Pulmonary Manifestations of Acute Lung Injury

More Than Just Diffuse Alveolar Damage

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• ***Context.***—**Acute pulmonary injury may occur as a result of myriad direct or indirect pulmonary insults, often resulting in hypoxemic respiratory failure and clinical acute respiratory distress syndrome. Histologically, most patients will exhibit diffuse alveolar damage on biopsy, but other histologic patterns may be encountered, such as acute eosinophilic pneumonia, acute fibrinous and organizing pneumonia, and diffuse alveolar hemorrhage with capillaritis.**

Objective.—**To review the diagnostic features of various histologic patterns associated with a clinical picture of acute lung injury, and to discuss key features in the differential diagnosis.**

Data Sources.—**The review is drawn from pertinent peer-reviewed literature and the personal experience of the authors.**

Conclusions.—**Acute pulmonary injury is a significant cause of morbidity and mortality. In addition to diffuse alveolar damage, pathologists should be aware of alternate histologic patterns of lung disease that may present with a similar clinical presentation because this may impact treatment decisions and disease outcome.**

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Acute respiratory distress syndrome (ARDS) is a significant cause of pulmonary morbidity and mortality. As a clinical term, acute lung injury (ALI) was previously defined along with ARDS by the 1994 North American–European consensus classification. Both met certain clinical and radiographic criteria and were distinguished by the PaO2:FiO2 ratio, which was less than 200 mm Hg in ARDS and 300 mm Hg in ALI.[1] Since 2012, an updated "Berlin definition" has eliminated the clinical term acute lung injury and categorized ARDS as mild, moderate, and severe based on a PaO2:FiO2 ratio less than 300, 200, and 100 mm Hg, respectively. The mortality rates based on this classification are 27%, 32%, and 45% for mild, moderate, and severe disease, respectively. Additional criteria include development of new or worsening respiratory symptoms within 1 week of a known clinical insult, bilateral opacities on chest imaging not fully explained by effusion, atelectasis, or nodules, and respiratory failure not fully explained by cardiac failure or fluid overload with objective assessment, such as echocardiography, if no risk factor is present. The mild category of ARDS, with PaO2:FiO2 between 200 and 300 mmHg, corresponds to the previous clinical term acute lung injury.[2,3]

The term acute lung injury is still useful from a pathologic standpoint to describe a group of entities that present with acute or subacute disease. Originally used by Katzenstein to encompass diffuse alveolar damage (DAD) and the entity previously known as bronchiolitis obliterans with organizing pneumonia, now known as organizing pneumonia (OP), the term was meant to reflect the relatively acute onset of both entities as well as the temporal uniformity of both processes.[4] Studies that have looked at patients meeting clinical criteria for ARDS have shown most patients have DAD histologically, whereas some patients may present with acute eosinophilic pneumonia (AEP) or diffuse alveolar hemorrhage (DAH).[5] Other entities that may be encountered include the more recently described acute fibrinous and organizing pneumonia (AFOP).[6] Most cases of OP do not generally meet criteria for ARDS but may be seen in the "mild" category using the Berlin criteria, with OP remaining in the pathologic differential diagnosis of the patient with a subacute, less fulminate clinical course.[7,8]

With DAD identified in most patients with ARDS, the value of obtaining a wedge biopsy from an acutely ill patient has been questioned. Although it is less informative when only done to confirm DAD in a patient with ARDS, judicious use of wedge biopsies may identify a treatable cause in patients failing empirical treatment for ARDS. Nearly one-third to three-fourths of patients undergo a change in therapy, most often when an infectious etiology is uncovered, emphasizing the crucial role of the pathologist in using special stains to identify microorganisms.[5,9]

The aim of this review is to provide a practical approach to a biopsy from a patient presenting with acute respiratory failure and to discuss diagnostic pearls and the differential

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diagnosis of the most commonly encountered histologic patterns, namely, DAD, AEP, AFOP, OP, and DAH.

DIFFUSE ALVEOLAR DAMAGE

Diffuse alveolar damage (DAD) is the most common histologic pattern identified in patients with ARDS.[5,9] Patients have hypoxemia, the degree of which categorizes the disease as mild, moderate, or severe according to the recent Berlin criteria, and most patients require mechanical ventilation.[10] The classically described radiographic pattern of diffuse bilateral pulmonary infiltrates ("white-out") is best seen on conventional chest x-ray. However, computed tomography scans often demonstrate patchy, nonhomogenous distribution with greater involvement of the dependent regions.[11] A detailed discussion of the pathogenesis of DAD is beyond the scope of this review. Briefly, an initial insult to the alveolar epithelium and capillary endothelium is propagated by proinflammatory cytokines and results in hyperpermeable alveolar tissue. The exudation of edema fluid and cellular breakdown products is followed by reparative attempts by the lung that are manifested as pneumocyte hyperplasia and fibroblastic proliferation.[12–14] Recent investigations have sought to correlate signaling pathways and mediators to each of these steps in pathogenesis.[12] A recently published review of molecular studies found tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), IL-8, and IL-18 as potential biomarkers of assessing morbidity and mortality, an area requiring further study.[15]

The histologic findings in DAD vary depending on when the biopsy is taken during the progression of the disease course. Generally, the findings within a biopsy are diffuse and temporally uniform, unless sequelae of previous lung injury are also present. Both acute (exudative) and organizing (proliferative) phases are recognized, and some authors also include a final fibrotic phase. The acute phase is seen in the first week following pulmonary insult followed by the organizing phase. Considerable overlap between the 2 is often seen, especially late in the first week, because the processes represent a continuum of injury and repair. Furthermore, a patient may suffer repeated insults, and histology may show features of acute injury superimposed on those of a repairing lung.[16]

The acute/exudative phase is usually readily recognized by the presence of eosinophilic hyaline membranes, along with intra-alveolar edema, capillary congestion, and interstitial widening (Figure 1). These findings may be seen as early as day 2, but prior to this point, damage is only identified ultrastructurally. Reaching a peak at days 4 to 5, hyaline membranes are composed of plasma proteins and cellular debris gathered into dense, glassy eosinophilic membranes found along alveolar septa with accentuation in alveolar ducts. Inflammatory cells are relatively sparse unless a preexisting infectious pneumonia is the cause of DAD. Thrombi may form quite extensively because of localized alterations in the coagulation pathway but should not be taken as evidence for an underlying thromboembolic disorder as the cause of pulmonary insult.[4,16,17]

The organizing/proliferative phase may be more difficult to appreciate on biopsy specimens. The hyaline membranes of the acute phase are incorporated into the alveolar septa through phagocytosis by macrophages or granulation tissue formation by proliferating myofibroblasts. Residual hyaline membranes may still be identified if the biopsy specimen is taken close to a week after pulmonary insult. The interstitium is expanded with loose, myxoid fibroblastic tissue that appears blue-gray, as opposed to eosinophilic dense collagen fibrosis (Figures 2 and 3). Type 2 pneumocyte hyperplasia and squamous metaplasia may be quite pronounced, and both may exhibit cytologic atypia that should not be mistaken for malignancy. Mitotic activity within pneumocytes may be present and likewise should not be confused with a malignant process. Thrombi and extensive vascular remodeling may also be seen. Resolution of DAD may eventually follow the organizing phase, but residual functional impairment experienced by most surviving patients is the consequence of continued interstitial collagenous fibrosis and airspace remodeling.[4,16–18]

Most potential etiologies that elicit DAD are not evident by histology alone but require relevant clinical and laboratory data. Etiologic agents include infection, sepsis, shock, trauma, transfusion, inhalants, drug reactions, metabolic disorders, and collagen vascular/immune-mediated diseases among others.[1,7,19,20] Acute interstitial pneumonia is the clinical term for idiopathic DAD, in which no known causative etiology can be identified. Hamman-Rich syndrome, historically referring to rapidly progressive idiopathic lung disease, appears to correspond with acute interstitial pneumonia.[21–23]

The infectious etiologies most frequently cited are *Legionella*, *Mycoplasma*, and *Rickettsiae*, but almost any infectious agent can cause DAD in a patient with immunosuppression, as is often encountered in the critical setting.[5,19] Although granulomas and viral inclusions may be present in some cases and should be sought, the routine use of stains for fungi, mycobacteria, and bacteria in all cases of DAD must be emphasized. This is especially crucial for the detection of *Pneumocystis*, which in some instances may elicit little to no tissue response.[24] Immunohistochemical staining for viruses, including cytomegalovirus, herpes simplex viruses, and the respiratory viruses, should also be considered in immunocompromised patients.

The mortality rate from DAD is generally reported as being between 40% and 60%, but based on the Berlin criteria, one study reported respective mortality rates of 27%, 32%, and 45% for mild, moderate, and severe disease.[1,7,10] Variations of ventilation techniques and fluid management are newer management approaches that have improved outcomes. Corticosteroid therapy, although often given empirically, has given mixed results, as have therapies with surfactant replacement and vasodilators, including nitric oxide.[10,13,25] In surviving patients, radiographs show improvement, and pulmonary function typically recovers in 6 months to a year. However, patients with significant fibrosis from DAD may continue to have restrictive pulmonary disease.[10,26]

The differential diagnosis of DAD depends on whether the acute/exudative phase or the organizing/proliferative phase is more prominent in a biopsy specimen. In patients with the acute/exudative phase showing hyaline membranes on biopsy, the differential is primarily with AEP, AFOP, and occasionally DAH (see respective sections below).

It should also be noted that hyaline membranes can also be superimposed on otherwise typical findings of usual interstitial pneumonia (UIP) or other chronic interstitial lung diseases in what has been termed acute exacerbation. Although the patient will usually have a known clinical history of chronic lung disease, acute exacerbation may

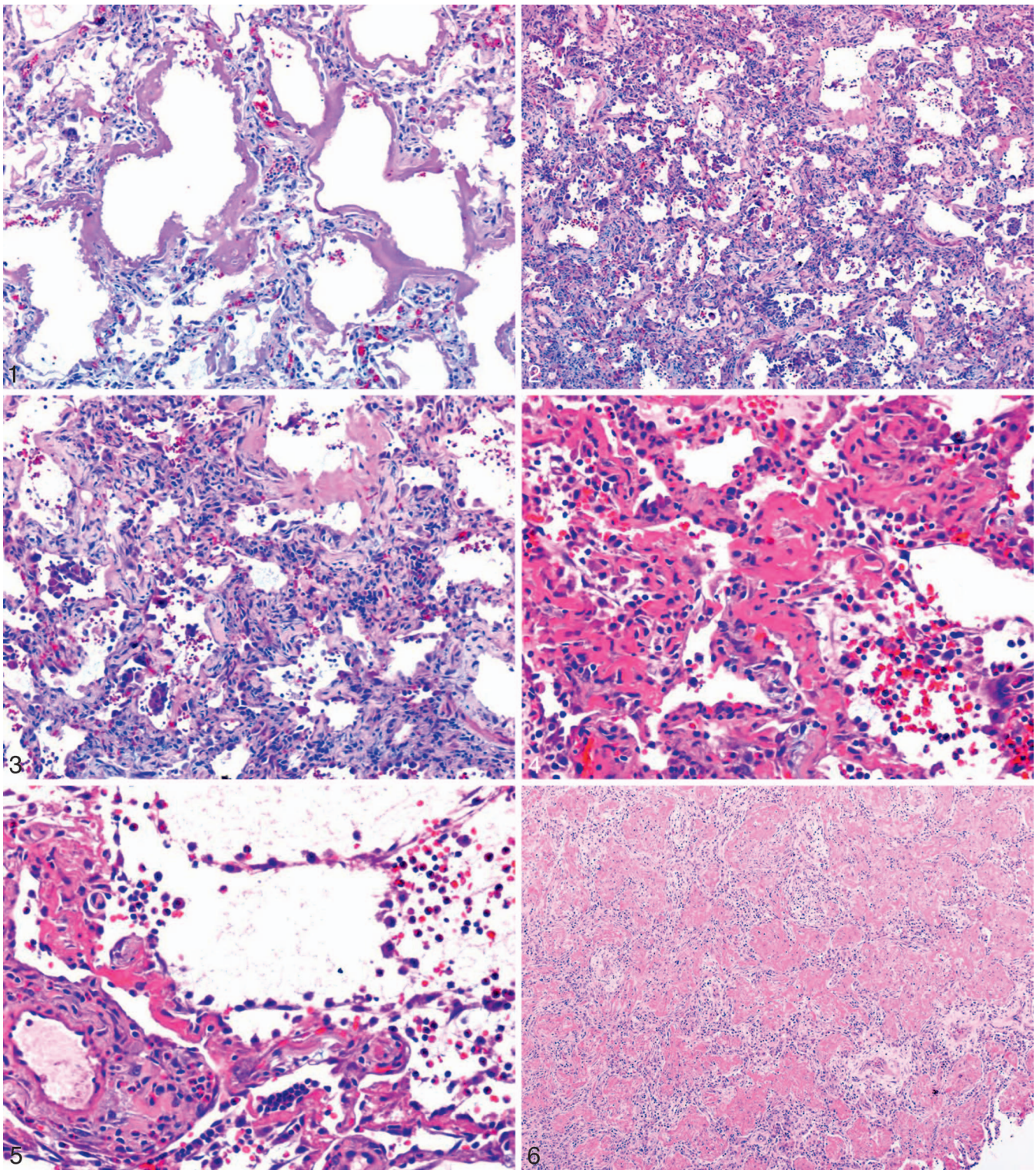

Figure 1. *Diffuse alveolar damage, acute phase. Prominent hyaline membranes line alveolar spaces. The interstitium shows mild edematous widening (hematoxylin-eosin, original magnification ×200).*

Figure 2. *Diffuse alveolar damage, organizing phase. A residual hyaline membrane can be seen in the upper right. The interstitium shows prominent expansion by myxoid fibroblastic tissue. Prominent type 2 pneumocyte hyperplasia is also present (hematoxylin-eosin, original magnification ×100).*

Figure 3. *Diffuse alveolar damage, organizing phase. The myxoid interstitial fibrosis and marked type 2 pneumocyte hyperplasia are characteristic of this phase. Dense collagenous fibrosis is not a feature (hematoxylin-eosin, original magnification ×200).*

Figure 4. *Acute eosinophilic pneumonia. Similar to diffuse alveolar damage, hyaline membranes and pneumocyte hyperplasia may be present, but prominent eosinophils are additionally present (hematoxylin-eosin, original magnification ×400).*

occasionally be the initial presentation of a patient with subclinical disease. Examination of the background lung for histologic features of usual interstitial pneumonia in particular, such as patchy subpleural honeycomb change and fibroblast foci, should aid in this distinction.

The organizing phase of DAD characterized by bluish gray, loose, myxoid, interstitial fibrosis is contrasted with other interstitial lung diseases showing denser, collagenous fibrosis, such as usual interstitial pneumonia and nonspecific interstitial pneumonia (NSIP). Type 2 pneumocyte hyperplasia is another feature of DAD that is not as pronounced in NSIP; yet in some instances, the separation of fibrotic NSIP from organizing DAD is nearly impossible. Organizing fibroblastic tissue within airspaces, particularly in alveolar ducts (alveolar duct fibrosis), may be seen in organizing DAD but does not constitute the dominant findings, as in cases of OP. The localization of fibrosis to the intraluminal spaces, rather than within the interstitium, also characterizes OP. Finally, neither hyaline membranes nor marked type 2 pneumocyte hyperplasia are prominently seen in OP.[23,27]

ACUTE EOSINOPHILIC PNEUMONIA

Eosinophilic pneumonia (EP) is most often encountered in the subacute clinical setting, but it may also present with ALI and respiratory failure, termed acute eosinophilic pneumonia (AEP). The patient with AEP typically has clinical ARDS, often accompanied by fever. Unlike subacute/chronic EP, peripheral blood eosinophilia may be absent in the acute setting.[28,29] AEP and EP share underlying etiologies—including inhalational injury, drug reaction, or infection, particularly parasitic or fungal—or may be idiopathic.[28,30,31] AEP has also been reported as a consequence of recent initiation of cigarette smoking.[32,33]

AEP is generally characterized by varying degrees of intra-alveolar fibrin, macrophages, and eosinophils. Hyaline membranes similar to those seen in the acute phase of DAD may also be seen (Figures 4 and 5). Eosinophils, some with microabscess formation, may infiltrate the interstitium and even blood vessel walls. Although AEP shares the features of hyaline membranes and intra-alveolar fibrin with DAD and AFOP, respectively, the presence of abundant eosinophils and macrophages is uncharacteristic of these entities and instead points to EP.[28–30]

Eosinophils should be sought in all cases with histologic findings of DAD. Distinction from DAD is crucial because AEP responds exquisitely to corticosteroids, with patients showing dramatic improvement upon initiation of the correct therapy. The rapid response to corticosteroids is also witnessed histologically, and tissue eosinophilia may be markedly diminished to absent in patients with EP if biopsied after the initiation of steroid therapy.[27–29,34]

ACUTE FIBRINOUS AND ORGANIZING PNEUMONIA

Acute fibrinous and organizing pneumonia (AFOP) is characterized by alveolar spaces filled with organizing fibrin balls but lacking the presence of hyaline membrane formation (Figure 6). Intra-alveolar organizing fibroblastic tissue, some with central fibrinous cores, may be seen but should not constitute the dominant finding, as in cases of OP. Neutrophils, eosinophils, and macrophages should not be seen, but within the alveolar septa, there may be a chronic inflammatory infiltrate with mild interstitial widening. Fibrosis is also essentially absent. Most cases feature a patchy distribution with bilateral basilar infiltrates seen on chest imaging.[6,35]

Acute fibrinous and organizing pneumonia was originally described in patients with an ALI pattern that did not meet strict criteria for DAD or OP. A slight majority of patients in the initial study presented acutely with severe respiratory distress and rapid progression to death, suggesting AFOP may be a variant of DAD. However, another group of patients presented subacutely similar to OP, with cough and dyspnea of few weeks' duration, did not require mechanical ventilation, and eventually recovered. Neither the degree of fibrin within the alveolar space nor any other clinical or histologic feature was shown to distinguish these 2 groups.[6] However, a recent study of cases of OP found a correlation between increasing amounts of fibrin seen on biopsy and a worse response to steroid therapy.[36,37] As such, the presence of fibrin should be mentioned in cases otherwise consistent with OP to indicate a potential atypical response to steroids. Although some cases are idiopathic, the known etiologies are similar to those in DAD and OP, such as infection, collagen vascular disease, drug reaction, or environmental exposure. Special stains for microorganisms should be performed in all cases. AFOP has also been reported following hematopoietic stem cell transplantation and lung transplantation.[6,35,38–41]

A definitive diagnosis of AFOP should be made only on large biopsy specimens because organizing alveolar fibrin may be seen as a nonspecific reaction adjacent to other processes, such as abscesses, granulomas, or neoplasms, and to ensure the absence of otherwise diagnostic features of entities within the differential diagnosis of DAD, OP, and EP.[6,37,42] DAD may prominently feature organizing fibrin, but there should always be typical hyaline membranes, however focal, present. Hyaline membranes should be sought in all cases with organizing fibrin to properly classify cases as DAD and not AFOP. Eosinophilic pneumonia, likewise, may have abundant intra-alveolar fibrin and mimic AFOP. The marked presence of eosinophils would preclude a diagnosis of AFOP, but cases of EP treated with steroids prior to biopsy may especially resemble AFOP because eosinophils rapidly disappear following treatment. AFOP should also lack significant macrophage accumulation, as is found in EP. Organizing fibroblastic tissue may be seen in AFOP but not as the dominant finding, as in cases of OP. Abundant fibrin may be seen in vasculitic processes, acute bacterial pneumonia, or in subpleural parenchyma adjacent

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Figure 5. *Acute eosinophilic pneumonia. Eosinophils are present within the hyaline membrane and alveolar space as well as in the interstitium, best seen in the lower left (hematoxylin-eosin, original magnification ×400).*

Figure 6. *Acute fibrinous and organizing pneumonia. As opposed to hyaline membranes, organizing intra-alveolar fibrin is present. Mild chronic inflammation, myxoid fibrosis, and pneumocyte hyperplasia may be present, but marked significant eosinophils and neutrophils should be absent (hematoxylin-eosin, original magnification ×100).*

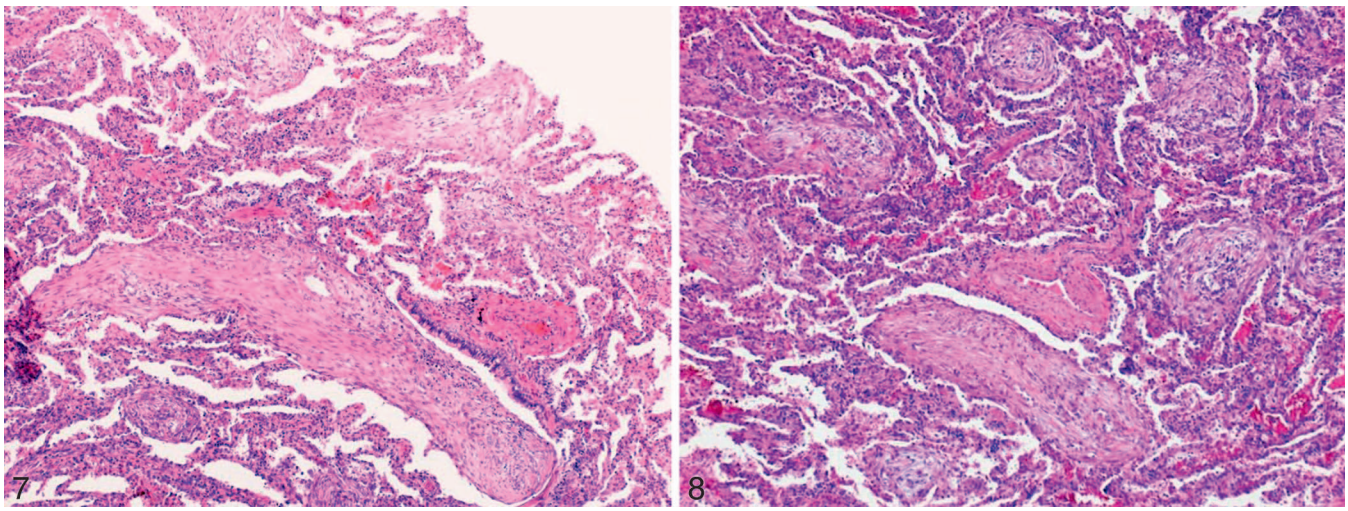


Figure 7. *Organizing pneumonia. Organizing fibroblastic tissue is present within alveolar spaces. Mild chronic inflammation is present in the interstitium of involved areas. In this example, organizing fibroblastic tissue can be seen within a tangential section of a bronchiole (hematoxylin-eosin, original magnification ×200).*

Figure 8. *Organizing pneumonia. Organizing fibroblastic tissue is within airspaces as opposed to the interstitium (hematoxylin-eosin, original magnification ×200).*

to acute pleuritis. These cases, or ones with marked neutrophils, should not be classified as AFOP.[6,27,43,44]

ORGANIZING PNEUMONIA

Organizing pneumonia (OP) is a nonspecific term for proliferations of fibroblastic tissue within small airways, alveolar ducts, and alveolar spaces. In this sense, OP may be present as a component of a variety of pathologic processes, such as hypersensitivity pneumonitis or eosinophilic pneumonia, or as a reactive process to adjacent unrelated mass lesions. An "OP pattern" refers to a specific pattern of patchy, bronchiolocentric disease and corresponds to the entity formerly termed bronchiolitis obliterans–organizing pneumonia. For the sake of ease in this review, OP is used simply to refer to the latter pattern of disease, because this pattern is frequently a consideration in the histologic differential diagnosis of ALI. Organizing pneumonia can be secondary to a number of underlying etiologies, such as infection, collagen vascular disease—especially rheumatoid arthritis or Sjögren disease rather than systemic lupus erythematosus—or drug reaction. Organizing pneumonia may be idiopathic in origin and clinically designated cryptogenic organizing pneumonia.

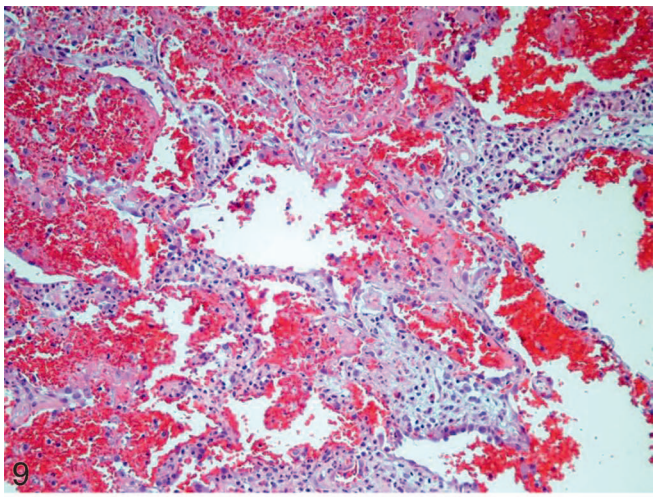
Organizing pneumonia generally presents in a subacute clinical course with patients who have had a few months of cough and dyspnea rather than fulminant respiratory failure. However, by the recent Berlin definition, some patients found to have OP meet criteria for mild ARDS. The patient with OP in the more typical subacute setting may report a recent history of upper respiratory infection. Computed tomography scan demonstrates patchy airspace consolidation in a peribronchial, lower lobe–predominant distribution.[8,27,45]

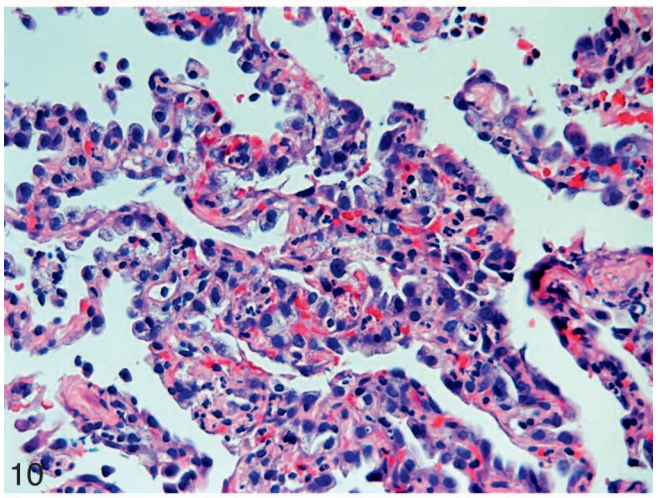
Histologically, the OP pattern is characterized by a temporally uniform proliferation of intra-alveolar organizing fibroblastic tissue in a patchy peribronchiolar distribution. Organizing fibroblastic tissue within bronchiolar lumens (bronchiolitis obliterans) is present in most cases, but not always. Organizing fibroblastic plugs are composed of loose, myxoid tissue with a bluish gray appearance on hematoxylin-eosin stains (Figures 7 and 8). The alveolar septa in involved areas typically show mild to moderate chronic inflammation, but significant fibrosis or architectural remodeling should not be present. Type 2 pneumocyte hyperplasia may be seen but is usually mild in degree. Foamy macrophages may also be evident, secondary to airway obstruction. Neutrophils, eosinophils, and granulomas should be absent, and the intervening lung tissue should be relatively normal. [8,27,46,47]

Similar to AFOP, the diagnosis of OP is best made on a large biopsy, given that OP may represent a secondary reaction to or as a component of a variety of other processes. The histologic pattern of OP is distinguished from AFOP by the fact that organizing intra-alveolar fibrin is the dominant finding in AFOP, whereas organizing fibroblastic tissue should be the dominant finding in OP. As previously noted, how much fibrin is needed to call a case AFOP instead of OP is under investigation, but the presence of any fibrin appears to potentially portend a worse than expected response to steroids compared with conventional OP.[36,37] Diffuse alveolar damage may contain organizing fibroblastic tissue within alveolar ducts in particular, but this is not the dominant finding, and OP lacks the hyaline membranes or acute DAD and does not show the prominent interstitial myxoid fibrosis or prominent type 2 pneumocyte hyperplasia of the organizing phase of DAD. The presence of eosinophils, fibrin, and intra-alveolar macrophages should discriminate OP from AEP or EP.[8,27]

DIFFUSE ALVEOLAR HEMORRHAGE

Diffuse alveolar hemorrhage may present with life-threatening respiratory failure. Diffuse alveolar hemorrhage differs to some degree from the other types of ALI in that, with the exception of certain drug reactions and infections, the condition almost always occurs in a relatively narrow setting of immune-mediated injury, and nearly all patients





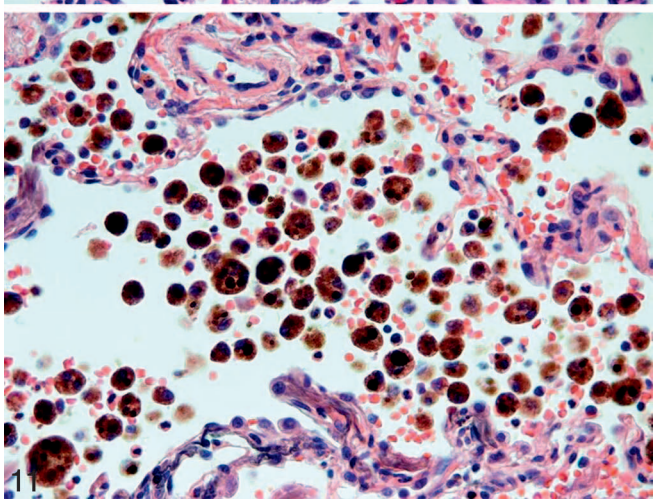


Figure 9. *Diffuse alveolar hemorrhage with capillaritis. In this relatively acute example, fresh blood and fibrin are present, but hemosiderin has not yet appeared. The alveolar septa show infiltration by neutrophils, and pneumocyte hyperplasia is prominent (hematoxylin-eosin, original magnification ×200).*

Figure 10. *Diffuse alveolar hemorrhage with capillaritis. Vascular damage is difficult to directly visualize, but neutrophils are prominent within the alveolar septa as opposed to within the airspaces. Neutrophilic debris may be seen and pneumocyte hyperplasia is prominent (hematoxylin-eosin, original magnification ×400).*

Figure 11. *Diffuse alveolar hemorrhage, hemosiderin deposition. Hemosiderin typically begins to form within 48 hours after the process starts and is characterized by coarse retractile material within macrophages in this image. Hemosiderin may also be present in the interstitium (hematoxylin-eosin, original magnification ×400).*

present with clinically significant hemoptysis. In the lung, DAH most commonly occurs in the setting of microscopic polyangiitis but may also occur in the setting of collagen vascular diseases, anti–glomerular basement membrane antibody syndrome (Goodpasture syndrome), and anti–phospholipid antibody syndrome, among other immune disorders. Although not classic, cases of granulomatosis with polyangiitis (Wegener granulomatosis) may occasionally present with pure diffuse alveolar hemorrhage histologically.[48–51]

Regardless of etiology, all cases of DAH appear similar histologically and are usually accompanied by capillaritis in the alveolar walls. Vascular damage may be difficult to visualize, but capillaritis is characterized by a preponderance of neutrophils within the alveolar septa as opposed to the alveolar spaces. Fibrin thrombi and neutrophilic debris may also be present as clues to vascular injury. Type 2 pneumocyte hyperplasia is usually prominent and, unless the hemorrhage is extremely acute, generally in less than 48 hours, hemosiderin deposition and hemosiderin-laden macrophage accumulation should be present (Figures 9 through 11). The etiology is usually sorted out on clinical and serologic grounds, but the finding of giant cells should raise the possibility of granulomatosis with polyangiitis.[48–51]

Diffuse alveolar hemorrhage is usually readily distinguished from other histologic patterns of ALI. However, DAH may form hyaline membranes on occasion; conversely, some cases of DAD may have prominent hemorrhage. The finding of prominent hemosiderin should prompt a search for capillaritis, but serologic studies may be needed to discriminate in difficult cases. Similarly, as DAH resolves, organizing fibroblastic tissue may form but prominent hemosiderin deposition typically remains present at this stage, which should aid in discrimination from OP.[49–52]

CONCLUSIONS

In spite of improving treatments and outcome date, clinical ARDS remains a significant cause of morbidity and mortality. Although most patients with clinical ARDS will have DAD histologically, pathologists should be aware of the potential alternative histologic patterns that may occur in the setting of respiratory failure, namely, AEP, AFOP, OP, and DAH. The role of the pathologist in elucidating a precise etiology is generally limited to identification of potential infectious etiology. Interpretation of findings in a small biopsy, particularly OP or organizing intra-alveolar fibrin, should be done with caution and preferably in a multidisciplinary fashion. Molecular biomarkers for DAD in particular are evolving, and will ultimately serve to expand our knowledge of ALI, which will hopefully improve treatment and outcomes.

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