Imaging of interstitial lung disease in systemic sclerosis: computed tomography versus ultrasound

Interstitial lung disease related to systemic sclerosis (SSc-ILD) is a main prognostic determinant of the disease. High-resolution computed tomography is the reference tool to detect SSc-ILD in the clinical arena. It enables the diagnosis, quantification and monitoring of lung involvement, providing robust information for the management of the disease; yet its cost and especially radiological burden can make it unappealing to SSc patients, who are often young women in their reproductive age, who require serial testing to assess the natural history of the disease. Recently, lung ultrasound has been proposed as a nonionizing technique to detect and semiquantifiy SSc-ILD. This new application of ultrasound seems interesting, as it is fast, inexpensive and can easily be performed at the patient's bedside with a handheld device. Magnetic resonance is the current gold standard for noninvasive virtual histological discrimination of different tissues. Despite still being underused for the evaluation of the lungs, it has successfully been employed in a few studies for the depiction of morphologic changes in patients with ILD. Although very promising, until now no other imaging modalities are able to provide all the information yielded by chest high-resolution computed tomography, which remains the gold standard technique for assessing pulmonary fibrosis. However, in a novel perspective of sustainability of our medical methods, the possibility to use radiation-free technologies to assess SSc-ILD seems extremely attractive and justifies further efforts in this field. The next challenge is to keep the high levels of information achieved with modern diagnostic imaging, preferably with the use of less risky techniques.

KEYWORDS: B-lines ■ high-resolution computed tomography ■ interstitial lung disease ■ lung ultrasound ■ pulmonary fibrosis ■ ultrasound lung comets

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Systemic sclerosis (SSc) is a complex, clinically heterogeneous disease, characterized by extensive vascular alterations, autoantibodies and fibrosis. Interstitial lung disease (ILD) is a frequent cause of death in SSc patients. It is characterized by histopathologically nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP) and occurs to various extents [1,2]. The clinical features of ILD are dyspnea and cough that may cause respiratory failure. For this reason, the diagnostic approach to ILD is of paramount importance to detect early modifications and then to monitor the evolution [3]. In this perspective, the imaging of the lung is today, together with pulmonary function tests, the fundamental aid to the clinician to reach a satisfactory understanding of the disease advancement.

In this article, the advantages as well as the limitations of the imaging techniques available today are analyzed and new perspectives proposed.

High-resolution computed tomography for the assessment of ILD

Open lung biopsy is considered the gold standard to diagnose ILD related to SSc (SSc-ILD); however, high-resolution computed tomography (HRCT) is the reference tool to detect pulmonary abnormalities in SSc [4]. In fact, HRCT is more sensitive than chest x-ray in identifying parenchymal modifications, and the extent and pattern of ILD. HRCT provides parenchymal detail due to high spatial resolution, with a resolution capacity of 200–300 µm, and it is now widely accepted as the reference technique for noninvasive diagnosis of ILD [5,6]. Computed tomography (CT) features of SSc-ILD are present in 55–65% of all SSc patients and in up to 96% of those with abnormal pulmonary function test results [7]. SSc-ILD affects juxtapleural, posterior and basilar portions of the lungs, with initially subtle alterations of increased ground glass opacities, defined as increased lung attenuation in the absence of architectural distortion, as well as accentuated reticular markings. These alterations may progress to pulmonary fibrosis, defined as architectural distortion with reticular intralobular interstitial thickening, traction bronchiectasis and bronchiolectasis and honeycomb cystic change. These hallmark CT features of SSc-ILD are similar to those of NSIP [8]. Honeycomb cystic changes are reported in 11–37% of patients with SSc-ILD. As honeycomb cystic change is typically a marker for UIP and pulmonary fibrosis [9], these findings suggest

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that patients with SSc-ILD may have a mixture of UIP and NSIP patterns, although the prevalence of NSIP has been reported to be higher [2]. However, the differential diagnosis between NSIP and UIP does not influence the management or the therapeutic approach as, unlike in idiopathic interstitial pneumonias, it seems that no significant association could be found between results of lung biopsy and survival in ILD-SSc [2].

It has been incorrectly assumed that SSc-ILD is more common and severe in patients with the diffuse cutaneous SSc. In the recent Scleroderma Lung Study, limited cutaneous SSc patients presented with more extensive pulmonary fibrosis, possibly reflecting a delay in diagnosis and progression of lung disease prior to study entry [10]. The rate of progression of SSc-ILD is similar in limited and diffuse cutaneous SSc patients, after adjustment for baseline differences in the degree of pulmonary fibrosis. Therefore, all SSc patients should be evaluated carefully for lung involvement, irrespective of disease extent [11].

High-resolution computed tomography has also been used to predict outcome in addition to characterizing the nature and extent of SSc-ILD. The absence of lung disease at an initial CT evaluation is a superior predictor of excellent long-term prognosis with regard to SSc-ILD [12].

Criteria have been developed for scoring the severity and extent of SSc-ILD based on disease distribution, relative proportions of reticulations and ground glass opacities, and presence of fibrosis on CT scans at one or more levels throughout the chest. However, the scoring of these lung modifications still remains a problem. Although many scores have been proposed (Warrick [13], Wells [14] and Kazerooni [15] are the most used), to date, no agreement has been reached on how disease should be scored on CT, with different methods used in randomized controlled trials in SSc [16].

Limitations

Differential diagnosis of ILD

For many years, the ground glass appearance has been thought to correspond to reversible, inflammatory histology, whereas honeycombing appearance – a reticular pattern associated with subpleural cysts – was associated with irreversible, fibrotic histology [17,18]. It is now well established that ground glass opacity is not indicative of active inflammation and likely represents microscopic pulmonary fibrosis that is below the resolution of CT [8]. Furthermore, the limitations of ground glass opacity as a predictive marker of active or reversible inflammation have been reinforced by longitudinal studies of CT change with and without treatment, and recent studies indicate that ground glass opacity is irreversible despite therapy [19]. It appears that ground glass on CT may reflect either fibrosis or inflammation. This appears to be corroborated by the observation that reversible inflammatory disease is present at biopsy in less than 25% of SSc cases [2], despite the prominence of ground glass on CT. Thus, the widespread use of the phrase "an alveolitis on CT", as a synonym for ground glass, is highly misleading [20,21], and we cannot consider HRCT as the ideal imaging test to distinguish between fibrosis and inflammation.

Radioprotection issues

A main limitation to the extensive employment of HRCT for a tight follow-up of SSc patients is the significant radiation exposure of this examination. The issue of the dangers of medical imaging has been extensively emphasized in recent literature [22–24]. The high level of radiation exposure provides immense benefits when appropriate, yet may result in an increased incidence of radiation-induced cancer in the future [25]. The long-term risk associated with radiation exposure should be considered in the risk–benefit assessment behind appropriate prescription of diagnostic testing.

The rheumatological patient is especially vulnerable to cancer effects of diagnostic procedures, owing to clinical and radiobiological reasons. The diagnostic work-up is largely based on ionizing radiation testing, such as cardiac catheterization for pulmonary hypertension, chest HRCT for ILD, gallium scintigraphy for lung inflammation, cardiac stress scintigraphy and cardiac CT for detecting occult coronary artery disease [26,27]. These techniques are time honored, objective and quantitative and provide robust diagnostic information; yet their cost, radiological burden, environmental impact (for scintigraphy) and long-term risks are especially unappealing in SSc patients, often young women in their reproductive age, who require serial testing to assess the natural history of the disease. From the radiobiological viewpoint, we now know that women are more sensitive to the cancer effects of radiation compared with males (the risk is approximately 37% higher in females than males), and that the female breast is a highly radiosensitive organ [28]. The radiation issue, albeit totally neglected to date, might provide an iatrogenic link between the observed puzzling relation between SSc and breast cancer, usually appearing on average 20 years after SSc onset [29].

Lung ultrasound for the assessment of ILD

Background & physical basis

The assessment of the lung has always been considered off limits for ultrasound, as it is standard textbook knowledge that "because ultrasound energy is rapidly dissipated by air, ultrasound imaging is not useful for the evaluation of the pulmonary parenchyma" [30]. However, this is true in a normal, aerated lung, but the presence in the lung of other structures besides air opens the previously locked pulmonary acoustic window, and allows one to gain an insight into pulmonary interstitium, which can be directly imaged and quantified. Ultrasound lung comets (ULCs, also called 'B-lines') are an echographic image detectable with lung ultrasound (LUS) [31]. This image consists of multiple comet tails fanning out from the lung surface. They originate from thickened interlobular septa, thus they may be present in water-thickened septa (i.e., pulmonary edema) or collagen-thickened septa (i.e., pulmonary fibrosis). In the presence of extravascular lung water or pulmonary fibrosis, the ultrasound beam finds subpleural interlobular septa thickened by edema or collagen. The reflection of the beam creates a phenomenon of reverberation, generating a series of very closely spaced pseudointerfaces that result in the image of an ultrasound lung comet (FIGURE 1).

In patients with heart failure, interlobular septa are thickened by water, and ULCs represent an early sign of pulmonary interstitial edema, well related to the increase in cardiac natriuretic peptides [32], radiographic signs of pulmonary congestion [33], invasive measurement of extravascular lung water and pulmonary capillary wedge pressure [34]. In pulmonary fibrosis, interstitial lobular septa are thickened by collagen tissue accumulation and, therefore, ULCs are generated by air fibrosis and not by air–water impedance mismatch.

Lung ultrasound examination can be performed using any commercially available 2D scanner. It has successfully been performed with many different probes, such as sector, linear, convex and microconvex probe. The examination may be performed with patients in the sitting, near-supine or supine position. LUS is performed by moving the probe longitudinally along anatomical reference lines (FIGURE 2). In each intercostal space, the number of ULCs is recorded. The sum of the ULCs found on each scanning site yields a score denoting the extent of pulmonary fibrosis in the lung. The full white screen in a single scanning site is considered, when using a cardiac probe, as corresponding to ten ULCs (FIGURE 3). For clinical purposes, ULCs may be semiquantified from mild to severe degree, similar to the method used for most echographic parameters. ULCs have a very satisfactory intraobserver and interobserver variability: approximately 5 and 7%, respectively [33].

Clinical implications

Recently, it has been demonstrated that LUS, by evaluation of ULC number, is able to identify pulmonary fibrosis in SSc patients [35,36]. A total of 33 SSc patients have been studied by LUS and chest HRCT, independently performed within 1 week. ULC score was obtained by totaling the number of ULCs on the anterior and posterior chest, which was then compared with pulmonary fibrosis quantified by HRCT with the previously described 30-point Warrick score. Presence of ULCs was observed in 51% of SSc patients, with significantly higher values in the diffuse than in the limited form. A statistically significant positive linear correlation was found between ULCs and Warrick score ($r = 0.72$; $p < 0.001$). This is the first study evaluating the presence of a LUS sign of interstitial fibrosis in SSc patients, in comparison with the gold standard HRCT. Previous studies had evaluated this echographic sign in different forms of ILD, including pulmonary fibrosis and sarcoidosis, underlining that diffuse parenchymal lung disease should be considered in the presence of multiple ULCs distributed over the whole surface of the lung [37,38]. In 1997, Lichtenstein and colleagues first described the presence of ULCs in patients with CT-documented diffuse interstitial pulmonary fibrosis [39].

The clinical impact of LUS implementation for the assessment of pulmonary fibrosis would be tremendous, as this is a highly versatile technique: it is inexpensive, it can be performed at the patient's bedside with a hand-held device, the learning and interpretation curves are very short [40] and the performing time is very quick (<10 min for a total chest assessment). Moreover, the technique is nonionizing, and LUS can easily be coupled with standard echocardiography, which evaluates other major prognostic determinants in SSc patients (i.e., pulmonary hypertension and cardiac involvement).

However, to date, no other imaging modalities are able to provide all the information yielded by chest HRCT, which remains the gold standard technique for assessing pulmonary fibrosis, also because it is the only tool that allows the evaluation of the whole lung. It

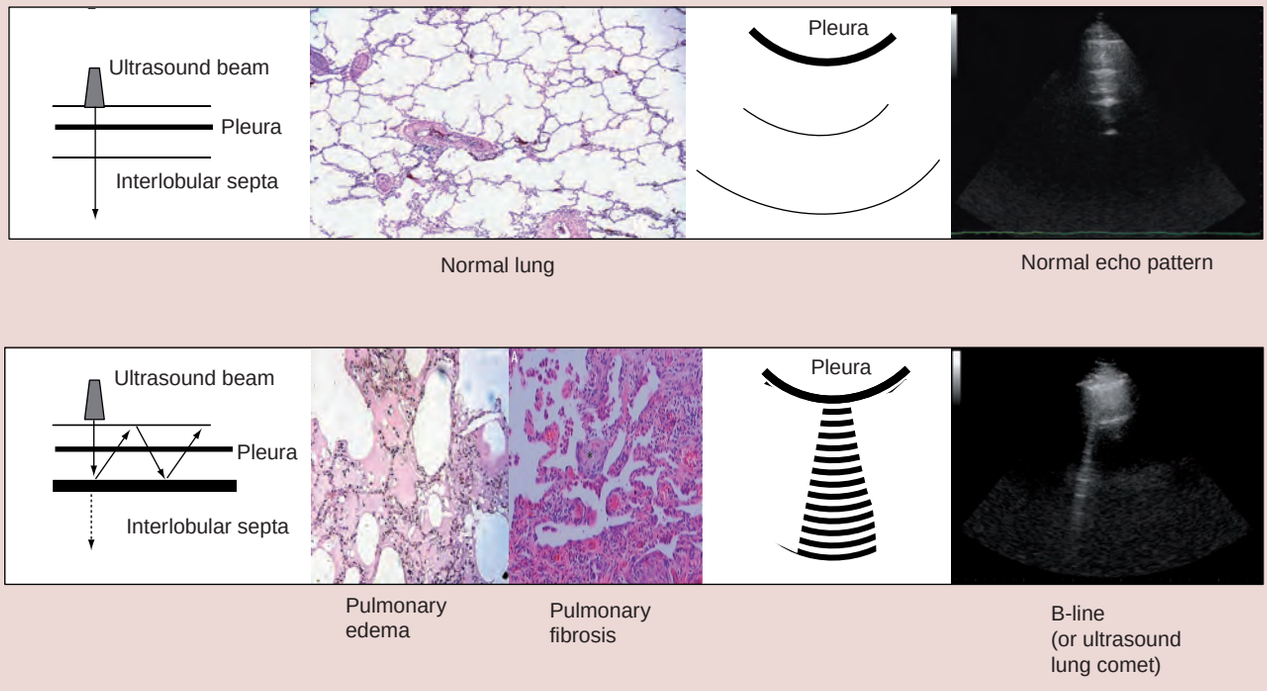

Figure 1. The hypothesized physical and anatomic basis of ultrasound lung comets: reflections of the ultrasound beam by the thickened interlobular septa give rise to the 'comet-tail' artifact.
Modified with permission from [33].

is mandatory that other, possibly multicenter, studies provide additional data on the usefulness of LUS in the assessment of SSc-ILD. No data on LUS follow-up in SSc patients are available yet, nor on the accuracy of this method to assess the eventual response to therapy, nor on the correct timing of starting LUS evaluation and follow-up. Nevertheless, although LUS will probably never replace the meaningful information of chest CT, it is likely that this additional tool could become useful to support CT, especially for the follow-up of SSc patients during treatment. From the scientific viewpoint, ULCs are attractive as a proximal biomarker of pulmonary fibrosis, of special interest in viewing the ongoing development of novel methods to prevent scarring and alleviate the symptoms of fibrosis. A direct, quantitative, early and radiation-free imaging biomarker would greatly facilitate the validation of new therapies in this field [41].

Limitations

Lung ultrasound has limitations that are essentially patient dependent. Obese patients are frequently difficult to examine owing to the thickness of their rib cage. The presence of subcutaneous emphysema or large thoracic dressings alters or precludes the propagation of ultrasound beams to the lung periphery. A limit of ULCs may arise from the differential diagnosis between cardiogenic and fibrotic ULCs. Cardiogenic watery ULCs may be difficult to visually distinguish from pneumogenic fibrotic ULCs. Usually, diagnosis is obvious from a patient's history and/or from dynamic, serial evaluation, as only cardiogenic ULCs are cleared by diuretic therapy. In SSc patients, unless a significant cardiac involvement is present, there is no other reason for ULC visualization apart from the presence of fibrosis. Although cardiac involvement is frequent in these patients, it is often subtle and not-so-frequently leads to overt pulmonary congestion. However, in patients with SSc-related heart failure or in SSc patients with heart failure owing to other etiologies, this technique may be misleading. Moreover, being a sign of both interstitial edema and fibrosis, LUS is currently not able to distinguish an active phase of lung inflammation, such as alveolitis, from established pulmonary fibrosis. LUS is an echographic method, thus subjective and qualitative; although a semiquantitative index of ULCs has been provided and successfully employed, there is no doubt that quantitative radiological imaging provides a more established and robust quantitative support to the diagnosis of pulmonary fibrosis.

Future perspective

A main goal of new imaging modalities in SSc would be to help in the differentiation of the two main stages of SSc-ILD: potentially reversible alveolitis and established pulmonary fibrosis. Detecting alveolitis is an important diagnostic clue in assessing disease severity in SSc patients. A greater deterioration in pulmonary function, a larger extent of pulmonary fibrosis on HRCT over time and an increased mortality have been reported in patients with untreated alveolitis [42]. As previously mentioned, there is not always consensus on the correspondence between specific CT signs and histopathological findings. The therapeutic dilemma is to know when to initiate appropriate treatment and whether or not to prescribe immunosuppressive agents. Immunosuppressive agents can diminish or stop

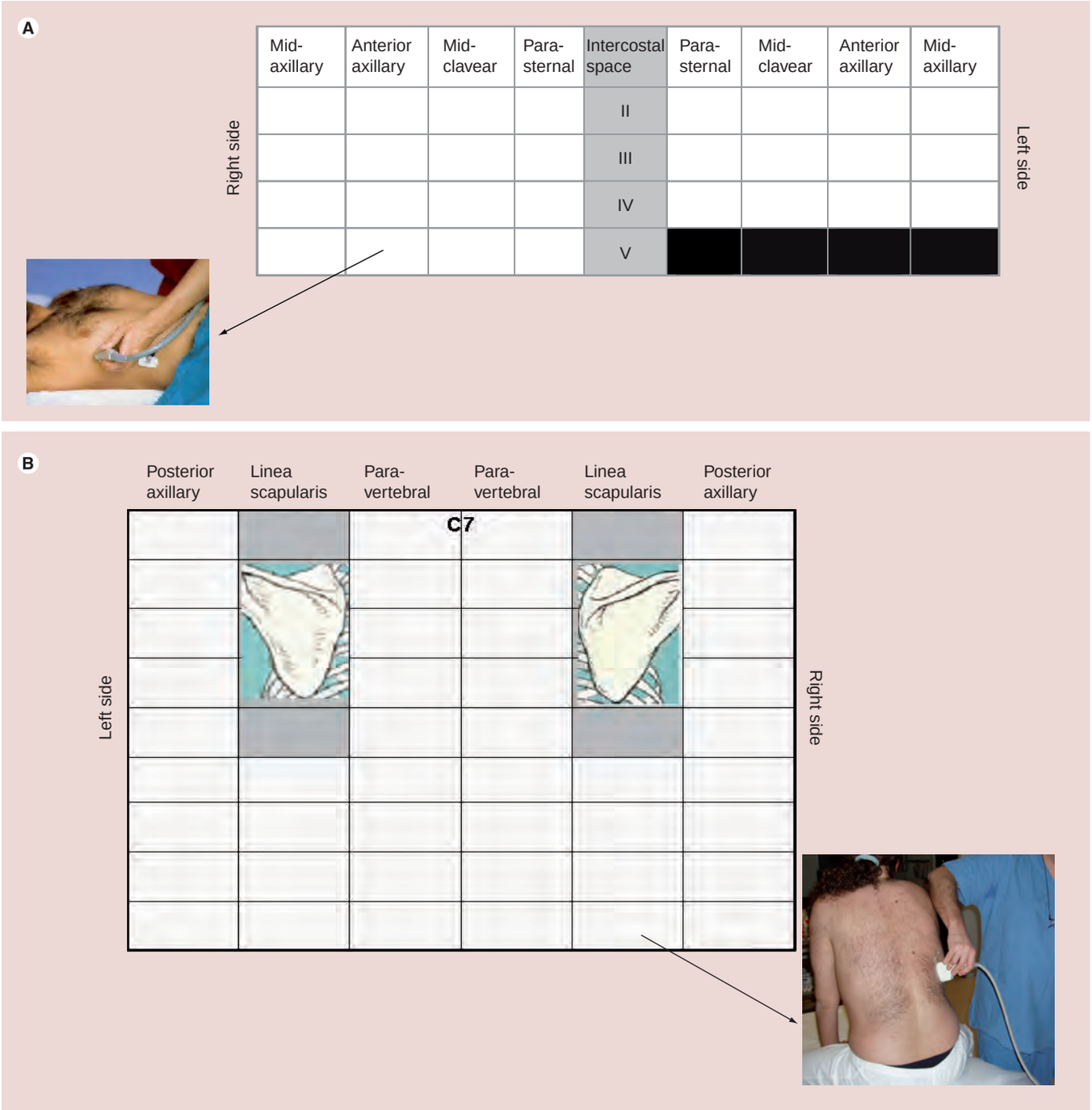

Figure 2. Methodology of lung ultrasound scanning on anterolateral (A) and posterior chest (B).
Modified with permission from [33,35].

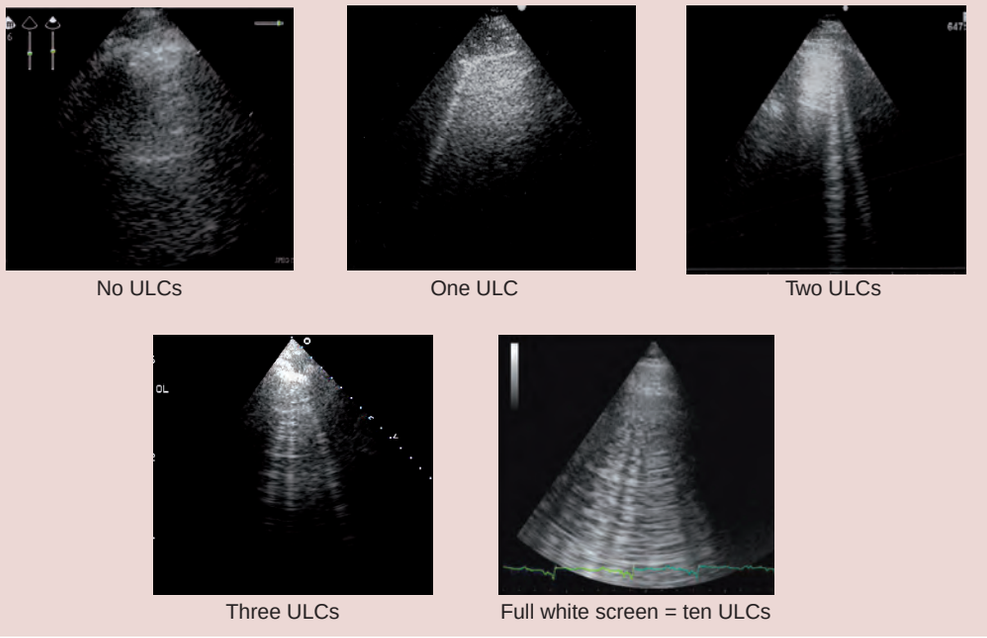

Figure 3. How to enumerate ultrasound lung comets: each hyperechogenic vertical stripe, spreading from the pleural line and extending to the edge of the screen is an ultrasound lung comet. A whole white screen, making it almost impossible to distinguish and enumerate different ULCs, is considered as corresponding to a plateau value of ten ULCs.
ULC: Ultrasound lung comet.

the fibrotic process; however, the response to treatment is variable and there are troublesome side effects [43].

For a long time, only chest x-ray and CT have been used to image lung structure, whereas nuclear medicine was employed to assess lung function. During the past decade, significant progress has been achieved in the field of LUS, as highlighted previously, and, although less developed, also in MRI of the lung, even if these techniques have not yet routinely entered the clinical arena of chest imaging. The application of magnetic resonance in lung disease has in fact long been limited by technical problems, namely a low signal-to-noise ratio owing to the low proton density of the lung, and artifacts due to cardiac and breathing motion or to air/soft tissue transition. However, MRI is the current gold standard for noninvasive virtual histological discrimination of different tissues; thus, at least theoretically, MRI should help in the differentiation between inflammation and fibrotic tissue. There are currently no data available on the use of MRI in patients with SSc-ILD, and to date, only a few studies have addressed the use of MRI for depiction of morphologic changes in patients with ILD. Primack *et al.* found that the MRI patterns correlated well with pathologic features seen on lung biopsy in a small group of patients with different forms of ILD [44]. A few studies have also focused on the differentiation between alveolitis and fibrosis in ILD. In an early study, McFadden *et al.* found that signal intensity on MRI correlated with disease severity and response to treatment, as a decrease in signal intensity could be observed on follow-up in some patients [45]. Further evidence that MRI is a suitable tool for the assessment of disease activity comes from experimental studies. Kersjes *et al.* investigated rabbits with bleomycin-induced lung damage and correlated MRI findings with histopathology [46]. They demonstrated that lesions in the alveolitic phase displayed high pre- and post-contrast signal intensity on T1-weighted and also on T2-weighted images, whereas with progressive fibrosis the signal intensity and contrast enhancement showed a marked decrease. Vinitski *et al.*, who chose a similar experimental approach in rats, demonstrated a close correlation between signal intensities at different stages of the disease and lung water content [47]. Other studies, however, failed to demonstrate differentiation of acute and chronic changes in ILD by calculating T1 and T2 proton relaxation times [48,49].

With MRI, the diagnostic benefits would stem from its ability to visualize changes in lung structure, while simultaneously imaging different aspects of lung function, such as perfusion, respiratory motion, ventilation and gas exchange. Recent technological refinements have led to a

considerable improvement of MRI image quality, which may open avenues for the use of MRI in selected patients with ILD [50]. With the increasing availability of MRI systems and with the advances in technology, the role of this imaging modality will be rapidly expanding. However, current limited availability and high cost of MRI may delay its wide use in the clinical arena.

In a novel perspective of sustainability of our medical acts, the possibility to use radiation-free technologies to assess SSc-ILD, such as ultrasound and MRI, seems extremely attractive and justifies further efforts in this field. The next challenge is to keep the high levels of information achieved with modern diagnostic imaging, but with a preferential use of less risky techniques. Both LUS and MRI look promising, but certainly more validation studies are needed to clearly establish their role. No doubt, however, that it is now time to pay a greater attention to economic, biologic and cultural sustainability of our imaging techniques [24].

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Executive summary

- High-resolution computed tomography (HRCT) is the reference tool to detect interstitial lung disease related to systemic sclerosis (SSc-ILD), although it carries a non-negligible radiological burden.
- Recently, lung ultrasound has been proposed as a nonionizing technique to detect and semiquantify SSc-ILD.
- If this technique were confirmed to be a reliable tool for the evaluation of SSc-ILD, it would be of tremendous impact on SSc management.
- A main issue in SSc-ILD is the differential diagnosis between pulmonary fibrosis and inflammation.
- To date, chest HRCT is not able to clearly differentiate fibrosis from inflammation.
- MRI is the current gold standard for noninvasive virtual histological discrimination of different tissues; thus, at least theoretically, MRI should help in the differentiation between inflammation and fibrotic tissue.
- To date, chest HRCT remains the gold standard technique for assessing SSc-ILD.
- It is likely that in the next few years, additional tools could become useful to support computed tomography, especially for the follow-up of SSc patients during treatment.

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