The Fleischner Society diagnostic criteria for IPF
Clinical implications

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Idiopathic Pulmonary Fibrosis is a debilitating, relentlessly progressing disease with a median survival of about 3-5 years. The introduction of antifibrotic agents, pirfenidone and nintedanib marked the beginning of a new era in the management of IPF[1]. These two agents have been tested only in the context of IPF[2-4]. This means that the precise diagnosis of IPF is not just an academic exercise but has direct clinical implications.

The latest guidelines for the diagnosis of IPF by ATS/ERS/JRS/ALAT date back to 2011[5]. According to them, the presence of a definite UIP pattern (presence of honeycombing in a predominantly peripheral bibasilar distribution) after exclusion of alternative diagnoses, is considered diagnostic of UIP/IPF obviating the need for surgical lung biopsy (SLB). Thus, honeycombing was a prerequisite in order to avoid tissue based diagnosis. When the patient presented with a possible UIP pattern (presence of traction bronchiectasis/bronchiolectasis in a predominantly peripheral bibasilar distribution but without honeycombing) and inconsistent with UIP pattern, surgical lung biopsy was advised in the diagnostic algorithm in order to establish diagnosis.

It is important to note that back then; there was no approved therapy for IPF. The main focus was to create clinical trial based guidelines in order to ensure the formation of a well characterized population of patients to enroll in clinical trials. The arrival of pirfenidone and nintedanib has created the need for new guidelines. The recently published diagnostic guidelines by the Fleischner Society[6] represent a major step forward. They incorporate findings during the last decade and are clinical practice oriented[7]. Several points are worth mentioning that have direct implications for clinical practice.

1. INTRODUCTION OF PRETEST PROBABILITY

An important new feature is the introduction in the diagnostic algorithm of pretest clinical probability[8]. According to the Fleischner Society guidelines, a clinical context of IPF includes all of the following: age >60, absence of significant exposure and no evidence of collagen vascular disease. Male sex is another factor that has been linked to an increased clinical likelihood of IPF[9-11]. When the clinical context is indeterminate for

IPF, a diagnostic biopsy is required to make a confident diagnosis, regardless of the pattern on HRCT.

2. UPGRADE OF POSSIBLE UIP PATTERN TO PROBABLE

The possible UIP pattern according to the 2011 guidelines (ie reticular pattern with bibasilar and peripheral traction bronchiolectasis/bronchiolectasis) has been upgraded to probable. This is not just a formality but has direct clinical implications. The presence of a probable UIP pattern within the clinical context of IPF obviates the need for tissue based diagnosis. This is a major breakthrough as honeycombing is no longer a prerequisite to avoid surgical lung biopsy. Peripheral distribution of fibrotic findings plays a pivotal role[12].

3. INTRODUCTION OF INDETERMINATE FOR UIP PATTERN

A new CT category is introduced, indeterminate for UIP. It would be extremely convenient to easily categorize everything in boxes but this is not possible and IPF is no exception to this. IPF is actually a great mimic from a radiology point of view[13]. In almost one third of cases

with UIP there is evidence of fibrosis that does not follow a predominantly peripheral and bibasilar distribution. In these patients even if in the clinical context of IPF, SLB is necessary in order to secure diagnosis.

4. INTRODUCTION OF SUBPLEURAL SPARING IN THE CT FEATURES MOST CONSISTENT WITH NON-IPF DIAGNOSIS

Subpleural sparing is considered a strong predictor of NSIP pathology[14]. Until know it was not included in diagnostic guidelines. Fleischner Society gives an important diagnostic role to subpleural sparing. Alongside upper or mid-lung predominant fibrosis and peribronchovascular predominance are considered as most consistent with non-IPF diagnosis.

5. FORMAL INTRODUCTION OF "WORKING DIAGNOSIS OF IPF"

As mentioned earlier, there are cases where SLB is necessary to secure diagnosis. However, in clinical practice this is not always feasible for a variety of reasons,
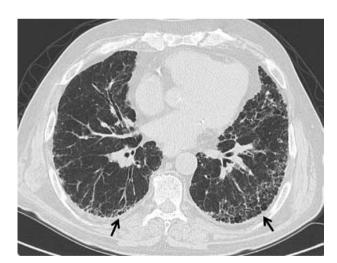

FIGURE 1. Cystic airspaces with well-defined walls in several layers. The cysts share walls abutting the pleura (black arrows). In conclusion, there is honeycombing in a subpleural distribution. This is a UIP pattern based on the 2011 ATS/ERS/JRS/ALAT guidelines and a typical UIP pattern according to the diagnostic criteria of the Fleischner Society. In the appropriate clinical setting this is diagnostic of IPF according to both guidelines.

FIGURE 2. Fine reticular pattern with traction bronchiolectasis (white arrows). No honeycombing is seen. According to the 2011 ATS/ERS/JRS/ALAT guidelines this is a possible UIP pattern and a surgical lung biopsy is mandatory to secure diagnosis. According to the diagnostic criteria by Fleischner society this is considered a probable UIP pattern and in the appropriate clinical setting a diagnosis of IPF can be established without the need for tissue confirmation.

FIGURE 3. Fine reticulation and areas of increased attenuation (ground glass) following a peribronchial distribution. There is mild bronchial distortion (white arrows). Characteristically, the abnormal findings spare the subpleural area (subpleural sparing). This is a pattern most consistent with a non-IPF diagnosis. Surgical lung biopsy demonstrated findings compatible with hypersensitivity pneumonitis.

TABLE 1. Fleischner Society diagnostic criteria for IPF. Clinical implications

- It is mandatory to define the clinical likelihood for IPF before interpreting other diagnostic tests (pretest probability)

- Appropriate clinical context for IPF requires all of the following: age >60, absence of significant exposure and no evidence of collagen vascular disease

- Honeycombing is no longer required for a non invasive diagnosis of IPF

- In the appropriate clinical context, the presence of fibrosis (traction bronchiectasis) in a predominantly basal and subpleural distribution (probable UIP pattern) leads to a confident diagnosis of IPF

- The presence of fibrotic changes in the absence of predominantly peripheral distribution is indeterminate for UIP and mandates tissue based diagnosis

- Subpleural sparing points to a non IPF diagnosis

- Tissue based diagnosis is not feasible in every patient. In such cases, experts can establish a "working diagnosis" of IPF based on history, clinical examination, HRCT findings, pulmonary function tests, progression over time

i.e. poor performance status or refusal of the patient. It is also important to keep in mind that in patients with Interstitial Lung Diseases (ILDs), SLB can trigger an acute

exacerbation. Worryingly, the clinical context of IPF (male sex, increased age) actually increases the risk for acute exacerbation[15,16]. Thus the decision on a surgical biopsy should not be taken lightly but after careful examination of the clinical benefit versus clinical risk for each patient.

The Fleischner Society diagnostic criteria for IPF were much needed. The previous ATS/ERS/JRS/ALAT guidelines were outdated and actually impossible to follow in every day clinical practice given the significant new findings in the field of IPF. Refining the role of HRCT regarding the diagnostic certainty of underlying UIP pathology gives us the ability to confidently establish a diagnosis of IPF without subjecting the patient to potentially life threatening diagnostic procedures. Also, defining pretest probability and embedding it into the diagnostic algorithm makes common clinical sense (unfortunately not always common practice) a central pillar of the diagnostic algorithm. Finally, taking consideration of real-life difficulties into account rationalize the term "working diagnosis" and made it a part of these diagnostic criteria. However, the practical application of these guidelines is not an easy task. The identification of the probable UIP pattern, the differentiation between probable UIP and indeterminate for UIP pattern, establishing a "working diagnosis" of IPF and in general applying differential diagnostics within the spectrum of ILDs, requires expert knowledge from multiple specialties in the context of a reference center[17]. The upcoming ATS/ERS/JRS/ALAT guidelines for IPF are greatly anticipated.

REFERENCES

1. Bouros D. Idiopathic Pulmonary Fibrosis: The dawn of a new era. Pneumon 2014; 27:117-9.
2. Noble PW, Albera C, Bradford WZ. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomized trials. Lancet 2011; 377:1760–9.
3. King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfe nidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2083–92
4. Richeldi L, du Bois RM, Raghu G, et al INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2071–82.
5. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824.
6. Lynch DA, Sverzellati N, Travis WD et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Published online November 15, 2017 http://dx.doi.org/10.1016/S2213-2600(17)30433-2.

7. Tzilas V, Valeyre D, Tzouvelekis A, Bouros D. Taking a giant step in the diagnosis of idiopathic pulmonary fibrosis. Lancet Respir Med. Published online November 15, 2017 http://dx.doi.org/10.1016/S2213-2600(17)30443-5.

8. Tzilas V, Tzouvelekis A, Chrysikos S, et al. Diagnosis of Idiopathic Pulmonary Fibrosis "Pragmatic Challenges in Clinical Practice". Front Med (Lausanne) 2017; 4:151.

9. Brownell R, Moua T, Henry TS, et al. The use of pretest probability increases the value of high-resolution CT in diagnosing usual interstitial pneumonia. Thorax 2017; 72:424-9.

10. Fell CD, Martinez FJ, Liu LX, et al. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2010; 181:832-7.

11. Salisbury ML, Xia M, Murray S, et al. Predictors of idiopathic pulmonary fibrosis in absence of radiologic honeycombing: A cross sectional analysis in ILD patients undergoing lung tissue sampling. Respir Med 2016;118:88-95.

12. Tzilas V, Bouros D. Usual interstitial pneumonia pattern in the diagnosis of idiopathic pulmonary fibrosis? Lancet Respir Med 2016; 4:770-2

13. Sverzellati N, Wells AU, Tomassetti S, et al. Biopsy-proved idiopathic pulmonary fibrosis: spectrum of nondiagnostic thin-section CT diagnoses. Radiology 2010; 254:957-64.

14. Silva CI, Müller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 2008; 246:288-97.

15. Hutchinson JP, McKeever TM, Fogarty AW, et al. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997-2008. Eur Respir J 2016; 48:1453-61.

16. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease in the United States. 2000 to 2011. American journal of respiratory and critical care medicine 2016; 193:1161-7.

17. Tzilas V, Bouros D. Reference centers for interstitial lung diseases. Pneumon 2016; 29:15-7.