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High-resolution computed tomography and magnetic resonance imaging protocols in the diagnosis of fibrotic interstitial lung disease: overview for "non-radiologists"

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Abstract. Fibrotic interstitial lung diseases (ILDs) include a number of pulmonary disorders characterized by infiltration of inflammatory cells in lung parenchyma and fibrosis resulting in decreased lung compliance. Idiopathic pulmonary fibrosis (IPF) represents the most common ILD. ILDs can be divided in two anatomopathological and radiographic patterns: usual interstitial pneumonitis (UIP) and non-specific interstitial pneumonitis (NSIP). The different radiological features of UIP and NSIP are discussed. The American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association guidelines for the diagnosis and management of IPF have identified several characteristic high-resolution computed tomography (HRCT) features of UIP. However, even if these guidelines recommend to avoid surgical lung biopsy in case of confident UIP diagnosis on HRCT, they present some limitations, the most important of which is represented by interobserver agreement. Magnetic resonance imaging (MRI) can be considered as a radiation-free alternative to HRCT for several lung diseases. However, the clinical value of MRI for IPF diagnosis remains to be proven. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 300-306)*

Key words: fibrotic interstitial lung diseases, idiopathic pulmonary fibrosis, high-resolution computed tomography, magnetic resonance imaging

1. Definition

Fibrotic interstitial lung diseases (ILDs) include a large collection of pulmonary disorders, the common anatomic features of which are infiltration of inflammatory cells in lung parenchyma and fibrosis resulting in decreased lung compliance.

The pathophysiology of ILDs is characterised by four overlapping biological mechanisms (1):

1. activation of the inflammatory cascade, caused by tissue injury;
2. reaction of the vascular endothelium, followed by increased permeability;
3. activation of leukocytes, with release of mesenchymal growth factors;
4. remodelling and fibrosis, caused by the perpetuation of tissue inflammation and fibroblast differentiation into myofibroblasts, which leads to extracellular matrix deposition.

The development of pulmonary fibrosis drives clinical manifestations, which include cough (linked to bronchiolar distortion), dyspnea (due to ventilation/perfusion mismatching), and inspiratory crackles (caused by the reduction of surfactant).

The increased lung stiffness explains the results of pulmonary function tests typical of restrictive lung

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disease. In addition, the diffusing capacity for carbon monoxide is usually reduced, reflecting the diminished capillary bed and thickened alveolar capillary membrane (2).

2. Epidemiology

Idiopathic Pulmonary Fibrosis (IPF) represents the most common ILD.

The annual incidence of IPF in the US was estimated at 6.8-16.3 per 100,000 persons (3). Agabiti and coworkers reported an incidence of 7.5 per 100,000 persons in the Lazio region of Italy, thus indicating that incidence rates in southern European regions may be similar to those observed in northern Europe and North America (4).

3. Patterns of fibrotic interstitial lung diseases

Fibrotic ILDs can be related to two different anatomo-pathological and radiographic patterns: usual interstitial pneumonitis (UIP) and non-specific interstitial pneumonitis (NSIP). The main features of UIP and NSIP are summarized in Table 1.

The UIP pattern consists of reticulation, traction bronchiectasis and honeycombing appearance, that are predominantly located in the sub-pleural regions and in the lower lobes (5). The ground-glass opacities are less represented than reticulation (6).

The NSIP pattern consists of bilateral ground-glass areas in the lung, sometimes with extensive distribution in association with reticular opacities, traction bronchiectasis, and consolidation with sub-pleural sparing (7). Honeycombing is present in few cases, less frequently than in UIP.

Although UIP and NSIP are not interchangeable and are considered as two different entities, they can be associated with the same clinical manifestations. The most common clinical features are progressive dyspnea, cough, and hypoxemia. Often, there are also extra-pulmonary manifestations, like joint pain, rash, and Raynaud phenomenon, though these are more common in NSIP than in UIP.

NSIP carries a much more favourable prognosis than UIP because of a better response to corticosteroids, whereas UIP exhibits a good response to combination of N-acetyl-L-cysteine, prednisone, azathioprine, and warfarin or to pirfenidone.

Known causes for ILD include the following categories:

- infectious;
- granulomatous (e.g. sarcoidosis and hypersensitivity pneumonitis);
- pneumoconiosis caused by occupational or environmental inhaled agents;
- connective tissue disorders (e.g. scleroderma, rheumatoid arthritis);
- focal fibrosis.

The absence of known causes of ILD is one of the major criteria for IPF diagnosis, which may be familial (8).

3a. Usual interstitial pneumonitis

UIP is the most severe form of lung fibrosis and is most prevalent in men aged 50-60 years.

Most cases are idiopathic and are termed IPF. Other causes of the UIP pattern include domestic and occupational environmental exposures, connective tissue disease, and drug toxicity.

Histologically, the disease is characterised by the coexistence of scattered fibroblastic foci, with heterogeneous distribution that alternates interstitial

Table 1. HRCT features of NSIP and UIP.

Features	UIP	NSIP
Ground-glass areas	Yes, but less than in NSIP and represent an index of activity/exacerbation of disease)	Yes, bilateral
Reticular opacities	Yes	Yes
Traction bronchiectasis	Yes/no	Yes
Honeycombing	Yes (basal and sub-pleural regions)	Yes, but in few cases (sub-pleural sparing)
Centrolobular nodules	No	Yes

inflammation and honeycombing, and normal lung areas.

In 2011, the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) defined the guidelines for diagnosis of UIP pattern using high-resolution computed tomography (HRCT) features (8).

The UIP patterns have been categorized into three different groups: confident, possible, and inconsistent with UIP.

A UIP pattern is defined as confident based on the coexistence of all the following features: basal and sub-pleural distribution, reticular opacities, honeycombing (clustered cystic air spaces) and ground-glass opacities less extensive than reticulation. In addition, the presence of these HRCT aspects must be associated with the absence of features suggestive of inconsistent UIP pattern.

A possible UIP pattern is characterized by basal and sub-pleural distribution, reticular abnormalities and absence of inconsistent UIP features.

An inconsistent UIP pattern is defined by the presence of one of the following aspects: upper or mid-lung predominance, peri-bronchovascular predominance, extensive ground-glass abnormality, micronodules, air trapping, non-honeycomb cysts or consolidation.

Although the 2011 ATS/ERS/JRS/ALAT guidelines suggest avoiding surgical biopsy in the presence of a conclusive HRCT diagnosis of UIP, clinical practice indicates that a multidisciplinary discussion which involves radiologists, pulmonologists and pathologists is recommended. Furthermore, Walsh and coworkers demonstrated that inter-observer agreement it is only moderate among thoracic radiologists with different level of experience, thus supporting the need of a multidisciplinary approach and, possibly, a revision of these criteria in order to improve inter-observer agreement (9).

Another limitation can be represented by the possible coexistence of UIP and NSIP in different parts of the lung (10). Furthermore, the presence of emphysema can hamper the identification of honeycombing (11, 12). Even if it is still unclear if emphysematous areas represent a comorbidity or a distinct phenotype of fibrosis, Sverzellati and coworkers reaffirmed that coexistence of emphysema and UIP pattern worsens patients' outcome (13).

Other studies revealed the discrepancy between atypical HRCT pattern and histological diagnosis of UIP (14). In particular, Pezzuto, Sergiacomi and coworkers identified a subgroup of patients with diagnosis of IPF by lung biopsy, in the absence of basal predominance of honeycombing and reticular abnormalities on HRCT (15).

Figures 1 and 2 present two cases of UIP pattern, as shown by HRCT (and also MRI) scans.

3b. Non-specific interstitial pneumonitis

NSIP is the second most common interstitial fibrosis and is most prevalent in middle-aged adults (16). Many authors focussed on the fact that some cases of interstitial pneumonias were not included in UIP, desquamative interstitial pneumonitis (DIP), or atypical interstitial pneumonitis (AIP), based on the histopathological features (17). Travis and coworkers were the first that described these pneumonias as "non-specific interstitial pneumonias" (18). NSIP is divided in idiopathic NSIP, when it is not associated

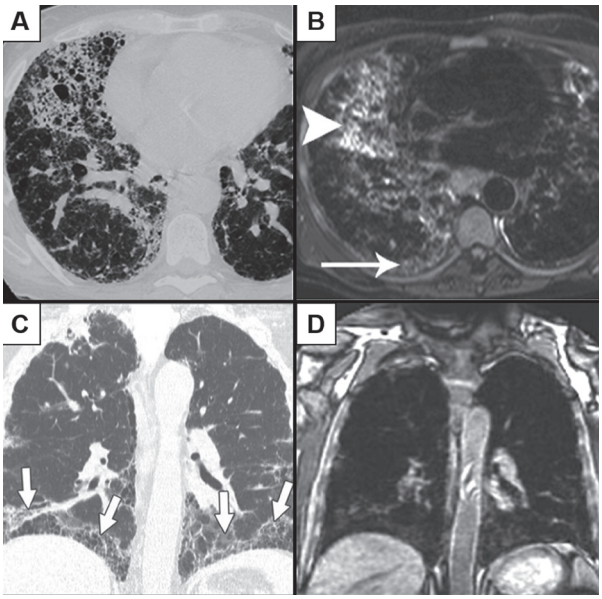

Fig. 1. Volumetric HRCT and MRI scan show a UIP pattern. Honeycombing is well shown in CT scan (A). In case of extensive honeycombing, fibrotic tissue is well represented also in T1 pre-contrast GRE sequence at MRI (B). However, a CT scan is necessary to well define the pattern (C) when the fibrotic tissue is not massive at MRI (D), which makes difficult the diagnosis and the definition of fibrosis extension. HRCT = high-resolution computed tomography; MRI = magnetic resonance imaging; GRE = gradient recalled echo.

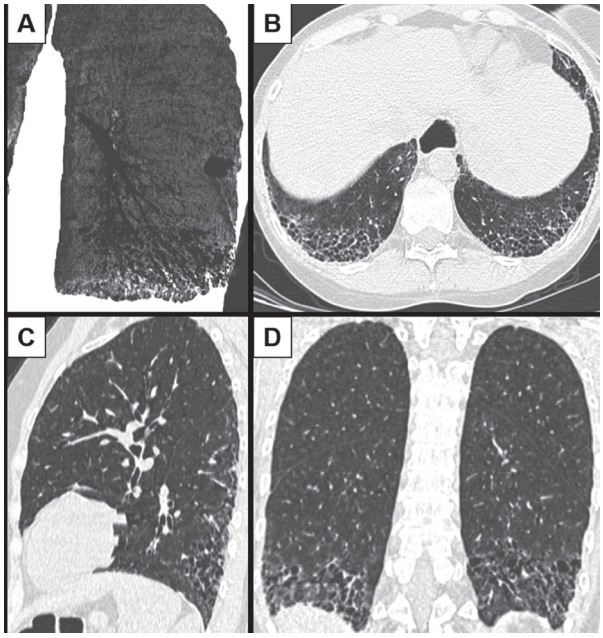

Fig. 2. Volumetric HRCT Scan (thickness 1.25 mm; 100 KV; 250 mA) of a 32 years old women affected by scleroderma showing fibrotic changes in the lower lung. The multiplanar reconstruction allows to better represent the basal predominance of fibrosis and the absence of consolidation or nodules in the lung (A-C). MinIP reconstruction well represents the basal bronchiectasis and the absence of honeycombing excluding the diagnosis of confident UIP (D). HRCT = high-resolution computed tomography; MinIP = minimum intensity projection; UIP = usual interstitial pneumonitis

with a specific disease, and secondary NSIP, when it is associated with connective tissue disorders like systemic lupus erythematosus, scleroderma, Sjögren's syndrome, polymyositis, dermatomyositis, and with hypersensitivity lung disease, drug toxicity, and slowly resolving diffuse alveolar damage (19, 20).

Histologically, NSIP is characterised by subpleural and symmetrical parenchymal changes with a peribronchovascular distribution. In particular, Travis and coworkers distinguished a "cellular NSIP" and a "fibrosing NSIP": the cellular type is characterised by chronic interstitial inflammation with little fibrosis, whereas in the fibrosing NSIP there is a preservation of the alveolar architecture with interstitial thickening due to fibrosis (21).

The radiological features are very important for differentiating NSIP from UIP and also for prognosis.

The preliminary chest X-Ray is not specific because it can show only infiltrates predominantly located in the lower lobes, a reticular pattern, and bronchiectasis. The HRCT is more specific than plain

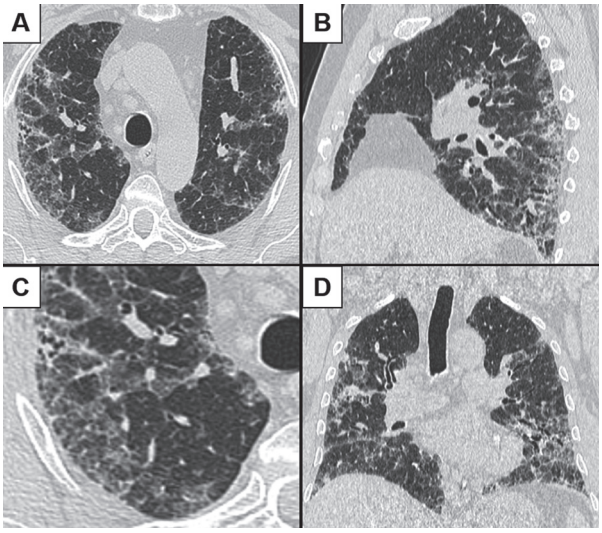

Fig. 3. Volumetric HRCT scan a NSIP pattern. Diffuse ground-glass opacities are showed, with no honeycombing or bronchiectasis and lower lung predominance, as evidenced in the axial plane (A), coronal plane (B), axial plane at higher magnification (C), and sagittal plane (D). HRCT = high-resolution computed tomography; NSIP = non-specific interstitial pneumonitis

film, due to the detection of bilateral ground-glass areas in the lung, sometimes with extensive distribution, with or without reticular opacities and traction bronchiectases, whereas honeycombing is a rare sign (22). However, the most specific sign of NSIP is sparing of the immediate sub-pleural lung (23).

Figure 3 shows representative HRCT scans from a patient presenting with a NSIP pattern.

4. High-resolution computed tomography protocol

Based on the current state of art, chest-radiography for ILD diagnosis and classification is considered misleading for several reasons: up to 10% of cases of false negative exams (especially early in the disease course), different X-Ray and HRCT or pathological examination pattern interpretation, and technical limitations due to 2-D summation of overlapping structures of the thorax (24-27). The best diagnostic tool in fibrotic ILD evaluation is the use of thin-section CT images (0.625-mm to 1.5-mm slice thickness) with a high spatial frequency reconstruction algorithm (28).

Two general approaches are available for acquiring HRCT images (29, 30). The first method (intro-

duced in the early 1980s) consists in obtaining discontinuous axial HRCT images spaced at 10-mm to 20-mm intervals throughout the lungs (31). The second method uses the ability of multiple detector CT scanners to provide volumetric single breath-hold datasets allowing spaced, contiguous and/or overlapping HRCT images to be reconstructed.

Prosch and coworkers in 2012 surveyed the protocols used by members of the European Society of Thoracic Imaging to evaluate patients with ILD and highlighted that most radiologists use to set the protocol on the patient and prefer volumetric CT acquisition because they consider 3D information very useful (32). In fact, volumetric scan allows obtaining multiplanar reconstruction that, in addition to axial planes, facilitates the evaluation of fibrosis distribution and the detection of bronchiectasis and pulmonary vascular disorders (33, 34). Furthermore, it is possible to produce 3D maximum intensity projection reconstructions providing advantages for the detection and characterization of nodules with respect to the differentiation between centrilobular and perilymphatic distribution, and minimum intensity projection reconstructions for the detection and quantification of subtle emphysema and for better identification of bronchiectasis (35).

Although novel CT techniques have substantially decreased the radiation dose, radiation exposure in volumetric acquisition is still high (36). Due to the need for repeated HRCT exams in fibrosing ILD patients and according to the well-known ALARA (As Low As Reasonably Achievable) principle, it is mandatory to minimize radiation dose when diagnostically feasible. To this end, it is suggested to increase pitch, utilize low mA or kVp using tube current modulation schemes, and tightly restrict the scan range to the body region of clinical concern. However, newest CT technologies promise to reduce drastically the dose up to 80% compared to current HRCT exams.

5. Magnetic resonance imaging technique

Magnetic resonance imaging (MRI) has been established as a radiation-free alternative to CT for several lung diseases, thus accounting for the growing interest in MRI for lung parenchyma evaluation. The low proton density in the lung and the fast signal decay due to susceptibility artefacts at air-tissue interfaces represent the most important limitations of MRI study of the lung, though the most recent technical advances have helped MRI to overcome these limitations (37).

Due to the lack of studies performed in ILD patients, MRI is currently used for research purposes only and its clinical value remains to be proven. However, MRI could be useful for the visualization and recognition of morphological changes and their patterns, the assessment of the inflammatory activity of the disease, and the evaluation of the effects of lung morphologic changes on functional parameters such as contrast enhancement and perfusion (38).

T2-weighted images demonstrate very well the interstitial fibrotic changes in peripheral and perihilar regions. The hyperintensity due to the increased proton density in interstitial space in fibrotic ILD must be differentiated from the extracellular interstitial water in patients with congestive hearth failure. However, mild interstitial changes, in particular in the sub-pleural portions, are more difficult to visualize, thus demonstrating the superiority of CT (39). Because of their higher spatial resolution, Fat suppression post-contrast T1-weighted, 3D gradient-echo sequences can increase the signal of altered sub-pleural lung tissue, improving the visualization of fibrosis in this region.

Honeycombing, which manifests with reticular changes and irregular cystic degeneration of the lung, can also be assessed using this technique (40). Though differentiation of active inflammation from fibrosis is difficult to achieve with 1.5 MRI exam, recent studies suggest the higher sensitivity of 3.0-T MRI to detect increased water content in the areas of inflammation, as inflammatory and fibrotic changes of the lung interstitium are hyperintense and isointense, respectively, on T2 weighted sequences compared to the signal of chest wall muscle (41-44). Precious information for differentiating ground-glass opacities, reticulations and honeycombing in fibrosing ILD could come from T2 mapping technique. In fact, Buzan and coworkers found different T2 relaxation times for the three different patterns (45). Furthermore, Jacob and coworkers reported that T2 relaxation data can be sensitive enough to identify lung inflammation in a rat model of bleomycin-induced lung injury (46).

6. Conclusions

As recommended by current ATS/ERS/JRS/ALAT guidelines, HRCT represents the gold standard for the diagnosis of IPF and differentiation between UIP and NSIP patterns. However, although these guidelines suggest to avoid surgical biopsy in the presence of a confident HRCT diagnosis of UIP, clinical practice suggests that a multidisciplinary discussion involving radiologists, pulmonologists, and pathologists is recommended to improve inter-observer agreement. Finally, MRI can be considered as a radiation-free alternative to HRCT for several lung diseases, though its clinical value for IPF diagnosis remains to be proven.

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