Pathogenesis, Imaging, and Evolution of Acute Lung Injury

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KEYWORDS

• Organizing pneumonia • Diffuse alveolar damage • CT • Fibrosis

KEY POINTS

- Acute lung injury exists on a continuum ranging from organizing pneumonia to diffuse alveolar damage.
- The site of injury in all forms of ALI is at the level of the type I alveolar epithelial cell, capillary endothelial cell, and intervening basement membrane.
- Imaging manifestations in diffuse alveolar damage (DAD), acute fibrinous and organizing pneumonia (AFOP), and organizing pneumonia (OP) share numerous patterns likely related to the same site of initial injury.
- Once the injury occurs, repair depends on the presence of type II pneumocytes and integrity of the basement membrane.
- Although the lung can repair itself in cases of ALI, in many cases permanent fibrosis occurs, which can be severe.

INTRODUCTION

There are numerous etiologies of acute lung injury (ALI) with the insult causing disruption of the framework of the lung with damage centered on capillary endothelium and alveolar epithelium and the intervening shared basement membrane.[1] This damage leads to cell death, exudation of proteinaceous and cellular material into the alveoli and interstitium, subsequent organization with alveolar collapse, and attempts at repair. ALI exists on a clinical, radiologic, and pathologic spectrum ranging from the milder organizing pneumonia (OP) pattern of injury to the extremely severe diffuse alveolar damage (DAD) pattern of injury. Acute fibrinous and OP (AFOP) is a pathologic finding highlighted by the exudation of fibrin and exists somewhere along the spectrum between OP and DAD. ALI remains a significant cause of patient morbidity and mortality, a fact highlighted by the SARS-CoV-2 (COVID-19) pandemic. Even if a patient survives the ALI, resultant pulmonary fibrosis can lead to chronic debilitation. This article discusses the clinical, radiologic, and pathologic findings of ALI, focusing on the stages of injury and pathways to repair or fibrosis.

DIFFUSE ALVEOLAR DAMAGE

Causes and Exudative Phase

DAD is the pathologic finding corresponding to a severe lung injury of which there are numerous causes including inhalation lung injury, drug toxicity, shock, and sepsis.[2] However, the most common cause of DAD is infection, which was true even before the dramatic increase in ALI seen during the COVID-19 pandemic.[3] In addition, DAD is a common pathologic process seen in acute exacerbations of underlying fibrotic lung disease.[4] In instances where the underlying cause of DAD is unknown, it is termed acute interstitial pneumonia. Although these various etiologies may seem distinct clinically, the underlying pathologic process remains constant. During the first week of injury, termed the acute exudative phase,

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there is diffuse damage to the alveolar epithelial cells, capillary endothelial cells, and intervening basement membranes with subsequent cell death and denudation of the alveolar walls.[5–10] Because of the increased capillary permeability, fluid, proteinaceous material, fibrin, and neutrophils flow into the alveoli.[6,11,12] In severe cases, damage to the blood-oxygen interface leads to leakage of red blood cells into the alveoli.[13] Hyaline membranes, eosinophilic structures composed of cellular debris, plasma proteins, and surfactant from pneumocyte death, line the alveolar walls and are the hallmark of the acute stage of DAD.[2,5]

The alveoli and alveolar septa also become infiltrated with myofibroblasts and fibroblasts as part of the normal healing process. Myofibroblasts are beneficial to closing open wounds, whereas the extracellular matrix proteins, cytokines, and growth factors released by fibroblasts are essential for wound healing.[14] However, if these cells are not removed in a timely manner, they can lead to permanent fibrosis, which can begin in less than a week after injury.[1] Myofibroblast contracture in the lungs can create distortion of the alveolar and bronchial architecture and promotes, in conjunction with the lack of surfactant because of pneumocyte death, alveolar collapse.[15,16] In addition, persistent fibroblastic activation, leading to the continued deposition of collagen in the alveoli and interstitium, can lead to permanent lung fibrosis.

On computed tomography (CT), the exudative phase of DAD is manifest as basilar predominant, but often diffuse ground-glass opacity (GGO) with areas of consolidation that are often dependent but are patchy or nodular (**Fig. 1**). Sparing of the anterior portions of the lungs is common. Septal thickening, caused by a combination of edema, interstitial inflammation, and alveolar collapse, is often most pronounced in the posterior aspects of the lungs because of their dependent nature.[17,18] Focal areas of spared, normal attenuated secondary lobules, termed lobular sparing, or more confluent subpleural sparing are common throughout the spectrum of ALI.[8,19,20] Bronchial dilation and volume loss are often mild in this phase.[20] The injury is essentially always bilateral and usually symmetric, although asymmetric injury can occur (**Fig. 2**).

Organizing Phase of Diffuse Alveolar Damage

Although there is overlap between phases because of the varying severity and distribution of injury, typically 1 week after the acute phase of DAD the organizing phase begins, eventually becoming the predominant finding by 3 weeks postinjury.[21] Although there are many components to the organizing phase, it is most denoted by two processes: extensive volume loss caused by alveolar collapse; and organization of the exudative material filling the alveoli, alveolar ducts, and interstitium into whorls or plugs of fibroblasts and activated myofibroblasts embedded in connective tissue matrix.[22–25] These organizing plugs are similar if not identical to those seen in OP and AFOP. However, compared with OP, in DAD there is more severe architectural destruction and alveolar collapse, which can become permanent in some cases.[5,9,24,26] Nonetheless, in some instances, a pathologists may have difficulty in differentiating a severe case of OP and DAD on biopsy.[1,15] This organizing phase of DAD is also commonly referred to as the proliferative phase denoting the proliferation of epithelial and connective tissue cells in an attempt to repair the damage and re-expand the collapsed alveoli.

CT findings mirror the pathologic organization and volume loss. Although the injury may still be lower lobe–predominant with anterior sparing, in some cases the injury is so widespread that no zonal distribution can be elucidated. GGO and consolidation remain the predominant finding, although the extent of consolidation often increases (see **Figs. 1** and **2**). There is more extensive volume loss compared with the exudative phase, secondary to a combination of alveolar collapse and possible early fibrosis. During this stage of injury, reticulation and airway dilation can develop rapidly[8,19,27,28] and are associated with a decreased likelihood of survival.[2,28–30] It should be noted that the airway dilation seen in DAD, AFOP, or OP may not be permanent and can resolve with lung repair and alveolar re-expansion (see **Fig. 2**; **Fig. 3**). Therefore, because bronchiectasis is often used to define a permanent airway dilation,[31] the term of traction bronchiectasis, although still widely used to describe this often transitory finding, may not be technically correct. Distended and distorted subpleural secondary lobules, which can mimic cicatricial emphysema, may also form but can also abate after lung repair likely related to increased lung volumes (see **Fig. 3**).

Lung Repair and Fibrosis in Diffuse Alveolar Damage

Mechanisms of lung repair after DAD are extremely complex and rely on the presence of type II pneumocytes, a repairable basement membrane, and a fibrinolytic system to remove the OP plugs. Because type I pneumocytes cannot themselves regenerate, lung repair in any form of ALI

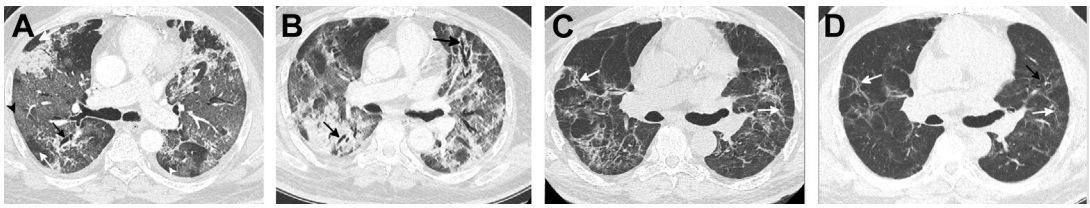

Fig. 1. (*A–D*) Diffuse alveolar damage caused by COVID in a 61-year-old man. (*A*) Axial image from a CT scan shows diffuse GGO with associated septal thickening (*black arrowhead*) and scattered areas of consolidation. Areas of subpleural (*white arrows*) and lobular (*white arrowhead*) sparing are present. There is minimal bronchial dilation (*black arrow*) and only mild volume loss. (*B*) Axial CT imaging at the same level 10 days later demonstrates increasing peribronchiolar consolidation with persistent lobular and subpleural sparing. There is associated increased volume loss with increased dilation of many airways (*black arrows*) despite being on a ventilator with high positive end pressures. (*C*) Axial CT image 5 months later shows areas of peribronchiolar GGO with architectural distortion (*white arrow*). Areas of bronchial dilation are improved but persist in some areas concerning for permanent bronchiectasis. Lung volumes are improved. (*D*) Axial CT image 12 months after the initial injury shows continued improvement of GGO and architectural distortion. However, persistent linear bands of subpleural and peribronchiolar GGO persist (*white arrows*) and represent permanent fibrosis and the residual dilated airways represent permanent traction bronchiectasis (*black arrow*). Overall, the degree of fibrosis is mild given the severity of lung injury. Importantly, the lung continued to heal even 5 months after the initial injury, so be wary of calling fibrosis early after a lung injury. (*Courtesy of* S Kligerman, MD, San Diego, California.)

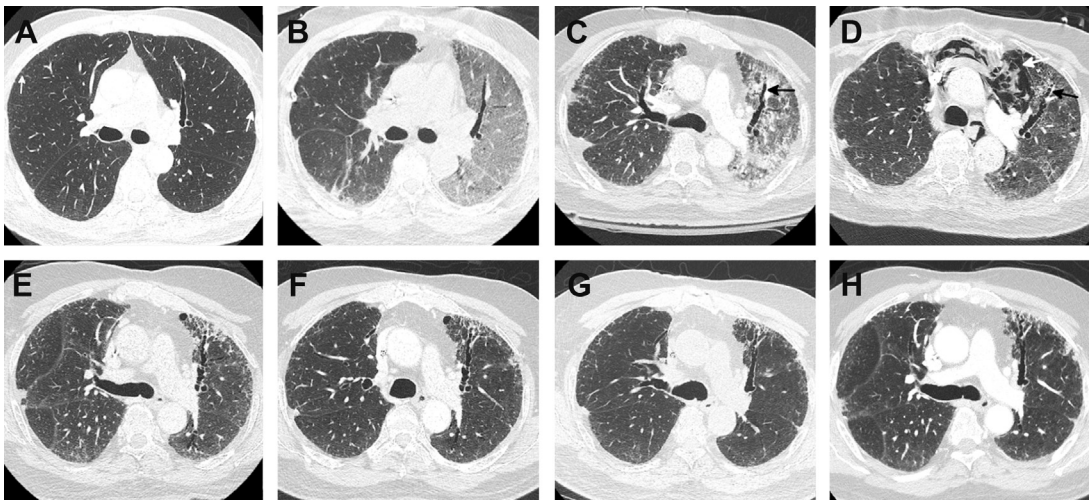

Fig. 2. (*A–H*) Asymmetric diffuse alveolar damage in a 64-year-old man with poorly differentiated pancreatic adenocarcinoma status post right lung wedge resection for an isolated pulmonary metastasis. He underwent Whipple procedure in January 2017. His course was complicated by pancreatic leak, severe sepsis, and acute kidney injury. (*A*) Baseline scan from 2016 at the level of the left upper lobe bronchus shows minimal scattered subpleural reticulation (*white arrows*) but otherwise no evidence of significant fibrosis. (*B*) Four days after Whipple procedure, on February 1st, the patient developed acute respiratory distress syndrome with diffuse left lung GGO with mild areas of opacity on the right. There is no significant airway dilation or volume loss. Although the injury is asymmetric, findings are consistent with the exudative phase of DAD (*C*). Two weeks later, finding of the organizing phase of DAD is seen with increased consolidation and volume loss with increasing bronchial dilation (*arrow*). (*D*) In mid-March, GGO and consolidation have improved but there is persistent dilation of the anterior segment left upper lobe bronchus (*black arrow*). Pneumomediastinum (*white arrow*) is present and is a common complication during prolonged ventilation in patients with DAD. (*E*) CT image at the same level in late May shows improved lung aeration with continued decrease in GGO but persistent airway dilation and subpleural reticulation concerning for permanent fibrosis. (*F–H*) CT images at the same level from 10 months (*F*), 1 year (*G*), and 4 years (*H*) post-DAD show stable findings with asymmetric anterior predominant fibrosis with traction bronchiectasis involving the left upper lobe anterior segmental bronchus and subpleural reticulation. The fibrosis has not progressed because no additional episodes of lung injury had occurred after the initial injury in February 2017. (*Courtesy of* S Kligerman, MD, San Diego, California.)

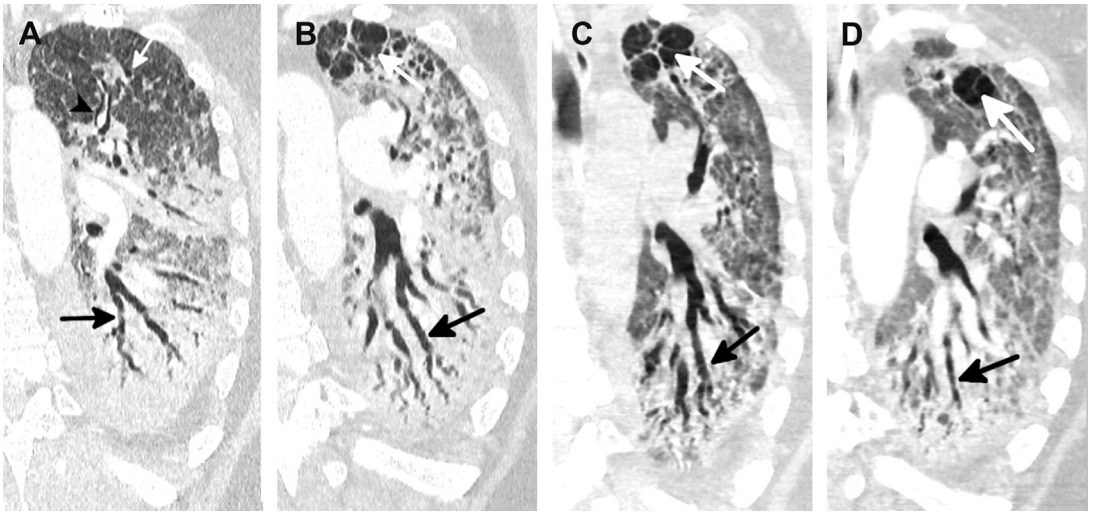

Fig. 3. Rapid development of cystic change in a nonsmoking patient with diffuse alveolar damage caused by dermatomyositis. (*A*) Coronal oblique CT image through the left lung shows lower lobe–predominant consolidation with areas of ground-glass opacity and bronchial dilation (*black arrow*). A few areas of pulmonary interstitial emphysema are present (*black arrowhead*). There are a few areas of lucency in the lungs (*white arrow*). (*B*) Coronal oblique CT image 1 week later shows increasing diffuse consolidation with increasing bronchial dilation (*black arrow*). There has been development of upper lobe parenchymal cystic change (*white arrow*) with an appearance suggesting of secondary lobules that have been pulled apart secondary to the extensive volume loss, suggestive of cicatricial emphysema. (*C*) Coronal oblique CT image 8 days later shows decreasing consolidation with slight improvement in lung volumes. Bronchial dilation (*black arrow*) and cystic change with an appearance of distended pulmonary lobules (*white arrow*) are seen but slightly improved. (*D*) Coronal oblique CT image 1 month later shows decreasing airway dilation *(black arrow)* as the injury begins to heal and lung volumes improve. Additionally, the subpleural cystic change has significantly improved (*white arrow*), likely related to decreased tension on the apical lobules as the lung volumes have increased. (*Courtesy of* S Kligerman, MD, San Diego, California.)

relies on the presence of type II pneumocytes to proliferate and then differentiate into type I pneumocytes, which then re-epithelialize over the denuded, and ideally repaired, basement membrane.[1] Additionally, type II pneumocytes secrete surfactant, which decreases the surface tension at the air/liquid interface of the lung.[32] This allows for some degree of lung repair and alveolar re-expansion.[15] Absence of type II pneumocytes would lead to permanent alveolar collapse. In addition, in areas with extensive basement membrane infoldings because of the initial injury, granular pneumocytes attempting to repair and re-epithelialize the denuded basal lamina can proliferate over apposed septa, thereby fusing the partial or completely collapsed alveoli into a single thickened septum leading to permanent alveolar volume loss.[9] Lastly, if the OP plugs are not removed by fibrinolysis,[15] two possible outcomes may occur. If the plugs remain in the alveoli, there is often epithelization and incorporation of these interalveolar buds into the interstitium.[6,8,9] This fibrosis by accretion is an important mechanism of lung remodeling not only in ALI but also seen in usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP).[1,2,6,8,9,15] The organizing plugs of fibroblastic tissue may also remain in the alveolar lumens and form large swaths of concretions, completely obliterating whole areas of lung in a process sometimes referred to as obliterative fibrosis.[15]

If the patient survives the exudative and organizing phase of DAD, consolidation and GGO slowly improve. Although findings on CT may return to normal in a small percentage of patients,[33] most patients have some degree of residual fibrosis because of mechanisms described previously.[1] In most cases the fibrosis often involves less than 25% of the lung (see **Figs. 1** and **2**).[33–35] The limited degree of fibrosis in comparison with the extensive parenchymal involvement seen earlier in the injury suggests that a healing response has occurred with reorganization of the damaged epithelial basement membranes and aeration of previously collapsed alveoli. However, in some patients the degree of permanent injury is so extensive that lung transplant is performed; 7% of lung transplants in the United States performed from August 1, 2020 to September 30,

2021 were performed secondary to COVID-19-related DAD.[36] Another question commonly posed is when the findings seen on CT during lung repair of ALI represent permanent fibrosis versus continued healing. Although there is no set time point as to when imaging findings demarcate fibrosis, in the author's experience, lung injury can continue to improve up to 6 months after the initial injury so the word fibrosis should be used sparingly before that time (see **Fig. 1**).

The distribution of post-DAD-related fibrosis is variable, although areas of reticulation, bronchiectasis, and cystic spaces are often present. Although the fibrosis is classically described as being most pronounced in the anterior, nondependent portions of the lung, fibrosis can occur in numerous patterns (see **Figs. 1** and **2**), and in some instances the pattern could be classified as UIP (**Fig. 4**).[17,19,28,33] The fibrosis seen with DAD should not progress unless subsequent episodes of lung injury occur.

Association of Diffuse Alveolar Damage with Usual Interstitial Pneumonia

An association between organizing lung injury and UIP was described in 1973 and has been confirmed in many studies.[37,38] This association is documented in the setting of an acute exacerbation, or accelerated phase, of UIP where imaging and histologic findings of DAD, or less commonly of OP, are superimposed on underlying UIP pattern of fibrosis (**Fig. 5**). This acute injury often leads to rapid clinical deterioration and even death.[4,39–42] In 2016, the definition of acute exacerbation was changed and importantly does not exclude infection as an underlying trigger to the lung injury (**Table 1**).[39,43] The imaging and histology often coincide findings of DAD superimposed on an underlying UIP pattern, which can, on occasion, be difficult to recognize given the superimposed lung injury. If the patient survives, much of the ALI can resolve, although worsening fibrosis is often seen.[1] Basement membrane damage is a

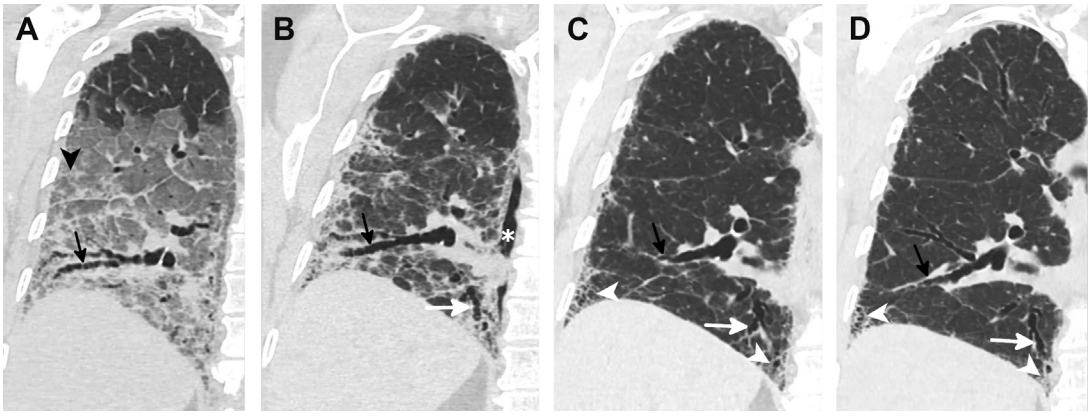

Fig. 4. (*A–D*) DAD pattern to UIP pattern in 3 months in a 71-year-old woman with no significant past medical history. (*A*) A few days after admission for shortness of breath, coronal CT image shows mid and lower lung–predominant GGO with septal thickening (*black arrowhead*) with mild volume loss and airway dilation. (*B*) Coronal CT image at the same level 2 weeks later shows normal evolution of DAD with decreasing GGO and increasing areas of subpleural and peribronchovascular consolidation. There is increased volume loss with increasing airway dilation (*black arrow*, *white arrow*). Pneumomediastinum (*asterisk*) has developed because of barotrauma from ventilation. Extensive work-up revealed no underlying cause and the patient was diagnosed with acute interstitial pneumonia. (*C*) Coronal CT image 3 months after initial injury shows what would be described as a probable UIP pattern with lower lobe subpleural reticulation (*white arrowheads*) and airway dilation most conspicuous in the posterior segment of the right lower lobe (*white arrow*). The dilation of the lateral segmental bronchus (*black arrow*) is significantly improved because of surrounding alveolar re-expansion from healing. (*D*) Coronal CT image 18 months after initial injury shows no change in what would be classified as a probable UIP pattern with permanent subpleural reticulation (*white arrowheads*) and traction bronchiectasis (*white arrow*). The lateral segmental bronchus (*black arrow*), which was significantly dilated during the acute injury, shows mild irregularities but tapers normally. Although a UIP pattern is commonly associated with progression, this fibrosis, secondary to DAD, has remained stable for more than 3 years because it represented sequela of a single severe lung injury and not repeated episodes of injury. (*Courtesy of* S Kligerman, MD, San Diego, California.)

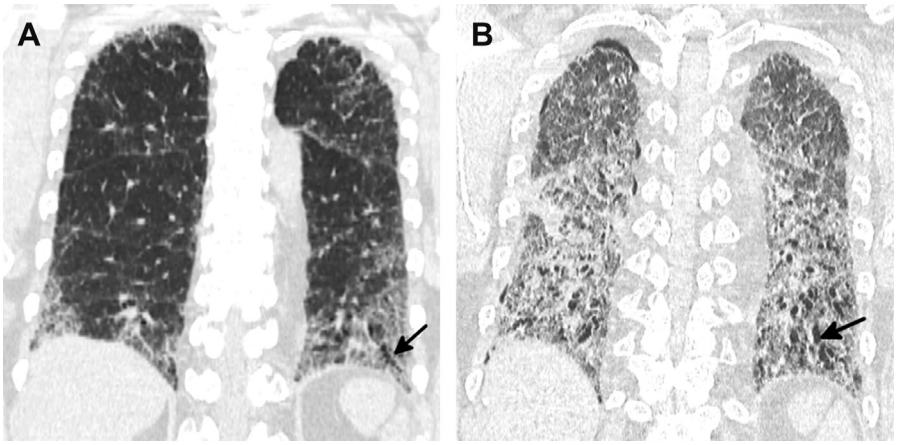

Fig. 5. (*A*, *B*) Acute exacerbation in 60-year-old man with UIP. (*A*) Baseline CT shows UIP pattern of fibrosis with lower lobe subpleural reticulation and traction bronchiectasis (*arrow*). Mild honeycombing, not seen in this image, was present. (*B*) Four months later, the patient was admitted to the hospital for rapidly developing shortness of breath. Coronal CT at the same level shows interval development of a DAD pattern of lung injury with diffuse but lower lobe–predominant ground-glass opacity and consolidation with increasing bronchial dilation (*arrow*). Given the baseline UIP pattern, this was termed an acute exacerbation. The patient received a lung transplant while in the hospital, which pathologically confirmed findings of DAD with underlying UIP pattern of fibrosis. (*Courtesy of* S Kligerman, MD, San Diego, California.)

common finding at electron microscopy in patients with UIP even in the absence of an acute exacerbation.[9,38,44] The relationship between UIP and the organization that occurs in response to acute or subacute lung injury is not entirely understood. However, the common histologic findings suggest that repeated episodes of lung injury and subsequent abnormal lung repair are partially responsible.

Table 1
Comparison between 2016 and 2007 criteria for acute exacerbation of idiopathic pulmonary fibrosis

	2016 Criteria[43]	2007 Criteria[39]
Definition	An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality	An acute, clinically significant, respiratory deterioration of unidentifiable cause
Underlying diagnosis	Previous or concurrent diagnosis of IPF	Previous or concurrent diagnosis of IPF
Clinical presentation	Acute worsening or development of dyspnea typically within 1 mo duration	Unexplained worsening or development of dyspnea within 30 d
CT findings	New bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern	New bilateral ground-glass abnormality and/or consolidation superimposed on a background of reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern
Exclusion	Deterioration not fully explained by cardiac failure or fluid overload	No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage Exclusion of alterative causes including left heart failure, pulmonary embolism, or any identifiable cause of acute lung injury

Abbreviation: IPF, idiopathic pulmonary fibrosis.

ACUTE FIBRINOUS ORGANIZING PNEUMONIA

AFOP is a histologic pattern of ALI that lies along a continuum somewhere between that of OP and DAD. The main histologic difference in AFOP is the presence of reddish fibrin "balls" within the alveoli intermixed with areas of OP.[29] However, hyaline membranes associated with DAD are absent. The underlying etiologies of AFOP mirror that of DAD and OP and include, but are not limited to, infection, autoimmune disease, drug toxicity, and toxic inhalation, such as e-cigarette/vaping-associated ALI.[45–49] The imaging findings and outcomes are variable depending on the study. For instance, in one study of 17 patients with AFOP, nine patients had a severe lung injury with imaging findings like those with DAD (**Fig. 6**) and demonstrated rapid progression to death.[29] The remaining patients had a subclinical course with imaging and recovery like that of OP.[24] In a more recent paper with 34 cases, the imaging findings had an OP pattern in 85% of cases and only two patients with a more severe pattern of injury akin to DAD on imaging died.[50] AFOP, like DAD and OP, can lead to pulmonary fibrosis.[1] Given the lack of ability to differentiate AFOP from either OP or DAD or imaging, this finding should remain a pathologic diagnosis and not an imaging one.

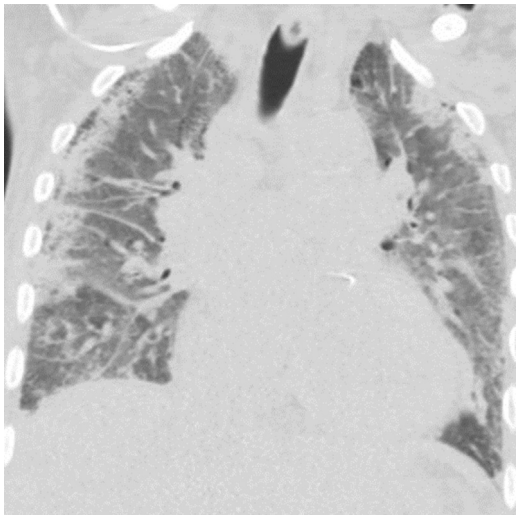

Fig. 6. AFOP in a 69-year-old man. Coronal CT image shows diffuse ground-glass opacity with areas of subpleural consolidation and septal thickening. Given the severity of lung injury, the patient was thought to have DAD. However, biopsy revealed AFOP, which is a pathologic pattern of lung injury where there is extensive deposition of fibrin in the airspaces alongside plugs of organizing pneumonia. The pattern of injury on imaging can range from a mild organizing pneumonia pattern to a severe DAD pattern. (*Courtesy of* S Kligerman, MD, San Diego, California.)

ORGANIZING PNEUMONIA

Etiology

The pathologic response of OP was first recognized during the turn of the nineteenth century in patients with "unresolved" pneumococcal pneumonias. OP was recognized as a distinct pathologic response to pulmonary infection where intra-alveolar exudates were transformed into connective tissue and is associated with the development of or occurs in conjunction with pulmonary fibrosis.[51]

OP is a nonspecific response to lung injury with the initial injury being the same as that seen with AFOP and DAD.[1] Like DAD, infection is the leading cause of OP, although numerous other etiologies include, but are not limited to, toxic inhalation, drug reaction, radiation, aspiration, and the sequela of a systemic inflammatory condition, such as that seen with certain collagen vascular diseases. In some, an inciting cause of the OP is never discovered, and the clinical entity is labeled cryptogenic OP. The underlying cause of OP, just like that of DAD and AFOP, is difficult to elucidate without contributory clinical and laboratory data because the imaging and pathologic findings are often identical to one another.[52]

Focal Imaging Patterns

On CT, numerous imaging patterns are associated with OP. These findings are most often diffuse, but focal abnormalities do occur. OP can present as a solitary pulmonary nodule or as a focal area of consolidation and/or GGO in 10% to 38% of patients.[35,53–55] Focal OP can have various appearances, which can range from benign-appearing areas of consolidation to nodules with spiculation or internal air bronchograms, which can mimic lung cancer or lymphoma, respectively. Architectural distortion, fibrosis, and marginal irregularities within and surrounding these nodules are correlated with alveolar collapse, interstitial inflammation, and fibrosis. A surrounding desmoplastic reaction similar to that seen with lung adenocarcinomas can also occur.[56,57] In many instances, focal OP is preceded by recent infection.[58] Additionally, with focal OP that is more consolidative than mass-like, the distribution is often peribronchovascular or subpleural (**Fig. 7**). Lobular or subpleural sparing, like that seen with diffuse forms, can occur. Unfortunately, in cases where the imaging does overlap with malignancy, lung biopsy may still be necessary if no prior imaging is available and there are no clinical findings to suggest OP. In rare instances where malignancy is still highly suspected, surgical excision is still sometimes necessary even if a biopsy shows OP

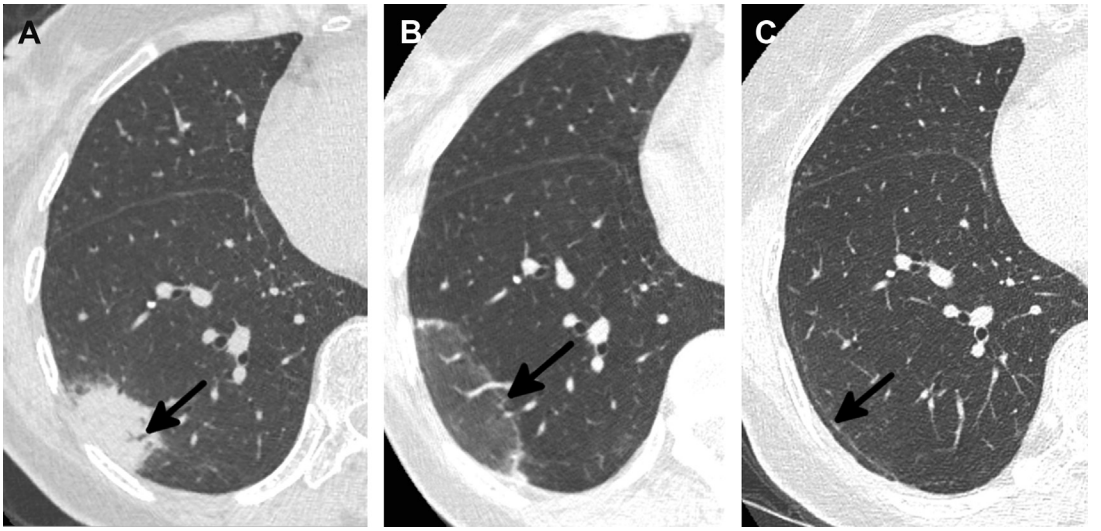

Fig. 7. (*A–C*) Focal mass-like areas of OP in a 44-year-old man with chest pain and abnormal chest radiograph. (*A*) Axial image shows a 3.8-cm subpleural right lower lobe mass with internal air bronchograms (*arrow*). The anterior edge of the mass shows mild ground-glass opacity. Although this was believed to represent an infection, the possibility of malignancy, including pulmonary lymphoma, was raised. The patient underwent biopsy, which showed OP. Subsequent *Coccidioides* titers were positive. (*B*) A few weeks after starting antifungals, axial CT image shows the lesion has expanded outward with near complete resolution of the consolidative portion, which has been replaced by nearly all ground-glass opacity (*arrow*). A remaining band of linear consolidation is along the periphery of the lesion consistent with a reverse halo sign. (*C*) Six months later, there is only a thin linear band of subpleural scarring (*arrow*) in the site of prior infection. (*Courtesy of* S Kligerman, MD, San Diego, California.)

because this pathologic finding can occur adjacent to a lung malignancy.[59]

Diffuse Imaging Patterns

Idiopathic and secondary causes of OP can present with various patterns of diffuse lung disease on imaging. Although some patterns are suggestive of a diagnosis of OP, in many instances the findings are nonspecific. The dominant finding in OP, which itself is completely nonspecific, is bilateral consolidation and/or GGO, occurring in 80% to 95% of cases.[19,60,61] However, it is the distribution of the opacities that helps to suggest the diagnosis of OP. These include subpleural or peribronchovascular predominant consolidation often with areas of lobular or subpleural sparing (**Fig. 8**).[62–64] In some instances, the subpleural consolidation forms linear bands that can parallel the underlying pleural surface. The peribronchovascular distribution may be related to the extensive epithelial damage involving peribronchiolar alveolar septa on pathology.[65] The areas of lobular sparing relate to the zonal distribution of injury where one lobular is filled with OP and the adjacent lobular is spared.[1] The cause of the subpleural sparing is unclear but may be related to clearance mechanisms via the subpleural lymphatics. Septal thickening is also a common finding and may be

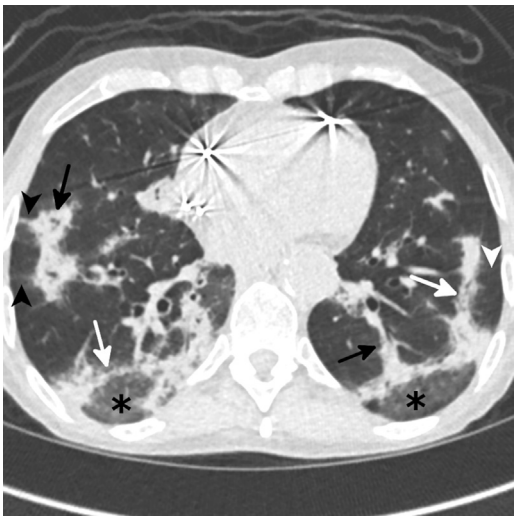

Fig. 8. Axial CT image in a 67-year-old woman being treated with nivolumab for metastatic non–small cell lung cancer shows classic imaging findings of organizing pneumonia including peribronchovascular (*black arrows*) and subpleural (*white arrows*) consolidation with areas of septal thickening (*black arrowheads*). The subpleural consolidation forms linear bands that run parallel to the pleural surface often with intervening subpleural sparing (*white arrowhead*). Additionally, ground-glass opacity is seen between the subpleural consolidation and the pleural surface creating a reverse halo sign (*asterisks*). (*Courtesy of* S Kligerman, MD, San Diego, California.)

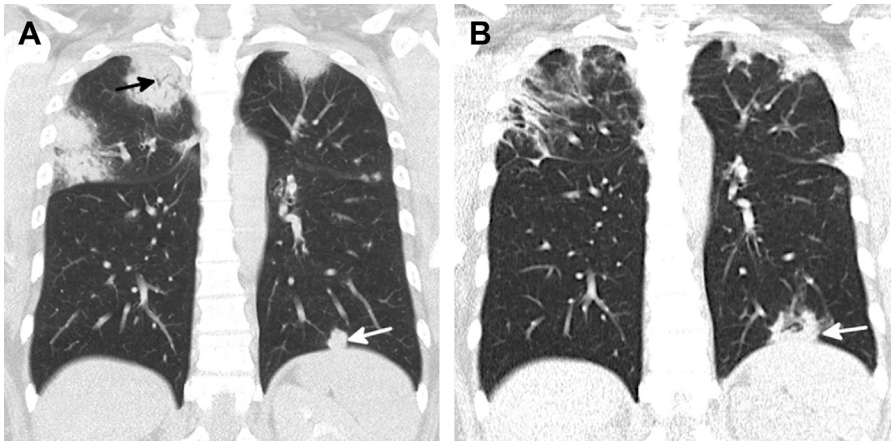

Fig. 9. Evolution of nodular and mass-like foci of organizing pneumonia in a 38-year-old woman with mixed connective tissue disease. (*A*) Coronal CT image shows numerous subpleural round subpleural masses (*black arrow*) and nodules (*white arrow*). (*B*) 16 days after the initiation of steroids, the areas of consolidation have improved with residual areas of subpleural and peribronchovascular consolidation. The lower lobe nodule now demonstrates a "reverse-halo" sign (*white arrow*). (*Courtesy of* S Kligerman, MD, San Diego, California.)

related to septal edema in acute injury, which can progress to septal fibrosis if the injury does not resolve.[1]

The "reverse halo" or "atoll" sign is a CT finding defined as a focal area of GGO surrounded by a ring, or halo, of consolidation (see **Figs. 7** and **8**; **Fig. 9**). It can occur with a unilateral or bilateral injury and is often preceded by a focus of nodular or mass-like consolidation. Over time, the nodule or mass expands outward with decreasing attenuation centrally creating this imaging finding (see **Figs. 7** and **9**). Why this occurs is unclear, but it may represent a healing response. Although initially thought to be a sign diagnostic of OP, it is seen with a variety of infections, infarction, noninfectious granulomatous abnormalities, and even adenocarcinoma in situ.[66,67]

In focal and diffuse forms, OP can appear as airway-centered or peribronchiolar nodules. These nodules are variable in size but are often subpleural and may demonstrate internal air bronchograms when large.[68] The distribution of nodules suggests that the initial site of injury involves the airway.[65] In many instances, these nodules coexist with additional parenchymal manifestations of OP, as discussed previously. This may help to differentiate these nodules from other pathologic processes that can have a similar appearance, such as parenchymal lymphoma, septic emboli, or granulomatosis with polyangiitis. In certain instances, diffuse tree-in-bud nodularity can represent OP on pathology (**Fig. 10**). This has been seen with inhalational injuries caused by synthetic marijuana and e-cigarette/vaping-associated ALI.[69,70]

Treatment of OP centers around removing known inciting factors and corticosteroids treatment, either alone or in conjunction with cytotoxic agents.[23,62,71] How steroids cause the plugs of OP to resolve in still unclear. Prognosis is usually good, and many cases demonstrate complete or near complete resolution with only minimal areas of scarring (**Fig. 11**). In most, the extent of lung

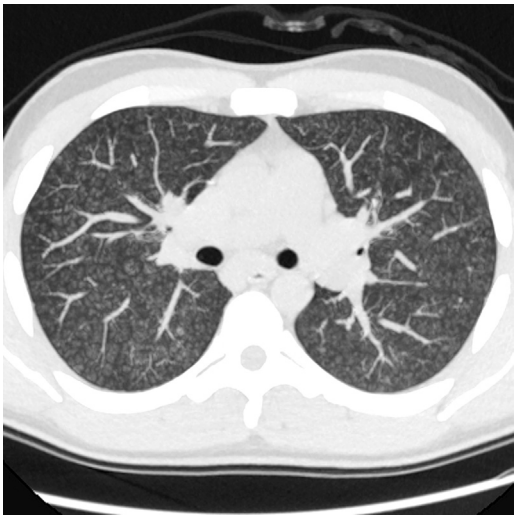

Fig. 10. Axial 10-mm-thick maximum intensity projection image shows diffuse ill-defined ground-glass centrilobular nodules in a 20-year-old man diagnosed with e-cigarette/vaping-associated acute lung injury. Biopsy was performed, which showed organizing pneumonia centered around the respiratory bronchioles caused by the toxic inhalation injury. (*Courtesy of* S Kligerman, MD, San Diego, California.)

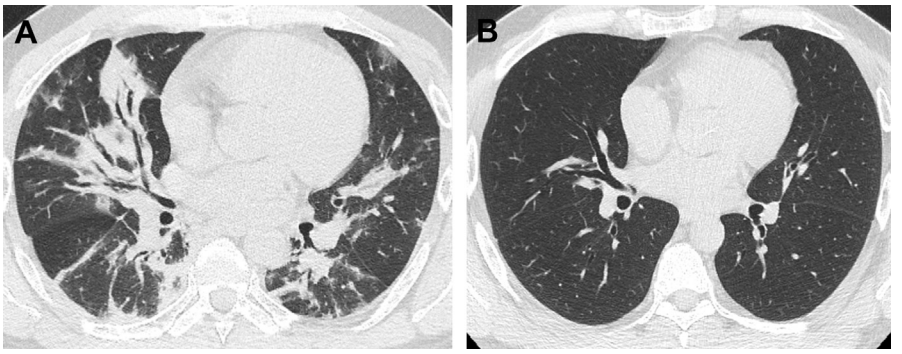

Fig. 11. Resolution of organizing pneumonia pattern of lung injury in a 45-year-old man with COVID-19-related pneumonia. (*A*) Axial image during admission shows peribronchovascular and subpleural consolidation. (*B*) Axial image 6 months later shows a complete resolution of lung injury on CT. (*Courtesy of* S Kligerman, MD, San Diego, California.)

injury is mild, and the lung repairs itself without permanent injury.[7,65,72–74] However, in certain instances, the degree of injury is severe leading to permanent damage and interstitial fibrosis.

Organization as a Pathway to Fibrosis

The pathways of injury in OP, AFOP, and DAD are essentially identical and exist along a continuum. The initial insult leads to injury of the alveolar and capillary epithelium with subsequent proteinaceous exudates filling the airspaces and distal airways.[8,65,72,75,76] Although the degree of injury is more severe in DAD than OP, both lead to alveolar epithelial necrosis, subsequent sloughing of the dead pneumocytes, and associated denudation of the alveolar basal lamina.[9,65,76] The basal lamina is an integral part in normal lung repair by providing an underlying scaffolding for the lung and aid in lung repair.[77,78] New parenchymal cells migrate from adjacent healthy alveoli, repopulate alveolar epithelial cells, and help unfold the pleated basal lamina.[9,65,78] Similar to that seen with DAD, infolding of the basal lamina can lead to permanent epithelial damage with alveolar collapse as repopulating epithelial cells epithelialize over the deformed and infolded basal lamina causing permanent apposition.[65,72] Additionally, intraluminal plugs of organizing fibrotic tissue are epithelialized by proliferating type II pneumocytes with subsequent incorporation into the interstitium.[8,9,65,72,76] Once in the interstitium, they share morphologic characteristics of and look identical to fibroblastic foci seen in UIP.[7,8]

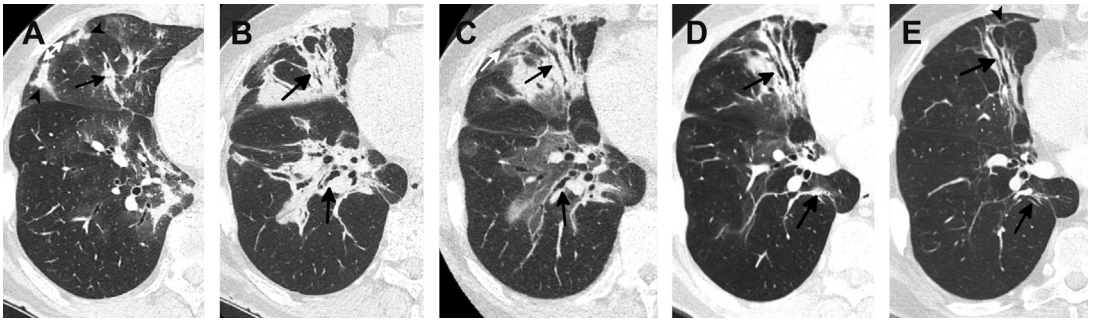

Fig. 12. (*A–E*) A 71-year-old man with metastatic colorectal cancer on an immune checkpoint inhibitor develops shortness of breath and cough. (*A*) Axial image during time of emergency department visit shows peribronchovascular (*black arrow*) and subpleural (*black arrowheads*) consolidation with areas of subpleural sparing (*double-headed white arrow*) caused by drug-induced organizing pneumonia. (*B*) Four days later, there is increasing peribronchovascular consolidation (*black arrows*) with persistent areas of subpleural sparing. (*C*) Ten days after initial injury and 4 days after initiation of steroids, consolidation has decreased with increased GGO in the previous areas of consolidation. Bronchial dilation (*black arrows*) in seen in certain regions. Conspicuous subpleural sparing *(white arrow)* is present. (*D*) Axial CT image 1 month after injury shows continued decrease in consolidation and decrease in GGO. Persistent airway dilation is present in the right middle lobe (*black arrows*). (*E*) Axial CT image 2 years after injury shows right middle lobe greater than right lower lobe peribronchiolar fibrosis (*black arrows*) with linear subpleural bands of scarring (*black arrowhead*). Overall, the degree of fibrosis is mild given the extent of lung injury. (*Courtesy of* S Kligerman, MD, San Diego, California.)

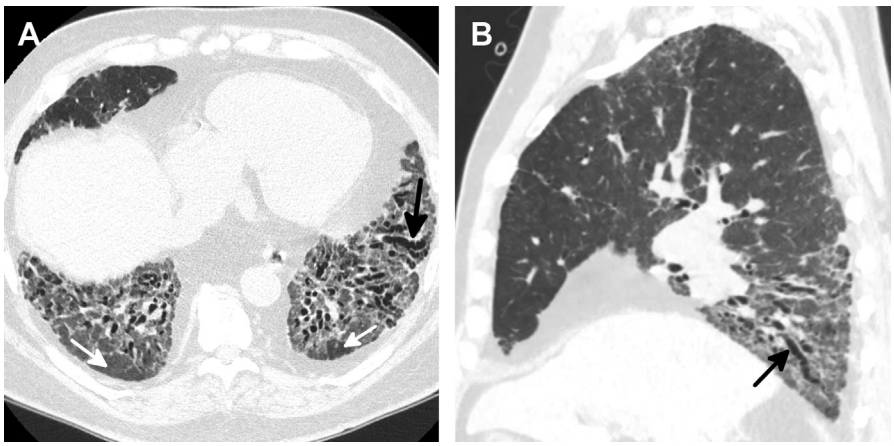

Fig. 13. (*A*, *B*) NSIP pattern of fibrosis 14 months after COVID-19-related pneumonia in a 54-year-old man with no past medical history. Axial (*A*) and sagittal (*B*) images show lower lobe–predominant fibrosis with ground-glass opacity, traction bronchiectasis (*black arrows*), and areas of subpleural and lobular sparing (*white arrows*) suggestive of an NSIP pattern of fibrosis. This pattern can occur after a single episode of acute lung injury. (*Courtesy of* S Kligerman, MD, San Diego, California.)

Given that the initial insult to the basal lamina is more severe in DAD than in OP, it is of little surprise that DAD can lead to fibrosis, as discussed previously. The development of fibrosis secondary to OP is less commonly reported in the radiology literature. In these cases, the distribution of fibrosis often mirrors the distribution of the initial injury and often shows peribronchiolar or

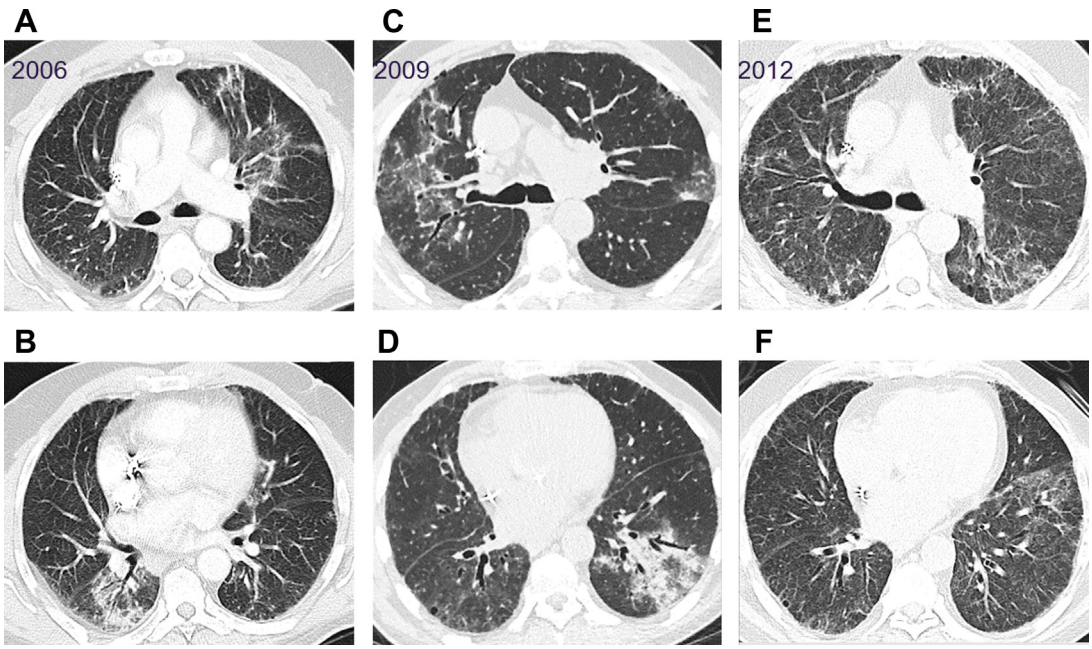

Fig. 14. (*A–F*) A 62-year-old man with reactive arthritis with numerous repeated episodes of OP caused by medical noncompliance. Axial images through the carina (*A*) and through the lower lobes (*B*) in 2006 show patchy areas of peribronchovascular consolidation and GGO, which was shown to be OP on biopsy. The abnormality resolved after steroid treatment. Axial images through the carina (*C*) and lower lobes (*D*) in 2009 show new areas of peribronchovascular consolidation and GGO because of OP. Mild areas of fibrosis are present in the right lower lobe and left upper lobe because of prior insult. Axial images through the carina (*E*) and through the lower lobes (*F*) in 2012 show more diffuse hazy peribronchovascular and subpleural GGO. Although some of this represents acute injury, many areas represented permanent fibrosis as demonstrated on continued follow-up imaging (not shown). Repeated episodes of lung injury can lead to worsening fibrosis after each insult. (*Courtesy of* S Kligerman, MD, San Diego, California.)

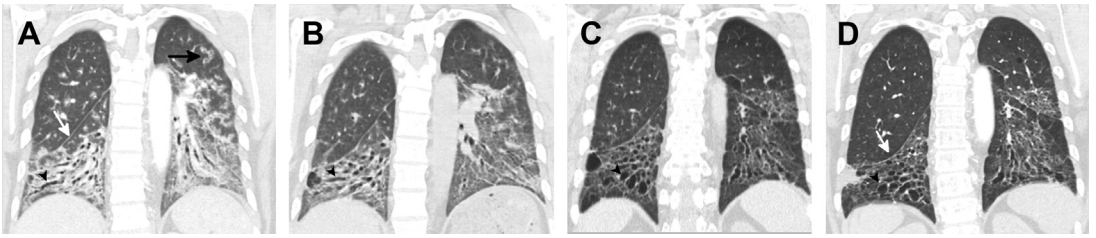

Fig. 15. Progression of OP with areas of NSIP to NSIP in a 39-year-old woman with scleroderma. (*A*) Coronal image shows extensive peribronchovascular GGO and consolidation (*black arrow*) with dilated airways (*black arrowhead*) and inferior displacement of the right major fissure (*white arrow*). Open lung biopsy showed predominantly OP with scattered areas of NSIP pattern of fibrosis. (*B*) After steroid treatment coronal CT scan shows decreasing GGO and near complete resolution of consolidation. Airway dilation *(black arrowhead)*, persists. It is unclear if the residual GGO represents areas of OP or fine fibrosis. Coronal CT images 12 months (*C*) and 18 months (*D*) after the initial CT show near complete resolution of GGO. There is extensive lower lobe–predominant fibrosis with lower lobe volume loss, manifest with inferior displacement of the major fissure (*white arrow*) and associated traction bronchiectasis *(black arrowhead)*. Conspicuous subpleural sparing is present. Bilateral lung transplant showed NSIP pattern of fibrosis with only a few plugs of OP. Although the author believes that OP is the pattern of injury that leads to an NSIP pattern of fibrosis, the concept remains controversial. (*Courtesy of* S Kligerman, MD, San Diego, California.)

subpleural bands of fibrosis with GGO, tractional bronchiectasis, and architectural distortion (**Fig. 12**). In other instances, diffuse OP can heal with a pattern identical to that of NSIP, which is reported to occur in up to 45% of patients (**Fig. 13**).[79] Fibrosis that occurs with OP secondary to a single event, such as a severe pneumonia, should not lead to progressive fibrosis. However, OP relapses are common, being seen 13% to 58% of patients.[23,53,60,62] With each repeated episode of insult, areas of fibrosis can develop (**Fig. 14**).

Lastly, OP is commonly associated with other pathologic forms of interstitial pulmonary fibrosis, most notably NSIP and less frequently UIP.[38,80] The relationship between NSIP and OP is controversial. However, OP is commonly seen in cases of NSIP, and in the American Thoracic Society study on NSIP, OP was seen in 52% of biopsy specimens[81] with similar findings seen in numerous additional studies.[82–84] Additionally, the presence of OP in patients with NSIP is associated with more rapid disease progression and a worse prognosis.[80] Given this clear relationship and evolution from OP to NSIP on imaging in many patients, the author believes that OP is the pathologic pattern of lung injury that may lead to an NSIP pattern of fibrosis in many cases (**Fig. 15**). However, this remains a controversial topic.

SUMMARY

ALI exists on a spectrum. Although there is a tendency to divide injuries into distinct entities, the primary site of injury in all remains the same with injury to the shared basement membrane between the capillary endothelium and type I pneumocyte, which leads to exudation, organization, and attempts at repair. The radiologic findings in ALI depend on the degree of injury and the subsequent healing response. Although ALI can heal without permanent injury, the development of fibrosis after injury is not uncommon and may be debilitating. When ALI does lead to fibrosis, other histologic and imaging patterns, such as those seen with NSIP, can occur, suggesting that the injury associated with organization may be the underlying cause.

CLINICS CARE POINTS

- The pathologic manifestations of acute lung injury exist on a spectrum including organzing pneumonia, acute fibrinous and organizing pneumonia, and diffuse alveolar damage.
- Given that acute lung injury exists on a spectrum, imaging and pathologic findings can overlap.
- Acute fibrinous and organizing pneumonia (AFOP) is a pathologic diagnosis. Imaging findings overlap with both organizing pneumonia and diffuse alveolar damage. There is no way to suggest the diagnosis of AFOP based on imaging alone.

- Organizing pneumonia, acute fibrinous and organizing pneumonia, and diffuse alveolar damage represent nonspecific patterns of lung injury with numerous causes. A radiologist can diagnose ALI but the clinican needs to find the underlying cause.
- No lung injury is truly idiopathicl; it is just that the underlying cause has not been elucidated.

DISCLOSURE

The author has nothing to disclose.

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