Alveolar Disease

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**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
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
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- 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).

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**Bronchiolitis Obliterans Organizing Pneumonia: Recently Described Clinopathological 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.

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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 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.

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Case 7105 (Chapter 2 – Alveolar Disease)
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 overpowers 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.
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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, non-diagnostic, 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 bronchial 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 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 bronchio-centric 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, technically 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.
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 membranes, 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 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 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)
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 microabsceses 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, air-spaces, 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)
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)