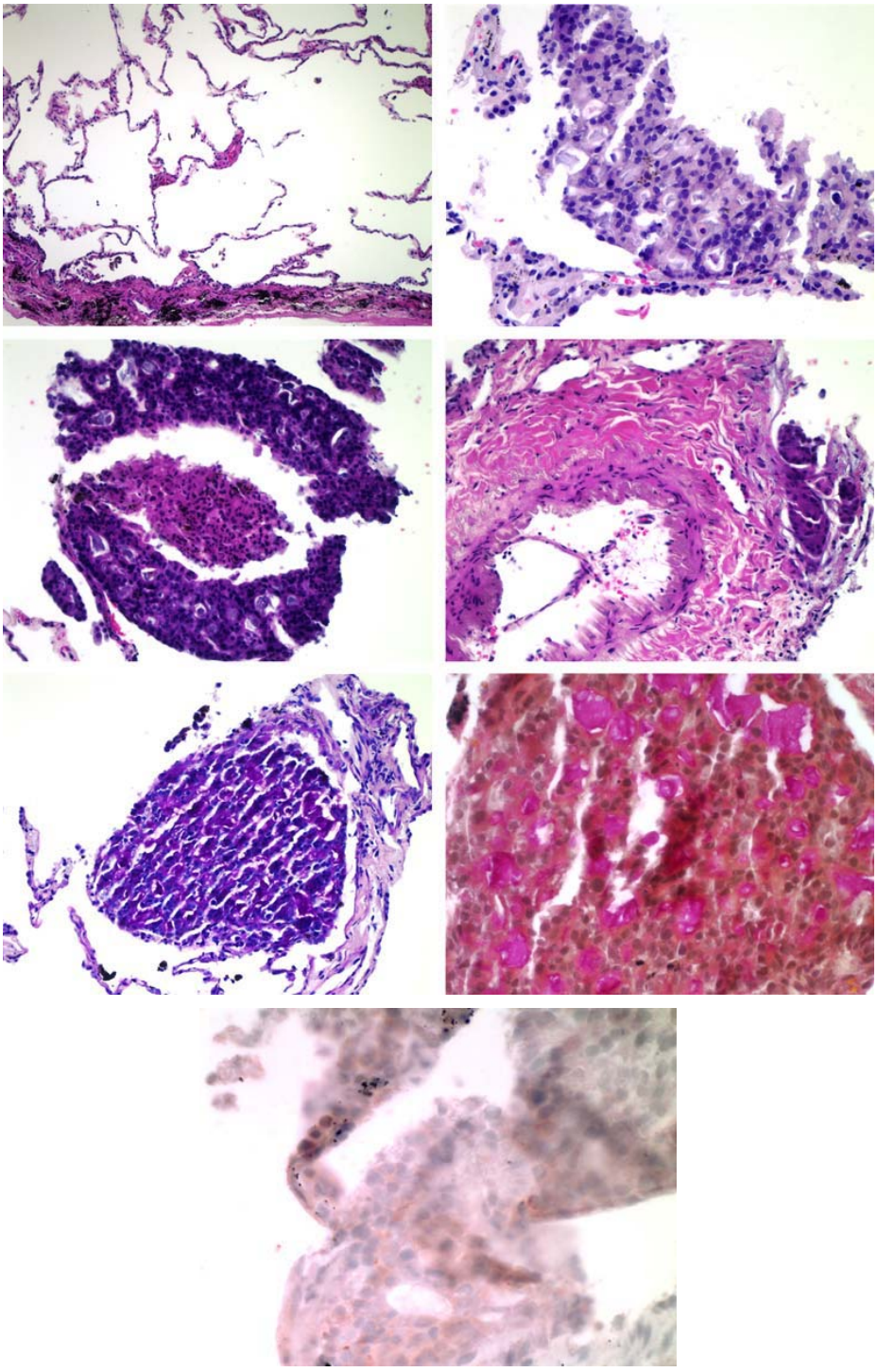
Diagnosis: Lung, biopsy: Adenocarcinoma, well differentiated, origin unknown.

The interpretation is complicated because of the relatively small piece of neoplastic tissue, which is mostly detached from lung tissue. There is central comedo-like necrosis in the middle of the tumor, and this leads me to believe this is a malignant tumor. There is also lymphangitic spread around an artery. Glandular spaces contain basophilic mucus. I favor a diagnosis of well differentiated adenocarcinoma.

To further evaluate the case, I performed several recut sections, histochemistry, and immunochemistry. Our recut showing additional tissue demonstrates emphysematous lung with a scar and additional pieces of the carcinoma. As in your section, these cells have surprisingly uniform nuclei for a malignancy, but I believe there is hyperchromatism and angularity of nuclei in a few regions. We found one mitosis and additional areas of necrosis. Mucicarmine and periodic acid-Schiff stains show production of mucus. I was concerned about carcinoid tumor and metastatic adenocarcinoma of the prostate. Insufficient tissue remained in the block to provide meaningful evaluation. There is no tissue on our slides stained for chromogranin, synaptophysin, and prostate specific antigen. A few cells of the tumor have weak staining for prostate acid phosphatase, which does not provide me with a diagnosis. The relative monotony, small glands, and apparent cribiform structure in some areas makes me consider adenocarcinoma metastatic from a prostate primary.

Thank you for referring this case in consultation. This is a confirmation of my telephone call. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6835 (Chapter 9 – Lung Tumors)

10 Pleural Tumors

Contents

DIFFUSE MALIGNANT MESOTHELIOMA

The term mesothelioma has been applied to two very different neoplasms. The first is the diffuse malignant mesothelioma (DMM), which covers the serosal surface, has both epithelioid and mesenchymal characteristics histologically, is virtually always fatal, and is caused by asbestos. The second is the fibrous mesothelioma, which forms a discrete mass, usually can be cured by resection, and is not related to asbestos. It is derived from the submesothelial fibroblast and thus has a histogenesis different from DMM. Its radiographic appearance as a baseball in the chest differs dramatically from DMM, but a needle biopsy of the tumor may show hyperchromatic spindle cells difficult to differentiate from a fibrosarcomatous or desmoplastic subtype of DMM.

All fibrous tumors of the pleura can recur. Recurrence occurs more commonly in those arising from the parietal pleura, because those arising in the visceral pleural have been resected in a lobectomy. About 10% appear cytologically worrisome and may metastasize. Even a few mitoses are noteworthy for malignant potential.

Other names for the tumor are solitary fibrous mesothelioma, localized fibrous mesothelioma, localized fibrous tumor, pleural fibroma, and submesothelial fibroma. Localized fibrous tumor may lie within the lung and without any obvious connection to the visceral pleura. Theoretically, such a tumor arises from mesothelial rests embedded in septa. Such intrapulmonary fibrous tumors may simulate a bronchial hamartoma. When multiple, which occurs rarely, they may raise the false suspicion of metastatic sarcoma. Solitary fibrous tumor arises in many sites in the body including the mediastinum.

Features of fibrous tumors of the pleura include the following:

- Visceral or parietal pleura
- Subpleural
- Blunt invagination into lung
- Spindle cells
- Cellular fascicles like schwannoma
- Large vessels like angiofibroma
- Little pleomorphism
- Few mitoses

From: *Current Clinical Pathology: Lung Pathology: A Consultative Atlas*
By S. Houser, U. J. Balis, and E. J. Mark © Humana Press, Totowa, NJ

- Usually benign
- Not related to asbestos

Macroscopically, as the name "localized fibrous tumor of the pleura" indicates, the typical lesion is round or oval and well circumscribed. The lesions may range from several millimeters to many centimeters in diameter, including examples measuring up to 36 cm and weighing up to 5000 g. Larger lesions may be multilobulated. The cut surface of a resected specimen is rubbery and firm with a whorled pattern. Central myxoid change and hemorrhage may occasionally be seen and are more commonly encountered in large tumors. Tumors arise more commonly from the parietal than the visceral pleura. Rarely, tumors arise from the thoracic surface of the diaphragm, from the mediastinum, or in the lung, where they are thought to arise from a pleural invagination in a lobular fissure. A vascular pedicle may be present, particularly on one arising from the parietal pleura.

Microscopically, dark spindled nuclei may have stippled or homogeneously dense chromatin with occasional vacuolar change and inconspicuous nucleoli. Density of the nuclei varies from richly cellular to poorly cellular. The nuclei are separated by fibrillar collagen. The cells form fascicles or storiform arrays and also grow without any reproducible pattern. Mitoses are very rare in benign tumors. Regions with numerous large blood vessels are common. Entrapment of surface epithelioid mesothelial cells or entrapment of pneumocytes as the tumor grows within the lung may cause gland-like spaces, but these are not intrinsic parts of the neoplasm.

Ultrastructurally, the neoplastic cells have spindled nuclei with heterochromatin and occasional admixed polygonal cells. Nuclei may be mildly indented. Nucleoli are not prominent. Cytoplasm contains microfilaments and rough endoplasmic reticula with cisternae. Mitochondria are generally scarce. The cells are arranged in groups and surrounded by collagen. Intercellular junctions are often discernible. The cells do not produce basement membrane.

The differential diagnosis depends on the pattern seen on routine staining and includes DMM of the fibrosarcomatous pattern, hemangiopericytoma, schwannoma, leiomyoma, sclerosing epithelioid fibrosarcoma, sclerosing epithelioid hemangioendothelioma, inflammatory pseudotumor, fibrous histiocytoma, sclerosing hemangioma, and carcinoid with sclerosis. Immunochemistry is not usually necessary for diagnosis, but it may be useful in cases with one or more of these differential diagnoses. Typically, the cells of the solitary fibrous tumor stain for vimentin and for CD34 and do not stain for epithelial, endothelial or histiocytic markers.

Seventy years ago, solitary fibrous tumors of the pleura outnumbered DMM, but with the great increase in the numbers of the latter tumor owing to the widespread use and dissemination of asbestos, DMM now outnumbers solitary fibrous tumor. DMM is a new disease. It was virtually unknown until the 1930s and not accepted as a distinct entity by some pathologists until the 1940s. The association with asbestosis was established in the late 1950s. The tumor continues to increase in incidence. The first wave of disease occurred in miners and milers of asbestos. The second wave occurred in insulators and other tradesmen who applied asbestos. The third wave is occurring now in persons who have worked around the material but were not hired to apply it, including plumbers, maintenance workers, and mechanics. The fourth wave is now beginning among people who do not know they have been exposed, such as electricians and school teachers.

A central issue regarding the pathology of the pleura is the diagnosis of DMM and, as discussed in Chapter 8, distinguishing it from reactive pleural disease. Once the diagnosis

of malignancy is assured, the next challenge to the pathologist is distinguishing DMM from carcinomatosis or sarcoma. Until a few years ago, this was the only practical concern, since the clinical import of distinguishing DMM from carcinomatosis or sarcoma was moot. There are now surgical and chemotherapeutic protocols specific for malignant mesothelioma, so now its precise diagnosis is important. However, there is generally more to lose from the standpoint of patient care with overdiagnosis of DMM rather than underdiagnosis, because the malignant disease, if present, will make itself evident clinically soon enough, and little or nothing will be lost from the standpoint of therapy in a delay in diagnosis. One manner of reporting an equivocal case is as follows: "The histology observed here may appear in patients who subsequently develop DMM."

DMM presents in the following histological forms:

Predominately Epithelioid	*Predominately Mesenchymal*
Squamoid	Myxoid
Tubuloalveolar	Angiosarcomatoid
Signet ring	Fibrosarcomatoid
Anaplastic	Desmoplastic

DMM derives from cells lining a schizocoelom. Embryologically, the cells forming the surface of the cavity after the mesoderm splits are schizoid. They acquire the potential to act either like epithelial cells or mesenchymal cells. The tumor displays only the epithelioid features in about 50% of cases, only the mesenchymal features in 10%, and both features in 40%. The differential diagnosis for the epithelioid form is pleural carcinomatosis. The differential diagnosis for the mesenchymal form is usually malignant fibrous tumor of the pleura. The biphasic form has no significant differential diagnosis.

Pleural carcinomatosis indicates metastasis from any source. Overlying mesothelial cells may show highly atypical reactive hyperplasia that simulates DMM.

The entity pseudomesotheliomatous adenocarcinoma of the lung indicates a subpleural adenocarcinoma of the lung, which spreads extensively in the pleura to simulate a DMM and where the subpleural primary may have been disguised by the pleural tumor. Synchronous DMM and carcinoma of the lung has been reported several times. Asbestos can cause both tumors at the same time. Pleural hyaline plaque resulting from asbestos occurs in about one-fourth of cases of DMM.

Diffuse Malignant Mesothelioma: Cellular Characteristics of Epithelioid Forms

- Epipleural and intrapleural
- Elongate tubuloalveoli and micropapillae
- Bland nuclei
- Squamoid cytoplasm
- Rare signet cells within myxoid degeneration
- Mucicarmine rarely may be positive
- Epithelioid cells positive for one or more: keratin, calretinin, WT-1, HBME-1
- Mesenchymal cells positive for keratin
- Epithelioid cells have long thin microvilli on ultrastructural examination

Pleural Carcinomatosis: Cellular Characteristics

- Intrapleural (not epipleural)
- Rounded glands
- Pleomorphic and hyperchromatic nuclei
- Vacuolated cytoplasm

- Signet cells in lymphatics and in fibrosis
- Mucicarmine and periodic acid-Schiff (PAS) often positive
- Cells usually positive for one or more: CEA, Leu M-1, B 72.3, TTF-1,
- Ber-EP4, MOC 31

Mesenchymal types of DMM may resemble sarcomas which are metastatic to the pleura.

Diffuse Malignant Mesothelioma: Histology of Mesenchymal Types

- Variety of patterns: storiform, densely cellular, poorly cellular, cambium layer
- Spindled cells with dark nuclei
- Myxoid matrix
- Blood filled channels lined by bizarre cells, to be distinguished from epithelioid hemangioendothelioma or primary or metastatic angiosarcoma in the pleura
- Necrosis of collagenous areas
- Microinvasion of adipose tissue

Pleural Sarcomatosis (Metastases With Spindle Cell Element)

- Renal cell carcinoma
- Synovial sarcoma
- Malignant fibrous histiocytoma
- Epithelioid hemangioendothelioma

Desmoplastic DMM presents special problems. The tumor is so poorly cellular that one may consider it to be scar tissue. Even metastases may appear much like fibrous tissue. Useful features are very broad bundles of keloidal collagen, highly regimented nuclei parallel to the surface, cellular cambium layer under the serosal surface, and necrosis. Storiform pattern is a useful finding since it is uncommon in reactive mesothelial proliferation. Ectatic blood vessels appear in DMM. Angiosarcoma enters the differential diagnosis when hemorrhage obscures the underlying malignancy.

Desmoplastic Diffuse Malignant Mesothelioma

- Poorly cellular
- Keloidal collagen
- Highly regimented nuclei parallel to surface
- Cambium layer
- Storiform pattern
- Necrosis
- Tumor grows over or under pleural hyaline plaque

Diffuse Malignant Mesothelioma: Recently Described Forms

- Well differentiated
- Osteocartilagenous
- Lipid-rich
- Glycogen-rich
- Lymphohistiocytoid
- Rhabdoid
- Small cell
- Deciduoid
- Pleomorphic

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LETTERS

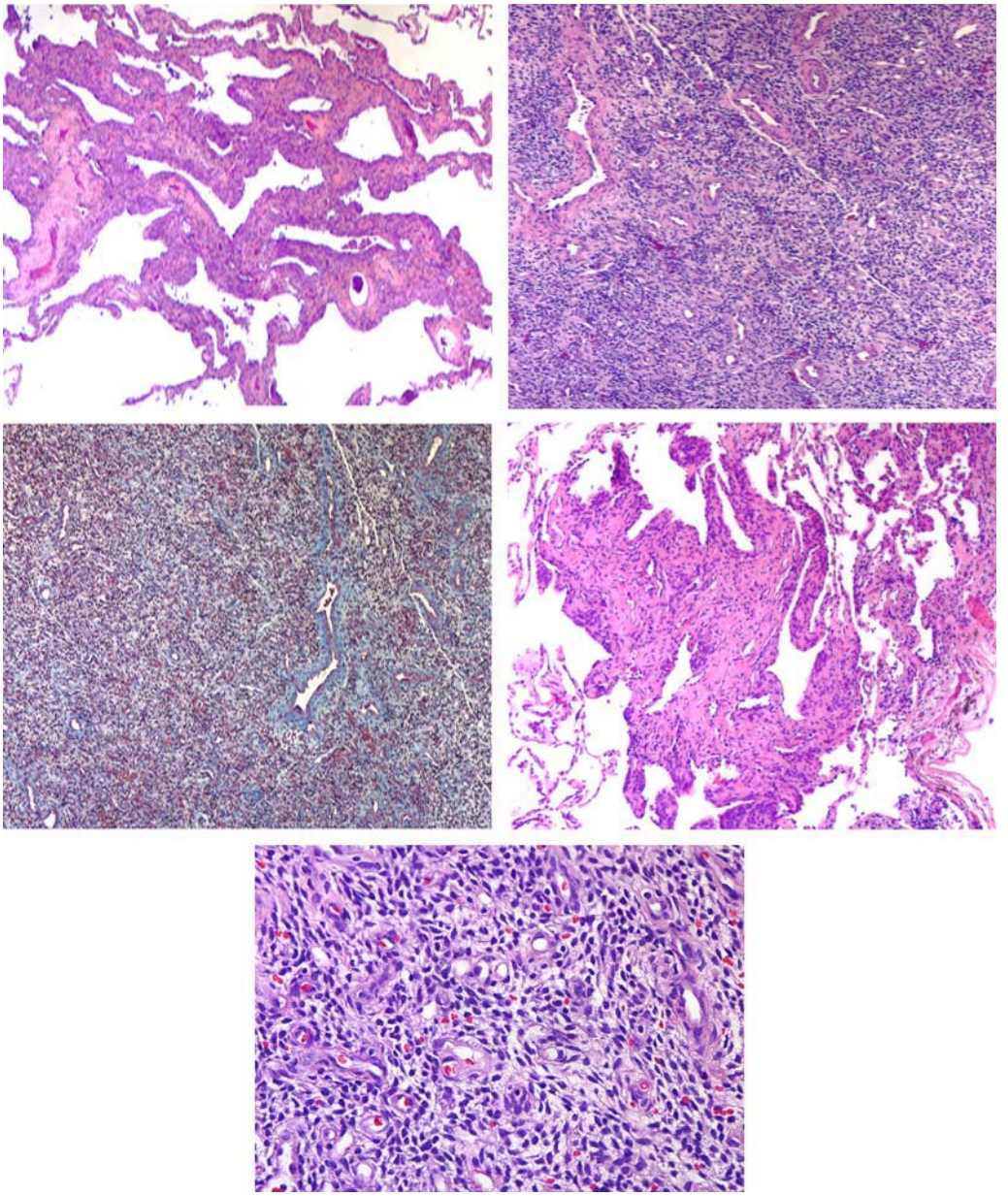
Case 6633

Diagnosis: Lung, wedge resection: Intraparenchymal fibrous tumor of the pleura.

The small oval and spindled cells in fascicles and the prominent blood vessels (trichrome stain) comprising this well-circumscribed neoplasm indicate a fibrous tumor of the pleura. Occasionally such tumors arise within the lung, where they are presumed to arise from submesothelial fibroblasts entrapped in lobular septa. In Europe such intrapulmonary tumors are called type III fibrous mesotheliomas. Sometimes fibrous tumors have regions with uniform small cells, such as present in areas here, and a needle biopsy of such areas can raise the differential diagnosis of small cell tumors. We generally do not make a diagnosis of hemangiopericytoma in the lung unless the pathology is absolutely classic for that diagnosis, in part for the clinical reason that the diagnosis implies a lack of predictability in behavior. I suspect that the prognosis in this case is excellent. The principal alternative diagnosis is a metastatic low grade fibrosarcoma, but I do not favor that interpretation. The lung also contains a few tumorlets of chemodectoma type.

Thank you for referring this case in consultation. Other pathologists in the department have reviewed this case and essentially concur with the above. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6633 (Chapter 10 – Pleural Tumors)

Case 6770

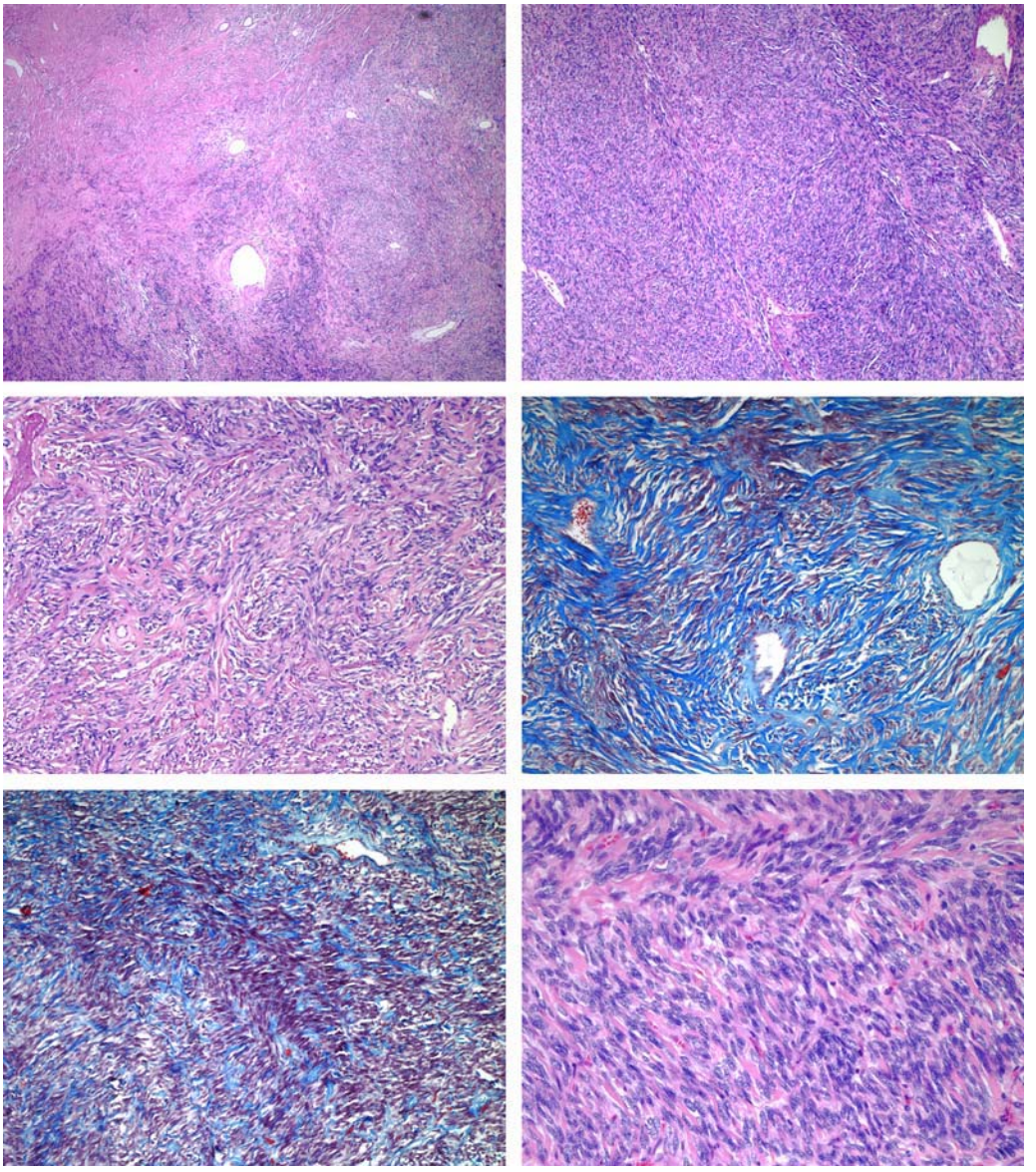
Diagnosis: Lung, wedge excision: Fibrous tumor of the pleura, intrapulmonary.

This mass consists of fascicles of spindled cells (trichrome stain) producing herringbone and storiform patterns. The variation in cellularity from one region to another and the prominent ectatic blood vessels (trichrome stain) characterize a fibrous tumor of the pleura. Despite areas that are highly cellular, no mitoses are present, and such cellular areas do not alter the diagnosis. Although biopsies of such areas might prove troublesome, the overall histology in this case is that of a fibrous tumor. Tumors within the lung and not attached to visceral pleura are thought to arise from submesothelial fibroblasts in interlobular septa.

When localized fibrous tumors of the pleura arise from the parietal pleura of chest wall, recurrence is possible in the stalk that attached the tumor to the chest wall. In tumors that arise in the lung, clear surgical resection margins usually are more easily obtained.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6770 (Chapter 10 – Pleural Tumors)

Case 6689

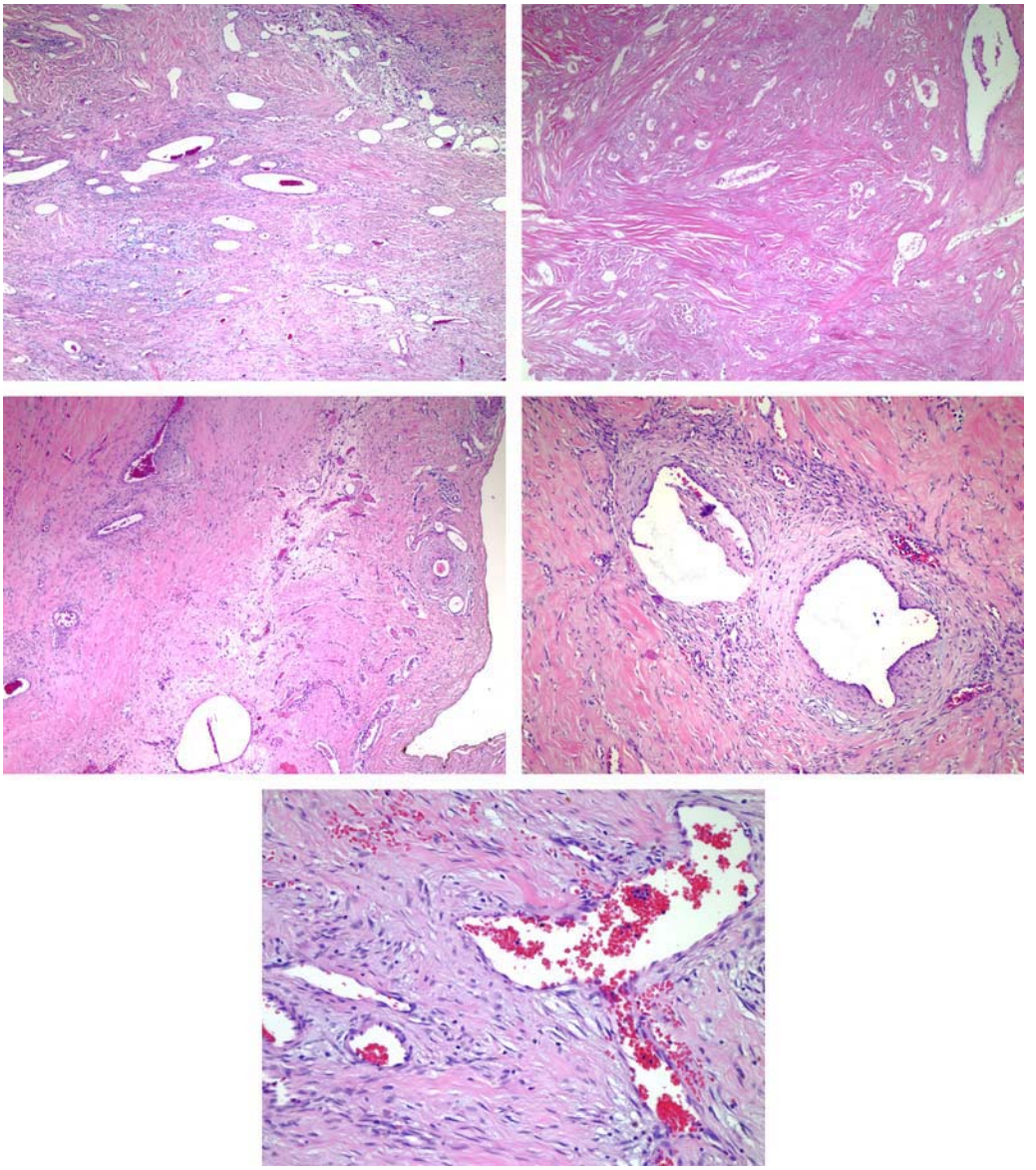
Diagnosis: Lung, wedge resection: Fibrous tumor of the pleura (fibrous mesothelioma), with extensive recent infarction and pleural adhesions.

The intrinsic lesion is a proliferation of spindled cells forming fascicles in an orderly manner and separated by collagen along portions of the perimeter of the infarcted center. This spindle cell proliferation with ectatic blood vessels characterizes a fibrous tumor of the pleura. I searched for mitoses, and I find none. There is entrapment of epithelial-lined airspaces at the perimeter of the tumor. The infarction could have arisen either from thrombosis or from torsion of the pleural nodule. I suspect the latter. The necrosis is a few weeks old based on the capillary proliferation at the perimeter of the necrosis and on the character of the fibrous pleural adhesions. The prognosis of intrapulmonary fibrous tumors of the pleura is better than that for tumors in the chest wall because surgical resection is generally more successful for the intrapulmonary tumors.

In the differential diagnosis, I considered hyalinizing granuloma, benign metastasizing leiomyoma, and amyloidoma. I do not favor these interpretations.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6689 (Chapter 10 – Pleural Tumors)

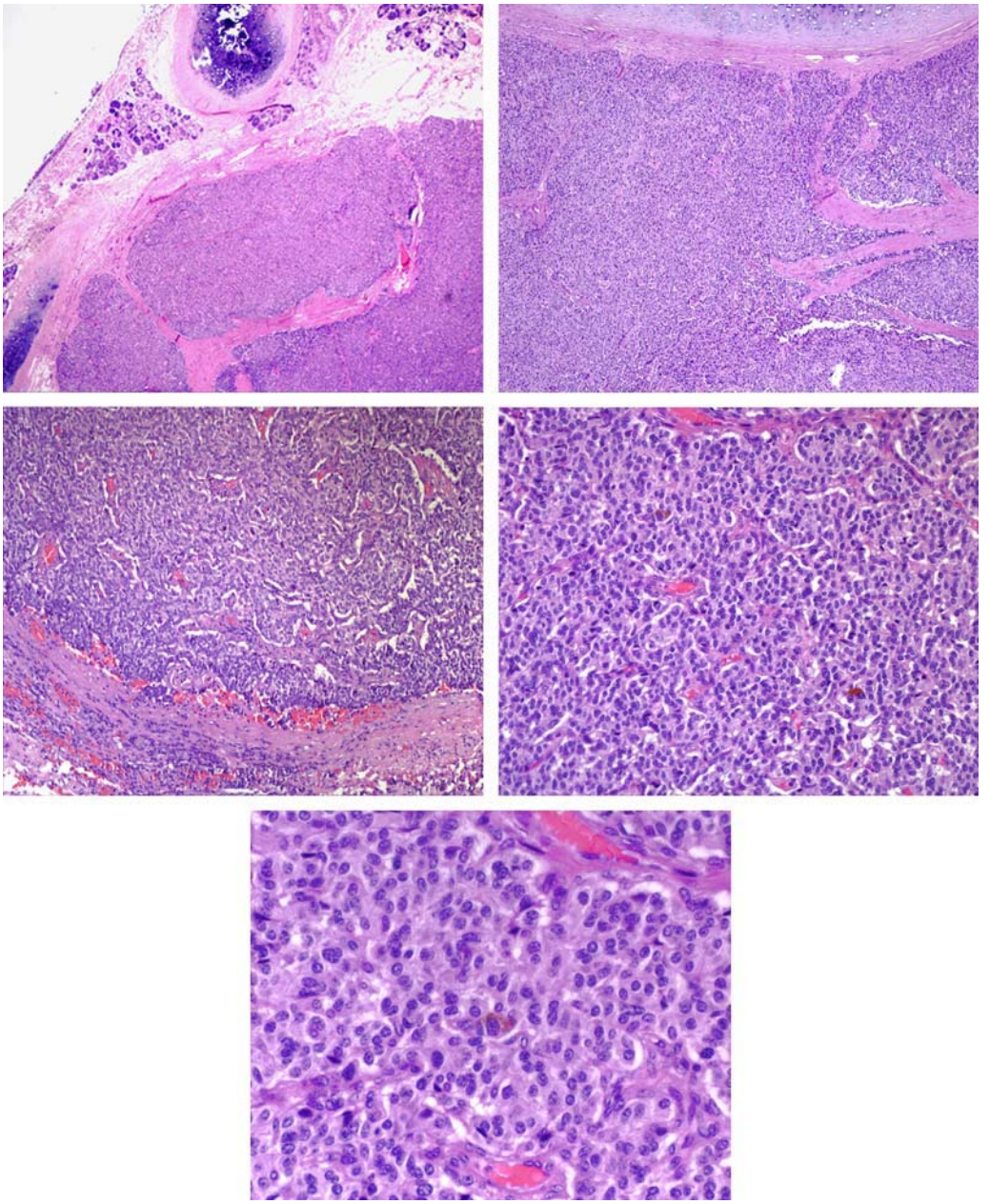
Case 6552

Diagnosis: Parietal pleura, open biopsy: DMM.

Epithelioid cells have pleomorphic nuclei with coarsened nuclear membranes sufficient for a diagnosis of malignancy. The location and appearance of the cells on the histochemical and immunochemical staining indicate a mesothelial proliferation. Therefore, I believe this is a DMM of the pleura. The appearance of the process at surgery is consistent with that interpretation. I believe there is invasion of dense of connective tissue planes in the parietal pleura. The tumor elicits desmoplastic inflammation and fibrosis in reaction to the invasion.

Thank you for referring this case in consultation. Other pathologists in the department have reviewed the case and concur with the above. Your special stains are hereby returned.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6552 (Chapter 10 – Pleural Tumors)

Case 6814

Diagnosis: Parietal pleura, thoracoscopic biopsy: DMM, well differentiated.

Clinically, the patient was found to have an effusion in the right hemithorax. She developed pain in the right mid upper back and epigastrium. She lost weight. The pleural effusion increased. The back pain worsened. Multiple thoracenteses were performed. No etiology was discovered for the recurrent pleural effusion. Approx 1 yr and 10 mo after initial detection of the pleural effusion, thoracoscopy was performed. The surgeon described the pleural space as loculated and saw no obvious tumor. Biopsies were obtained. Frozen section examination was interpreted as showing reactive mesothelial cells. Final pathological diagnosis of malignant mesothelioma of epithelioid type was made. Clinical, laboratory, and radiographic studies disclosed no other tumor in the body. The patient developed mild discomfort in the right side of the chest and lost weight.

Histopathologically, the pleura contains a malignant epithelioid tumor. The malignant cells have relatively small and oval and hyperchromatic nuclei with inconspicuous nucleoli and eosinophilic cytoplasm. The malignant epithelioid cells grow in sheets. The malignant epithelioid cells form cohesive nests, glandular structures, and numerous micropapillae. The malignant epithelioid cells grow upon the serosal surface. The malignant epithelioid cells invade fibrous lamellae of endothoracic fascia of chest wall. There is a moderate amount of desmoplastic inflammation and fibrosis in response to invasive tumor in adipose tissue.

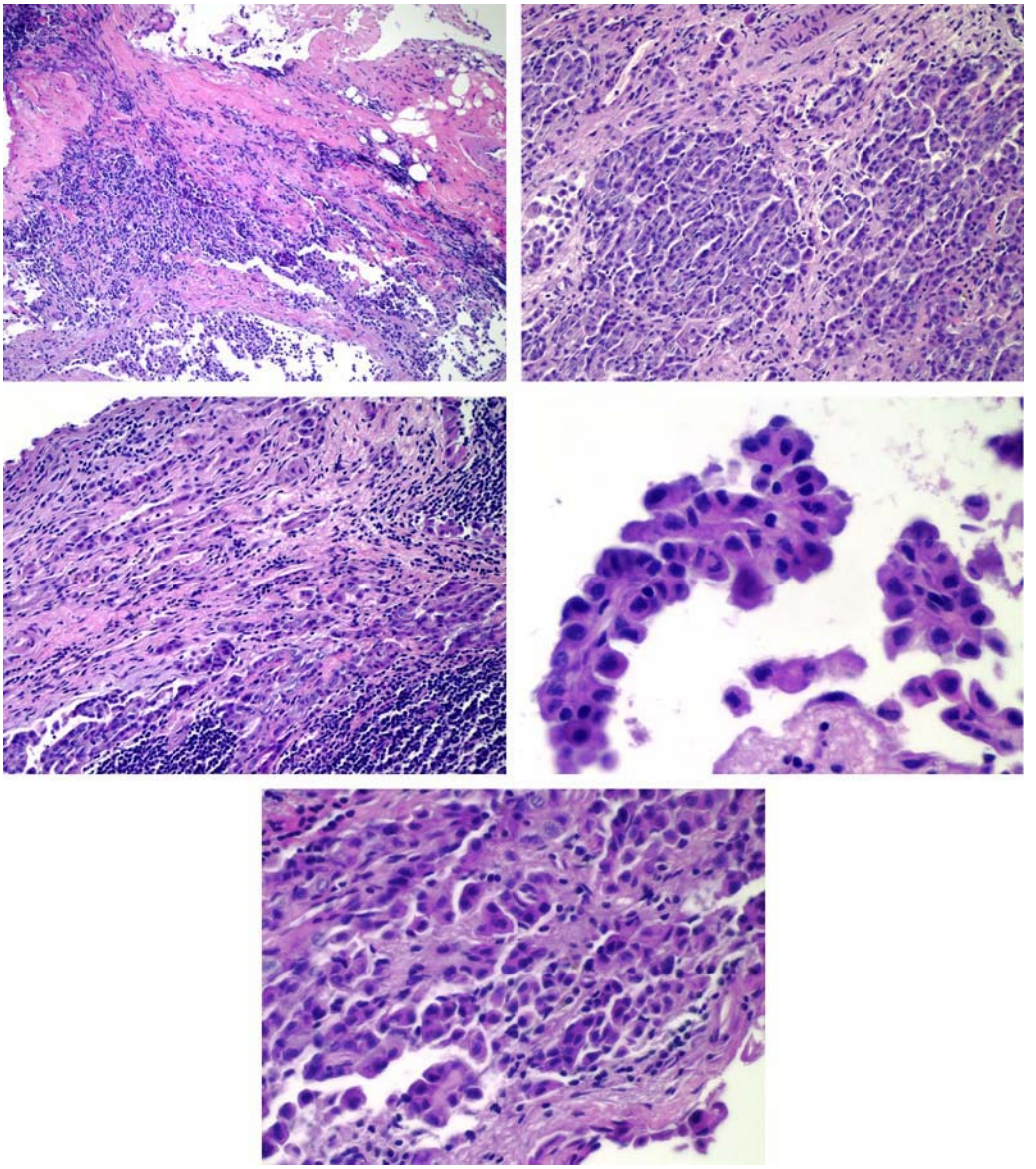
Cytopathologically, the preparations contain clumps and micropapillae of highly atypical mesothelial cells. The nuclei are relatively regular, but there is an increase in the ratio of nucleus to cytoplasm. Intercellular windows are visible. The highly atypical mesothelial cells are similar to the invasive malignant epithelioid cells in the histological preparations of the pleura.

The histopathological and cytopathological findings taken together indicate a DMM of the pleura. The DMM is well differentiated. Histopathologically, no alveolated lung parenchyma is present.

The patient may have been exposed to asbestos in school buildings where she worked. Asbestos is the only established cause of DMM in patients in the United States who have not received prior radiotherapy at the site of the tumor. All of the exposures to asbestos which occur prior to the development of a DMM contribute to its pathogenesis. All of the types of asbestos can cause DMM.

I conclude that the patient has developed a DMM of the pleura. I conclude that asbestos to which the patient was exposed caused the DMM.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6814 (Chapter 10 – Pleural Tumors)

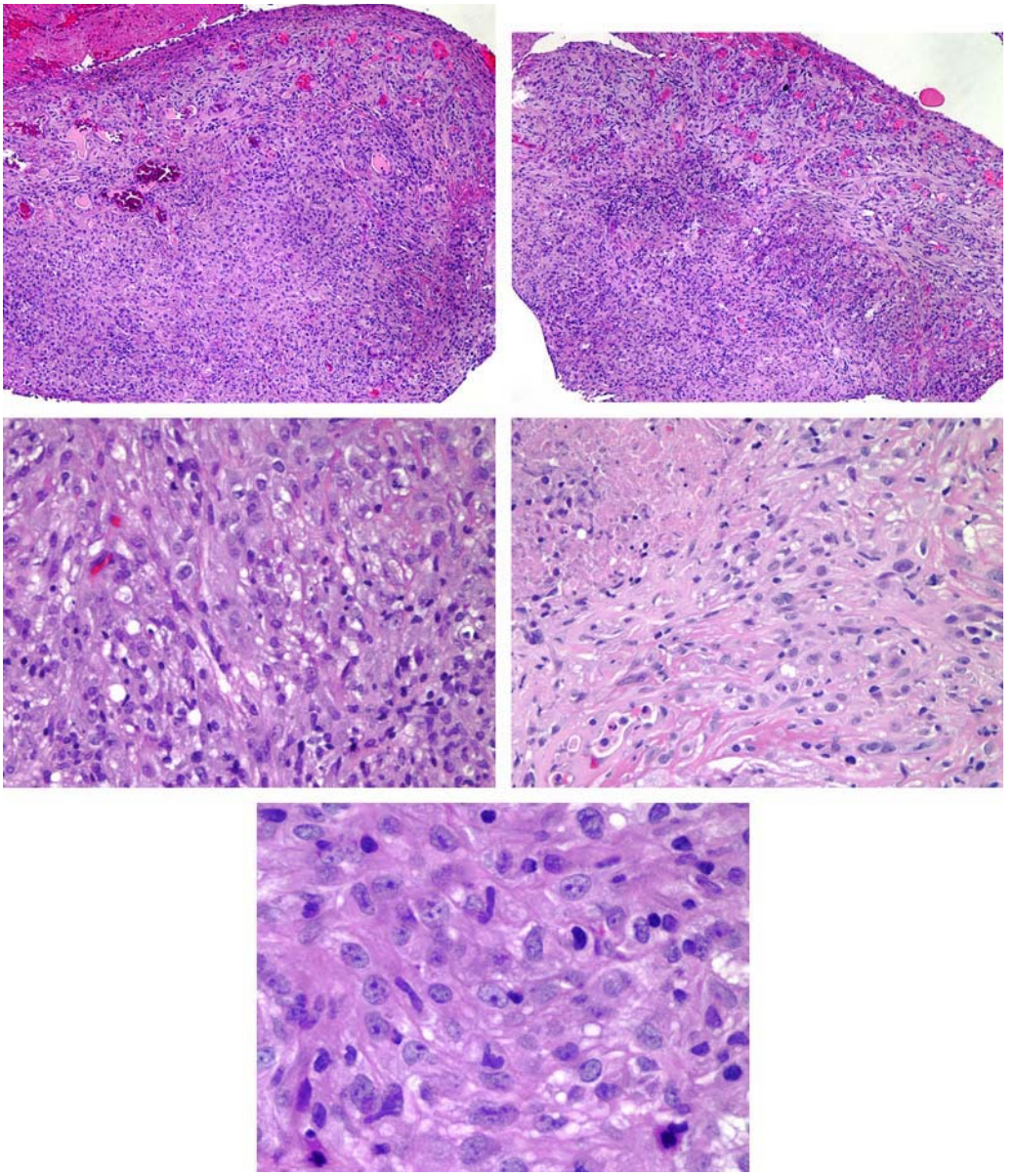
Case 6559

Diagnosis: Pleura, open biopsy: Malignant epithelioid tumor, consistent with DMM.

Nuclear pleomorphism suffices for a diagnosis of malignancy. The nuclei are relatively regular for most metastatic carcinomas to the pleura but are in keeping with DMM. Your immunopathological studies are consistent with that interpretation. However, I cannot absolutely exclude metastatic carcinoma from the kidney or bladder. These tumors may stain negatively with CEA and LeuM1, and I have seen both of these metastatic tumors presenting as pleural effusions and diffuse pleural thickening. If no tumors have been found in the kidney or bladder, then DMM becomes even more certainly the diagnosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. Your special studies are hereby returned. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6559 (Chapter 10 – Pleura Tumors)

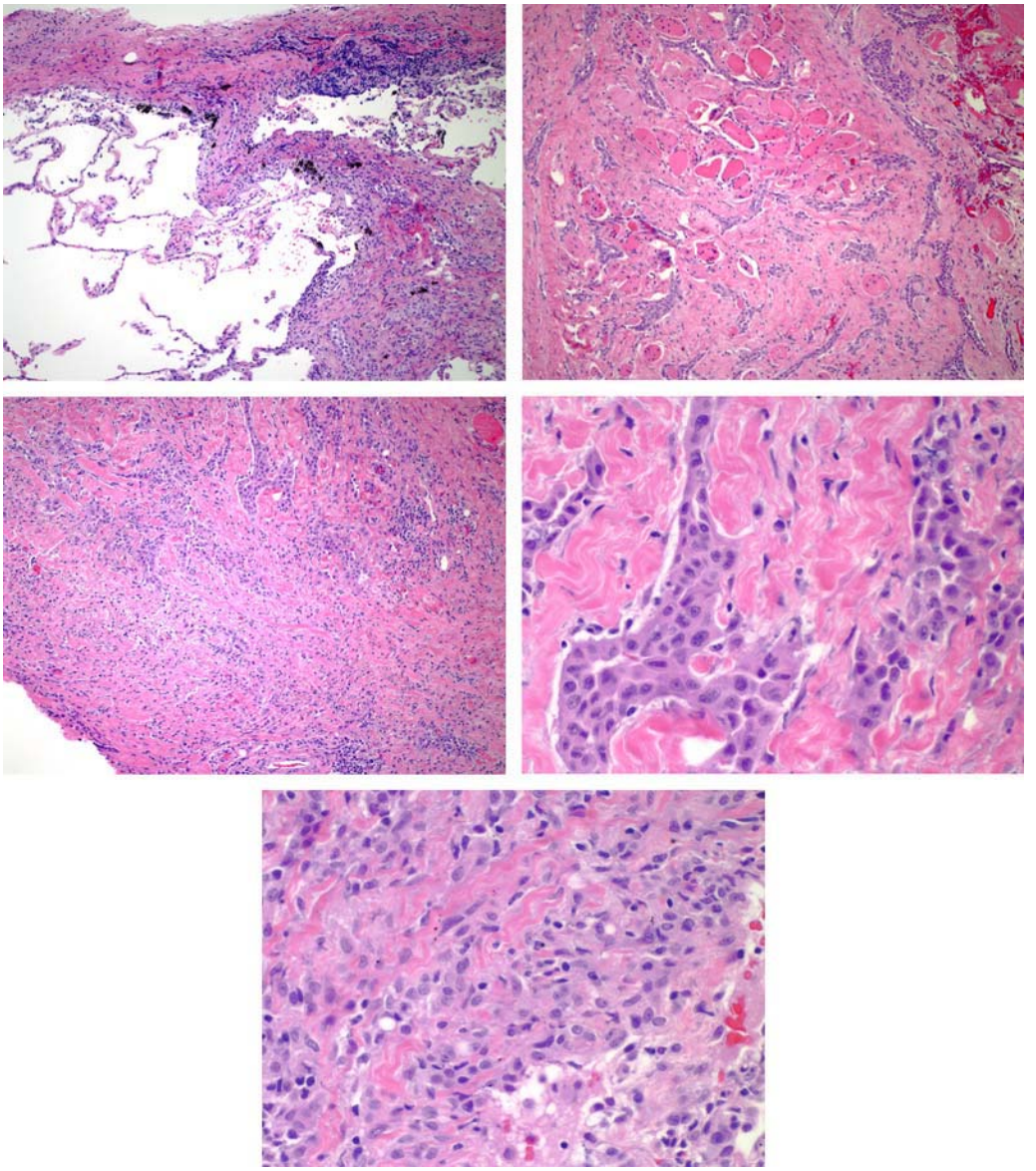
Case 6878

Diagnosis: Parietal and visceral pleura and lung, stripping: DMM.

This case is difficult because the cells are so uniform and bland even though there is invasion into skeletal muscle and into lobular septa of the lung. However, I cannot envision a manner by which cells could be located so deeply without being malignant. The cells appear mesothelial, so I believe this is a DMM. Your immunopathological studies serve to exclude adenocarcinoma. The principal differential diagnosis in this case is epithelioid angiosarcoma. There are occasional malignant cells with large vacuoles of the type seen with epithelioid angiosarcomas, and epithelioid angiosarcomas can stain positively for keratin. I favor DMM, however, both on a statistical basis and because the bland nature of the cells is in keeping with a mesothelial origin.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. All of your special stains are hereby returned. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6878 (Chapter 10 – Pleural Tumors)

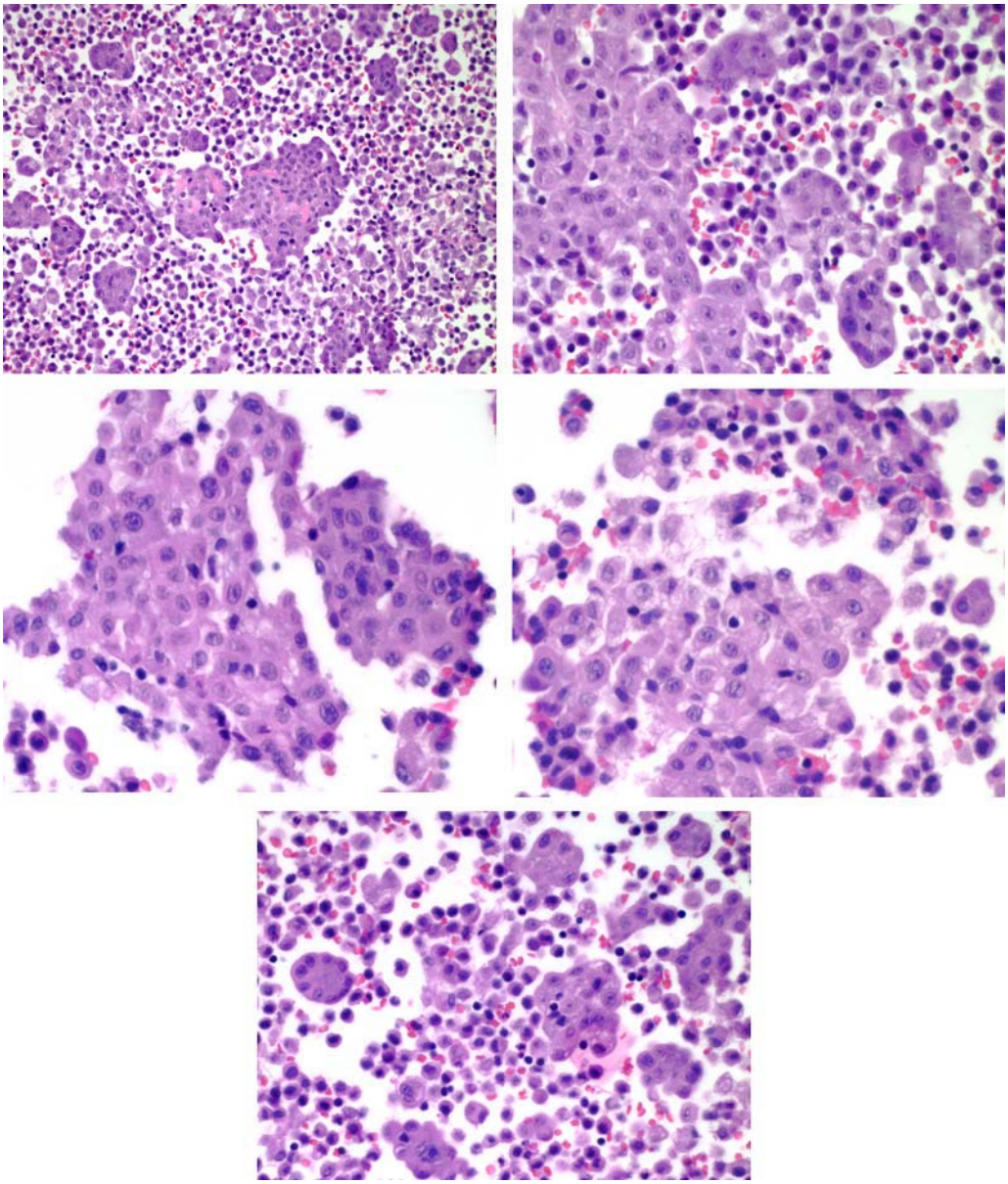
Case 6799

Diagnosis: Peritoneal fluid, cell block: Highly atypical mesothelial proliferation, consistent with DMM.

Numerous tightly packed nests and papillary projections of cells with pleomorphic nuclei are admixed with inflammatory cells. The cytological and architectural features of the cells make me believe that these are mesothelial, and your histochemical and immunochemical stains corroborate this interpretation. I am in general reluctant to make an absolute diagnosis of DMM on cytological grounds alone. However, in this case with the reported history of caking of the omentum and the highly atypical mesothelial cells on the cytological preparations, I believe that the correct clinicopathological diagnosis is a DMM.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6799 (Chapter 10 – Pleural Tumors)

Case 6777

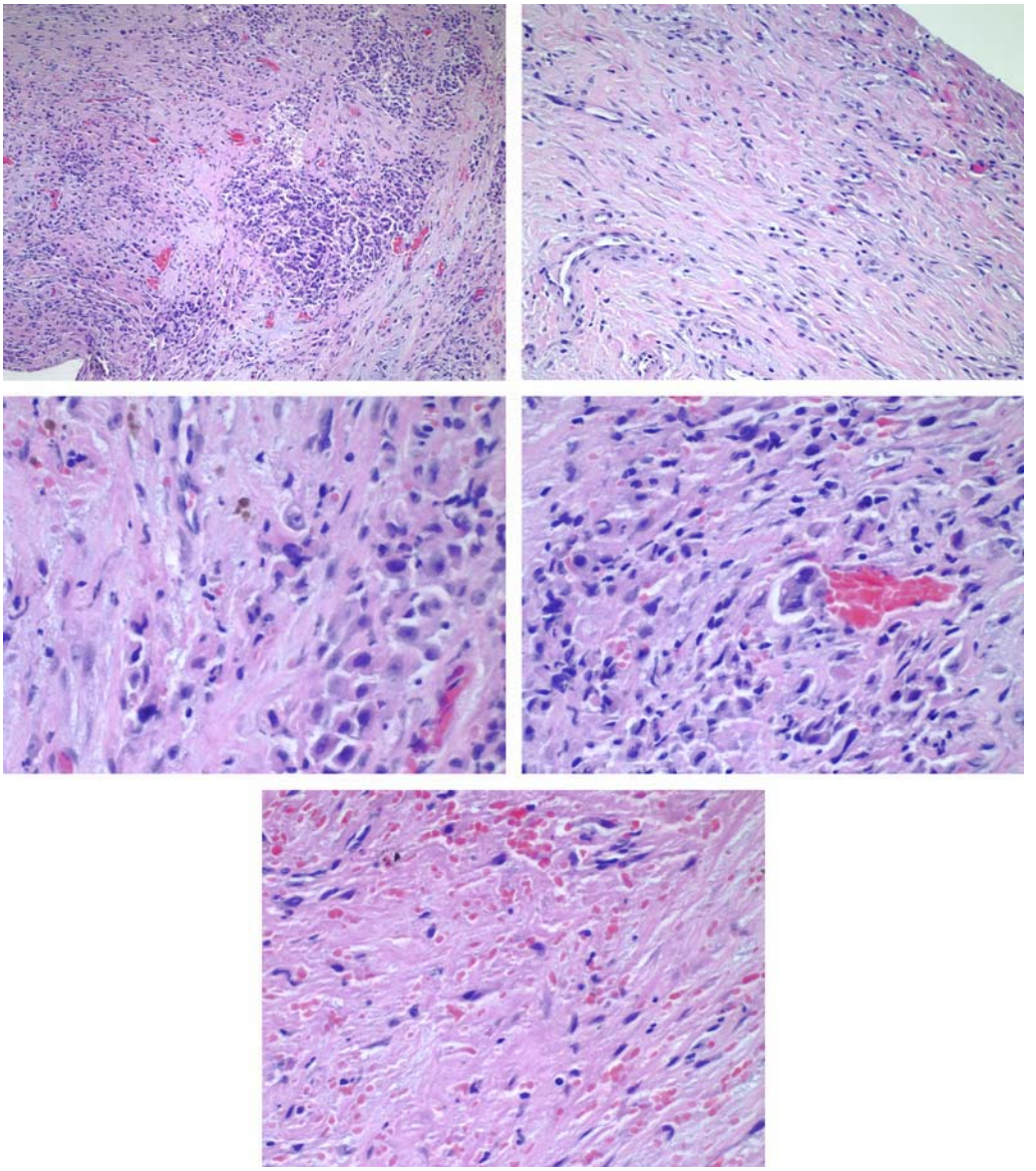
Diagnosis: Parietal pleura, open biopsies: DMM.

Sheets of malignant epithelioid cells have vacuolization in some areas and squamoid appearance in other areas. This picture is what is occasionally seen in early phase of DMM with predominantly squamoid histology. Although the nuclear pleomorphism here is more marked than usually observed in such cases, I do not believe the appearance of the tumor on routine stains is suggestive of pleural carcinomatosis, and your histochemical and immunochemical studies are against adenocarcinoma as well. A few of the malignant cells are spindled, and this biphasic pattern is consistent with DMM.

In the differential diagnosis, I considered a highly atypical reactive process because of the presence of organizing fibrin with ingrowth of capillaries and reactive mesothelial cells in areas of the biopsy. However, the nuclear features are beyond what I can accept for a reactive condition. In the differential diagnosis, I also considered epithelioid angiosarcoma because of the large vacuolar spaces and erythrocytes dispersed between the malignant cells. However, immunochemical and ultrastructural studies performed here exclude an endothelial origin of the tumor. The electronmicrographs (to be reported separately) are consistent with a DMM.

Thank you for referring this case in consultation. Other pathologists in the department have reviewed the case and essentially concur with the above. Please keep me informed of any follow-up.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6777 (Chapter 10 – Pleural Tumors)

Case 6751

Patient: 53-yr-old female

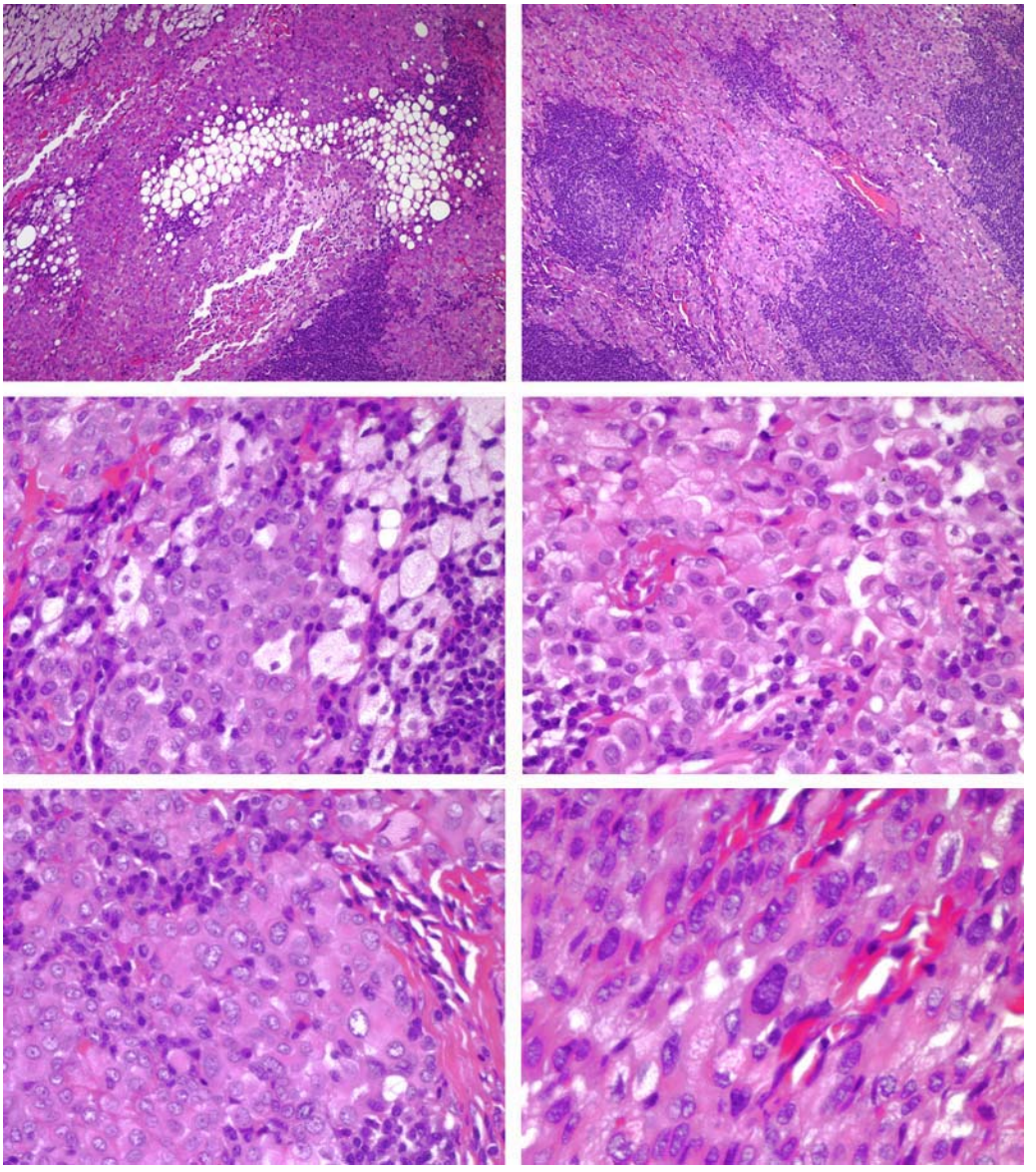
Diagnosis: Mediastinum, open biopsy: Malignant tumor, consistent with DMM.

This case is difficult. The fibroadipose tissue is infiltrated by cells which are primarily mononuclear with abundant cytoplasm. The squamoid features and the relatively innocuous nuclei in many areas make me believe that this is a DMM in early phase. I am convinced this is malignant by virtue of occasional pleomorphic nuclei with clumped chromatin as well as the infiltration through fibroadipose tissue and between lymphoid nodules. Your immunologic studies are consistent with DMM. I have seen other examples of DMM presenting with a diffusely infiltrative pattern reminiscent of a lymphoma, as is the case here.

Our differential diagnosis was broad. It included malignant lymphoma, lymphoepithelial carcinoma, thymoma, malignant melanoma, Rosai-Dorfman disease, panniculitis, sebaceous gland carcinoma, and reactive mesothelial proliferation. We do not favor any of these interpretations.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. I look forward to working again with you in the coming years. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6751 (Chapter 10 – Pleural Tumors)

Case 7090

Diagnosis: Parietal pleura, thoracoscopic biopsy: DMM.

The 62-yr-old patient experienced pain in his right chest. The pain was especially noted on deep breathing. He had also experienced shortness of breath for approx 4 mo and had become acutely short of breath during the 24 h before admission to hospital. He had been recently evaluated for congestive cardiomyopathy and started on therapy, which included digitalis and diuretics.

Radiographic studies of the chest showed an effusion in the right hemithorax. Thoracentesis was performed. A cytological examination of the pleural fluid was initially interpreted as adenocarcinoma. Subsequent to the thoracentesis, pleuritic chest pain continued. The patient became uncomfortable most of the time. Chemotherapy was begun. The patient then chose to discontinue chemotherapy. The patient became unable to walk more than 50 ft and required oxygen.

Video-assisted thoracoscopy was performed. The surgeon saw tumor studding of the entire parietal pleural surface including anterior and posterior chest wall, apex and diaphragm with exudate on the visceral pleural surface. Biopsies were obtained. Talc pleurodesis was performed. Clinical, radiographic, and laboratory studies disclosed no other tumor in the body. A pathological diagnosis of malignant mesothelioma was established. Pain became severe. The patient died approx 3 mo after initial cytopathological diagnosis of malignancy.

Histopathologically, the pleural biopsy is 6 mm in greatest diameter on the slides. The specimen is composed of a malignant epithelioid tumor. The nuclei are dark with obscured internal architecture and inconspicuous nucleoli. The nuclei are moderately or markedly enlarged. The nuclei vary in shape from round to oval to polygonal to spindled. Cytoplasm is abundant and eosinophilic. The malignant cells grow in a variety of patterns, including sheets, nests, and indian files. The malignant cells form tubuloalveolar and microcystic structures. Infiltrating malignant cells elicit a small amount of desmoplastic fibrosis, which in some areas is edematous and inflamed and in other areas sclerotic.

Cytopathologically, malignant epithelioid cells appear in sections of a cell block of pleural fluid and in smears of pleural fluid. The epithelioid cells are mesothelial cells, which are highly atypical. The cells form many micropapillae. Occasional cells have solitary large cytoplasmic vacuoles. Intercellular windows are visible between some of the cells. Neutrophils are admixed with the highly atypical mesothelial cells. In retrospect, the highly atypical and malignant mesothelial cells are the same malignant epithelioid cells that appear in the biopsy.

Immunochemical studies were performed on the biopsy. The malignant cells reportedly stained for calretinin, cytokeratin 7, pankeratin, epithelial membrane antigen, and thrombomodulin. The malignant cells reportedly did not stain for carcinoembryonic antigen, Ber-EP4 antigen, or CD15 antigen. These slides are not available for review.

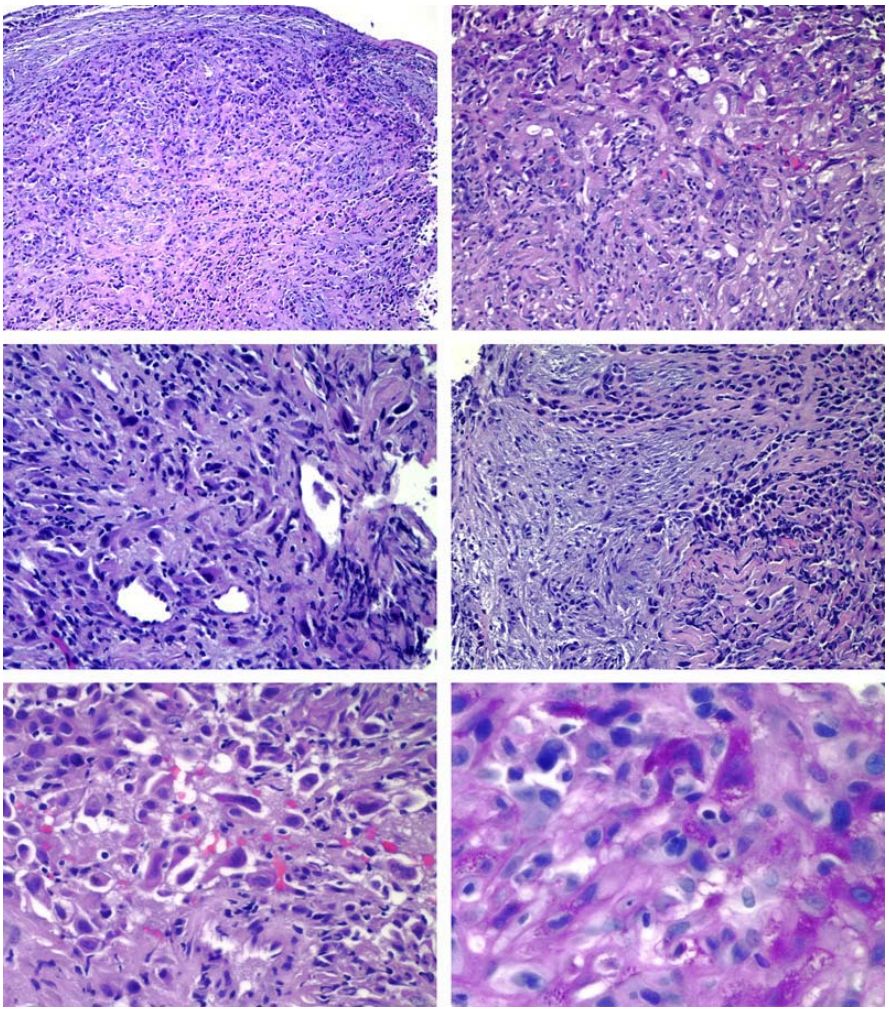
Histochemical and immunochemical stains have been performed on the cell block of pleural fluid. Histochemically, the malignant cells do not stain for cytoplasmic mucin with a mucicarmine stain. The malignant cells contain granules in the cytoplasm which stain positively with a periodic acid-Schiff stain. The malignant cells do not stain with an alcian blue stain. Immunochemically, the malignant cells stain positively for Ber-EP4 with high background staining on initial analysis and do not stain on a repeat analysis

performed at a higher dilution. The malignant cells stain positively for calretinin. The malignant cells stain positively for cytokeratin 5/6. The malignant cells do not stain for carcinoembryonic antigen. The histopathological and cytopathological findings including the histochemical and immunochemical results indicate a DMM of the pleura.

The patient was exposed to asbestos. Asbestos is the only established cause of DMM in patients in the United States who have not received prior radiotherapy at the site of the tumor. All of the exposures to asbestos which occur prior to the development of a DMM contribute to its pathogenesis. All of the types of asbestos can cause DMM.

I conclude that the patient developed a DMM of the pleura. I conclude that the asbestos to which the patient reportedly was exposed caused the DMM. I conclude that the DMM spread and caused death.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7090 (Chapter 10 – Pleural Tumors)

Case 6577

Diagnosis: Parietal pleura, open biopsy: DMM.

The 73-yr-old patient experienced progressive shortness of breath and dyspnea on exertion over an interval of 1 yr. During the latter part of this interval, he also experienced pleuritic pain in the left chest, anorexia, and weight loss. Radiographic studies of the chest showed a large effusion in the left hemithorax. Thoracentesis was performed. No diagnosis was established. Thoracoscopy was performed. The surgeon lysed adhesions, obtained biopsies of the pleura, and performed a talc pleurodesis. A pathological diagnosis of malignant mesothelioma was established. Clinical, radiographic, and laboratory studies showed no other tumor in the body. The patient died approx 2 mo after initial pathological diagnosis of malignancy. The cause of death was mesothelioma according to the Certificate of Death. No autopsy was performed.

Histopathologically, the parietal pleura is thickened relatively uniformly to approx 4 mm by a hypercellular tumor which is composed of spindled cells. The nuclei are elongated and hyperchromatic. The nuclei are separated by finely fibrillar collagen. The malignant cells grow in fascicles and form storiform arrays throughout the specimen. The spindled cells infiltrate fibroadipose tissue of chest wall, encircle blood vessels and nerves, and, in areas, comprise the pleural surface. Portions of the surface are eroded and covered by fibrin, into which grow the spindled cells. No lung parenchyma is available for review.

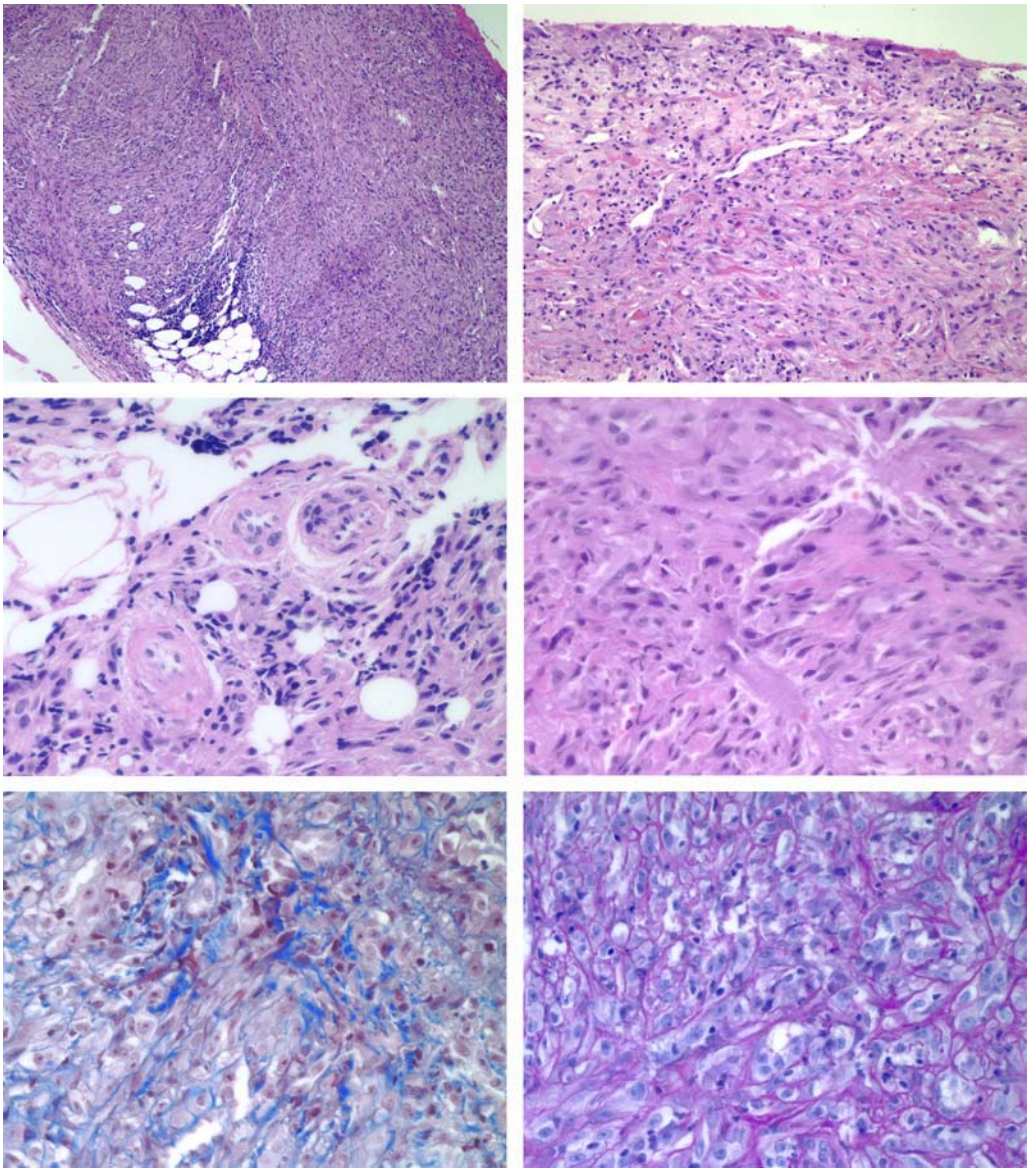
Immunochemically, the spindled cells stain strongly for keratin. The malignant cells reportedly stained positively for calretinin and reportedly did not stain for carcinoembryonic antigen, LeuM1 antigen, Ber-EP4, B72.3 antigen, S-100 antigen, or HMB-45 antigen. These results are consistent with a DMM.

The trichrome stain shows production of collagen by the malignant cells. The elastic tissue stain shows disruption of the elastic fibers of parietal pleura by the malignant cells. The periodic acid-Schiff stain shows an absence of intracytoplasmic globular material. These results are consistent with a diagnosis of DMM.

The patient was exposed to asbestos for many years according to the medical records. Asbestos is the only established cause of DMM in patients in the United States who have not received prior radiotherapy at the site of the tumor. All of the exposures to asbestos which occur prior to the development of a DMM contribute to its pathogenesis. All of the types of asbestos can cause DMM.

I conclude that the patient developed a DMM of the pleura. I conclude that the asbestos to which the patient reportedly was exposed caused the DMM. I conclude that the DMM caused death.

Sincerely yours,
Eugene J. Mark, M.D.



Case 6577 (Chapter 10 – Pleural Tumors)

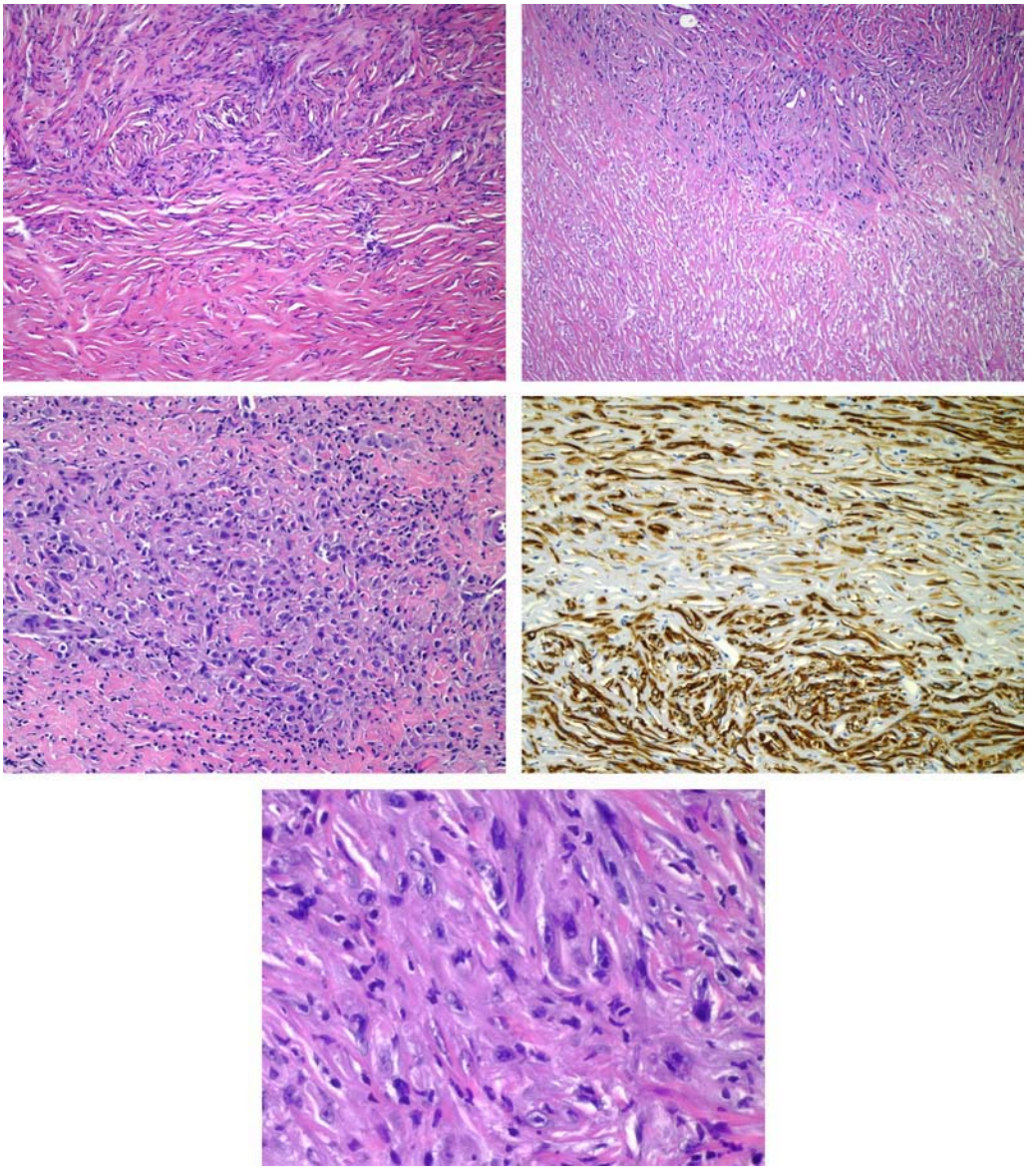
Case 6987

Diagnosis: Pleura, open biopsy: DMM, desmoplastic subtype.

The pleura is thickened to 6 mm by a spindle cell proliferation. The storiform pattern in richly cellular areas and keloidal pattern in poorly cellular areas suggest DMM of mesenchymal type and desmoplastic subtype. In some regions the nuclei of the spindled cells are pleomorphic and have large nucleoli. The focal necrosis in conjunction with these patterns suffices for a diagnosis of malignancy despite the absence of demonstrable invasion into either soft tissue of chest wall or into lung in my opinion. The spindled cells stain as mesothelial cells with your keratin stain. No lung parenchyma is present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6987 (Chapter 10 – Pleural Tumors)

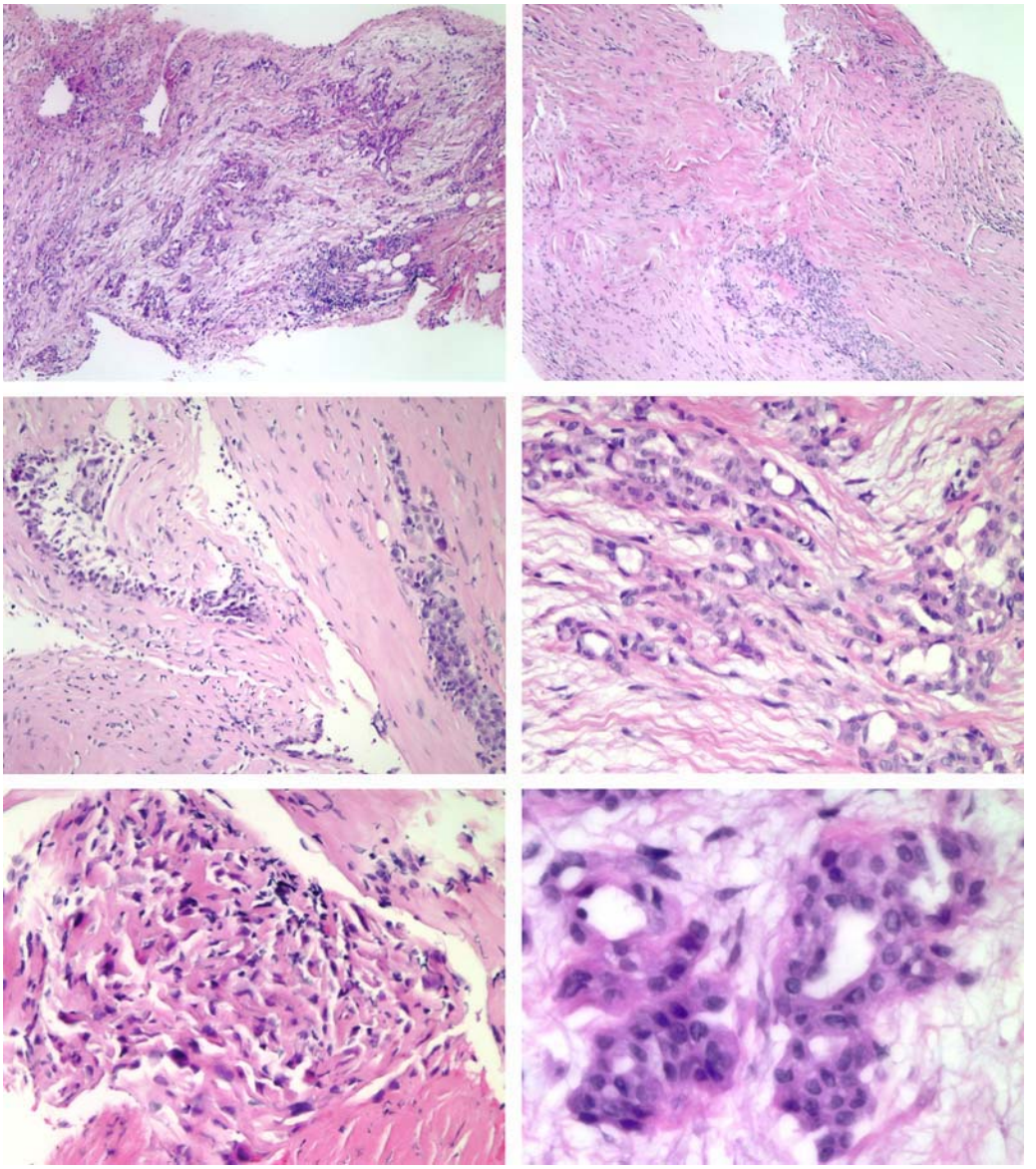
Case 6576

Diagnosis: Pleura, thoracoscopic biospy: DMM.

This relatively small biopsy provides evidence of both the epithelioid and mesenchymal components of a malignant tumor, which facilitates the diagnosis of DMM. Distinct glandular architecture is produced in one region, and these cells stain negatively for mucin with mucicarmine and stain negatively for carcinoembryonic antigen. A sarcomatous area is present in another region. Spindled cells and intermediate cuboidal cells in this region stain positively for keratin and are malignant by virtue of hypercellularity. The three other very unusual biphasic tumors which can present in the pleura (synovioma, renal cell carcinoma, hemangioendothelioma) would not have the morphology apparent here. Therefore, I believe one can make a diagnosis of DMM on this specimen. The clinical and surgical findings are consistent with that interpretation.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have any questions. I have retained one slide stained with hematoxylin and eosin for our permanent teaching collection in pulmonary pathology and hereby return all of the remainder, which include all of your special studies. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6576 (Chapter 10 – Pleural Tumors)

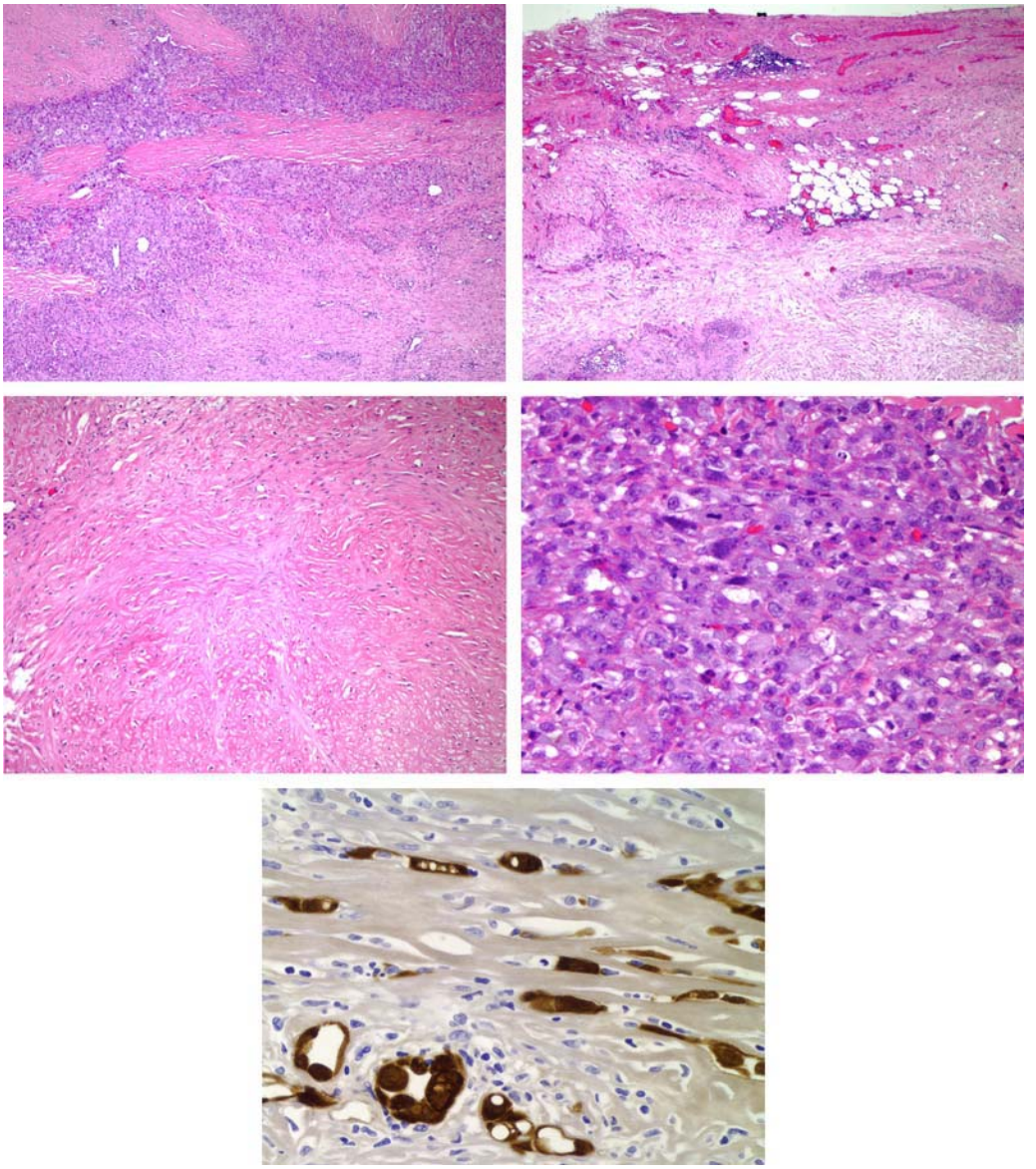
Case 6919

Diagnosis: Parietal pleura, pleurectomy: DMM.

There is a classic admixture of malignant mesenchymal and malignant epithelioid tumor creating a pleural rind more than 1 cm in thickness on average. The mesenchymal portion has fascicular and storiform patterns characteristic of DMM. The epithelioid portion is rather more anaplastic than generally observed at the time of the first biopsy of DMM but consistent with the diagnosis. Tumor invades into fibroadipose tissue and reaches to endothoracic fascia. Your immunopathological studies (calretinin) confirm the mesothelial nature of this malignant neoplasm. No lung parenchyma is present.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. Your special stains are returned under a separate cover. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6919 (Chapter 10 – Pleural Tumors)

Case 7089

Diagnosis: Parietal pleura, open biopsy:

1. **DMM.**
2. **Pleural hyaline plaque.**

Clinically, the 64-yr-old patient experienced discomfort in the right chest of 3 wk duration. Physical examination revealed dullness to percussion and diminished breath sounds to auscultation in the right lower chest. Radiographic studies of the chest showed an effusion in the right hemithorax. Thoracentesis and needle biopsy of the pleura were performed. No definite diagnosis was established. The patient experienced increasing dyspnea. Pleural fluid reaccumulated. The patient developed a low grade fever.

Video-assisted thoracoscopy was performed. The surgeon saw multiple tumor nodules throughout the parietal and visceral pleura. Biopsies were obtained. A frozen section diagnosis of malignant neoplasm was made. Talc pleurodesis was accomplished. A final diagnosis of malignant neoplasm most consistent with DMM of intermediate grade with epithelioid and microcystic features was made. Clinical and radiographic studies showed no other tumor in the body.

Histopathologically, the parietal pleura is thickened both linearly and in a nodular fashion up to approx 6 mm by a malignant neoplasm with biphasic features. The majority of the tumor is epithelioid, whereby the cells have large and hyperchromatic and moderately pleomorphic nuclei with inconspicuous nuclei and abundant eosinophilic cytoplasm. The epithelioid cells grow in sheets and indian files. In the nodules the malignant epithelioid cells form microcysts. Some of the malignant epithelioid cells contain large cytoplasmic vacuoles. The malignant epithelioid cells grow upon the serosal surface in a monolayer and bilayer. The malignant epithelioid cells are enmeshed in some areas within fibrin. The malignant cells infiltrate as tubuloalveolar structures and single cells into fibroadipose tissue and elicit desmoplastic inflammation. A minority of the tumor is mesenchymal, whereby hyperchromatic spindled nuclei are separated by collagen and form fascicles. The pathological findings including the variety of patterns of growth and the character of the cells and their manner of spread characterize a DMM of the pleura.

Histopathologically, a prior needle biopsy of the pleura shows a few highly atypical epithelioid cells and a few highly atypical spindled cells. In retrospect, these cells represent the same DMM. These cells infiltrate through fibrous tissue in the needle biopsy. Cytopathologically, specimens of pleural fluid show highly atypical epithelioid mesothelial cells forming clumps and numerous micropapillae. These cells represent the same DMM. Histopathologically, pleural hyaline plaque is present. Paucicellular bundles of collagen in a basket-weave characterize pleural hyaline plaque that occurs after exposure to and inhalation of asbestos. No alveolated lung parenchyma is present.

Histochemically, a mucicarmine stain shows an absence of intracytoplasmic mucin in the malignant epithelioid cells of the DMM. A periodic acid-Schiff stain shows granular staining in the malignant epithelioid cells but no globular staining. Methenamine silver stain and acid-fast stain of the prior needle biopsy of the pleura show an absence of fungi and mycobacteria, respectively. An iron stain of the pleural tumor shows an absence of hemosiderin. The elastic-van Gieson and trichrome stains show production of collagen by the tumor, desmoplastic inflammation, and disruption of elastica by invasive tumor.

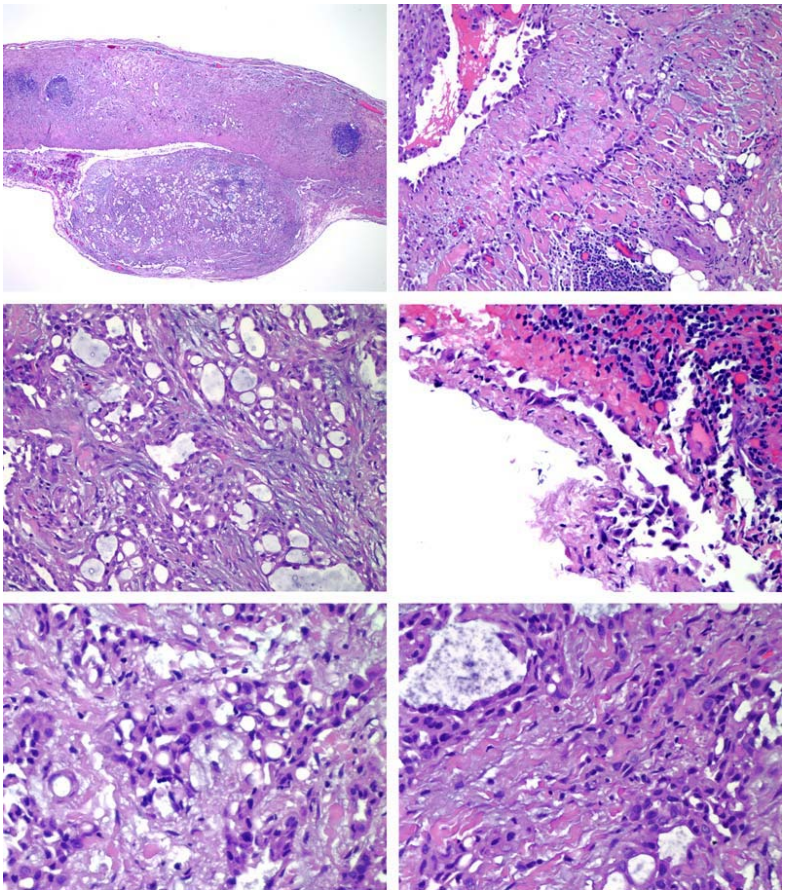
Immunochemically, the malignant cells stain for cytokeratin. The malignant cells do not stain for carcinoembryonic antigen, LeuM1 antigen, or epithelial membrane antigen. The histochemical and immunochemical findings corroborate the diagnosis of DMM.

Electron microscopy reportedly was performed. The electron micrographs reportedly showed neoplastic cells that are joined by well developed desmosomes and cell membranes that are covered by abundant long microvilli. The ultrastructural studies corroborate the diagnosis of DMM.

The patient was exposed to asbestos according to the medical records. Asbestos is the only established cause of DMM in patients in the United States who have not received prior radiotherapy at the site of the tumor. All of the exposures to asbestos which occur prior to the development of a DMM contribute to its pathogenesis. All of the types of asbestos can cause DMM.

I conclude that the patient has developed pleural hyaline plaque and a DMM of the pleura. I conclude that the asbestos to which he reportedly was exposed caused the pleural hyaline plaque and the DMM.

Sincerely yours,
Eugene J. Mark, M.D.



Case 7089 (Chapter 10 – Pleural Tumors)

Case 6798

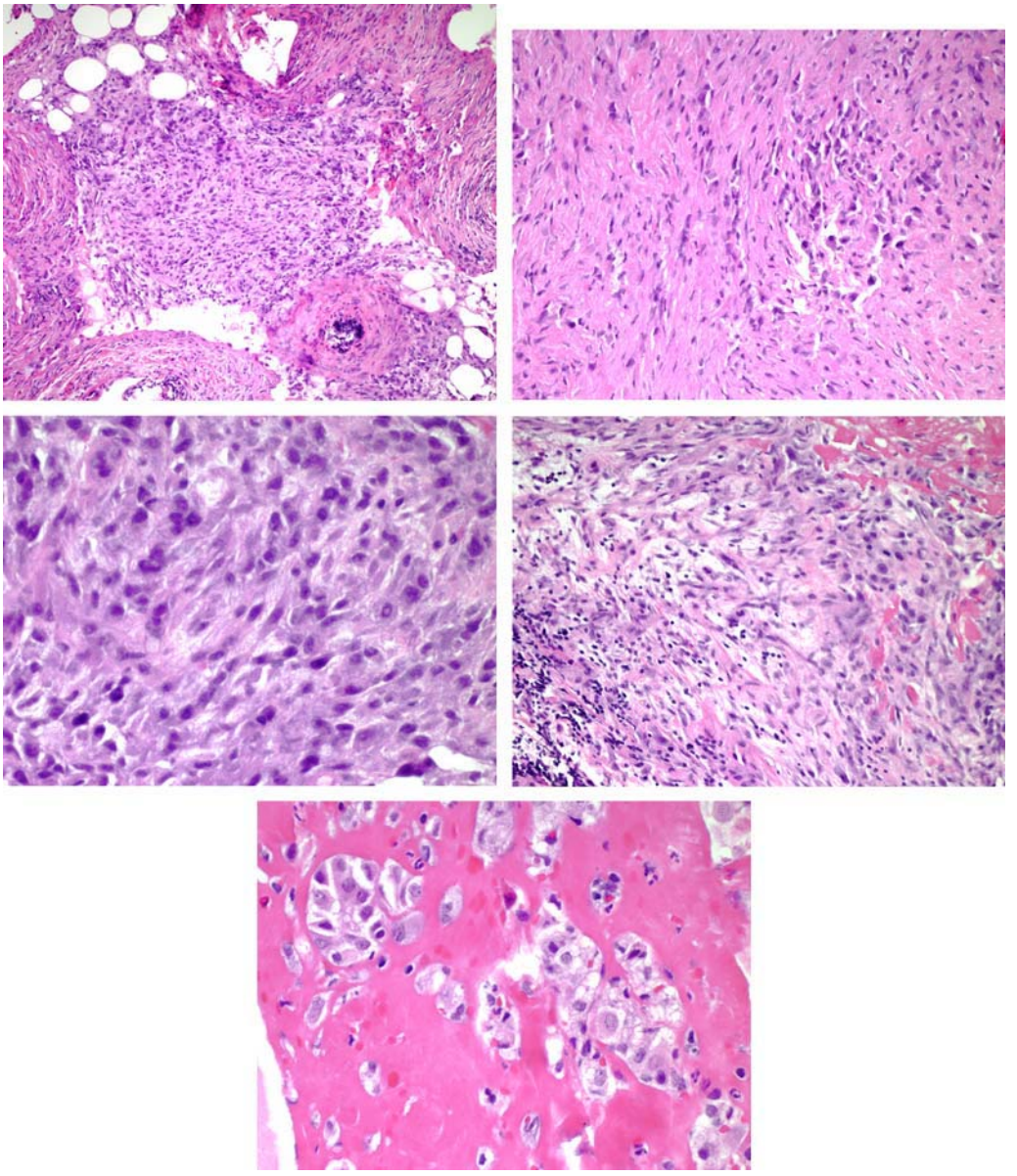
Diagnosis: Pleura, open biopsy: Malignant biphasic tumor, consistent with DMM.

The biopsy of the tumor mass used for frozen section shows numerous cells with pleomorphic nuclei. Malignancy seems established because of the pattern of invasion of fibroadipose tissue as well as the nuclear features. There are both epithelioid and mesenchymal aspects of the infiltrating tumor, and both epithelioid and mesenchymal aspects are malignant. This is the strongest point in favor of DMM in this case. I attempted to study the case further with immunopathological analysis and obtained several stains, but there was insufficient tissue remaining in the block for definitive interpretation. I cannot absolutely exclude a sarcomatoid carcinoma infiltrating pleura or chest wall, but I favor DMM.

The cell block of the fluid shows highly atypical mesothelial cells, which probably represent this tumor. However, highly atypical mesothelial cells can also develop on a serosal surface overlying infiltrating carcinoma.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6798 (Chapter 10 –Pleural Tumors)

Case 4438

Diagnosis: Peritoneum, omentum, ovaries, and fallopian tubes: DMM.

The 41-yr-old patient developed pain in the right upper quadrant of the abdomen and swelling of the abdomen. She had a history of hysterectomy for carcinoma *in situ* and tubal ligation. Computerized tomograms of the abdomen showed ascites and enlarged liver and spleen. Her abdomen enlarged progressively over the next 3 mo. Peritoneoscopy revealed multiple nodules on the peritoneum. A biopsy of one of these nodules was interpreted as infiltrating malignant tumor most consistent with well differentiated epithelioid mesothelioma. Exploratory laparotomy was performed. Multiple yellow lobulated nodules of tumor covered the omentum, fallopian tubes, ovary, bowel, and peritoneum. One nodule infiltrated the abdominal wall near the umbilicus. Tumor covered the appendix. A pathological diagnosis of well differentiated epithelioid mesothelioma was made. The patient was treated with repeated paracenteses and diuretics. Fluid reaccumulated in the abdomen. Pain developed in the abdomen. Approximately 15 mo after initial pathological diagnosis of malignancy, the patient developed fever and weakness thought to be due to viral infection. She also developed pleural effusions, subpulmonic effusions, subsuperior vena caval syndrome, palpable metastatic disease in the peritoneum with Sister Mary Joseph nodules.

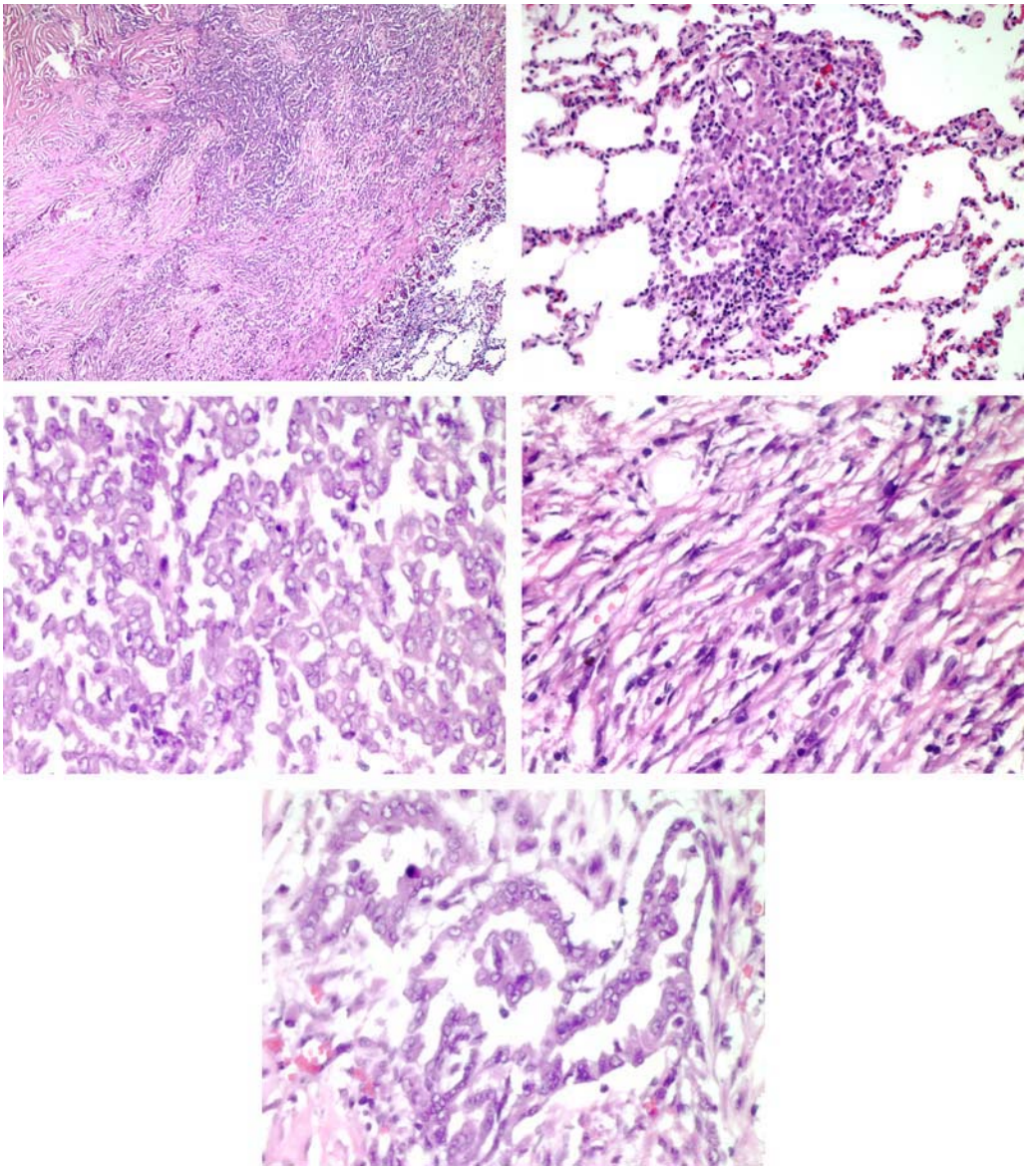
Histopathologically, the serosal surface of the omentum, fallopian tubes, and ovaries is covered by a DMM which is biphasic. The majority of the tumor is epithelioid. Large and relatively regular oval nuclei and pale eosinophilic cytoplasm comprise this portion of the tumor. The epithelial cells form long tortuous glands infiltrating into omentum. The epithelioid cells form a monolayer and bilayer over the serosal surface. Where the cells form a monolayer, they appear in the hobnail fashion. A minority of the tumor is mesenchymal. Elongate pale nuclei and indistinct fibrillar cytoplasm characterize these cells. The mesenchymal tumor forms nodules in a piece of skin and in the ovaries. Nodules of tumor are present on the serosal surface of the bowel. Separate biopsies of liver and of stomach are unremarkable. Appendix has fibrous obliteration of the lumen.

The malignant tumor stained positive for MAK6 keratin and CA125 keratin, weakly positive for epithelial membrane antigen, and negative for carcinoembryonic antigen, LeuM1 antigen, S-100 antigen, and PLAP. These results corroborate the diagnosis of DMM.

The patient was exposed to asbestos for many years previously. Asbestos is the only established cause of DMM in patients in the United States who have not received prior radiotherapy to the site of the tumor.

I conclude that the patient developed a DMM of the peritoneum. I conclude that the mesothelioma spread within the abdomen and within the chest. I conclude that the asbestos to which the patient reportedly was exposed caused her DMM.

Sincerely yours,
Eugene J. Mark, M.D.



Case 4438 (Chapter 10 – Pleural Tumors)

Case 7051

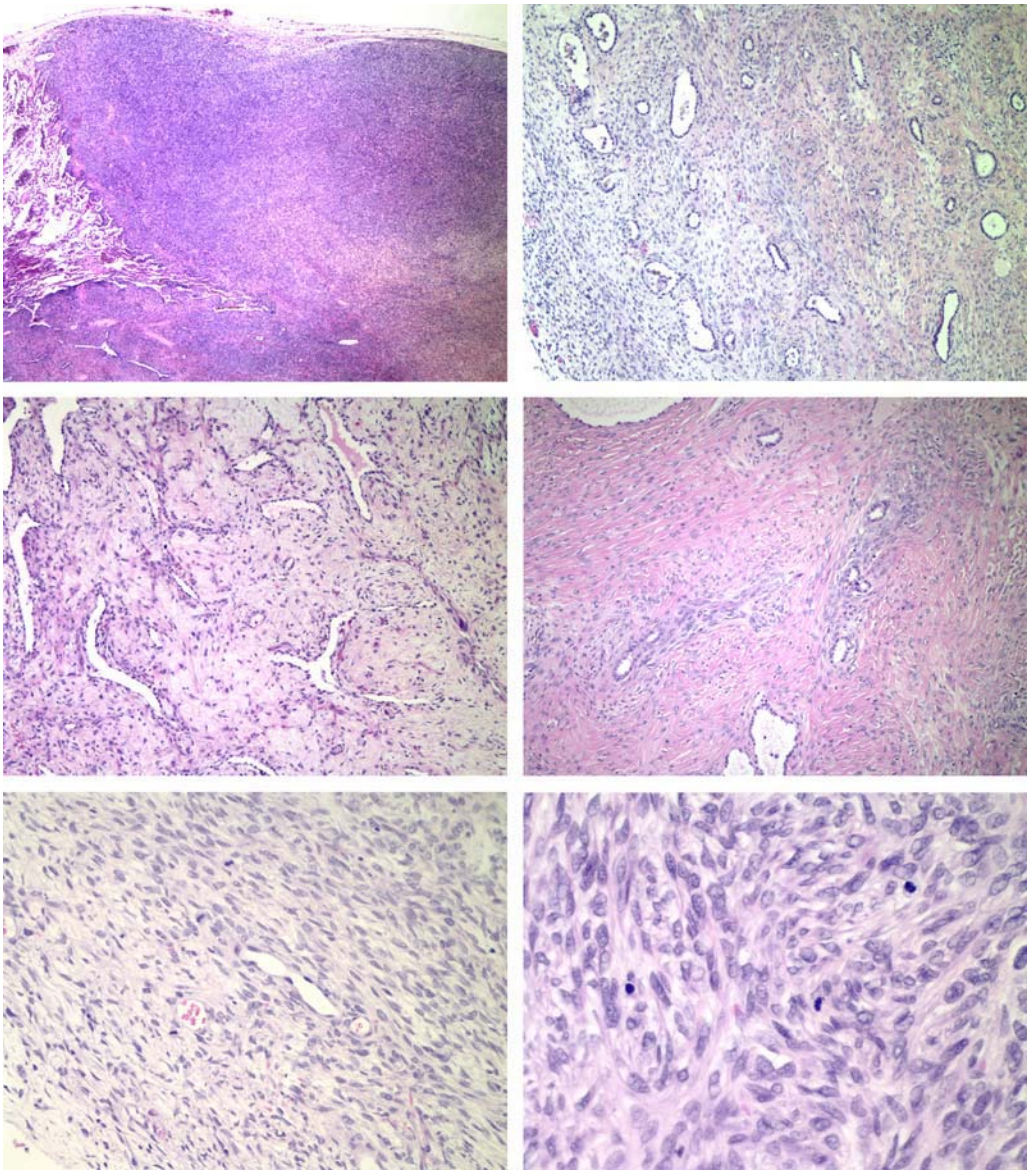
Patient: 62-yr-old female

Diagnosis: Lung, lobectomy: Malignant fibrous tumor (fibrosarcoma) of the pleura.

Regions of this tumor appear like a fibrous tumor of the pleura, in that fascicles of spindled cells expand interstitium at the periphery of the mass and entrap reactive pneumocytes. I agree that this lesion must be considered malignant because of the mitoses, and there are many apoptotic cells as well that simulate mitoses. The tumor is attached to the visceral pleura over a large area. Poorly cellular regions of the tumor are present as well, and some of these have a myxoid or chondroid appearance. This is not typical for fibrous tumor of the pleura, although I have seen small amounts of it in other examples. I favor a fibrous tumor of the pleura over a metastasis. The differential diagnosis includes principally metastatic synovial sarcoma or metastatic fibrosarcoma, but I believe the histology is more in keeping with a malignant fibrous tumor of the pleura. Some persons consider malignant fibrous tumor of the pleura to be a subtype of fibrosarcoma.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and all if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7051 (Chapter 10 – Pleural Tumors)

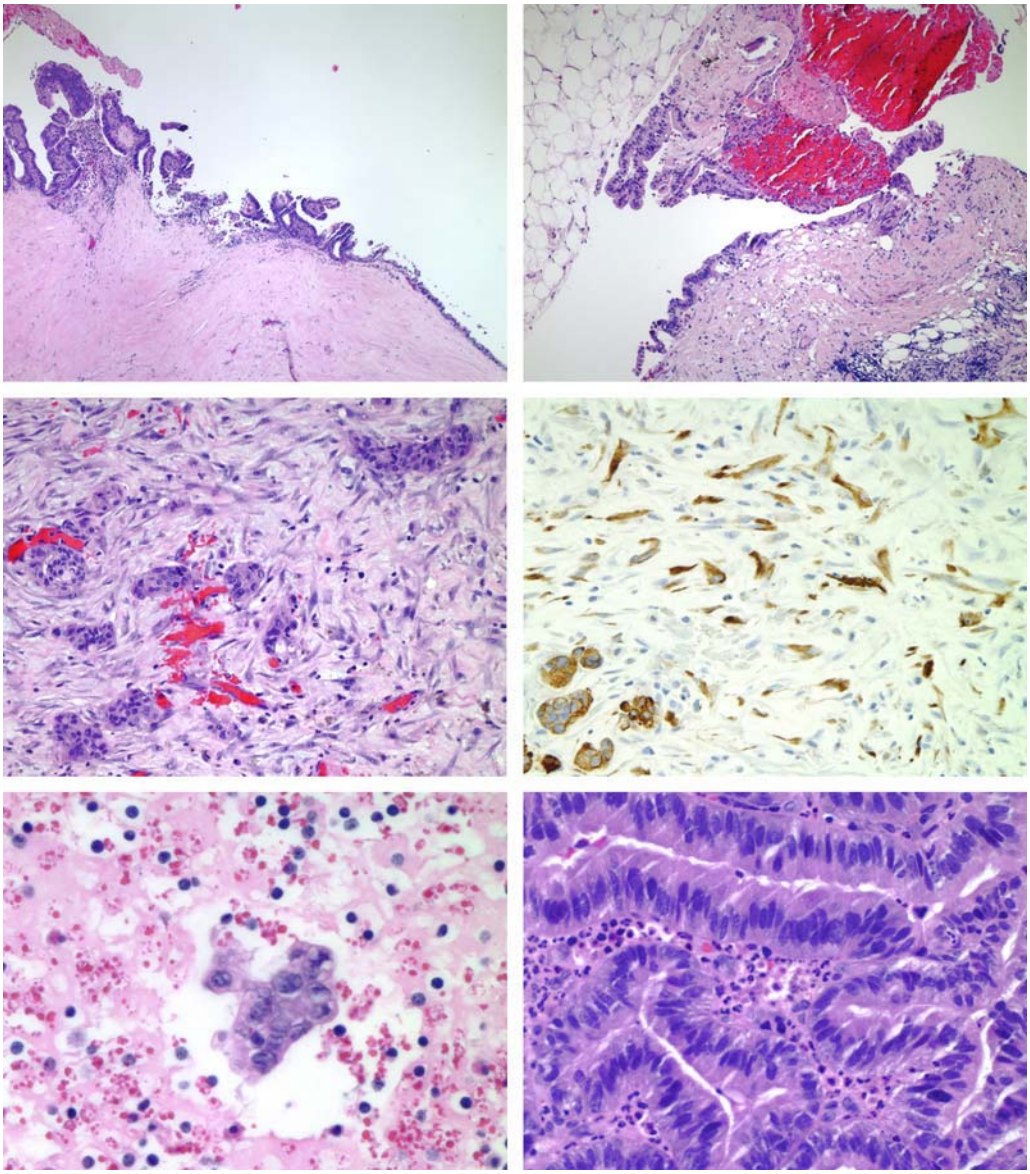
Case 6724

Diagnosis: Lung and pleura, open biopsy: Metastatic adenocarcinoma to the pleura.

This case is unusual in that the metastatic adenocarcinoma is virtually confined to the serosal surface and spreads there in a manner typical of a mesothelial proliferation. However, there are a few nests of adenocarcinoma within the pleura, probably invasive of pleura rather than within lymphatics. The distinct columnar palisading of the tumor cells with basal nuclei, apical pink cytoplasm and brush border are not those of a DMM. They suggest to me an origin in one of the following locations: biliary tract, pancreatic tract, gallbladder, colon, or lung. Occasionally carcinomas arising in the lung can have essentially only pleural spread when first discovered. These cases are referred to as pseudomesotheliomatous carcinomatosis of the lung. However, this metastatic pattern comes from a subpleural carcinoma of the lung, and no such subpleural carcinoma is apparent here. I interpret your mucicarmine stain as positive with small vacuoles in the tumor cells. I believe the bizarre spindled cells in the pleura, which stain for keratin, are reactive mesothelial cells and not malignant. The lung otherwise contains pigmented histiocytes consistent with cigarette smoking and focal interstitial fibrosis with carbon and silica consistent with inhalation of dusts.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6724 (Chapter 10 – Pleural Tumors)

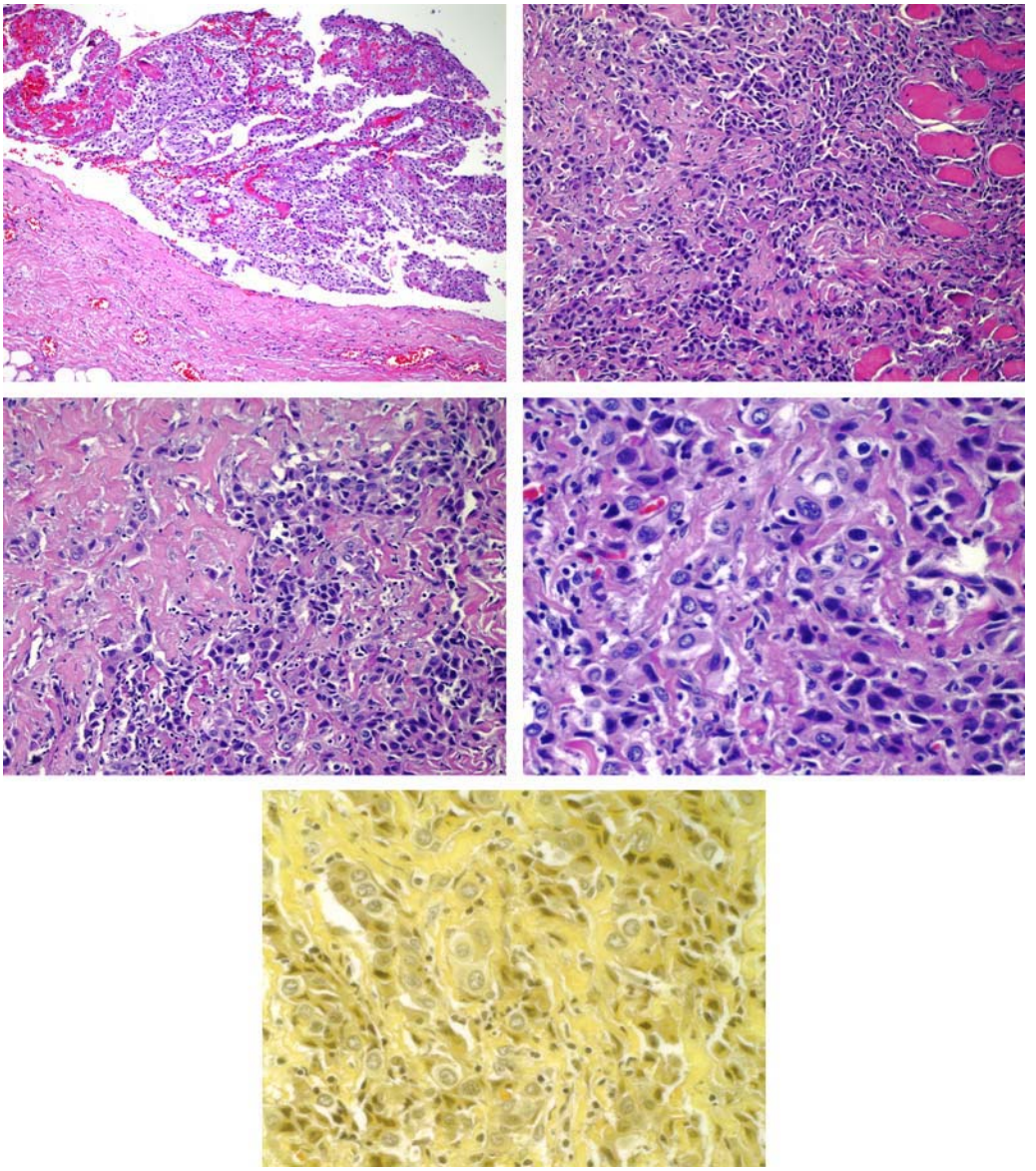
Case 7082

Diagnosis: Parietal pleura, open biopsy: Poorly differentiated carcinoma, invading pleura, with mesothelial hyperplasia and desmoplastic inflammation and fibrosis.

Malignant cells with pleomorphic nuclei have very abundant eosinophilic cytoplasm. The presence of reactive mesothelial cells in some regions of the biopsy makes me believe that the malignant cells are different lineage and thus carcinoma. The immunopathological results suggest an adenocarcinoma (and not a DMM). I agree with that interpretation based on the standard stains. We considered adenocarcinoma as a possibility and have stained the tumor for mucin. Mucicarmine, alcian blue and periodic acid-Schiff show no intracellular mucus. I do not know the origin of this tumor. Gastrointestinal tract and pancreas are possibilities. Some strips of pleura show dense hyaline sclerosis.

Thank you for referring this case in consultation. Please keep me informed of any follow-up and call if you have questions. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 7082 (Chapter 10 – Pleural Tumors)

Case 6899

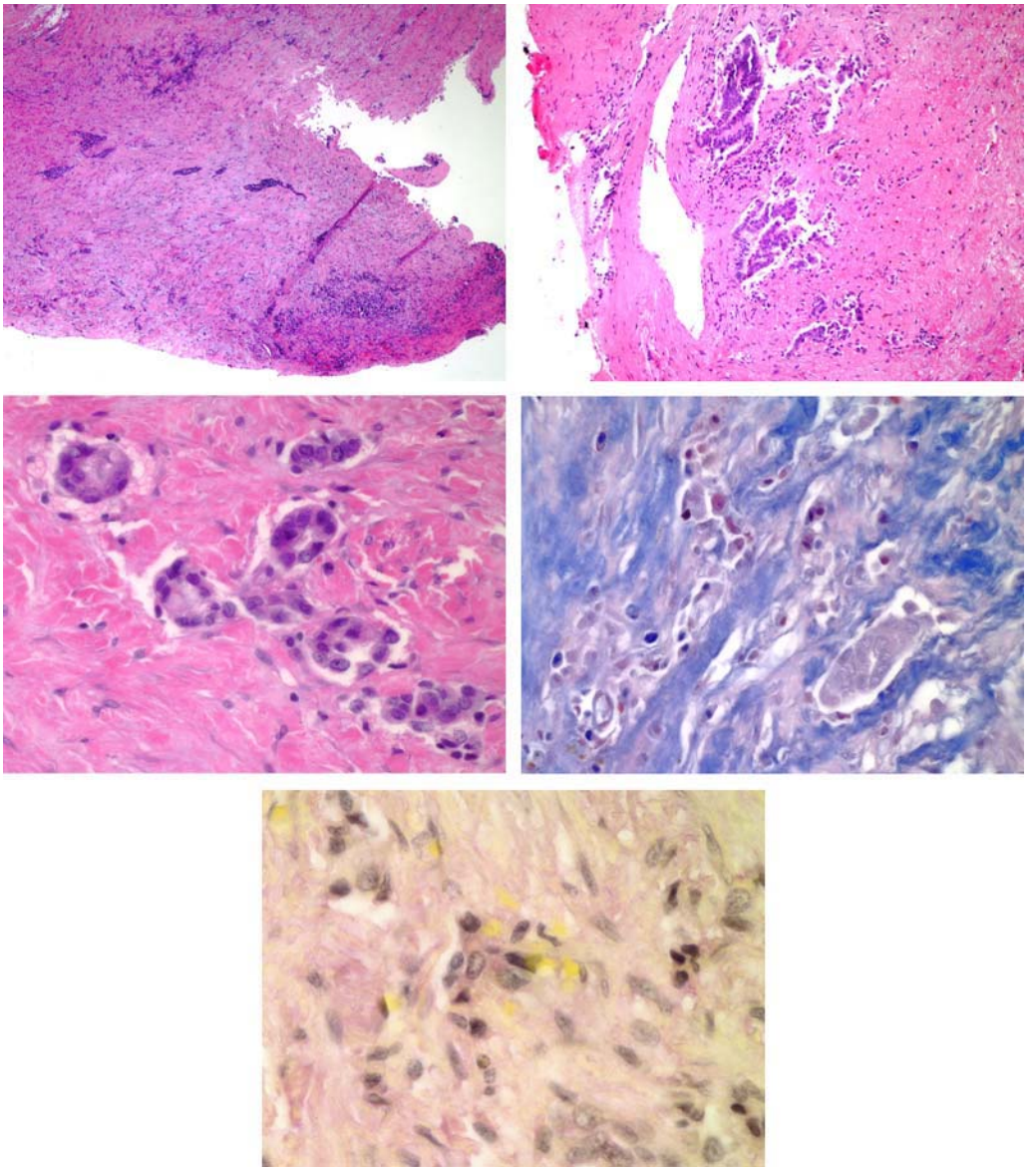
Diagnosis: Parietal pleura, open biopsy: Pleural carcinomatosis, in part lymphangitic, with reactive pleural fibrosis.

This case is difficult because there are two possibilities to explain the pleural fibrosis and atypical epithelioid cells. The first is that this is a form of pleural carcinomatosis which has elicited secondary pleural fibrosis. I believe this is the correct interpretation. The second is that this is a reactive fibrosing pleuritis with entrapped benign mesothelial cells. I do not favor this interpretation. In the differential diagnosis we also considered a desmoplastic DMM, but the distinct nesting and glandular appearance of the cells and their intralymphatic location are against that interpretation. We also considered pleural hyaline plaque for the regions of poorly cellular collagen, and this is a possibility, but I cannot make that diagnosis with certainty in the face of the fibrosing pleuritis.

We studied the case further with deeper sections and histochemistry to confirm the diagnosis. Collagen stains serve to confirm the lymphatic position of the epithelioid cells. A few of the epithelioid cells contain vacuoles of mucin on mucicarmine stain.

Thank you for referring this case in consultation. Please keep me informed of any follow-up. Delay was caused by sequential analysis by histochemistry. Your paraffin blocks are hereby returned. With best wishes,

Sincerely yours,
Eugene J. Mark, M.D.



Case 6899 (Chapter 10 – Pleural Tumors)

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