The Pathologist’s Approach to Acute Lung Injury

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Context.—Acute lung injury and acute respiratory distress syndrome are significant causes of pulmonary morbidity and are frequently fatal. These 2 entities have precise definitions from a clinical standpoint. Histologically, cases from patients with clinical acute lung injury typically exhibit diffuse alveolar damage, but other histologic patterns may occasionally be encountered such as acute fibrinous and organizing pneumonia, acute eosinophilic pneumonia, and diffuse hemorrhage with capillaritis.

Objective.—To review the diagnostic criteria for various histologic patterns associated with a clinical presentation of acute lung injury and to provide diagnostic aids and discuss the differential diagnosis.

Acute pulmonary injury may occur secondary to an extensive number of direct or indirect pulmonary insults and often results in acute hypoxemic respiratory failure. Most patients with this condition will have acute respiratory distress syndrome (ARDS) clinically. In 1994, the American-European Consensus Conference on ARDS formally defined ARDS as the presence of acute hypoxemia with (1) a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO₂/FIO₂) of 200 mm Hg or less, (2) bilateral infiltrates that are consistent with pulmonary edema radiographically, and (3) no clinical evidence of cardiac failure. A less severe category, termed acute lung injury (ALI), was defined by the same criteria but with a PaO₂ to FIO₂ of 300 mm Hg. While the definitions are not without their critics, they have provided a basis for a more uniform approach to the study of ALI/ARDS including epidemiology, pathogenesis, treatment, and clinical trial design. The actual incidence of ALI/ARDS has been difficult to approximate because of varying criteria for diagnosis. A population-based cohort study in King County, Washington, examined the incidence and mortality of ALI and ARDS by using the consensus criteria and found that the incidence of ALI was 78.9 per 100 000 person-years and the incidence of ARDS was 58.7 per 100 000 person-years. This same study reported an average mortality rate of 41.1% for ARDS and 38.5% for ALI. Although the average mortality rate in the study was lower than the historically reported mortality rates for ARDS of 50% to 60%, the mortality rate was found to increase with age and was 60% in persons older than 85 years. Therefore, in spite of the myriad advances in understanding the pathogenesis of ALI/ARDS, this entity clearly remains a significant cause of morbidity and mortality.

From a pathologic standpoint, most cases of clinical ALI and ARDS will have diffuse alveolar damage (DAD) histologically. Other histologic patterns encountered in a clinical setting of ALI/ARDS include acute fibrinous and organizing pneumonia (AFOP) and the more recently described acute eosinophilic pneumonia (AEP) and the more recently described acute fibrinous and organizing pneumonia (AEP). Organizing pneumonia (OP) is often included in the pathologic differential of clinical ALI. However, most patients with OP typically present with a subacute, less fulminating clinical course and generally do not meet clinical criteria for ALI, but OP will be discussed in this article primarily as part of the differential diagnosis. Diffuse alveolar hemorrhage may also occasionally present with clinical ALI/ARDS. It is important to note that clinicians think of ALI/ARDS in terms of the previously discussed clinical guidelines, while pathologists tend to use the term acute lung injury in reference to the pathologic findings—particularly in reference to small biopsies, as discussed below—when precise classification of findings is not possible. As such, communication is important to avoid any misinterpretation of the findings. The aim of this review is to cover the major features of the common histologic patterns seen in association with clinical ALI/ARDS, the differential diagnosis, and an approach to biopsy specimens.

Given that most biopsy specimens from patients with clinical ALI/ARDS will demonstrate a histologic pattern of DAD, some authors have questioned the value of obtaining a wedge biopsy specimen from patients with ALI/ARDS. Patel et al examined a series of wedge biopsy
samples obtained from patients with clinical ALI/ARDS and determined that while most specimens did show DAD, diagnostic findings were found that prompted a change in therapy in nearly one-third of cases. Most of these cases involved the discovery of a definitive infectious etiology. As will be discussed below, evaluation for an infectious cause is an important contribution that the pathologist can make in evaluating a biopsy specimen from a patient with acute lung injury.

**CLINICAL AND PATHOLOGIC OVERVIEW OF HISTOLOGIC PATTERNS ASSOCIATED WITH ALI/ARDS**

**Diffuse Alveolar Damage**

Diffuse alveolar damage is the classic histologic manifestation of ALI/ARDS. Clinically, patients present with severe hypoxemia and typically require mechanical ventilation. The histologic findings will vary depending on when a biopsy is obtained during the course of the disease.

Radiographically, patients with DAD are classically described as having diffuse bilateral pulmonary infiltrates (“white out”) by conventional chest x-ray. Computed tomography scans, however, often demonstrate that the distribution is actually nonhomogenous and is greater in the dependent portions of the lung. The pathogenesis of DAD has been widely studied, and an extensive review is beyond the scope of this article. Briefly, damage to the capillary endothelium and alveolar epithelium result in exudation of edema fluid and cellular breakdown products, with subsequent pneumocyte hyperplasia and fibroblastic proliferation as the lung attempts to repair the damage. The entire process is propagated by a complex and ever-expanding collection of cytokines and other cellular factors. The interested reader is referred to several excellent reviews on the pathogenesis of DAD/ARDS.

Histologically, DAD is typically divided into 2 phases: the acute/exudative phase and the organizing/proliferative phase. The acute phase generally occurs during the first week following pulmonary insult, with the organizing phase occurring after the first week; however, the processes actually represent a continuum and overlapping features may be encountered, particularly late in the first week. Some authors additionally include a final fibrotic phase. In cases related to a single insult, the disease progresses in a relatively linear fashion. However, in some cases, a patient may experience repeated insults that may lead to variable features within a biopsy specimen.

The acute/exudative phase is usually easily recognizable. The findings are generally diffuse and relatively uniform, but may occasionally be more focal. While the earliest changes may be seen only ultrastructurally, by day 2 intra-alveolar edema and interstitial widening are apparent. Hyaline membranes may be seen at this point and may reach a peak 4 to 5 days after the initial insult. Hyaline membranes are composed of cellular and proteinaceous debris and appear as dense, glassy eosinophilic membranes lining the alveolar ducts and alveolar spaces (Figure 1). Generally, inflammation is relatively sparse unless the DAD is evolving from a preexisting pneumonia. Thrombi may be present and may be quite extensive (Figure 2). The formation of thrombi in DAD is due to localized alterations in the coagulation pathway and should not be considered evidence of an underlying thromboembolic disorder in the patient.

The organizing phase may prove more problematic on biopsy specimen examination. This phase is characterized by relatively uniform interstitial fibrosis associated with quite pronounced type 2 pneumocyte hyperplasia (Figure 3). Squamous metaplasia may also be present and in some cases may be quite pronounced (Figure 4). The hyaline membranes characteristic of the acute phase gradually disappear as they become incorporated into the alveolar septa; however, residual hyaline membranes may be identifiable depending on the timing of the biopsy in the course of disease. Cytologic atypia may be quite pronounced in both the type 2 pneumocytes as well as squamous metaplastic areas and should not be confused with malignancy. Similarly, mitotic figures may be observed in the pneumocytes. The fibrosis in DAD tends to be loose and myxoid and will appear bluish-gray on hematoxylin-eosin sections, in contrast to the collagenous fibrosis typically seen in other disorders such as nonspecific interstitial pneumonia and usual interstitial pneumonia. Organizing fibroblastic tissue may be observed in air spaces, particularly the alveolar ducts (alveolar duct fibrosis), but this feature is typically not prominent and does not constitute the dominant finding as seen in cases of OP.

Following the organizing phase, some cases of DAD will gradually resolve while others may develop continued interstitial fibrosis with architectural remodeling and progressive respiratory compromise. Among patients who survive, most experience some degree of residual functional impairment.

The histologic findings of DAD may result from a large number of potential etiologies that include numerous infectious agents, drug reactions, collagen vascular/immune-mediated diseases, ingestant/inhalant exposure, shock, sepsis, and numerous other agents. Among the infectious etiologies, viruses (Figure 5), Legionella, Mycoplasma, and Rickettsia are most frequently cited, but it is important to note that most any infectious agent can produce DAD. This is of particular importance in the immunosuppressed patient, a context in which agents such as Pneumocystis jiroveci and other fungi are not infrequently encountered.

Diffuse alveolar damage in which no known causative etiology can be elucidated is clinically termed acute interstitial pneumonia, which also corresponds to cases historically referred to as Hamman-Rich syndrome.

Transfusion-related acute lung injury (TRALI) deserves mention in the discussion of DAD/ARDS, as TRALI is increasingly recognized from a clinical standpoint. Transfusion-related acute lung injury is a clinical syndrome associated with transfusion of plasma containing blood components and is most frequently associated with antibodies to white blood cells in transfused blood components. Patients may experience a wide range of respiratory compromise ranging from mild dyspnea to fulminate respiratory failure, which is fatal in 5% to 10% of cases, although most patients recover with supportive measures. Radiographs demonstrate findings essentially identical to those of ARDS.

As TRALI is typically a clinical diagnosis, reports of pathologic findings are few and generally restricted to fatal cases. As would be
expected given the clinical presentation, several case reports\textsuperscript{33} describe findings identical to those of DAD with classic hyaline membranes. Other reports describe only pulmonary edema with neutrophil accumulation within alveolar capillaries, although neutrophils within alveolar spaces have also been reported. It has been postulated that the lack of hyaline membranes in many reported cases suggests a differing pathologic mechanism from DAD, which has warranted further study.\textsuperscript{35–34}

**Acute Fibrinous and Organizing Pneumonia**

Acute fibrinous and organizing pneumonia (AFOP) is a more recently described histologic pattern associated with acute lung injury in which the alveolar spaces are filled with organizing fibrin balls, in contrast to the true hyaline membranes found in DAD. The process may be patchy or relatively diffuse. The alveolar septa may show mild interstitial widening or lymphocytic infiltrates, but significant eosinophils or neutrophils should not be seen (Figure 6). Organizing fibroblastic tissue may be present to varying degrees but is not the dominant finding, and the fibroblastic tissue may retain a central fibrinous core.\textsuperscript{4}

The differential diagnosis of AFOP is primarily with DAD and eosinophilic pneumonia (EP). Prominent organizing fibrin may be seen in some cases of DAD. Such cases also contain foci of more typical hyaline membranes, although they may be relatively focal. Hyaline membranes should be sought in all cases with prominent organizing fibrin and should be properly classified as DAD and not as AFOP. Eosinophilic pneumonia, described below, may have prominent intra-alveolar fibrin and greatly resemble AFOP histologically. Cases of AFOP should not have significant eosinophils and should also lack significant macrophage accumulation. As eosinophils disappear rapidly from tissue following initiation of steroid therapy, partially treated EP may be a consideration if a biopsy is obtained after administration of steroids. Peripheral blood eosinophilia is not a feature of AFOP and may help distinguish these cases on a clinical level. Cases of alveolar hemorrhage may also contain organizing fibrin but the presence of hemosiderin-laden macrophages and other features described in the hemorrhage section below should point to the correct diagnosis. Similarly, AFOP may have areas of organizing fibroblastic tissue but this is not the dominant finding, as seen in cases of OP.\textsuperscript{9}

A diagnosis of AFOP should only be made on a large biopsy specimen when one can be more certain that there are not otherwise diagnostic features of DAD or EP. Similarly, abundant fibrin may be encountered in acute bacterial pneumonias and cases with marked neutrophils should not be classified as AFOP. Additionally, organizing fibrin can occur as a nonspecific reaction adjacent to lesions such as granulomas, abscesses, or neoplasms or may occur in subpleural lung parenchyma adjacent to acute pleuritis.\textsuperscript{8} For these reasons, the finding of organizing alveolar fibrin on a small biopsy specimen should be interpreted conservatively and carefully correlated with clinical and radiographic information.

In the original study of AFOP, the overall mortality rate was similar to that seen in DAD and it was felt that AFOP likely represented a histologic variant of DAD. Acute fibrinous and organizing pneumonia was additionally found to be associated with a wide range of potential etiologies similar to those seen in DAD, and some cases were felt to be idiopathic. Most patients presented with severe respiratory failure. However, a significant number of patients with the AFOP pattern presented with a subacute clinical course not requiring mechanical ventilation and eventually recovered. Histologic features distinguishing these 2 prognostic groups were not identified. Therefore, while at least some cases of AFOP appear to be related to DAD, further study is needed to further define the significance of this pattern, particularly in regard to the subacute clinical cases.\textsuperscript{4} From a practical standpoint at this time, the primary issue for the practicing pathologist is recognizing the AFOP pattern as being associated with acute lung injury and understanding its spectrum of potential clinical associations.

**Eosinophilic Pneumonia**

Eosinophilic pneumonia most commonly presents with a subacute clinical course but occasional cases present with fulminate respiratory failure, often associated with fever. Such cases, termed *acute eosinophilic pneumonia* (AEP), may not be associated with the peripheral blood eosinophilia typical of chronic eosinophilic pneumonia.\textsuperscript{7} Both AEP and EP may be associated with underlying etiologies such as toxic inhalation, drug reaction, or infection, particularly with parasites or fungus, or may be idiopathic.\textsuperscript{35–38} Interestingly, AEP has also been reported in patients after recent initiation of cigarette smoking.\textsuperscript{39,40}

Eosinophilic pneumonia in general is characterized by intra-alveolar fibrin and macrophages in variable proportions, admixed with numerous eosinophils. Eosinophils may also be present in the interstitial tissue and eosinophilic microabscess formation may be observed. In some cases, eosinophils may infiltrate blood vessel walls.\textsuperscript{41,42} In AEP, these features may be present to varying degrees with the additional finding of hyaline membrane formation identical to that seen in the acute phase of DAD (Figure 7).\textsuperscript{7} The histologic differential of EP/AEP is primarily with DAD and AFOP, as described in the 2 previous sections. Churg-Strauss syndrome does not typically present with clinical ALI/ARDS but may arise in the histologic differential of EP. The finding of necrotizing vasculitis and granulomas should distinguish cases of Churg-Strauss syndrome from EP, along with clinical findings of systemic vasculitis.

The presence of eosinophils should be sought in all cases with histologic findings of DAD. The importance of this finding lies in the fact that AEP is exquisitely sensitive to steroid therapy, with most patients making a dramatic recovery when appropriate therapy is instituted.\textsuperscript{7,35,36,38}

**Diffuse Alveolar Hemorrhage With Capillaritis**

Occasionally, diffuse alveolar hemorrhage (DAH) with capillaritis will present with fulminate respiratory failure.\textsuperscript{5,4} Such cases demonstrate diffuse intra-alveolar blood admixed with hemosiderin-laden macrophages containing coarse hemosiderin granules. Capillaritis is evidenced by neutrophils within the alveolar septa with resultant vascular necrosis (Figure 8). Neutrophilic cellular debris or fibrin thrombi may also be observed. Capillary necrosis may be difficult to visualize but the histologic finding of significant neutrophilic infiltrates within the alveolar septa with minimal or absent involvement of the air spaces should strongly suggest capillaritis. Organizing fibroblastic tissue may be present and form “dumbbell” shapes crossing the alveolar septa (Figure 9). This feature evolves as capillaritis resolves. Some cases of DAH with...
Figure 1. Diffuse alveolar damage, acute/exudative phase. Alveolar septa show edematous widening and sparse inflammation and are lined by prominent hyaline membranes (hematoxylin-eosin, original magnification ×200).

Figure 2. Thrombi may be observed in cases of diffuse alveolar damage and are secondary to localized alterations in the coagulation pathway. Such findings should not be misinterpreted as pulmonary emboli (hematoxylin-eosin, original magnification ×200).

Figure 3. Diffuse alveolar damage, organizing phase. The alveolar septa are expanded by myxoid-appearing fibrous tissue and pneumocyte hyperplasia is prominent. A residual hyaline membrane is still visible (hematoxylin-eosin, original magnification ×200).

Figure 4. Organizing diffuse alveolar damage (DAD) with an unusually large amount of squamous metaplasia. The finding of more typical features of DAD elsewhere in the biopsy specimen, the distribution of the squamous epithelium along air spaces, and the lack of overt cytologic features of malignancy should help avoid misdiagnosis as carcinoma (hematoxylin-eosin, original magnification ×100).
capillaritis will also have hyaline membranes, which may occasionally be the dominant histologic component.44–46

The primary challenge upon encountering hemorrhage in a biopsy specimen is to determine if the hemorrhage is of pathologic significance or if it is related to trauma secondary to the biopsy procedure. Hemosiderin-laden macrophages are an important finding, which points to true alveolar hemorrhage. The hemosiderin in these macrophages is characteristically coarsely granular and golden brown, in contrast to the finely granular brown pigment encountered in the lungs of cigarette smokers (Figure 10, A and B). Iron stains may highlight the coarse nature of true hemosiderin, but one should keep in mind that pigmented “smoker’s type” macrophages may also contain stainable iron; therefore, morphologic features should take precedence over the finding of stainable iron alone. Hemosiderin-laden macrophages begin to develop as soon as 2 days after a bleeding episode and may persist for as long as several months. As such, the mere finding of hemosiderin-laden macrophages may not be indicative of acute or active hemorrhage. Other histologic findings that point towards active hemorrhage include cellular reactive changes in the adjacent alveolar septa and focal areas of air space organization.44–46 When hemorrhage is determined to be potentially significant from a histologic standpoint, the finding must be evaluated in the appropriate clinical context. From a clinical standpoint, significant alveolar hemorrhage is almost always associated with hemoptysis. While the focus of the article is on ALI, in a broader scope of ALI, in a broader scope of ALI, in a broader ADAM 17, in a broader scope of ALI, in a broader scope of ALI, in a broader scope of alveolar hemorrhage may be localized or diffuse, and localized hemorrhage in particular may occur secondary to a wide range of etiologies, particularly bronchiectasis or thromboembolism among others. A diagnosis of DAH should be entertained only when a patient presents with diffuse alveolar infiltrates. Diffuse alveolar hemorrhage may occur with or without associated capillaritis; however, it is typically the cases with capillaritis that may present with clinical manifestations of ALL.5 Diffuse alveolar hemorrhage with capillaritis most commonly occurs in association with immune-mediated disorders. The primary considerations include collagen vascular diseases (most commonly systemic lupus) and microscopic polyangiitis. Goodpasture syndrome (anti–glomerular basement membrane antibody syndrome) may present with DAH with or without associated capillaritis, and Wegener granulomatosis may occasionally present with a primary pattern of hemorrhage and capillaritis. Other entities that have been reported in association with DAH include primary antiphospholipid antibody syndrome, mixed cryoglobulinemia, Behçet syndrome, and Henoch–Schönlein purpura along with some drug reactions and some infections (human immunodeficiency virus, listeriosis).44–47 As most of the potential causes of DAH are immune mediated, specific patterns of immunoglobulin deposition may be observed by immunofluorescence, particularly Goodpasture syndrome. While interesting, in reality, such studies are rarely necessary in establishing a diagnosis from a clinical standpoint. A diagnosis of “alveolar hemorrhage” with a comment regarding the presence or absence of capillaritis is typically sufficient and the etiology is confirmed via clinical and serologic findings.

From a histologic standpoint, it should be noted that some cases of conventional DAD may present with fairly considerable intra-alveolar hemorrhage, which is more commonly fresh blood and seen in the acute phase. The presence of coarse hemosiderin, neutrophilic interstitial infiltrates, and capillaritis should raise the possibility of an immune-mediated lung injury.

Organizing Pneumonia

As stated previously, OP generally presents with a subacute clinical course without fulminate respiratory failure and is not generally encountered in patients with clinical ALI/ARDS. Indeed, the clinical finding of fulminate respiratory failure requiring mechanical ventilation militates against a diagnosis of OP. However, OP is frequently included in the pathologic differential diagnosis of ALI and, most importantly, is often a consideration in the differential diagnosis of the other histologic patterns associated with ALI.

The histologic pattern of OP, as defined in the current American Thoracic Society/European Respiratory Society consensus classification of interstitial lung disease, corresponds to the entity formerly termed bronchiolitis obliterans organizing pneumonia. The clinical term for idiopathic OP is cryptogenic organizing pneumonia (COP). The OP pattern may also be seen in association with a number of potential underlying etiologies such as infection, collagen vascular disease, and drug reactions, which must be excluded clinically before a clinical diagnosis of COP is made.29

The OP pattern is characterized by patchy accumulation of intra-alveolar organizing fibroblastic tissue, which is primarily centered around bronchioles. Intra-bronchiolar fibroblastic tissue (bronchiolitis obliterans) may or may not be present. The alveolar septa in involved areas generally exhibit mild chronic inflammation. Significant fibrosis should not be present, and the intervening lung tissue should be relatively normal (Figure 11).9,10,29

Organizing pneumonia is typically readily distinguished from DAD histologically. Some cases of organizing DAD may, however, contain comparatively prominent intra-alveolar or alveolar duct fibrosis and therefore, OP may arise in the histologic differential diagnosis. Organizing DAD is typically much more diffuse and, even when relatively prominent air space fibrosis is present, the dominant finding remains the diffuse interstitial expansion/myxoid fibrosis with marked pneumocyte hyperplasia. In OP, the air space organization is the primary finding and the interstitial changes are relatively mild, consisting of lymphocytic interstitial inflammation without significant interstitial fibrosis. Pneumocyte hyperplasia is similarly not as prominent. Organizing pneumonia is additionally a patchy, bronchiolocentric process with the intervening lung parenchyma appearing relatively normal.
Figure 7. Acute eosinophilic pneumonia. Hyaline membranes, essentially identical to those seen in diffuse alveolar damage, are present but contain numerous eosinophils on closer inspection (hematoxylin-eosin, original magnification ×400).

Figure 8. Neutrophilic capillaritis is characterized by prominent neutrophils within the alveolar septa. Necrosis of the capillary may be difficult to visualize, but neutrophilic debris, as seen here, or fibrin thrombi suggest underlying vascular damage (hematoxylin-eosin, original magnification ×400).

Figure 9. Healing capillaritis is characterized by organizing fibroblastic tissue. Often the organizing tissue bridges the previously damaged alveolar septa in a “dumbbell” fashion, as seen here (hematoxylin-eosin, original magnification ×100).

Figure 10. Hemosiderin secondary to alveolar hemorrhage typically consists of large, coarse granules (A) in contrast to the finely granular pigment associated with cigarette smoking (B) (hematoxylin-eosin, original magnifications ×400).

Figure 11. Organizing pneumonia is characterized by patchy intra-alveolar organizing fibroblastic tissue. The surrounding alveolar septa contain mild lymphocytic infiltrates (hematoxylin-eosin, original magnification ×100).
As with AFOP, a diagnosis of OP/COP should generally only be made on a large biopsy specimen, and only when the histologic pattern described above is present. Organizing fibroblastic tissue may occur as a component of a number of pathologic processes, such as hypersensitivity pneumonitis and Wegener granulomatosis, or it may occur as a nonspecific reaction adjacent to an unrelated lesion. That being said, the opinion that OP should only be diagnosed with certainty on a large biopsy specimen is controversial. Certainly, there are instances when a small biopsy specimen with organizing fibroblastic tissue may be considered consistent with OP/COP with careful clinical and radiographic correlation.

**APPROACH TO BIOPSY SPECIMENS IN PATIENTS WITH CLINICAL ALI/ARDS**

As with any lung biopsy, when evaluating a biopsy specimen from a patient with clinical acute lung injury, it is important to have as much clinical information as possible. Information regarding disease onset and progression, suspected underlying etiologies, radiographic information, and whether or not the patient is on mechanical ventilation are important to support or refute possible differential diagnoses.

With the exception of diffuse alveolar hemorrhage with capillaritis, which most commonly occurs in a relatively narrow range of immune-mediated settings, all of the above histologic manifestations of ALI, and DAD in particular, may be associated with myriad potential underlying etiologic agents, or they may be idiopathic. In many cases the etiology will not be apparent from the histologic findings alone. While the role of the pathologist is limited in elucidating the etiology, the one thing that can and should be done in every case is careful evaluation for potential infectious etiologies. Special stains for microorganisms, namely an acid-fast stain, a Gomori methenamine-silver or similar silver stain, and a bacterial stain such as Brown-Brenn or Brown-Hopps should be obtained, and cases should also be carefully scrutinized for viral cytopathic changes. This should be done in all cases but is of particular importance in cases of DAD and AFOP, which may harbor fungal, pneumocystis, mycobacterial, or bacterial infections that may affect the clinical treatment (Figure 12, A and B).
The entities discussed herein are diagnosed with greatest certainty on a wedge biopsy specimen, and as previously stated, a definitive diagnosis of AFOP or OP should generally be made on a large biopsy specimen. In practice, however, one may be more frequently presented with a small biopsy specimen, particularly in the initial stages of the clinical workup. In some cases, one may be fortunate and hyaline membranes may be detectable, enabling a diagnosis of DAD, or one may be able to identify features of eosinophilic pneumonia (Figure 13, A and B) or capillaritis. More frequently, a precise diagnosis may not be possible. Important features to evaluate include (1) presence of intra-alveolar edema and/or myxoid interstitial fibrosis, (2) presence of marked pneumocyte hyperplasia, especially with bizarre cytologic features, and (3) presence of alveolar fibrin or debris. If such features are present, particularly in a patient with known respiratory failure, it is appropriate to provide a descriptive diagnosis with a comment that the findings are suggestive of, or consistent with, acute lung injury (Figure 14). When a diagnosis of acute lung injury is suspected, additional features to assess include evaluation for the presence of (1) microorganisms and viral inclusions, (2) eosinophils, suggesting the possibility of AEP, and (3) coarse hemosiderin and capillaritis, suggesting an immune-mediated vasculitis.

It cannot be emphasized enough that clinical correlation and communication with the clinician are critical to avoid overinterpretation of findings in small biopsy specimens, and it is generally better to be conservative, especially if correlating information is not available. While the above features may point to acute lung injury in the proper clinical setting, they are not specific taken alone and out of context.

Hemorrhagic small biopsy samples may also be problematic. Fresh hemorrhage secondary to the biopsy procedure is very common, and blood and associated fibrin within air spaces should not be overinterpreted as hyaline membranes. Fibrin associated with procedural effect is generally loose and wispy. Only well-formed hyaline membranes with a dense, glassy eosinophilic quality should be taken as evidence of DAD. Similarly, procedural-related hemorrhage should not be overinterpreted as a chronic hemorrhage syndrome. Features of chronic hemorrhage such as macrophages with coarse hemosiderin granules and associated reactive pneumocytes, or definitive evidence of capillaritis, should be present before suggesting this diagnosis.

In summary, ALI and ARDS clinically represent a significant cause of pulmonary morbidity and mortality. Most patients with these conditions will have a histologic pattern of DAD, but AFOP, AEP, and DAH with capillaritis may also be encountered and constitute important considerations in the differential diagnosis. Determination of potential infectious etiologies is important from the pathologic perspective, and caution should be used in interpreting small biopsy specimens.

References


