Imaging Features of Autoimmune Disease-Related Interstitial Lung Diseases

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Abstract: Interstitial lung diseases (ILDs) associated with autoimmune diseases show characteristic signs of imaging. Radiologic signs are also used in the identification of ILDs with features suggestive of autoimmune disease that do not meet the criteria for a specific autoimmune disease. Radiologists play a key role in identifying these signs and assessing their relevance as part of multidisciplinary team discussions. A radiologist may be the first health care professional to pick up signs of autoimmune disease in a patient referred for assessment of ILD or with suspicion for ILD. Multidisciplinary team discussion of imaging findings observed during follow-up may inform a change in diagnosis or identify progression, with implications for a patient's treatment regimen. This article describes the imaging features of autoimmune disease-related ILDs and the role of radiologists in assessing their relevance.

Key Words: autoimmune, HRCT, ILD, interstitial lung disease

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Interstitial lung disease (ILD) may develop as a consequence of an autoimmune disease such as rheumatoid arthritis (RA), systemic sclerosis (SSc), or myositis and is associated with morbidity and premature mortality.[1–5] Although most cases of autoimmune disease-related ILD are observed in patients who have already been diagnosed with an autoimmune disease, in some cases, ILD is the first sign of an autoimmune disease to be identified.[1,2,6–8] A retrospective study found that among 114 patients referred to an ILD clinic, 15% received a new diagnosis of collagen vascular disease as a result of evaluation for ILD.[6] Prospective data from 679 patients with RA-ILD showed that in 14% of cases, ILD was diagnosed 1 to 5 years before RA.[2] An analysis of US health care claims data reported that 4% to 6% of patients with SSc had ILD documented more than 1 year before their first claim for SSc.[7]

Patients with autoimmune diseases who are at high risk of ILD, including all those diagnosed with SSc and patients with other autoimmune diseases who have risk factors, should be screened for ILD using high-resolution computed tomography (HRCT).[9–13] Patients with unexplained respiratory symptoms should also undergo HRCT. In some cases, a radiologist may be the first health care professional to pick up signs of autoimmune disease in a patient referred for the assessment of ILD or due to suspicion of ILD. It is vital that radiologists are able to identify signs of autoimmune disease on HRCT and flag them in multidisciplinary team (MDT) discussions. This article describes the imaging features of autoimmune disease-related ILDs and the role of radiologists in identifying these signs and assessing their relevance.

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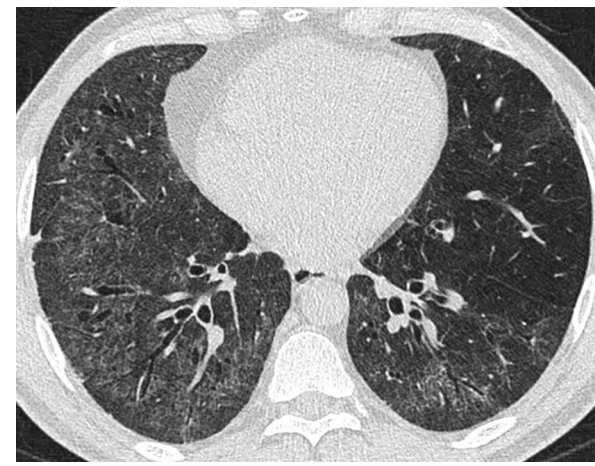

FIGURE 1. Axial HRCT image of a patient with fibrotic NSIP. There is basal predominant peripheral ground glass opacification. Traction bronchiectasis within the ground glass opacification indicates that this represents fine fibrosis.

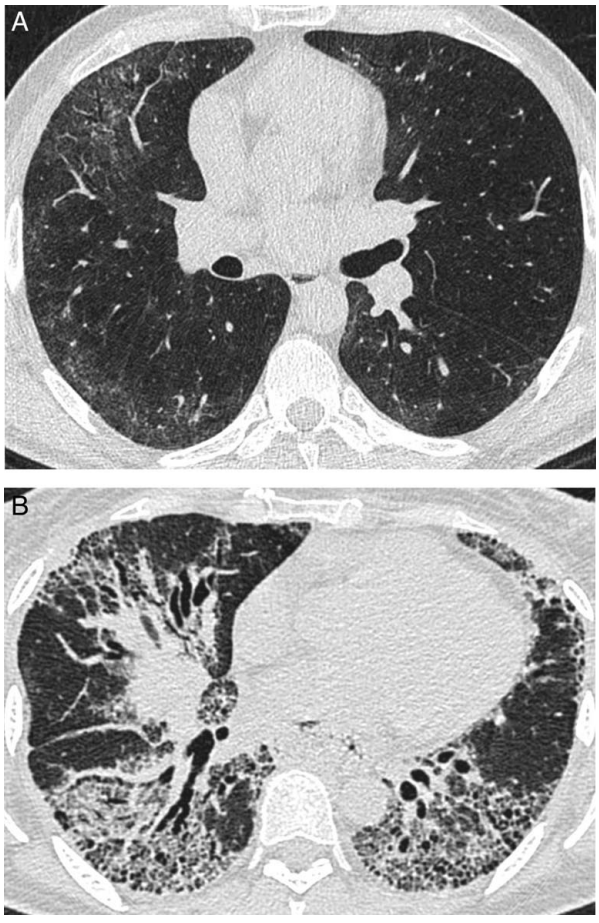

FIGURE 2. (A) Axial HRCT image of a patient with fibrotic NSIP. There is basal predominant ground glass opacification with subtle sparing of the subpleural lung; (B) Axial HRCT image of a patient with fibrotic NSIP demonstrating coarse fibrosis in the lower lobes with marked traction bronchiectasis and possibly subpleural honeycombing. The right oblique fissure is markedly retracted due to fibrosis-induced volume loss.

IMAGING FEATURES OF AUTOIMMUNE DISEASE-RELATED ILDS

In all cases of suspected ILD, an appropriate protocol should be followed in the performance of a volumetric HRCT scan.[14] There are no specific requirements for patients with autoimmune disease-related ILDs, and contrast agents are not needed. Typical features of autoimmune disease-related ILDs evident on HRCT scans include ground glass opacity, reticulation, traction bronchiectasis, honeycombing, and consolidation.[15] Radiologic signs are also used in the identification of ILDs, with features suggestive of autoimmune diseases that do not meet classification criteria for a specific autoimmune disease, such as interstitial pneumonia with autoimmune features.[16–18] Extra-pulmonary manifestations of autoimmune diseases may also be visible on HRCT, for example, in bone/soft tissue.

IMAGING FEATURES THAT SUGGEST AN AUTOIMMUNE TRIGGER FOR AN ILD

In some patients with ILD, the radiologist may be the first to suggest an autoimmune trigger. These patients may previously have been diagnosed with idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), unexplained organizing pneumonia (OP) or fibrotic OP, overlapping patterns, or multicompartment disease. Although a usual interstitial pneumonia (UIP) pattern on CT is characteristic of IPF, in a substantial minority of patients, UIP may be the first manifestation of an undiagnosed autoimmune disease. Indeed, UIP is the HRCT pattern most frequently observed in patients with RA-ILD.[19,20] The radiologist has a key role to play in differentiating IPF from ILD due to a connective tissue disease (CTD-ILD). In a study conducted in 196 patients, an increased prevalence of 3 novel CT signs in patients with CTD-UIP compared with IPF-UIP was observed, namely the anterior upper lobe sign (concentration of fibrosis within the anterior aspect of the upper lobes with concomitant lower lobe involvement), straight edge sign (isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane, without substantial extension along the lateral margins of the lungs on coronal images), and exuberant honeycombing sign (honeycomb-like cyst formation constituting more than 70% of

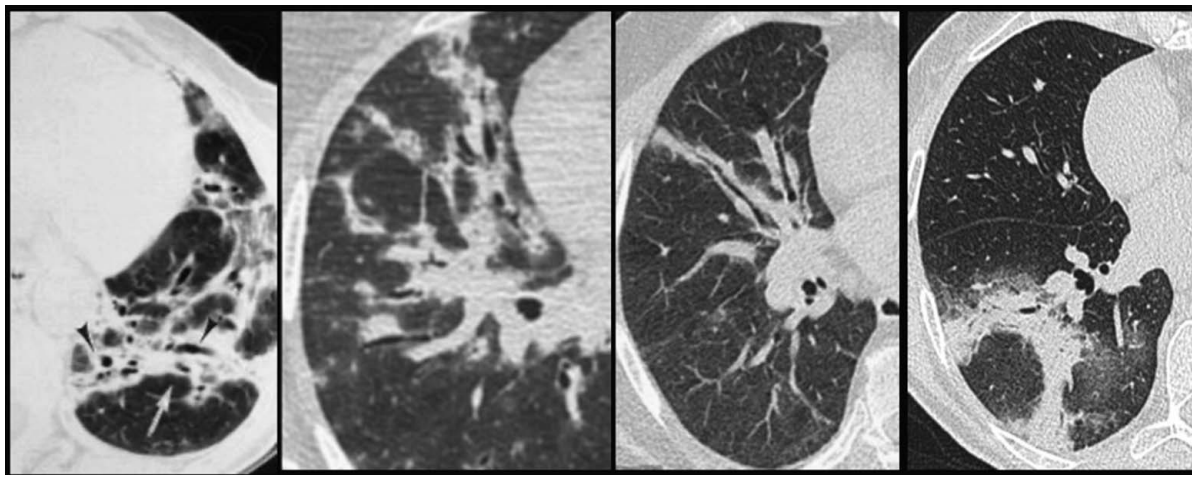

FIGURE 3. Cropped HRCT images depicting features of nonfibrotic organizing pneumonia (OP) bronchocentric consolidation, partial band-like consolidation containing air bronchograms, band-like consolidation containing air bronchograms and perilobular consolidation.

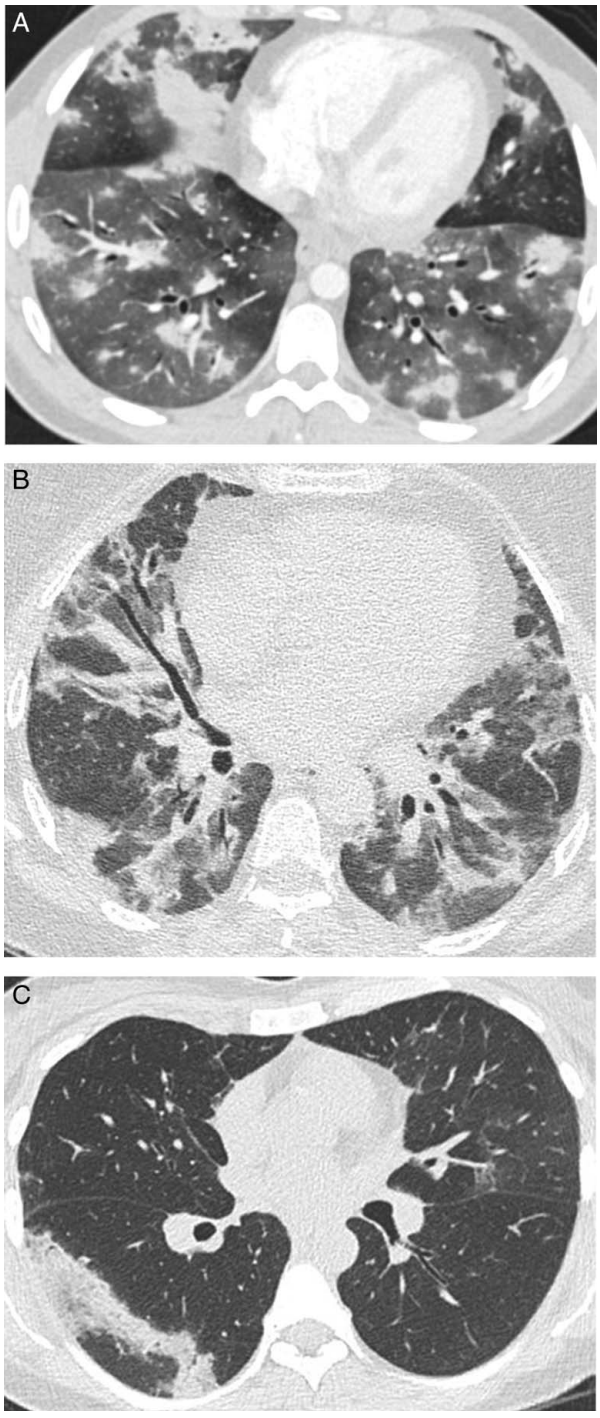

FIGURE 4. Axial HRCT images (A–C) in patients with organizing pneumonia (OP) depicting focal areas of bronchocentric consolidation and perilobular consolidation.

fibrotic portions of the lung), with the highest specificity (94.0%) and sensitivity (25.4%) reported for the straight edge sign.[21] In another study conducted on 150 patients, the straight edge sign and anterior upper lobe sign were also significantly more common in patients with CTD-UIP than IPF-UIP, with the highest specificity (95.7%) observed for the straight edge sign.[22] Although, in many cases,

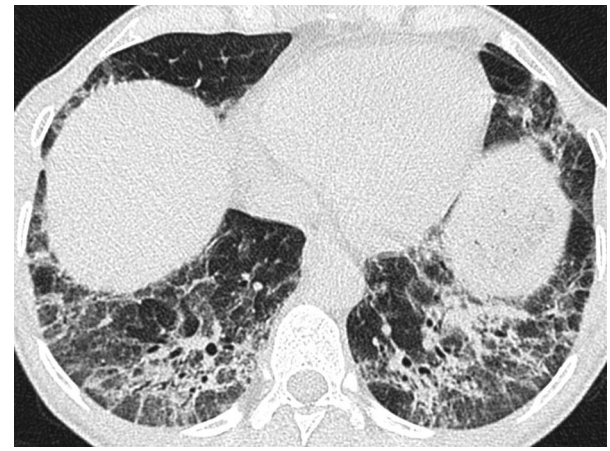

FIGURE 5. Axial HRCT images of a patient with fibrotic organizing pneumonia (OP) depicting perilobular opacities in the lower lobes containing traction bronchiectasis and coarse reticulation.

multidisciplinary evaluation of medical history and serum biomarkers will allow CTD-UIP to be differentiated from IPF, the identification of these novel CT features in the setting of UIP may influence diagnosis. However, the relevance of these features needs to be confirmed in large independent cohorts.

Patients diagnosed with idiopathic NSIP, particularly young female patients, should be assessed for an underlying autoimmune disease. Although the classification of idiopathic interstitial pneumonias published by the American Thoracic Society and European Respiratory Society in 2013 recognized idiopathic NSIP as a distinct clinicopathologic entity,[23] a substantial number of patients presenting with idiopathic NSIP meet criteria for an undifferentiated CTD.[24,25] NSIP is also recognized as a defining CT pattern in the European Respiratory Society/American Thoracic Society research statement on interstitial pneumonia with autoimmune features.[16] The most common HRCT feature of NSIP is a profusion of bilateral ground glass opacities,

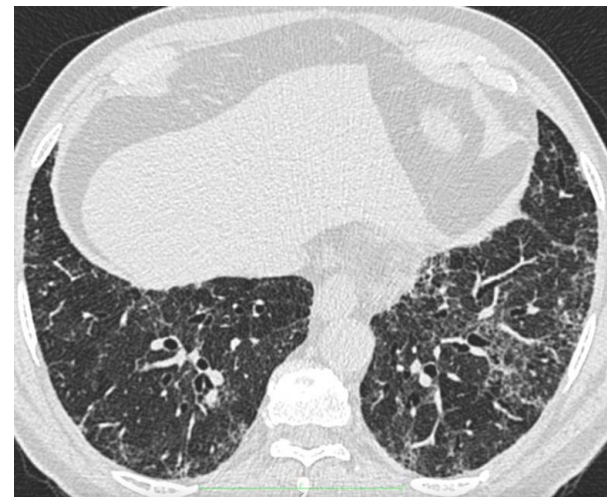

FIGURE 6. Multicompartment disease. Axial HRCT image of the patient with rheumatoid arthritis and interstitial fibrosis. There is freestanding bronchiectasis (ie, not related to fibrosis) in the right lower lobe. full color online

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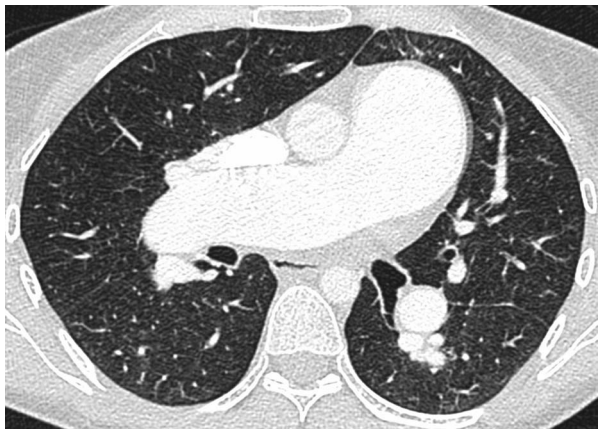

FIGURE 7. Axial HRCT image of the patient with systemic sclerosis and pulmonary arterial hypertension. The main pulmonary artery and segmental pulmonary arteries in the left lower lobe are enlarged.

often with reticular opacities.[23,26] When fibrosis is present, traction bronchiectasis may be seen (Fig. 1). Subpleural sparing, a relative paucity of honeycombing and less coarse fibrosis may help to distinguish NSIP from UIP (Fig. 2A). However, in 1 study, only the proportion of ground glass opacities and a relative lack of coarseness of parenchymal abnormalities on HRCT were independently associated with a histologic diagnosis of NSIP as opposed to UIP.[27] Patients with fibrosing SSc-ILD may show intense lower lobe traction bronchiectasis that is apparently disproportionate to the extent of fibrosis. In these cases, retraction of the oblique fissures is often present, reflecting the true extent of the fibrosis (Fig. 2B).

Unexplained OP should alert the radiologist to the possibility of an autoimmune disease, with an adverse drug reaction being the other important diagnosis to consider. OP may present as patchy or migratory consolidation, which is often strikingly bronchocentric, may be subpleural, or may present as a band-like pattern containing an air bronchogram (which distinguishes it from atelectasis) (Figs. 3 and 4). Perilobular opacities create a distinctive pattern peripherally (Fig. 4A-C) or, when located more centrally, appear as 'reverse halos.' OP may be associated with marked

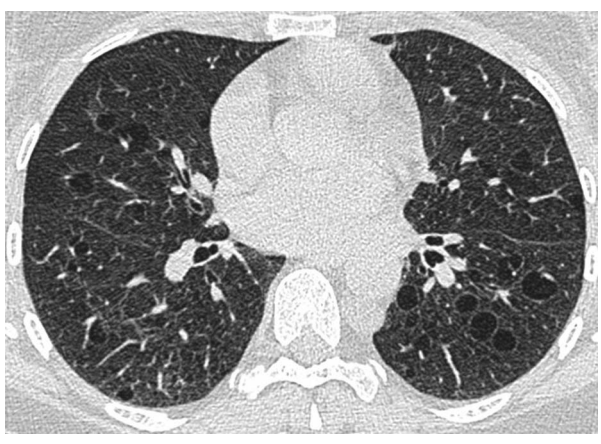

FIGURE 8. Axial HRCT image of the patient with Sjögren syndrome with multiple thin-walled cysts randomly distributed throughout both lungs.

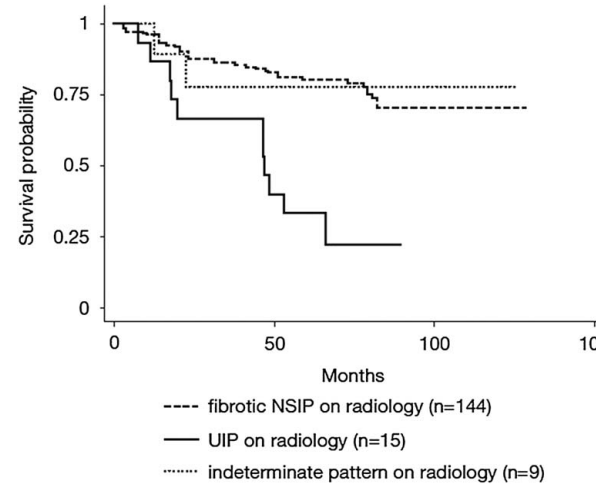

FIGURE 9. Survival among patients with fibrotic CTD-ILDs based on the radiologic pattern.[33] Reproduced from Thorax, Walsh SLF et al, volume 69, pages 216–222, copyright 2014, with permission from BMJ Publishing Group Ltd.

inflammation manifesting as ground glass opacities, with considerable overlap with NSIP. Although most patients with OP respond to anti-inflammatory therapy, a small subgroup progresses to a fibrosing variant, despite prolonged treatment. These patients sometimes have features that overlap with fibrotic NSIP (bronchocentric consolidation, reticular opacities, perilobular opacities, traction bronchiectasis) (Fig. 5). These overlapping patterns on HRCT can be distinctive and are a common imaging presentation in patients with antisynthetase syndrome.[28,29]

Patients presenting with multicompartment disease in addition to ILD should be investigated for an underlying autoimmune disease. Examples of this include interstitial fibrosis with freestanding bronchiectasis (ie, bronchiectasis unrelated to the fibrosis) in patients with RA (Fig. 6), and patients with systemic sclerosis and pulmonary arterial hypertension (Fig. 7). Lymphocytic interstitial pneumonia with airway wall thickening may indicate Sjögren's syndrome (Fig. 8).

PROGNOSTIC RELEVANCE OF IMAGING FEATURES IN PATIENTS WITH AUTOIMMUNE DISEASE-RELATED ILDS

Autoimmune disease-related ILDs have a variable clinical course.[3,4] As in all ILDs, certain imaging findings in patients with autoimmune disease-related ILDs have been associated with a greater risk of progression. A UIP pattern has been strongly associated with the risk of progression and mortality in patients with RA-ILD[30–32] and other autoimmune diseases[33,34] but reported associations between HRCT patterns (and patterns on histology) and outcomes in patients with SSc-ILD are conflicting.[35–37] In a retrospective study using data from 153 patients with RA-ILD, a UIP pattern on HRCT was included in a multivariable model for predicting the risk of mortality (along with age $\geq$ 60 y, $\geq$ 20% fibrosis on HRCT, emphysema on HRCT).[32] In a retrospective cohort of 168 patients with various fibrosing CTD-ILDs, HRCT pattern (UIP, NSIP, or indeterminate) was significantly associated with mortality (Fig. 9).[33]

Across ILDs, a greater extent of fibrosis on HRCT portends a worse prognosis.[3,32,38,39] In a nationwide

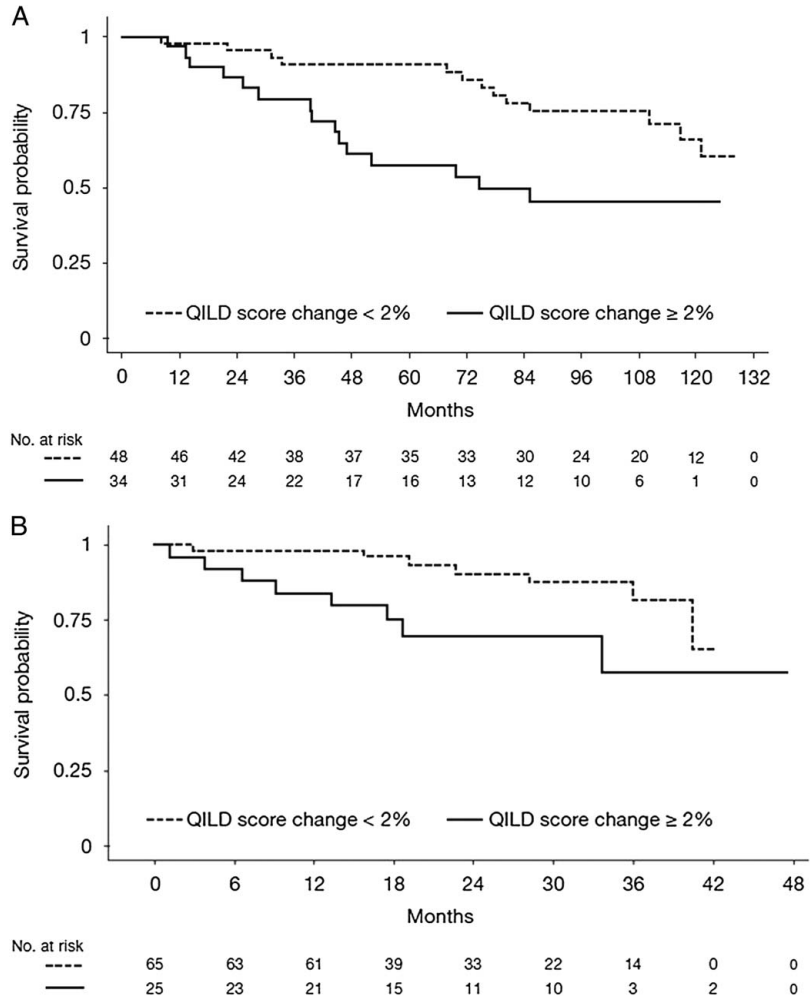

FIGURE 10. Survival probability among patients with SSc-ILD based on changes in quantitative ILD score over 12 months in Scleroderma Lung Study I (a) and over 24 months in Scleroderma Lung Study II (b).[39] Reproduced from Chest, Volkmann ER et al, volume 161, pages 1310–1319, copyright 2022, Elsevier Inc.

Norwegian cohort of patients with SSc, standardized mortality ratios (compared with the general population) ranged from 2.2 in patients with no fibrosis on HRCT to 8.0 in patients with >25% fibrosis at baseline.[3] A relationship has also been observed between a greater extent of traction bronchiectasis or honeycombing and higher mortality.[33,40,41] More recently, the presence of pleuroparenchymal fibroelastosis on HRCT, characterized by fibrosis of the visceral pleura and subpleural parenchyma with upper lobe predominance, has been shown to correlate with a greater rate of decline in lung function and increased mortality in patients with autoimmune disease-related ILDs.[42–44]

Acute exacerbations of autoimmune disease-related ILDs, which are characterized by acute respiratory deterioration and evidence of new ground glass attenuation or widespread alveolar abnormality on HRCT, are associated with very high mortality[45] and may be more common in patients with a UIP pattern on HRCT.[46,47]

ASSESSING DISEASE PROGRESSION

An increase in the extent of ILD on HRCT has been linked to increased mortality in patients with SSc-ILD[39,48] (Fig. 10) and other fibrosing ILDs.[49] The OMERACT international consensus initiative deemed the overall extent of ILD on HRCT to be an appropriate radiologic method for monitoring the progression of CTD-ILDs but did not provide any guidance on the frequency of HRCT scans.[50,51] Expert panels on the monitoring and management of SSc-ILD have also agreed that an increase in the extent of ILD on HRCT indicates progression.[9,13] The criteria for progressive pulmonary fibrosis published by international pulmonology societies in May 2022 included the evidence of radiologic progression, which could include an increased extent or severity of traction bronchiectasis and bronchiolectasis; new ground glass opacity with traction bronchiectasis; new fine reticulation; and/or new or increased honeycombing.[52] However, it is important to be aware that these criteria have not been validated and that visual assessment of HRCT scans does not enable radiologists to predict the progression of ILD nor to assess the worsening of ILD with any degree of accuracy. There is often not a close relationship between progression identified based on pulmonary function tests and based on visual assessment of HRCT scans, which is probably less sensitive to change.[48,53,54] In a retrospective study of 129 patients with

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SSc who had a median time between HRCT scans of 16 months, no significant correlations were found between change in semi-quantitative CT score (extent of lung fibrosis) and change in FVC % predicted or DLco % predicted over the same period.[55] In a sub-study of the SENSCIS trial in patients with SSc-ILD, only weak correlations were observed between changes in qualitative HRCT parameters (honeycombing, reticulation, and/or fibrotic ground glass opacity) and the rate of decline in FVC over 52 to 60 weeks.[54] In a sub-study of the INBUILD trial in patients with progressive pulmonary fibrosis, changes in the extent of fibrosis and other qualitative HRCT parameters over 52 weeks were small, despite a marked decline in FVC.[56]

Quantitative computed tomography softwares have demonstrated better performance than visual assessment in predicting the progression of ILD, including in patients with autoimmune disease-related ILDs,[38,39,57,58] but are not widely available in clinical practice. Work continues on artificial intelligence applications that may provide a more accurate prediction of prognosis for an individual patient with ILD or interstitial lung abnormalities.[59]

IMPORTANCE OF MULTIDISCIPLINARY DISCUSSION OF IMAGING FINDINGS

Ideally, a review of imaging findings by an expert radiologist should be part of an MDT discussion of all information available on a patient with an autoimmune disease-related ILD.[60–65] A surgical lung biopsy is rarely required in patients with autoimmune disease-related ILDs found to have ILD on HRCT. MDT discussion of imaging findings is not only important for informing an initial diagnosis. Imaging findings observed during follow-up may inform a change in diagnosis or identify progression,[62,63] both of which have implications for prognosis and treatment.[52] The variable course of ILD can make it challenging to make therapeutic decisions. MDT discussion of imaging findings may result in changes being made to a patient's treatment regimen. For example, the identification of a UIP pattern on HRCT, or evidence of progression of pulmonary fibrosis, may lead clinicians to take a more aggressive approach to pharmacological treatment [9,13,52,66–68] or to refer a patient for the evaluation for lung transplant [69] or autologous stem cell transplant. Changes to how patients are counselled about their prognosis and about palliative care options that may help to preserve their quality of life should also be considered if there is evidence of progressive fibrosis.[70]

In conclusion, imaging plays a fundamental role in the diagnosis and assessment of autoimmune disease-related ILDs. Radiologists need to be able to identify signs of autoimmune disease on HRCT and features that may have relevance to prognosis and treatment. Ideally, imaging findings should be discussed as part of an MDT discussion at the diagnosis of ILD and during the follow-up of patients with progressive disease.

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