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Imaging of Acute Lung Injury

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KEYWORDS

- Acute lung injury (ALI) • Acute respiratory distress syndrome (ARDS)
- Diffuse alveolar damage (DAD) • Acute interstitial pneumonia (AIP)
- Acute fibrinous organizing pneumonia (AFOP) • Acute eosinophilic pneumonia (AEP)

KEY POINTS

- Acute lung injury (ALI) is the clinical syndrome associated with patients who have diffuse alveolar damage on histopathology.
- A variety of diseases may mimic ALI, including hydrostatic edema, infection, aspiration, organizing pneumonia, interstitial lung disease, and acute eosinophilic pneumonia.
- Treatment of ALI is mainly supportive, and no pharmacologic treatment (eg, corticosteroids) has been shown to be convincingly beneficial.
- The key role of imaging is to identify diseases that mimic ALI so that appropriate specific treatment may be instituted.

INTRODUCTION

Acute lung injury (ALI) is a common cause of acute respiratory symptoms in the hospitalized patient, accounting for more than 10% of admissions to the intensive care unit¹ and affecting nearly 200,000 people in the United States yearly.² ALI is unique from other causes of dyspnea in its pathophysiologic mechanism of disease. Injury to the alveolar epithelium and capillary endothelium increases alveolar barrier permeability, resulting in airspace edema and inflammation. Because of this unique pattern of injury, the natural history, treatment, and prognosis of ALI differs significantly from other acute lung diseases. The diagnosis of ALI is typically based on clinical and radiographic criteria; however, because these criteria can be nonspecific, diagnostic uncertainty is common. A multidisciplinary approach that synthesizes clinical, imaging, and pathologic data, when available,

can ensure an accurate diagnosis. Imaging represents a cornerstone modality in the detection, characterization, and follow-up of patients with suspected ALI, but radiologists must also have a comprehensive knowledge of the clinical and pathologic findings seen in patients with ALI. The goal of this article is to provide a review of ALI with an emphasis on this multidisciplinary approach.

CLINICAL Definitions

ALI, acute respiratory distress syndrome (ARDS), and diffuse alveolar damage (DAD) all refer to a similar pathophysiologic process; however, they are not synonymous. The first challenge in understanding this topic is to be aware of the subtle, yet important, differences between these 3 terms (**Table 1**). DAD is a histopathologic pattern of injury

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Table 1
Definitions of diffuse alveolar damage, acute lung injury, and acute respiratory distress syndrome

Term	Definition
DAD	A histopathologic pattern of injury characterized by alveolar epithelial injury, proteinaceous edema, hyaline membranes, edema, and eventually fibroplasia
ALI	The clinical syndrome associated with any patient that has DAD pathologically
ARDS	A clinical syndrome defined by 4 criteria: 1. Acute onset (occurring within 1 wk of an insult or after the onset of symptoms) 2. Bilateral opacities on chest radiography (opacities not explained by effusions, collapse, or nodules) 3. Exclusion of cardiac failure or fluid overload as a cause of symptoms (echocardiography often obtained, particularly when there are no risk factors for hydrostatic edema) 4. Reduced oxygenation (3 levels of severity) a. Mild: $200\text{ mm Hg} < \text{Pao}_2/\text{Fio}_2 \leq 300\text{ mm Hg}$ b. Moderate: $100\text{ mm Hg} < \text{Pao}_2/\text{Fio}_2 \leq 200\text{ mm Hg}$ c. Severe: $\text{Pao}_2/\text{Fio}_2 \leq 100\text{ mm Hg}$

characterized by alveolar epithelial injury, proteinaceous edema, hyaline membranes, edema, and eventually, fibroplasia. The pathologic manifestations of DAD are discussed in greater detail later.

ALI and ARDS, on the other hand, are both clinical syndromes. ARDS was most recently defined in a 2012 consensus statement.³ It is characterized by the acute onset of hypoxemia and diffuse parenchymal opacities on chest radiograph not explained by cardiogenic edema or fluid overload. ARDS is further categorized into mild, moderate, and severe forms based on the severity of hypoxemia as defined by the ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen ($\text{Pao}_2/\text{Fio}_2$ ratio). ALI, on the other hand, refers to the clinical syndrome associated with any patient who has DAD pathologically, but its use is not limited by the strict clinical criteria that define ARDS. To add further confusion, an older consensus paper⁴ defined ALI using similar criteria to ARDS, except with less severe hypoxemia. This definition of ALI was subsequently removed in the 2012 classification because practitioners had been using the term ALI to describe patients who clinically appeared to have ARDS, but did not meet the oxygenation criteria. Presently, the most accurate use of the term ALI is to describe any clinical symptoms or findings that are associated with histopathologic DAD, which include both cases that meet criteria for ARDS and those that do not meet criteria for ARDS.

In many cases, a definitive pathologic diagnosis is not available in patients with ALI or ARDS; thus, the diagnosis is often presumed and based on the exclusion of other causes of acute lung symptoms. As discussed earlier, DAD and ARDS are not synonymous. Not all patients who meet clinical and radiographic criteria for ARDS will have DAD on

pathology. DAD mimics that may meet clinical criteria for ARDS are shown in **Box 1**. In a study of ARDS patients undergoing autopsy,⁵ only 45% of patients who met criteria for ARDS had DAD on pathology. In the group with mild ARDS, only 14% had DAD on pathology. The most common alternative (non-DAD) diagnoses in this study included pneumonia (49%), no significant lung abnormality (14%), emphysema (7%), pulmonary hemorrhage (6%), and malignancy (5.5%). In another study of open lung biopsy in patients with nonresolving ARDS (persistent hypoxemic respiratory failure >1 week after admission),⁶ 58% had DAD on pathology. The most common alternative (non-DAD) diagnoses in this study were interstitial fibrosis (37%), organizing pneumonia (OP; 26%), and alveolar hemorrhage (14%). It is also important to note that not all patients with DAD on histopathology meet clinical

Box 1
Clinical and radiographic mimics of acute lung injury

- Hydrostatic pulmonary edema
- Rare causes of pulmonary edema (high altitude, high permeability such as interleukin-2 infusion, neurogenic, postobstructive)
- Pneumonia without ALI
- Aspiration
- Diffuse alveolar hemorrhage
- Acute hypersensitivity pneumonitis
- Organizing pneumonia
- Acute eosinophilic pneumonia
- Acute fibrinous organizing pneumonia

criteria for ARDS, although they can still be considered to have ALI.

Demographics and Causes of Acute Lung Injury

ALI may affect patients of any age, including pediatric patients,⁷ but its highest incidence is seen in patients over the age of 75.² There are a variety of causes that may be pulmonary or extrapulmonary in origin (**Box 2**). The most common causes vary depending on referral patterns and specialties at different institutions. In an analysis of 21 academic and community hospitals in the state of Washington, the most common causes of ARDS were pneumonia with sepsis (46%), sepsis from a non-pulmonary source (33%), aspiration (11%), transfusion (3%), drug overdose (3%), pancreatitis (3%), and other (14%).² In a study of ARDS patients at the Mayo Clinic in Rochester, Minnesota, the most common causes were idiopathic (21%), stem-cell or solid organ transplantation (17%), connective tissue disease (16%), acute exacerbation of idiopathic pulmonary fibrosis (IPF; 12%), drugs (10%), and radiation therapy (2%).⁸

As ALI and ARDS are diagnoses of exclusion, a search for alternative causes of dyspnea and diffuse lung opacities is important. This is particularly true in patients without common risk factors for ALI or ARDS, such as pneumonia or sepsis, because these patients have a higher mortality than those with common risk factors but may have steroid-responsive disease.⁹ There are currently no pharmacologic

therapies for ALI or ARDS. Therefore, an aggressive diagnostic workup early after presentation, and the identification of steroid-responsive diseases that clinically mimic ALI may have a significant impact on outcomes.¹⁰ Diagnostic studies that may be obtained in the evaluation of patients with suspected ALI or ARDS are focused on clinical entities that may mimic DAD. Diagnostic evaluation may include echocardiography, pulmonary artery pressure measurements obtained from pulmonary artery catheterization, bronchoalveolar lavage, blood cultures, sputum analysis, connective tissue disease serologies, and other laboratory tests. Imaging is a vital component of this diagnostic evaluation. Although chest radiographs are routinely obtained in all hospitalized patients with acute dyspnea and comprise one of the principal criteria for ARDS, computed tomography (CT) may also be helpful in the detection of treatable causes of acute respiratory failure.

Bronchoscopy often represents the first invasive diagnostic test obtained when an initial clinical evaluation is unrevealing. In particular, bronchoscopy with alveolar lavage increases diagnostic accuracy for certain infections, diffuse alveolar hemorrhage, and acute eosinophilic pneumonia (AEP). Open lung biopsy is often helpful, although only occasionally obtained. In a study of 57 patients meeting clinical criteria for ARDS, but without a clear precipitant, open lung biopsy led to the initiation of new treatments in 60% of patients and the termination of unnecessary treatment in 37% of patients.¹¹ The most common changes in treatment included the administration of corticosteroids (46%), cyclophosphamide (14%), and antimicrobial therapies (9%). One caveat in interpreting this study: corticosteroids were given to patients with DAD on lung biopsy, but this is not currently considered the standard of care.

Box 2

Pulmonary and extrapulmonary causes of acute lung injury and acute respiratory distress syndrome associated with diffuse alveolar damage pathologically

Pulmonary

Pneumonia
Aspiration
Inhalational injury
Pulmonary contusion

Extrapulmonary

Sepsis (extrapulmonary)
Surgery
Drugs
Pancreatitis
Transfusion
Connective tissue disease
Trauma

Mortality

Studies of mortality are heterogeneous with regards to the population studied. Some studies have evaluated patients with clinical ARDS, whereas others have evaluated those with pathologic evidence of DAD. The studies that included ARDS patients were undoubtedly a mix of those with and without DAD. Regardless, the average mortality of these entities is high compared with other common causes of hypoxemia, such as cardiogenic pulmonary edema. Recent advances in supportive techniques, such as the introduction of low tidal volume ventilation, would predict an improvement in outcomes compared with prior decades; however, despite the positive results from randomized trials, adherence to lung-protective ventilation strategies is less than complete.¹²

Although some observational trials¹³ and a systematic review¹⁴ have shown a reduction in ARDS mortality over time, another review of the literature¹⁵ reported no significant change in mortality between 1994 and 2006. The overall pooled mortality in this review was 44.3%. More recent data comparing ARDS mortality by severity, based on the 2012 criteria, reported 28-day mortalities of 30%, 35%, and 43% for mild, moderate, and severe ARDS, respectively.¹ Among patients who meet the clinical criteria for ARDS in whom histopathology was obtained, mortality also varies depending on the presence or absence of DAD. In one recent study, the odds ratio for mortality in patients with ARDS and DAD was 1.8 compared with patients who had ARDS without DAD.¹⁶ Although most patients who die with ARDS succumb to multiorgan failure or shock, the presence of DAD on histopathology was associated with a higher risk of death from respiratory failure.¹⁷ Among patients with DAD, mortality may also vary depending on the clinical context. For example, the mortality of patients with DAD due to an acute exacerbation of IPF is as high as 86%.⁸

Treatment

Treatment of ALI is primarily supportive through supplemental oxygen and mechanical ventilation, if necessary. The main pharmacologic treatment is aimed at any underlying cause, if one can be identified, such as infection. The use of corticosteroids in patients with protracted hypoxemic respiratory failure is controversial. Although one study demonstrated a benefit of using corticosteroids for a subset of ARDS patients with persistent respiratory failure of at least 7 days' duration,¹⁸ a multicenter, double-blind randomized controlled trial of steroids versus placebo in patients with ARDS of at least 7 days' duration¹⁹ showed no significant difference in the 60-day mortality comparing the corticosteroid group (29.2% mortality) with the placebo group (28.6% mortality). Interestingly, the steroid group in this study showed a greater number of ventilator-free days, improved oxygenation, and improved blood pressure compared with the placebo group. It is possible that the benefits of steroid therapy in this population may have been counteracted by drug-related complications of this therapy. Alternatively, there may be a subset of patients for whom steroid therapy was beneficial. For example, because DAD and OP often coexist, it is possible that a subset of patients had steroid-responsive OP following ARDS, but this remains to be investigated.

PATHOLOGY

DAD is the main pathologic correlate to the clinical entity ALI. The term diffuse in this setting refers to the global involvement of the alveolus such that both the endothelial (alveolar capillary) and the epithelial (pneumocyte) components are affected. The histologic appearance of this process evolves over the course of the injury from an early exudative or injury phase, through a proliferative or organizing phase, and finally into a healed or resolved phase.²⁰

The proliferative phase is characterized by alveolar septal thickening from interstitial edema and mild inflammation. Ultrastructural analysis by electron microscopy reveals that this phase is initially characterized by necrosis of type 1 pneumocytes, endothelial cell damage, and sloughing of the alveolar basement membranes. This loss of the alveolar integrity results in leaking of fibrin-rich proteinaceous fluid into airspaces. After 1 or 2 days from the initial injury, this fluid admixes with the cytoplasm and nucleoplasm of the dead cells and forms homogeneous eosinophilic hyaline membranes, which lie in close apposition to the alveolar septa (Fig. 1). Hyaline membranes become better developed over the course of the next 3 to 5 days. During this time, there is recruitment of inflammatory cells into the region.

The organizing phase begins near the end of the first week following injury and is characterized by re-epithelialization and fibroplasia. The alveoli show growth of type 2 pneumocytes along their surface. These cells are thought to differentiate into type 1 pneumocytes as the repair process continues. The alveolar septa are thickened by

Fig. 1. Late proliferative phase DAD. The alveolar septa are thickened by edema and mild chronic inflammation. There are well-developed hyaline membranes along the alveolar septal surface. The airspaces show filling with edema (hematoxylin-eosin, original magnification $\times 200$).

interstitial accumulation of granulation tissuelike fibrosis composed of fibroblasts, myofibroblasts, and small vessels. These fibroblasts and myofibroblasts can also extend into the airspaces, resulting in consolidated regions of OP. It is important in pathology to recognize this overlap of OP and DAD because the nonspecific presence of OP may be a sign of either a steroid-responsive process (as in cryptogenic OP) or organizing DAD that may not be as easily treatable.

The healed or resolved phase is characterized by either a return to normal pulmonary alveolar architecture or a progression to fibrosis. As the type 2 pneumocytes proliferate, the regions of OP may be incorporated into the interstitium where the fibroblasts undergo apoptosis. Apoptosis results in a relatively normal-appearing lung following resolution of the injury. Alternately, the involved regions may show extensive architectural remodeling by fibrosis, which may be manifest as either large areas of alveolar lobular collapse with fibrosis, airspace enlargement with fibrosis, or microscopic honeycomb fibrosis.

A second pattern of lung injury that may occur in isolation or may be associated with DAD is OP. This nonspecific injury pattern is characterized by consolidation of alveolar ducts and alveolar spaces by branching rounded polypoid plugs of granulation tissue (**Fig. 2**).^{21,22} The underlying lung architecture is preserved, and the regions of alveolar consolidation are often patchy and frequently bronchiolocentric. The fibrous plugs are rich in mucopolysaccharides and have a slight basophilic appearance on hematoxylin and eosin staining (rather than the eosinophilic appearance seen with established dense fibrosis in scar tissue). There are often numerous associated intra-alveolar macrophages with foamy cytoplasm. Alveolar

Fig. 2. OP. The lung parenchyma shows consolidation by numerous rounded polypoid plugs of granulation tissuelike fibrosis. There is mild alveolar septal interstitial inflammation (hematoxylin-eosin, original magnification $\times 40$).

septal inflammation is variable, but may be nearly absent.

Acute fibrinous organizing pneumonia (AFOP) is a term used to describe a pattern of ALI that histologically lies within the spectrum between DAD and OP. Similar to DAD, the airspaces show accumulation of fibrin, and similar to OP, this fibrin-rich material is arranged into polypoid plugs.²³ Like the other 2 patterns of ALI, AFOP is histologically nonspecific and may be observed in several types of toxic insults. Identification of hyaline membranes should prompt the diagnosis of DAD rather than AFOP, and identification of numerous eosinophils should prompt a diagnosis of eosinophilic pneumonia (which frequently shows abundant intra-alveolar fibrin).

IMAGING

Radiographic Findings of Acute Lung Injury

Chest radiographs typically are the first imaging modality obtained in patients with suspected ALI. Although the chest radiograph is a fast and inexpensive test, its findings are nonspecific and interobserver agreement for ALI is only moderate.²⁴ Figueroa-Casas and colleagues²⁵ assessed the diagnostic performance of chest radiographs for ARDS compared with CT and found that chest radiographs had a sensitivity of 73%, specificity of 70%, positive predictive value of 47%, and negative predictive value of 88%.

Bilateral lung opacities are one of the primary criteria for ARDS (**Fig. 3**) and will be seen,

Fig. 3. Chest radiograph of ARDS. Diffuse lung consolidation with air bronchograms is present on a frontal chest radiograph of a patient with ARDS. Diffuse lung opacity on chest radiograph comprises one of the principal criteria for the diagnosis of ARDS.

therefore, in all patients with ARDS whether or not it is associated with DAD pathologically. The differential of bilateral lung opacities on chest radiographs is thus broad and includes ALI, infection without ALI, aspiration, hydrostatic pulmonary edema, diffuse alveolar hemorrhage, acute hypersensitivity pneumonitis, OP, and AEP.

The distinction between diffuse lung consolidation and layering pleural effusions or bilateral atelectasis may be challenging. Good radiographic technique is important in avoiding this pitfall. Ideally, patients should be imaged in an upright or semiupright position at maximal inspiration. In the supine position, pleural effusions may layer posteriorly and extend from base to apex, mimicking diffuse lung consolidation (Fig. 4). When the patient is imaged in an upright position, the pleural effusions layer toward the lung bases and cause more typical blunting of the costophrenic angles. Atelectasis may be distinguished from consolidation by signs of volume loss, such as fissural displacement, diaphragmatic elevation and mediastinal/hilar deviation. In many cases of atelectasis, however, these signs are lacking.

Computed Tomography Findings of Acute Lung Injury

Compared with chest radiographs, CT is more sensitive in the detection of early disease and is more accurate in the characterization of abnormalities and formulation of a differential diagnosis. The typical CT findings of ALI are symmetric or diffuse ground-glass opacities and/or consolidation (Fig. 5). Smooth interlobular septal thickening may be seen in association with ground-glass opacity (ie, crazy paving) (Fig. 6); however, interlobular

septal thickening as an isolated finding is not typical. These findings overlap significantly with hydrostatic pulmonary edema, certain infections (particularly viruses, atypical bacteria, and *Pneumocystis jirovecii*), diffuse alveolar hemorrhage, acute hypersensitivity pneumonitis, and AEP.

The distribution of abnormalities on CT varies depending on the cause of ALI: pulmonary versus extrapulmonary. ALI from an extrapulmonary cause (eg, pancreatitis) classically shows an even gradient of lung opacity from anterior to posterior (Fig. 7). The anterior lung is normal or shows ground-glass opacity, whereas the posterior lung shows confluent consolidation. The specificity of this pattern for ALI is unclear, however. ALI from a pulmonary cause does not tend to show this gradient, but instead demonstrates more heterogeneous opacities and nondependent areas of consolidation (Fig. 8).

Role of Computed Tomography in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome

The results of CT scans in patients meeting clinical criteria for ARDS have been shown to change management in greater than 25% of cases. Management changes in the study by Simon and colleagues²⁶ included changes in antibiotic therapy against bacteria or fungi (12.7%), drainage of pleural effusions (7.8%), correction of misplaced lines or tubes (4.9%), diuresis (2.9%), and anticoagulation (2.5%). The role of CT scan in patients with ALI or ARDS is 2-fold. First, CT is able to confirm the presence of abnormalities that are compatible with ALI. As discussed previously, chest radiographs are limited in their ability to

Fig. 4. Pleural effusions mimicking ARDS. Supine frontal chest radiograph (A) shows diffuse opacities. The distinction between lung consolidation and layering effusions is difficult when imaging patients in the supine position. An upright chest radiograph (B) in the same patient shows that these opacities represent layering effusions and there is no significant lung consolidation.

Fig. 5. DAD without ARDS. Extensive bilateral ground-glass opacity is seen on this axial CT image in a patient with DAD due to drug toxicity. Although DAD was present on open lung biopsy, the patient did not meet clinical criteria for ARDS because of a P_{aO_2}/F_{iO_2} ratio greater than 300 mm Hg.

distinguish diffuse lung opacities from pleural effusions and atelectasis. CT is more specific in this distinction and thus may target patients who will benefit from drainage of pleural effusions or recruitment techniques to reduce atelectasis.

Second, CT may identify patients with lung disease that is incompatible with ALI and suggestive of an alternative cause. A careful search for CT findings suggestive of these alternative causes has the potential to change management by detecting a disease that may be responsive to specific pharmacologic intervention. Infection should be considered in cases in which nondependent areas of consolidation are present. Greater than 90% of patients with pneumonia will show these nondependent opacities.²⁷ Tree-in-bud opacities are strongly suggestive of infection or aspiration²⁸

Fig. 6. Crazy paving in ALI. Axial CT image demonstrates a combination of ground-glass opacity and interlobular septal thickening, also known as the crazy-paving pattern. In the acute setting, this pattern is most commonly seen with pulmonary edema, ALI, infection, and hemorrhage. This patient had DAD from sepsis.

Fig. 7. ALI from an extrapulmonary cause. Axial CT shows a gradient of density from anterior to posterior. The anterior lung shows dense consolidation. This distribution suggests an extrapulmonary cause of ALI. The cause of ALI in this patient was sepsis from an abdominal source.

(**Fig. 9**). Pulmonary edema should be considered in patients with smooth interlobular septal thickening, pleural effusions, or cardiomegaly. In the study by Komiya and colleagues,²⁹ findings suggesting hydrostatic pulmonary edema over ALI included an upper lung or central distribution of ground-glass opacity and the presence of peribronchovascular interstitial thickening (**Fig. 10**). Findings of fibrosis (irregular reticulation, traction bronchiectasis, and honeycombing) suggest interstitial lung disease (ILD). Of note, CT findings of fibrosis may develop in patients with ALI over time; however, they are not usually present within the first week after clinical presentation.

OP is another entity that may clinically mimic ALI. Both OP and ALI may have an acute or subacute clinical presentation with hypoxemia and

Fig. 8. ALI from a pulmonary cause. In contrast to **Fig. 7**, this axial CT image shows more heterogeneous opacities with focal nondependent areas of consolidation. This distribution suggests a pulmonary cause of ALI. The cause of ALI in this patient was pneumonia.

Fig. 9. ARDS due to infection without ALI. An axial CT image shows extensive bilateral centrilobular nodules and tree-in-bud opacities in a patient with viral infection. Although this patient met clinical criteria for ARDS, they did not have DAD on pathology.

bilateral opacities on chest radiographs. On CT, OP shows characteristic findings of patchy, bilateral, often rounded areas of peribronchovascular and subpleural consolidation (**Fig. 11**). As OP tends to be a highly steroid-responsive disease, distinction from ALI has a significant impact on treatment. It is important to note that DAD and OP show significant pathologic overlap and often coexist (**Fig. 12**). This overlap is termed organizing DAD. In most cases, DAD is the predominant finding and OP is a secondary finding; however, in rare cases, the opposite is true. CT may be helpful in determining the relative contributions of DAD versus OP to the overall disease burden and may be able to predict steroid responsiveness in cases of organizing DAD.

The Subacute to Chronic Appearance of Acute Lung Injury

ALI shows a typical evolution over time on CT that mirrors the pathologic stages of DAD.^{30,31} Initially, ground-glass opacity and/or consolidation are seen in isolation. Over time (1–4 weeks), findings

Fig. 11. OP. Focal areas of patchy, bilateral, peribronchovascular consolidation are seen on this axial CT of a patient with OP.

of fibrosis may develop, including irregular reticulation and traction bronchiectasis (**Fig. 13**). In diseases such as IPF, reticulation and traction bronchiectasis represent irreversible fibrosis; however, in the setting of ALI, these findings may eventually resolve over time. Despite this fact, the development of bronchiectasis, in particular, is a poor prognostic sign. In the study by Chung and colleagues,³² the development of varicoid bronchiectasis was associated with higher mortality, seen in 43% of patients who died but only 7% of survivors.

ALI may eventually lead to permanent fibrosis with or without honeycombing; however, in most cases, the extent of fibrosis is limited. As many as 90% of patients who survive the acute stage of clinical ARDS will show some signs of fibrosis 6 to 10 months after the onset of symptoms.³³ The presence and extent of these findings correlate with the severity of ARDS and duration of mechanical ventilation using high peak inspiratory

Fig. 10. ARDS due to edema without ALI. Two axial CT images through the upper (A) and lower (B) lungs show bilateral ground-glass opacity and consolidation. The presence of peribronchovascular interstitial thickening and interlobular septal thickening suggests hydrostatic pulmonary edema over ALI.

Fig. 12. Organizing DAD. An axial CT image shows bilateral ground-glass opacity and focal areas of consolidation. Open lung biopsy showed features of both DAD and OP. The focal areas of peribronchovascular and subpleural consolidation on CT corresponded to OP, whereas the more symmetric ground-glass opacities corresponded to DAD.

pressures or high oxygen levels. This fibrosis typically has an anterior, subpleural distribution (**Fig. 14**). This distribution may be a result of barotrauma and oxygen toxicity in an area of lung that is relatively resistant to atelectasis.

SPECIFIC CAUSES OF ACUTE LUNG INJURY

ALI is most often caused by common etiologies, such as pneumonia. There are several uncommon

causes of ALI that deserve specific mention because of their unique clinical, pathologic, or radiographic features.

Acute Interstitial Pneumonia

Acute interstitial pneumonia (AIP), previously known as Hamman-Rich syndrome, is the idiopathic clinical disorder associated with histopathologic DAD. Patients are given a diagnosis of AIP when they meet clinical criteria for ARDS, but no cause is identified. Lung biopsy is required to confidently confirm the diagnosis and exclude mimics of AIP. Given that many patients with AIP have a prodromal illness, viral infection may be one of the potential inciting factors. The demographics and clinical course are similar to ARDS from an identifiable cause. Information on mortality is limited by small sample sizes and varies significantly from 20% to 100%.^{10,34}

Radiographic findings are similar or identical to nonidiopathic ARDS (**Fig. 15**). Chest radiographs demonstrate extensive bilateral lung opacities, and CT demonstrates diffuse ground-glass opacity and consolidation evolving over time to reticulation, traction bronchiectasis, and honeycombing.³⁵ In one study comparing AIP to nonidiopathic cases of ARDS,³⁶ AIP more frequently showed a lower lung and symmetric distribution. Honeycombing was also more common in the evolution of AIP,

Fig. 13. Evolution of CT findings of ALI over time. A baseline CT (A) at the onset of acute symptoms demonstrates extensive bilateral ground-glass opacity and consolidation. Three weeks later, a CT at the same level (B) shows the interval development of irregular reticulation. Axial minimum intensity projection images show the development of traction bronchiectasis over time when comparing images at the onset of symptoms (C) and 3 weeks later (D). This is the typical evolution of the CT findings of ALI over time.

Fig. 14. Post-ARDS fibrosis. Two axial CT images through the mid (A) and lower (B) lungs demonstrate an anterior distribution of irregular reticulation and traction bronchiectasis. This is a typical distribution of fibrosis from prior ARDS.

although this may have been due to the inclusion of patients with an acute exacerbation of ILD. Corticosteroids are often administered given the lack of any other effective treatment; however, they are unlikely to provide a significant benefit.

Acute Exacerbation of Interstitial Lung Disease

Over the past 2 decades, there has been an increased awareness of patients with ILD presenting with acute symptoms not attributable to infection, edema, or other identifiable causes. The cause of these acute symptoms is presumably related to the underlying ILD, although the trigger for the acute acceleration of disease is unknown. Although an acute exacerbation may be seen with any ILD, it is most common in patients with IPF. Silva and colleagues³⁷ reviewed 24 patients

with a diagnosis of acute exacerbation of interstitial pneumonia. This cohort was composed of patients with IPF (50%), connective tissue disease (33.3%), and idiopathic nonspecific interstitial pneumonia (16.7%). In a retrospective review of 147 patients with IPF, 9.6% developed an acute exacerbation during the 2-year observational period.³⁸ Thoracic surgery is one risk factor for the development of an acute exacerbation. Sakamoto and colleagues³⁹ showed a 7.7% incidence of acute exacerbation in IPF patients immediately after thoracic surgery.

Pathology in patients with acute exacerbation of ILD showed 1 of 3 patterns: (1) DAD, (2) OP, or (3) progressive fibrosis.⁴⁰ DAD comprises most cases. Criteria for the diagnosis of acute exacerbation of IPF include the following⁴¹:

1. Acute worsening of symptoms over 30 days or less
2. New bilateral radiographic abnormalities
3. Absence of infection or other identifiable abnormality

The radiographic findings of acute exacerbation of ILD are similar to those of ALI except the findings are often superimposed on the pre-existing fibrosis.³⁷ Signs of fibrosis may be present on imaging obtained before the onset of acute symptoms. If no prior films are available, the signs of fibrosis may be present at the onset of acute symptoms (Fig. 16), as opposed to other causes of DAD in which these signs may develop 1 to 4 weeks later. Three variants of acute exacerbation have been described based on the distribution of ground-glass opacity and consolidation on CT⁴²: (1) diffuse, (2) multifocal, and (3) peripheral (Fig. 17). In the study of Akira and colleagues,⁴² there were significant differences in survival based on this distribution, as follows: diffuse (0% at 100 days), multifocal (50% at 500 days), and peripheral (75% at 500 days).

Fig. 15. AIP. Diffuse ground-glass opacity is present on this axial CT image. This appearance is indistinguishable from nonidiopathic ALI, edema, infection, hemorrhage, acute hypersensitivity pneumonitis, and AEP. The lucencies that underlie the ground-glass represent pre-existing emphysema in a smoker.

Fig. 16. Acute exacerbation of IPF. Baseline axial CT (A) shows peripheral fibrosis with honeycombing in a patient with IPF. Two years later, the patient presents with acute dyspnea. A follow-up CT (B) shows both worsening of fibrosis and the development of diffuse ground-glass opacity, compatible with an acute exacerbation.

Acute Fibrinous Organizing Pneumonia

AFOP is a unique form of ALI.²³ Although its histopathologic features share features with DAD and OP, they do not meet strict criteria for either one; however, AFOP likely represents a variant of these patterns of injury. There are a variety of associations including rejection in lung transplantation,⁴³ connective tissue disease, drug toxicity, and infection. The clinical presentation may be acute or subacute. The CT findings include symmetric, bilateral ground-glass opacity, and nodular areas of consolidation.⁴⁴ These findings may be seen in isolation or in combination. These radiographic findings mirror those of both DAD and OP (Fig. 18). The clinical course ranges from rapid progression and death to complete recovery, similar to the wide clinical spectrum seen in patients with DAD or OP.

Acute Eosinophilic Pneumonia

AEP is a disorder that shares many characteristics with ALI. Most patients with AEP present with acute respiratory symptoms requiring admission

to the intensive care unit. Characteristic findings on histopathology include DAD associated with an increased number of tissue eosinophils.⁴⁵ Interestingly, a more recent review of the pathology of AEP showed findings resembling AFOP,⁴⁶ further emphasizing the close relationship between DAD and AFOP.

There are some important differences between AEP and ALI. Rhee and colleagues⁴⁷ performed a retrospective analysis of the clinical characteristics of 137 patients with AEP. Ninety-nine percent of patients were current smokers. Of these, 90% of patients described a change in smoking habits in the 1 month before developing AEP. This change in smoking habits included starting smoking, restarting smoking, or increasing the number of cigarettes smoked per day. The association between smoking and AEP was confirmed in the study by Uchiyama and colleagues,⁴⁸ in which 97% of patients were smokers. Another important difference between AEP and ALI is the significant clinical and radiographic response to corticosteroid treatment. In the study by Rhee and colleagues,⁴⁷ the average time to complete symptom resolution after

Fig. 17. Peripheral distribution of acute exacerbation of IPF. Peripheral irregular reticulation and early honeycombing are present on a baseline axial CT image (A) in a patient with IPF. Six months later, the patient presents with worsening cough and acute dyspnea. A follow-up CT (B) shows a peripheral distribution of new ground-glass opacity, compatible with acute exacerbation. This distribution has a significantly better prognosis than the diffuse or patchy distributions.

Fig. 18. AFOP. Axial CT (A) shows typical findings of AFOP with bilateral ground-glass opacity and focal, rounded areas of consolidation. Six months later (B), this progresses to severe fibrosis. In another patient with AFOP, the initial CT (C) shows similar findings to (A). In this patient, the follow-up CT (D) shows significant improvement in the findings. These 2 patients demonstrate the spectrum of changes over time in AFOP.

corticosteroid treatment was 7 days. In addition, 85% of chest radiographs showed complete clearing by 7 days.

The diagnosis of AEP presents several challenges. With the exception of the smoking history, the clinical presentation of AEP is nearly identical

to ALI. Peripheral eosinophilia is only seen in approximately 30% of patients. In addition, there is significant overlap between AEP and ALI on imaging. Chest radiographs in both show extensive bilateral lung opacities. The main findings of AEP on CT are ground-glass opacity (97% of patients) and interlobular septal thickening (68% of patients)⁴⁷ (Fig. 19). This combination of findings is more commonly seen in patients with pulmonary edema; however, AEP should be suspected in patients in whom edema is unlikely (eg, younger age, normal echocardiogram). The diagnosis of AEP is most often confirmed by the presence of an increased number of eosinophils on bronchoscopy or characteristic pathologic findings on lung biopsy. As opposed to ALI/ARDS, corticosteroids are routinely administered given the rapid response seen in most patients.

SUMMARY

ALI is a clinical entity that requires input from clinicians, radiologists, and pathologists. Multidisciplinary input is vital in ensuring appropriate diagnosis and treatment. The main role of imaging is to evaluate for diseases that may mimic ALI clinically, including infection, edema, hemorrhage, OP, ILDs, and AEP. Radiologists need to be aware of the typical findings of ALI, and how these findings

Fig. 19. AEP. Single axial CT through the mid lung in a patient who began smoking 1 month ago shows diffuse ground-glass opacity associated with interlobular septal thickening. Although the CT findings in isolation are nonspecific, when interpreted in the context of the clinical history, AEP is a leading diagnosis.

evolve over time, in addition to the features that distinguish ALI from these alternative causes.

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