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Approach to the Patient With Connective Tissue Disease and Diffuse Lung Disease

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Introduction

Diffuse lung disease (DLD) is common in patients with connective tissue disease (CTD) and an important cause of morbidity and mortality. High-resolution CT (HRCT) of the lungs is a critical component of the workup and management of patients with CTD and DLD. Nearly, all patterns of DLD (eg, usual interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia, etc.) can be seen in patients with CTD, and no one pattern is specific for a certain CTD. Moreover, while most patients undergoing HRCT may have a known diagnosis of CTD, in some patients DLD may be the first or only manifestation of a previously undiagnosed CTD. The purpose of this article is to review the current understanding of CTD and DLD and describe the role of the imager in the broader context of the multidisciplinary team that evaluates patients with CTD. We will discuss the clinical workup of patients with DLD and a known (or suspected) CTD and review the HRCT imaging patterns seen in patients with CTD.

Clinical Workup of DLD in Patients With a Known or Suspected CTD

Patients With Pre-existing CTD

Diagnosis of CTD using the American College of Rheumatology criteria utilizes a combination of clinical and serologic data. Despite the frequency of DLD in patients with CTD, presence of DLD is not included in the diagnostic criteria for CTDs with the exception of scleroderma.[1]

Many CTDs are known to be associated with the development of DLD; however, pulmonary manifestations are most commonly seen in patients with rheumatoid arthritis, scleroderma, Sjogren syndrome, lupus, myositis, and mixed CTD. CTD-related DLD is most commonly bilateral and symmetric, with involvement of the mid to lower lobes.[2] The utility of surgical biopsy in patients with known CTD and probable CTD-related DLD remains unclear[3,4] and is not often obtained. For this reason, the radiographic findings on HRCT are used to determine the primary pattern of DLD, with the common patterns discussed in more detail below.

Although beyond the scope of this article, it is important to always remember that patients with CTD may be on immunosuppression and therefore at increased risk of lung infections or drug reactions, and these should be included on the differential diagnosis as appropriate. Specific agents commonly used in the management of patients with CTD that have frequently been implicated in the development of pulmonary drug toxicity include cyclophosphamide and methotrexate.[5-7] A targeted history of relevant medication administration should be elicited when pulmonary drug toxicity is suspected. While the latency between drug initiation and development of pulmonary toxicity is variable, there is usually a temporal relationship between the start of the medication and the onset of symptoms. Cessation of the offending agent generally leads to improvement.[8]

In addition to DLD, there are other thoracic manifestations of CTDs including pulmonary hypertension and extrapulmonary manifestations of the various disorders including involvement of the esophagus, pleura, and pericardium.[9] Thoracic lymphadenopathy is also common in patients with CTD and is usually not considered suspicious unless it is very pronounced or if the patient has a known underlying malignancy.[10] However, patients with CTD-DLD are at increased risk of lung cancer, and this should always be considered if enlarging nodules/masses are observed, or if ground glass opacity (GGO)/consolidation insidiously progresses despite adequate immunosuppression.[11]

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Patients With DLD as the Initial Presentation of CTD

Although DLD is commonly diagnosed in patients with an established diagnosis of CTD, lung disease may be the initial presenting symptom of CTD in a minority of patients. It has been shown that approximately 15% of patients presenting with a presumed idiopathic interstitial pneumonia were newly diagnosed with CTD as a part of the workup of their DLD.[12] In another study of 68 patients diagnosed with idiopathic DLD, 19% were eventually found to have a diagnosis of CTD during a follow-up period of 11 years.[13]

For these reasons, clinical evaluation of patients presenting with DLD should include a thorough evaluation for the possibility of an underlying CTD. This approach includes an evaluation for key historical elements such as arthralgias, rash, dysphagia, muscle weakness, and Raynaud phenomenon.[14] Physical examination should also be performed with targeted attention to typical manifestations of CTD, which often involve the hands and skin. Finally, serologic evaluation should be performed in many patients, as will be discussed more fully below. In addition to diagnostic testing with the aim of identifying an underlying CTD, assessment of the patient's functional status is commonly performed including pulmonary function testing and 6-minute walk testing.[14]

Serologic Evaluation of All Patients With DLD

Serologic evaluation is a critical component of the evaluation of many patients presenting with DLD for several reasons. Positive autoantibody tests are an important component of the diagnostic criteria of CTDs. They are often helpful in refining a patient's diagnosis with signs and symptoms suggestive, but not diagnostic, of a specific CTD. Additionally, they represent an important screening test in patients with idiopathic DLD, such as idiopathic pulmonary fibrosis (IPF), to help exclude the possibility of CTD as a cause.[15]

Supporting this statement, the recently updated ATS/ERS/JRS/ALAT Clinical Practice Guidelines for the diagnosis of IPF again recommend performing routine serologic testing in all patients with newly diagnosed DLD.[2] While there are a number of autoantibodies that may be seen in patients with CTD, routine testing in the setting for DLD often includes the following: C-reactive protein, erythrocyte sedimentation rate, antinuclear antibodies (ANA), rheumatoid factor (RF), anti-CCP, and myositis antibodies.[2] It is important to note that false positive results occur in healthy patients, and that the sensitivity and specificity of auto-antibodies vary depending on the diagnosis. Therefore, serologic testing should not be interpreted in vacuum but in a multidisciplinary context, including clinical symptoms and physical exam findings suggestive of a particular CTD.

Acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate are nonspecific markers of systemic inflammation and are elevated in other inflammatory processes, infection, and in patients with malignancy. Antinuclear antibody (ANA) testing includes evaluation of both antibody titer and staining pattern. Low titers (such as 1:40) may be positive in up to 30% of normal patients; however, higher titers (such as 1:160 and 1:320) have false positive rates of only 5%-3% in normal patients, respectively.[16] ANA patterns include nuclear (which may be diffuse, speckled, or mixed), nucleolar, and centromeric distributions.[17] A positive ANA is highly sensitive for the diagnosis of systemic lupus erythematosus (SLE) and scleroderma (sensitivity 93% and 85%, respectively), with positive anticentromeric staining being a diagnostic criteria for scleroderma.[18,19] In contrast, some CTDs, specifically antisynthetase syndrome (AS), may be ANA-negative.[15]

In addition to the highly specific anticentromeric ANA staining pattern mentioned above, other autoantibodies are useful in diagnosis of scleroderma. Anti-topoisomerase I antibodies (anti-Scl70) are positive in the minority of scleroderma patients, and are highly specific (specificity 90%-100%).[20] Anti-Scl70 positivity is also associated with an increased risk of the development of pulmonary fibrosis.[21]

Both rheumatoid factor and anti-CCP antibodies are useful in the diagnosis of rheumatoid arthritis. A positive rheumatoid factor has an approximately 70% sensitivity and specificity for the diagnosis of rheumatoid arthritis, although the specificity of anti-CCP positivity is much higher at 95%.[22-24] High anti-CCP titers have been associated with increased risk of development rheumatoid arthritis associated DLD.[25]

The panel of myositis antibodies includes a number of tests, with at least one positive myositis antibody in 40% of patients with myositis. Myositis-specific antibodies associated with the presence of DLD include the antisynthetase antibodies and anti-MDA5. To date, 8 AS antibodies have been identified and implicated in causing clinical disease (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo).[26] Anti-Jo-1 is the most common, and the one most likely to be included in a standard autoimmune panel, but anti-Pl-7, anti-Pl-12, and others can cause disease and usually require an extended myositis panel to identify.[22,27,28] The implications of specific antibody positivity are areas of ongoing study.[15]

There are numerous additional autoantibodies which may be obtained depending on the clinical suspicion for a particular CTD. Antidouble stranded DNA and anti-Smith antibodies are highly specific for the diagnosis of SLE (specificities of 97% and 96%, respectively), and thus are useful for confirmatory testing when SLE is suspected.[29] Anti-RNP is another disease-specific autoantibody which is both highly sensitive and specific for the diagnosis of mixed CTD.[29] In the setting of suspected Sjogren syndrome, the combination of both anti-SSA and anti-SSB antibodies is highly suggestive. However, either of these autoantibodies alone can be seen in other CTDs.[30]

Treatment of CTD-related DLD

The diagnosis of an underlying connective disease in patients with DLD is not trivial, as the prognosis and treatment of CTD-associated DLD are distinct from idiopathic interstitial pneumonias.[31] Which patients with CTD-related DLD should receive immunosuppressive therapy is still an area of active investigation; however, trials have shown benefit particularly in patients with scleroderma-related lung

disease.[32] Multiple agents and approaches have been studied including prednisone, cyclophosphamide, rituximab, mycophenolate mofetil, and stem cell transplantation, with the relative benefits of each of these approaches beyond the scope of this article.[33-36] Consideration of multiple factors including severity of lung disease, rate of progression, histologic/radiologic pattern of lung disease, underlying CTD diagnosis, and patient demographics may be needed in order to determine the most appropriate course of management for an individual patient.

Patterns of DLD in CTD

Patients with CTD can present with nearly any pattern of DLD, and the appearance on imaging alone may be indistinguishable from the idiopathic interstitial pneumonias.[37-40] The most common patterns of lung parenchymal involvement include NSIP pattern, organizing pneumonia (OP), NSIP/OP overlap, and lymphoid interstitial pneumonia (LIP). UIP is occasionally seen in CTD patients (especially rheumatoid arthritis). Acute interstitial pneumonia may be an initial, fulminant presentation of lung involvement in a CTD. Each of these patterns will be reviewed below.

Usual Interstitial Pneumonia

A UIP pattern of fibrosis is generally defined as a basilar and peripheral predominant reticulation and honeycombing, with or without traction bronchiectasis, and an absence of features that suggest an alternative diagnosis.[41] Recent consensus statements from the Fleischner Society and American Thoracic Society have attempted to expand this definition, but is beyond the scope of this manuscript.[2,42] A UIP pattern of fibrosis is most commonly due to IPF, especially in men over the age of 60. CTD patients with a UIP pattern are more commonly younger and female, and less likely to have a smoking history. A UIP pattern in this demographic should raise the question of CTD or another non-IPF diagnosis.[43,44]

RA is the most common CTD to present with a UIP pattern of fibrosis, but this pattern is not exclusive to RA. Virtually any CTD can present with a UIP pattern in a minority of cases including systemic sclerosis, mixed CTD, myositis, and LIP (Fig. 1).[43] The CT findings of UIP-IPF and UIP-CTD may be indistinguishable; however, Chung et al. recently described 3 findings that occur more frequently in patients with UIP-CTD: the "anterior upper lobe sign," the "straight edge sign," and the "exuberant honeycombing sign" (Fig. 2). These signs were not sensitive for UIP-CTD, but specificities for each sign were greater than 87%, and when at least 2 of the 3 signs were present, the sensitivity was 95.5% with a positive likelihood ratio of 5.28.[43] These signs will be discussed in more detail in a separate chapter titled, "signs in imaging ILD."

Nonspecific Interstitial Pneumonia

NSIP is the most common pattern of DLD in patients with CTD.[38,45,46] Systemic sclerosis is the most common CTD to present with an NSIP pattern, but as with UIP, any CTD can present with this pattern. Importantly, idiopathic NSIP is a rare entity, and anytime an NSIP pattern is encountered on CT then an extensive workup for CTD must be pursued (see section on IPAF).[38,47]

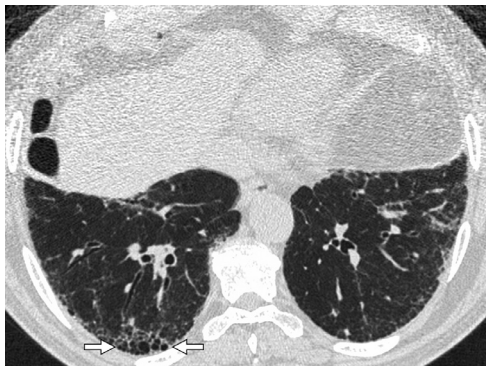

Figure 1 UIP pattern of fibrosis in a 77-year-old male with Sjogren syndrome. Axial HRCT image through the lung bases shows bilateral subpleural reticular abnormality, traction bronchiectasis, and honeycombing (arrows) at the right lung base. This patient was initially diagnosed with IPF, but serologic testing and rheumatologic evaluation revealed that the patient had Sjogren syndrome. The imaging findings in this case are indistinguishable from UIP-IPF.

The main imaging findings of an NSIP pattern include GGO, reticular opacities, and traction bronchiectasis/bronchiolectasis.[45] Like UIP, the craniocaudal distribution of NSIP on CT is similar in that it is a lower-lobe predominant disease. While NSIP may have a subpleural predominance, a peribronchovascular distribution may also be seen. NSIP tends to be more uniform (not patchy) in its distribution. Subpleural sparing is a very important clue to the diagnosis of NSIP although it is not seen in all cases[48] (Fig. 3).

Organizing Pneumonia

Organizing pneumonia may be seen in isolation, or in conjunction with an NSIP pattern (see mixed NSIP/OP section below). An isolated OP pattern is most often seen with the inflammatory myopathies, but like the other patterns can be seen in other CTDs as well.[49]

Imaging findings from OP-CTD are similar to those from other causes of OP and include symmetric, peripheral or perilobular GGO, and/or consolidation, with or without "reversed halos" or "atolls" (Fig. 4).[39,50,51]

Mixed NSIP/OP

Many patients with CTD may have a mix of NSIP and OP on imaging and histology, and this is an important combination of patterns to recognize (Fig. 5).[52,53] Trying to distinguish one pattern from the other has little impact in the overall multidisciplinary diagnosis of the patient. In fact, the presence of OP in histologic specimens of NSIP is well known. In patients who do not already carry a diagnosis of a CTD, recognizing this combination should prompt an extensive search for the presence of a CTD, in particular an extended myositis panel that includes antisynthetase antibodies.[53-55]

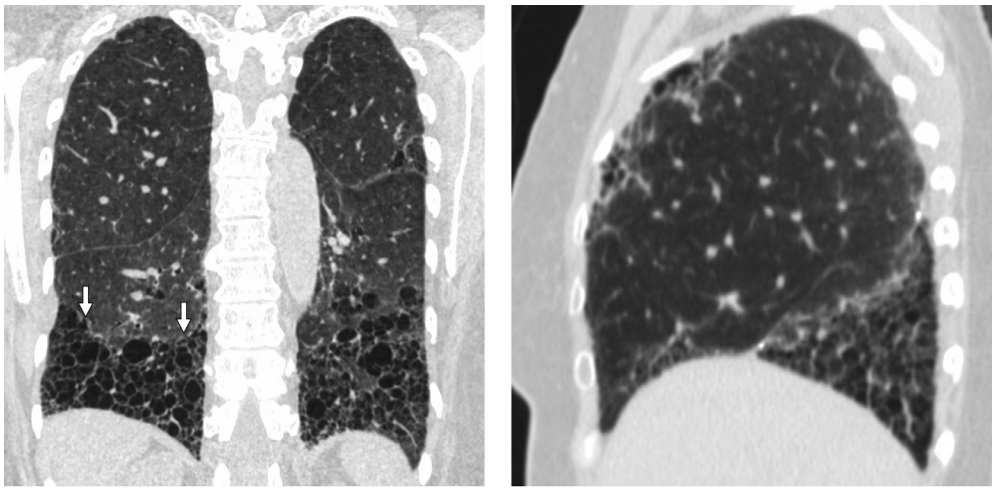

Figure 2 (a) Straight edge sign and exuberant honeycombing sign. Coronal MPR in a 69-year-old female with MCTD shows a UIP pattern with exuberant lower lobe honeycombing. The straight-edge sign is also present (arrows) with a fairly straight interface between fibrosis and normal lung orthogonal to the lateral chest wall. (b) Sagittal MPR from HRCT in a 52-year-old woman with Sjogren syndrome shows the anterior upper lobe sign. Fibrosis is concentrated in the anterior aspects of the upper lobes in addition to the posterior lower lobes.

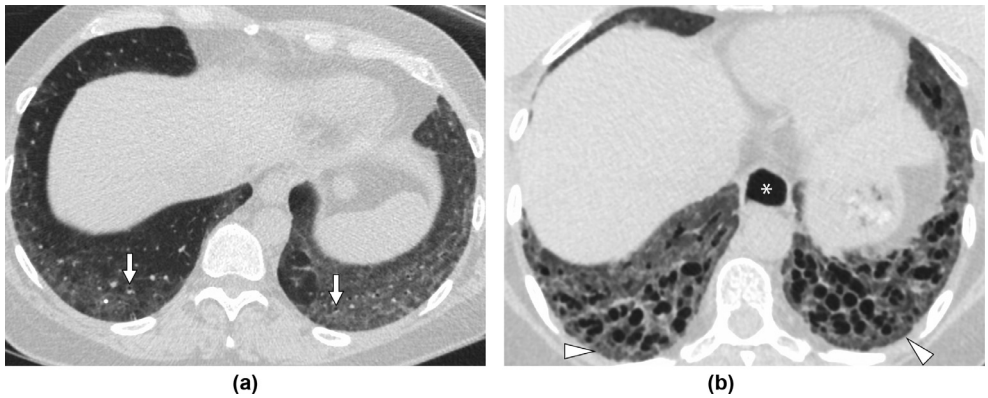

Figure 3 (a) A 41-year-old female with NSIP due to scleroderma. Axial HRCT through the lower lobes shows relatively diffuse GGO and mild traction bronchiectasis (arrows), which corresponded to NSIP on surgical lung biopsy. (b) A 49-year-old female with systemic sclerosis and NSIP pattern of fibrosis. Axial HRCT through the lower lobes shows a peribronchovascular distribution of fibrosis with severe traction bronchiectasis and relative subpleural sparing (arrow heads). Also note the dilated esophagus (asterisk), another clue to the presence of systemic sclerosis.

AS represents a subset of IM patients who test positive for autoantibodies to the aminoacyl-tRNA synthetase (antisynthetase) enzymes. Clinical features of AS includes DLD, myositis, arthritis, fever, Raynaud phenomenon, and mechanic's hands.[22,26] AS is important to recognize as there is a higher incidence of DLD than other inflammatory myopathy patients in general and AS antibodies are not always part of the autoimmune panel in patients being worked up for DLD.

Patients with AS and DLD usually present with gradual and progressive respiratory symptoms, but some may present with acute fulminant respiratory failure (discussed in DAD section below).[28,56] When presenting with subacute symptoms, CT usually shows a variable appearance of NSIP, OP, or both[57] (Fig. 5). Some cases of AS have been described as "extreme basilar predominant," but may otherwise be indistinguishable from other CTDs.[22,54] With treatment, the degree of consolidation may improve but fibrosis will persist, and a minority of patients may evolve to a UIP pattern of fibrosis.[27,28]

Lymphocytic Interstitial Pneumonia

LIP is most commonly seen patients with Sjogren syndrome and rarely with other CTDs or immunodeficiencies.[38,40,58] Like NSIP, idiopathic LIP is rare, and the diagnosis on imaging or histopathology should prompt workup for an underlying CTD or other systemic disease.

Histologically, LIP represents alveolar interstitial infiltration by lymphocytes and polyclonal plasma cells.[40] On imaging, this infiltration appears predominantly as GGO, a nonspecific finding.[39] Perivascular cysts are also a feature of

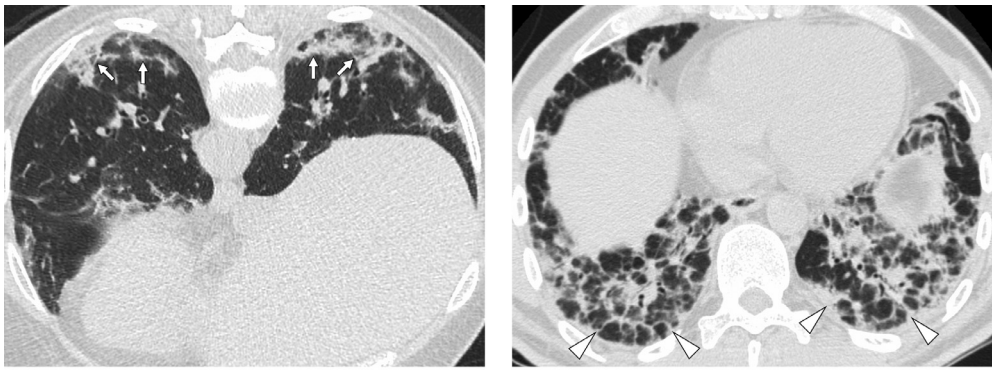

Figure 4 (a) A 63-year-old female with organizing pneumonia secondary to AS. Prone axial HRCT image through the lower lobes shows symmetric bilateral, peripheral consolidation with atolls typical of organizing pneumonia (arrows). The patient tested positive for anti-Jo-1, an antisynthetase antibody. (b) A 49-year-old male with dermatomyositis and organizing pneumonia. Axial HRCT shows symmetric, bilateral consolidation, and perilobular opacities (arrow heads), a pattern typical of organizing pneumonia.

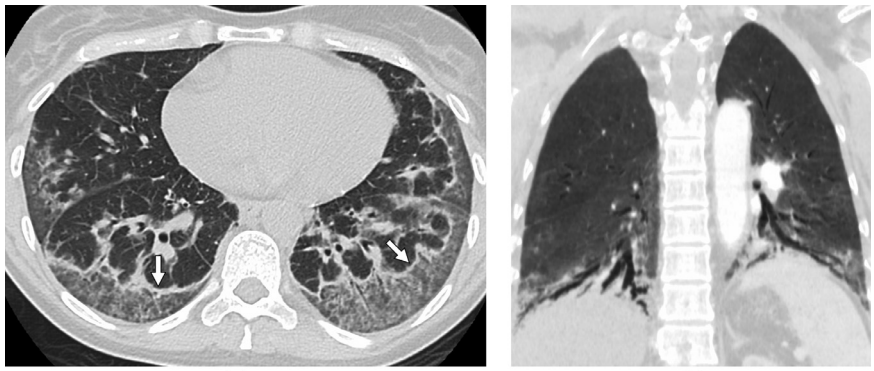

Figure 5 (a) A 45-year-old woman with systemic sclerosis and a mixed NSIP/OP pattern on imaging, subsequently proved on surgical lung biopsy. Axial HRCT image shows symmetric, peripheral GGO, and mild traction bronchiectasis (NSIP) and peripheral bands of consolidation (OP, arrows). This combination of findings on imaging or histology is typical of CTD. (b) A 53-year-old female with AS (anti-Pl-12). Coronal MinIP shows "extreme" basilar predominant fibrosis with traction bronchiectasis and consolidation. This distribution is especially seen in AS.

LIP and there is considerable overlap in appearance of the cysts with those of amyloid[22,39,59] (Fig. 6). A combination of GGO and cysts is most suggestive of LIP.

Acute Lung Injury/Diffuse Alveolar Damage

As discussed in the mixed NSIP/OP section above, CTD may occasionally present with an acute, fulminant respiratory illness with significant morbidity and mortality. As with other patterns of lung disease, ALI may be the initial manifestation of a previously undiagnosed CTD and has been observed with IM, systemic sclerosis, RA, and SLE. In particular, antisynthetase and other IM patients (such as anti-MDA-5 antibodies) have received attention as a cause of ALI with fulminant respiratory failure.[28,60]

Histologically, ALI/DAD evolves through 3 phases—acute exudative, organizing or proliferative, and chronic or

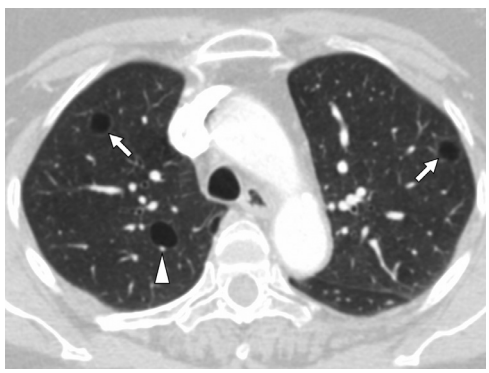

Figure 6 A 67-year-old female with Sjogren syndrome and lung cysts from LIP. Axial CT through the upper lobes shows a few round, thin-walled cysts (arrows). Note the vessel next to the posterior cyst in the right upper lobe (arrow head), typical of the perivascular distribution of LIP cysts. The number of cysts is typically fewer than in lymphangioleiomyomatois.

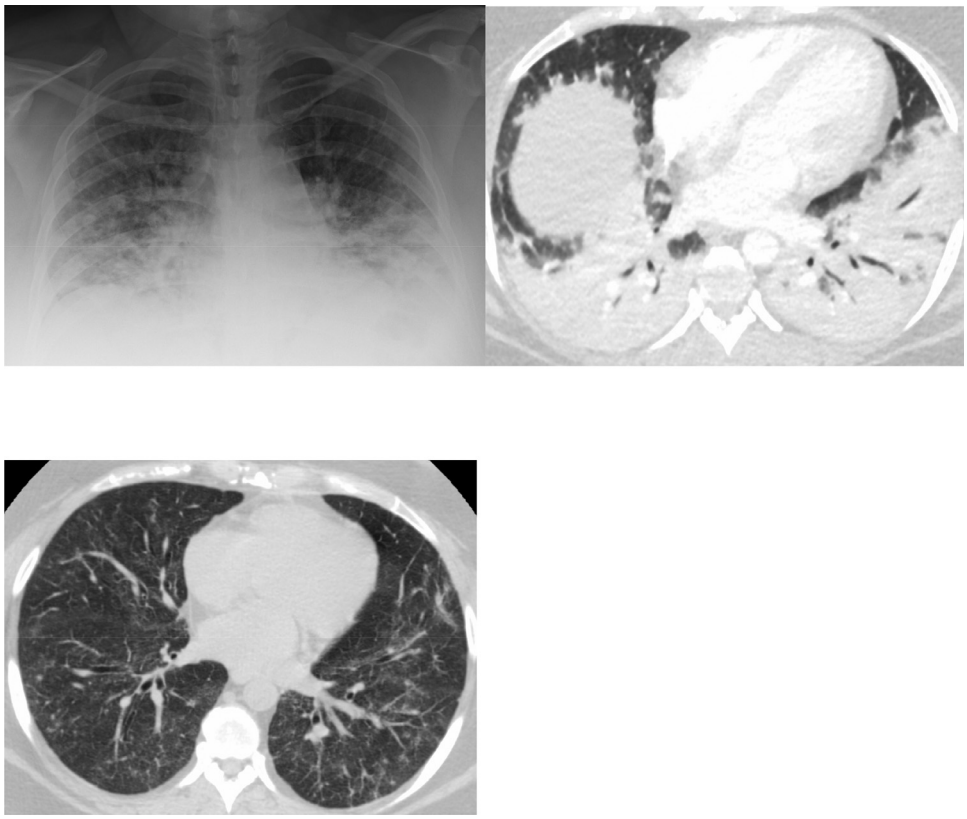

Figure 7 Acute lung injury as an initial presentation of AS in a 36-year-old female. Chest radiograph (a) and axial image from CT pulmonary angiogram (b) show confluent mid- and lower-lung predominant consolidation. The patient did not have signs of an infectious pneumonia, and extensive workup including CTD revealed anti-Jo-1 positivity. The patient was started on high-dose steroids for her AS and responded well with only mild residual fibrosis on follow-up CT (c).

fibrotic—and the findings on HRCT mirror the histologic evolution. ALI first appears as combination GGO, consolidation (with air bronchograms), and/or crazy paving pattern, which correlates with the acute exudative phase.[61] During this phase, the distribution of abnormalities may be more gravitational and affect the dependent portions of the lungs, and the findings are often relatively symmetric, which can help distinguish from pneumonia or aspiration. Small pleural effusions are often present.[61] Some findings of OP may be visible after days to weeks, and fibrosis may result in reticular abnormality and traction bronchiectasis that often has an anterior, upper-lung predominance[61] (Fig. 7).

Multicompartment Disease

Whereas IIPs are a primary abnormality of the lung parenchyma, in CTDs the lungs are merely one of many organ systems or compartments that can be affected by these systemic autoimmune diseases. Multicompartment thoracic disease includes abnormalities outside of the pulmonary parenchyma such as:

- Unexplained pleural or pericardial effusion/thickening
- Unexplained intrinsic airway disease (airflow obstruction, bronchiolitis, or bronchiectasis)
- Unexplained pulmonary vasculopathy

Especially when a patient has a DLD pattern described above in addition to one of these findings, a CTD should be considered (Fig. 8). While this may not be useful in cases of established CTD, it is particularly useful in the context of IPAF as described below.

Interstitial Pneumonia With Autoimmune Features

Some patients may present with DLD and symptoms suggestive of a CTD, yet they do not meet criteria for a specified CTD. Our institution was one of the first to attempt to categorize these patients as "undifferentiated CTD" and associated DLD,[62] and other groups described similar cohorts including "lung-dominant CTD" and "autoimmune-featured DLD."[63,64] In 2015, the term IPAF was proposed by an international task force to establish a framework under which to capture all of these patients that have DLD and an autoimmune "flavor."[52] While originally for research purposes, IPAF has gained some clinical acceptance as a diagnostic entity.

To make a diagnosis of IPAF, patients must meet criteria from at least 2 of 3 domains—clinical, serologic, and morphologic—yet not be classifiable as an established CTD. The clinical domain includes typical physical findings of a CTD and the serologic domain includes serologies discussed in the sections above. The morphologic domain is the one

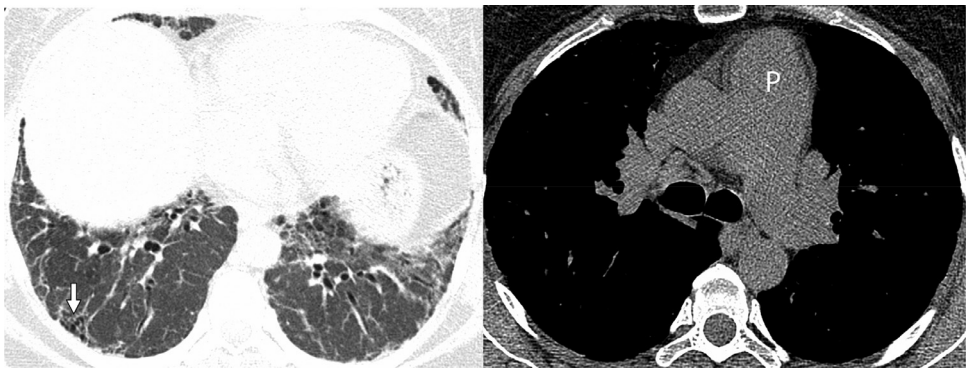

Figure 8 A 55-year-old female with DLD and multicompartment disease. Axial images from HRCT at lung windows (a) and soft tissue windows (b). The appearance of the lungs is consistent with a UIP pattern of fibrosis with basal predominant reticular abnormality, traction bronchiectasis, and mild honeycombing (arrow) at the posterior right lung base (a). Additionally, the pulmonary artery is enlarged at 3.7 cm ("P," b), with a PA:aorta ratio of greater than 1, suggestive of pulmonary hypertension and multicompartment disease (confirmed on subsequent cardiac workup as group I PAH). The patient was eventually diagnosed with IPAF based on clinical and morphologic domains and did not meet criteria for a specific CTD.

relevant to imagers and can be made either by imaging or histology. The "suggestive radiology patterns by HRCT" include:

- NSIP
- OP
- NSIP with OP overlap
- LIP

Note how each of these is a pattern frequently seen in CTD and described above. Moreover, note that UIP is conspicuously absent. While UIP may be seen in association with CTD, it is much more commonly seen in the setting of idiopathic disease (ie, IPF). Patients with a UIP pattern on CT can still have IPAF, but they do not get "credit" for it, meaning that they still need to fulfill 2 criteria by other means.[65]

To date, 6 retrospective studies have analyzed the clinical, serologic, and morphologic characteristics of IPAF cohorts.[66-71] These studies have reported widely variable ranges of patterns of DLD, but all of the above-listed patterns (including UIP) were observed in at least some patients, with NSIP being the most common overall.[72] Moreover, multicompartment involvement was a feature of many patients in these cohorts.

Conclusion

HRCT is indispensable in the diagnosis of CTD-DLD and the imager is a valuable member of the multidisciplinary diagnosis and management of these patients. Nearly any imaging pattern may be seen in patients with CTD-DLD, many patients may have a clinical or serologic overlap between multiple CTDs, and other patients may have an autoimmune "flavor" but not meet criteria for a specific disease (ie, IPAF). Moreover, patients may present with DLD as the first manifestation of a previously undiagnosed CTD. Therefore, it is important for the imager to remember CTD in the differential for DLD, especially when patients are young, female, nonsmokers, or have multicompartment involvement as described above.

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