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Structured multidisciplinary discussion of HRCT scans for IPF/UIP diagnosis may result in indefinite outcomes

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Abstract. Recent ATS/ERS/JRS/ALAT guidelines for the diagnosis and management of Idiopathic Pulmonary Fibrosis (IPF) have defined key features and specific high-resolution computerized tomography (HRCT) patterns for the diagnosis of UIP. The aim is the sorting of patients with suspected IPF into three subgroups, *confident*, *possible* or *inconsistent* with UIP patterns, after a multidisciplinary discussion (MDD). Specialists in respiratory diseases, radiologists and pathologists should reach IPF diagnosis based on either patients' clinical, radiological and laboratory data, either submitting patients to surgical biopsy. After ATS/ERS/JRS/ALAT recommendations have been applied, it has been identified a subgroup of patients showing uniform apical-basal distribution of honeycombing and reticular abnormalities that could not be categorized as *confident*, or *possible* nor *inconsistent* with UIP. These patients were subsequently diagnosed with IPF after MDD and lung biopsy. Inclusion of this pattern in the recommendation for IPF diagnosis would be worth considering. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 32-36)*

Key words: idiopathic pulmonary fibrosis, HRCT pattern, multidisciplinary discussion, guidelines, idiopathic interstitial pneumonia

Introduction

Is the application of ATS/ERS/JRS/ALAT guidelines about HRCT scans clinically useful for the diagnosis of IPF?

Procedural application of the recommendations has failed to provide results for those patients with uniform apical-basal distribution of honeycomb cysts and reticular abnormalities. All other HRCT criteria for IPF are fulfilled.

While waiting for a revision of the guidelines, interstitial lung disease (ILD) expert centers may need to develop a standardized method to improve the multidisciplinary discussion for those cases that do not meet the *confident/possible* or *inconsistent* IPF patterns, in order to avoid unnecessary invasive procedures.

Idiopathic pulmonary fibrosis (IPF) is a form of chronic, progressive fibrosing interstitial pneumonia of unknown etiology. Histopathological features and high-resolution computerized tomography (HRCT) patterns of usual interstitial pneumonia (UIP) are essential for the definition of IPF (1).

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ATS/ERS/JRS/ALAT guidelines for the diagnosis and management of IPF have established HRCT key features of UIP patterns, such as subpleural/basal predominance, reticular abnormalities and honeycombing with or without traction bronchiectasis. Thus, HRCT is essential to allow confident identification of IPF through a multidisciplinary discussion (MDD), in the context of the appropriate clinical setting (1). When one of the HRCT fundamental features is missing, or in those cases of CT patterns that are not typical of UIP, patients are addressed either as *possible* UIP pattern, either as *inconsistent* with UIP pattern. If this occurs, the diagnosis is only possible after recognition of histopathological features consistent with UIP on surgical lung biopsy (1).

Recent literature about the application of ATS/ERS/JRS/ALAT guidelines, have reported that patients with suspected IPF could be classified as *confident* IPF with a positive predictive value greater than 90%, avoiding surgery (1-3).

Other latest studies have suggested that qualified multidisciplinary teams are able to identify and diagnose IPF only in particularly limited disease, based upon a *possible* UIP pattern presentation, increasing the diagnostic sensitivity of HRCT scans without loosing specificity (4).

Nowadays, the guidelines establish a procedure that stresses the team effort of a multidisciplinary group for the identification and discussion of HRCT features, with the objective of describing a *confident* UIP pattern, a *possible* UIP pattern or an *inconsistent* with UIP pattern.

Methods

Study population

The study population included 124 patients referred to the Respiratory Medicine Unit of the University Hospital of Tor Vergata in Rome for suspected IPF or for revision of a diagnosis of interstitial pulmonary fibrosis. All patients underwent HRCT imaging of the chest, pulmonary function testing, blood tests searching for collagen vascular and autoimmune diseases and, if indicated, fiber-optic bronchoscopy with broncho-alveolar lavage (BAL) for microbiological and cytological tests and/or surgical lung biopsy.

The study group involved 37 females and 87 males (70.2%), average age was 69.0 ± 7,9 years. Fourteen (11,3%) of them were current smokers with a smoke history of 41,8 ± 17,6 P/Y and 70 (56,5%) were former smokers (28,7 ± 20,6 P/Y). Pulmonary function testing included forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV)(5) and carbon monoxide diffusion capacity (DLCO) (Jaeger Master Screen MS PFT Analyzer Unit; Jaeger, Würzburg, Germany) (5). Study patients showed restrictive disease pattern (FVC 75,1 ± 28,5% predicted; TLC 66,7 ± 17,7% predicted; RV 63,5 ± 17,3% predicted; DLCO 43.1 ± 17,3% predicted).

HRCT scan evaluation and UIP pattern definition

HRCT scans were evaluated systematically according to the ATS/ERS/JRS/ALAT guidelines. Imaging definition of *confident* UIP required all the following criteria: presence of reticular abnormality with basal and peripheral predominance; presence of honeycombing and absence of atypical features, such as upper or mid-lung predominance, peri-bronchovascular predominance, extensive ground glass abnormality (extent > reticular abnormality), profuse micronodules (bilateral, predominantly upper lobes), discrete cysts (multiple, bilateral, away from areas of honeycombing), diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes), consolidation in bronco-pulmonary segment(s)/lobe(s).

HRCT definition of *possible* UIP required the presence of reticular abnormality with basal and peripheral predominance and absence of atypical features, as listed above.

The definition of HRCT *inconsistent* with UIP pattern cases implied the presence of one or more of the atypical features that were previously described above.

Multiplanar HRCT chest scans were evaluated with standard and Minimum Intensity Projection (MinIP) algorithms for the detection of ground-glass opacities, linear attenuation and honeycombing patterns of traction bronchiectasis (6).

Multidisciplinary discussion (MDD)

MDD was performed for the final review of cases with suspected IPF, in order to decrease intra

and inter-observer variability. Each HRCT feature for the diagnosis IPF was recorded, analyzed, processed and discussed. Patients defined as *possible* UIP or *inconsistent* with UIP pattern that showed clinical, immunological, microbiological and cytological features indicative for IPF were recommended for surgical biopsy. Thereafter, these patients were evaluated with the help of a specialist in pathology, reaching the final diagnosis upon histological findings.

Statistical analysis

Data is presented as mean+standard deviation or percentage as most appropriate. Comparisons between groups were evaluated by t-test. Variance's correction was applied for multiple comparisons. *P* values <0.05 were considered significant. GraphPad Prism version 5.0 (Graphpad software, San Diego, CA, USA) has been used for all statistical analyses.

Results

"UIP pattern-Confident UIP" was found on HRCT imaging of the chest of 76/124 study patients (61,3%). Patient's clinical conditions, pulmonary functional tests and laboratory findings were reviewed in order to exclude any differential diagnosis. The entire group of patients was diagnosed with IPF.

20/124 patients (16,1%) showed the HRCT *possible* UIP pattern, since they presented with only two of the defining criteria, lacking honeycomb cysts, in the absence of features inconsistent with the UIP pattern (Table 1).

13/124 patients (10,5%) showed at least one of the seven HRCT features defined as *inconsistent* with UIP, and therefore they were classified as *inconsistent* with UIP (1).

Among the 48 patients whose HRCT scan was not recognized as a confident IPF pattern, 7/48 presented a *possible* UIP CT imaging pattern and 9/48 showed an *inconsistent* with UIP pattern. These 16 patients were selected for surgical lung biopsy: based on histological findings of possible of UIP, along with a consistent clinical history, they were all diagnosed with IPF.

HRCT features that could not be classified either as a *consistent* UIP pattern either as a *possible* UIP pattern were identified in 15/124 patients (12,1%). All these subjects showed the presence of both honeycombing and reticular abnormalities, with an apical-basal uniform distribution: thus basal predominance was lacking (Figure 1). However, these patients could not be classified as *inconsistent* with UIP, since they did not have apical-mid lung predominance (which is the first feature listed as in-

Table 1. ATS/ERS/JRS/ALAT High-Resolution Computed Tomography criteria for UIP patterns

Diagnosis	Features Ax+Coro y/n	1 y/n	2 y/n	3 y/n	4 y/n	5 y/n	6 y/n	7 y/n	8 y/n	9 y/n	10 y/n
UIP pattern	76/0	76/0	76/0	76/0	0/76	0/76	0/76	0/76	0/76	0/76	0/76
UIP possible	20/0	20/0	20/0	0/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20
UIP inconsistent	13/0	1/12	12/1	11/2	9/4	0/13	2/11	1/12	1/12	2/11	0/13
Indefinite	15/0	0/15	15/0	8/7	0/15	0/15	0/15	0/15	0/15	0/15	0/15

Legend:
1 Subpleural, basal predominance
2 Reticular abnormality
3 Honeycombing with or without traction bronchiectasis
4 Upper or mid-lung predominance
5 Peribronchovascular predominance
6 Extensive ground glass abnormality (extent > reticular abnormality)
7 Profuse micronodules (bilateral, predominantly upper lobes)
8 Discrete cysts (multiple, bilateral, away from areas of honeycombing)
9 Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)
10 Consolidation in bronchopulmonary segment(s)/lobe(s)
• UIP Pattern: Yes to 1-3 without any of 4-10 (listed as inconsistent with UIP pattern)
• Possible UIP Pattern: Yes to 1-2 without any of 3-10
• Inconsistent with UIP Pattern: Yes to any of 4-10

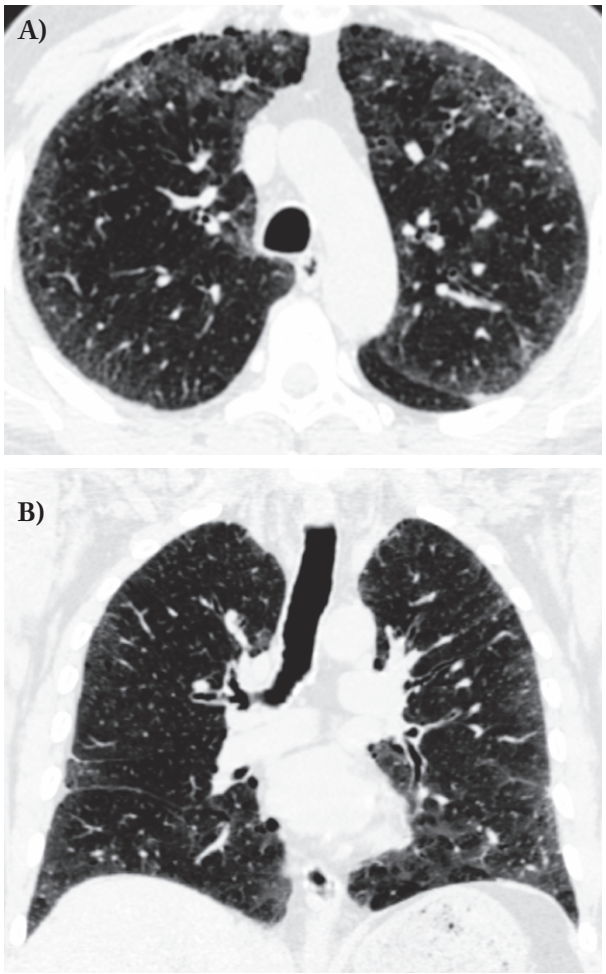

Fig. 1. Shown are the axial (1 A) and coronal (1 B) reconstruction of a HRCT categorized, according to criteria exposed in table I, as: 1) Subpleural, basal predominance NO; 2) Reticular abnormality YES; 3) Honeycombing with or without traction bronchiectasis YES; 4) Upper or mid-lung predominance NO; 5-10) other features inconsistent with UIP pattern NO

consistent with UIP). This explained why they were classified eventually as an *indefinite* UIP pattern (Table 1).

Seven of these patients were referred to lung biopsy: 3 patients presented lower lobe sub-pleural honeycombing at HRCT and 4 of them did not show it. A histological UIP probable pattern was found among all of these patients that were subsequently diagnosed with IPF.

Remarkable results was the fact that the "indefinite" subgroup appeared to be composed of heavy smokers (43,0 ± 21,9 pack years vs. 29,2 ± 19,3; non-corrected unpaired t-test p=0.039; variance corrected t-test p=0.07), if compared to patients with HRCT UIP pattern-Confident UIP, showing less reduced lung volumes (mean TLC 78,5 ± 17,1 % predicted vs. 63,7 ± 15,2%, compared to the confident UIP; non-corrected unpaired t-test p=0.0042; variance corrected t-test p=0.05) and also suggesting concurrent pulmonary emphysema.

Discussion

Pulmonary fibrosis may develop in a fraction of subjects affected by tobacco smoke-related emphysema (7, 8). Emphysema-associated IPF has been described as presenting with UIP pattern in the lower lobes, associated with paraseptal, centrilobular emphysema and bullae in the upper lobes (9). IPF associated with emphysema is also characterized by increased distribution of reticular opacities and microcysts in the upper lobes, and it has been shown that the sensitivity and specificity of HRCT for the diagnosis of IPF in patients with emphysema is significantly lower than in the absence of emphysema (10-11).

Although the cohort of patients in this study is rather limited, our findings are consistent with the belief that individuals with a history of heavy smoking are more likely to develop IPF over the years, also show a smaller number of typical HRCT abnormalities.

As recommended by ATS/ERS/JRS/ALAT 2011 guidelines, our multidisciplinary discussion could not classify as confident, nor as possible UIP, nor as inconsistent with UIP, only a specific subpopulation of patients that were then diagnosed with IPF/UIP, after surgical lung biopsy.

Even though larger studies may be useful for a better definition of the HRCT imaging of reticular and cystic abnormalities with upper to lower lobes distribution, our data can suggest that a fraction of IPF/UIP patients are excluded from the diagnosis of confident UIP when considering HRCT abnormal distribution solely as "sub-pleural, basal predominance" vs. "upper or mid-lung predominance".

Inclusion of this group of patients among the HRCT criteria for "consistent with UIP pattern" may allow a more accurate diagnosis of a greater amount of suspected IPF cases, without any invasive surgical or endoscopic procedure.

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