The diagnosis of IPF

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Clinical Classification

Diffuse parenchimal lung diseases

Exposure-related:
- occupational
- environmental
- medication

Idiopathic interstitial pneumonias

Idiopathic pulmonary fibrosis

Connective tissue Disease:
- Scleroderma
- Rheum. Arthritis
- Sjogren
- UCTD

Other:
- Sarcoidosis
- Vasculitis/DAH
- LCH
- LAM
- PAP
- Eosinophilic pneumonia
- Neurofibromatosis
- Chronic aspiration
- Inflammatory bowel disease

Desquamative interstitial pneumonia

Respiratory bronchiolitis interstitial lung disease

Acute interstitial pneumonia

Cryptogenic organising pneumonia

Non-specific interstitial pneumonia

Lymphocytic interstitial pneumonia
IPF is a rare disease that is considered a genetic disease. Median survival historically is only ~3-5 years. Progressive deterioration is inevitable, and considerable inter- and intra-patient variability exists. Worldwide prevalence is estimated to be at least 5 million people. Lung transplantation is an option, but limited therapeutic options are available.
The rising incidence of idiopathic pulmonary fibrosis in UK


- 15000 people in the UK have a diagnosis of IPF-CS
- each year, 5000 new cases of IPF
- each year, 5000 people with IPF-CS will die

“This means that in the UK, more people will die each year from IPF-CS than from ovarian cancer, lymphoma, leukaemia, mesothelioma or kidney cancer”
Incidence and prevalence of idiopathic pulmonary fibrosis: review of literature

- The incidence and prevalence of IPF are difficult to determine due to the lack of uniform diagnostic criteria

- Both prevalence and incidence estimates reported in the USA tended to be higher than those reported in Europe or Japan

- Prevalence and incidence estimates increased with increasing age

- In the USA, it seems that the incidence of IPF decreased in recent years, while in the UK incidence reported lately is higher than that reported previously. However, the recent incidence estimates in the USA are similar to the recent incidence estimates in the UK
The prevalence of IPF in Europe is ~ 120000 and an estimated 40000 new cases are diagnosed each year.

The prevalence of IPF in Lombardy region in 2010 is 3600 patients and incidence is 450.

In Lombardy, IPF prevalence increased while incidence remained stable in the last years (2005-2010).
### Familial Interstitial Pneumonia: 2-20% of cases

Heterozygous mutations in SFTPC (~1%), SFTPA2 (~1%), TERT (~15%), and TERC (~1%) are responsible for about 20% of all familial interstitial pneumonias (FIPs).

Sporadic IPF, in the absence of telomerase mutations, is often associated with telomere shortening, suggesting that pathways involved in familial disease may contribute to sporadic disease.

Most FIP families (80%) have evidence of vertical transmission suggesting single autosomal dominant mechanisms.

A common variant in the promoter of the MUC1B gene is associated with the development of both familial and sporadic IPF.
**Old definition of IPF**

- IPF is a distinct type of chronic fibrosing interstitial pneumonia
- Unknown cause
- Limited to the lungs
- Has typical HRCT findings
- Associated with a histologic pattern of usual interstitial pneumonia (UIP)

New definition of IPF

- IPF is a specific form of **progressive** fibrosing interstitial pneumonia
- Unknown cause
- Occurring in older adults
- Limited to the lungs
- Associated with a histological and/or **radiological** pattern of usual interstitial pneumonia (UIP)
Importance of early diagnosis of IPF

- Begin evaluation for lung transplant earlier
- Allows for earlier referral and enrollment in clinical trials (which are generally limited to patients with mild to moderate disease)
- Emerging evidence regarding response to therapy
- Exclude other more treatable diseases
Our results suggest that the recognition (or suspicion) of IPF should prompt early referral to a specialty center. The symptoms of early IPF are often subtle, and an accurate diagnosis of even established IPF may not be feasible for community based physicians. Early access would be facilitated by improved methods of early detection.

At present, ILD screening efforts are limited to those with known risk factors for ILD or those with a history of familial IPF. Innovative studies of circulating biomarkers and quantitative imaging methods may hold the key to more accurately identifying early disease.
Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis?

Cottin V and Cordier JF. Eur Respir J 2012; 40: 519

We further consider that pulmonary auscultation should still be included in the initial steps of the diagnostic algorithm in patients with chronic dyspnoea, especially in those with progressive dyspnoea, as well as in patients with chronic dry cough.

It cannot be ignored anymore that a longer delay in accessing a tertiary care centre is associated with a higher risk of death independent of the severity of IPF.
Chest auscultation has long been considered a useful part of the physical examination, going back to the time of Hippocrates."
Normal (Vesicular) Lung Sound
Low-pass-filtered noise
Typical frequency, 100–1000 Hz
Drop of energy at 200 Hz

Fine Crackle
Rapidly dampened wave deflection
Typical frequency, about 650 Hz
Typical duration, about 5 msec

Coarse Crackles
Rapidly dampened wave deflection
Typical frequency, about 350 Hz
Typical duration, about 15 msec
Don’t stop with “pulmonary fibrosis”

Reason for a specific diagnosis:

- many forms are treatable
- treatments depend on diagnosis
- prognosis varies
- clinical trial eligibility requirements
In idiopathic interstitial pneumonia, diagnosis is prognosis
Approach to the diagnosis of IPF

**Clinical**
- History
- Physical
- Laboratory
- PFTs

**Radiology**
- Chest X-ray
- HRCT

**Pathology**
- Surgical lung biopsy

Primary care physicians
- Pulmonologists
- Radiologists
- Pathologists

Multidimensional and multidisciplinary

The gold-standard of IIP diagnosis
Diagnosis is multidisciplinary

Modified from: Flaherty et al. Am J Respir Crit Care Med 2004; 170:904

Requires pulmonologists, radiologists and pathologists working together
“The diagnosis of IPF requires:

a) exclusion of other known causes of interstitial lung disease

a) the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy

a) specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy”
Chest radiograph in IPF

A normal chest x-ray does not exclude IPF
exercise PaO₂). The most useful clinical tool for distinguishing between subclasses is high-resolution computed tomography (HRCT) of the chest. The diagnostic utility of HRCT
An early and accurate diagnosis of IPF is critical, particularly with the advent of novel specific treatments that may have the potential to reduce disease progression.
Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate


- In a population of current and former smokers with at least 30 p/y, 55-74 years of age fibrotic interstitial lung disease was present at systematic CT in ~ 2% of patients, 37% of whom had progressive fibrotic disease on 2-year follow-up CT.

- Low dose CT scan appropriately detect subclinical fibrotic ILD likely corresponding to IPF at an early stage.
Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis

Cordier JF, Cottin V Eur Respir J 2013

The syndrome of combined pulmonary fibrosis and emphysema strikingly recapitulates the three major respiratory consequences of cigarette smoking, namely pulmonary fibrosis, emphysema, and lung cancer.

Among first-degree relatives of individuals with familial interstitial pneumonia, older age, male sex, and having ever smoked cigarettes are associated with the development of pulmonary fibrosis, suggesting that the development of ILD may result from an interaction between age, smoking and genetic factors.
IPF is a disease of ageing

In an apparent paradox, familial interstitial pneumonia predominantly occurs at a younger age as compared to non-familial IPF. Some clues as to why this may happen has arisen from the recent description of germline mutations in the genes hTERT and hTR associated to the telomerase complex.
Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study


20 of the 46 (43%, 95% CI 29-58) patients with IPF according to 2011 guidelines had a subsequent diagnosis of chronic hypersensitivity pneumonitis.

Almost half of patients diagnosed with IPF on the basis of 2011 criteria were subsequently diagnosed with chronic hypersensitivity pneumonitis, and most of these cases were attributed to exposure of occult avian antigens from commonly used feather bedding.
Reticular opacities
Traction bronchiectasis
Basal and subpleural predominance
Honeycombing

Classic IPF HRCT
## HRCT diagnosis of IPF

<table>
<thead>
<tr>
<th>IPF Findings</th>
<th>Consider Alternate Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UIS pattern (all four):</strong></td>
<td><strong>Possible UIS pattern (all three):</strong></td>
</tr>
<tr>
<td>Sub-pleural, basal predominance</td>
<td>Subpleural, basal predominance</td>
</tr>
<tr>
<td>Reticular abnormality</td>
<td>Reticular abnormality</td>
</tr>
<tr>
<td>Honeycombing with or without traction bronchiectasis</td>
<td>Absence of features listen as inconsistent with UIS</td>
</tr>
<tr>
<td>Absence of features listen as inconsistent with UIS</td>
<td></td>
</tr>
</tbody>
</table>

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**Am J Respir Crit Care Med 2011; 183: 788-824**
Use of prone Imaging
UIP: progression of fibrosis on CT

Early:
Reticular

Midcourse:
Subpleural honeycombing

Late:
Diffuse honeycombing
Inconsistent with UIP pattern (any of the seven):

- Upper or mid-lung predominance
- Peribronchovascular 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 bronchopulmonary segment(s)/lobe(s)

Am J Respir Crit Care Med 2011; 183: 788-824
Typical HRCT features of IPF in association with a compatible clinical profile obviate surgical biopsy

**BUT**

*High-Resolution Computed Tomography and the Many Faces of Idiopathic Pulmonary Fibrosis*
The spectrum of atypical HRCT appearances in IPF

- Exploration of biopsy-proven IPF (n=55)
- As expected, a high prevalence of atypical HRCT findings (n=34, 62%), as judged by three observers
- Alternative HRCT diagnoses analysed

Sverzellati N et al. Radiology 2010; 254:957-64
Alternative first choice diagnoses were NSIP (53%), chronic HP (12%), sarcoidosis (9%), “unclassifiable” (23%)

Cases with atypical appearances had the same IPF-like outcome as those with typical HRCT appearances

Sverzellati N et al. Radiology 2010; 254:957-64
UIP pattern (all four):

- Evidence of marked fibrosis/architectural distortion ± honeycombing in a predominantly sub-pleural/paraseptal distribution
- Patchy involvement of lung parenchima
- Fibroblastic foci
- Absence of features against a diagnosis of UIP

*Am J Respir Crit Care Med 2011; 183: 788-824*
<table>
<thead>
<tr>
<th>Probable UIP pattern</th>
<th>Possible UIP pattern (All three criteria)</th>
<th>Not UIP pattern (any of the six criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ Evidence of marked fibrosis/architectural distortion, ± honeycombing</td>
<td>❖ Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation</td>
<td>❖ Hyaline membranes</td>
</tr>
<tr>
<td></td>
<td>❖ Absence of other criteria for UIP</td>
<td>❖ Organizing pneumonia</td>
</tr>
<tr>
<td>❖ Absence of either patchy involvement or fibroblastic foci, but not both</td>
<td></td>
<td>❖ Granulomas</td>
</tr>
<tr>
<td></td>
<td>❖ Absence of features against a diagnosis of UIP suggesting an alternate diagnosis</td>
<td>❖ Marked interstitial inflammatory cell infiltrate away from honeycombing</td>
</tr>
<tr>
<td>❖ Absence of features against a diagnosis of UIP suggesting an alternate diagnosis</td>
<td>❖ Absence of features against a diagnosis of UIP suggesting an alternate diagnosis</td>
<td>❖ Predominant airways centered changes</td>
</tr>
<tr>
<td>OR</td>
<td>❖ Predominant airways centered changes</td>
<td></td>
</tr>
<tr>
<td>❖ Honeycomb changes only</td>
<td>❖ Other features suggestive of an alternate diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

OR
Morbidity increases with age

Co-morbidity a major constraint

In many patients, disease severity does not allow biopsy

In severe disease, a biopsy sometimes less useful
Early mortality was associated solely with the severity of lung function impairment at presentation, but mortality after 2 years of follow-up was primarily linked to the histopathologic diagnosis.

- Risk increases as gas transfer falls below 30-35%
- Prognostic value diminishes as gas transfer falls below 30-35%
Usefulness of BAL in diagnosis of IPF:

Should BAL cellular analysis be performed in the diagnostic evaluation of suspected IPF?

The most important application of BAL is in the exclusion of chronic HP; prominent lymphocytosis (>40%) should suggest the diagnosis.

Recommendation: BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, low-quality evidence).

Am J Respir Crit Care Med 2011; 183: 788-824
In cases requiring histopathology, the specificity and positive predictive value of UIP pattern identified by TBB has not been rigorously studied. While TBB specimens may show all the histologic features of UIP, the sensitivity and specificity of this approach for the diagnosis for UIP pattern is unknown.

Recommendation: TBB should not be used in the evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, low-quality evidence)
Usual interstitial pneumonia

scleroderma
RhA
DM/PM
Should serologic testing for connective tissues diseases be used in the evaluation of suspected IPF?

- CTD can present with a UIP pattern
- ILD has been described as the sole clinical manifestation of these conditions
- ILD can precede the overt manifestation of a specific CTD

**Recommendation:** serologic testing for CTD should be performed in the evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, very low-quality evidence)

*Am J Respir Crit Care Med 2011; 183: 788-824*
Serologic tests can help exclude other conditions

Connective tissue diseases

- ESR
- ANA
- CCP (for RA)
- CK
- Aldolase
- Anti-myositis panel with Jo-1 antibody
- ENA panel
  - Scl-70
  - Ro (SSA)
  - La (SSB)
  - Smith
  - RNP

Hypersensitivity pneumonitis

Hypersensitivity panel (if exposure history)
Complete history assessment

Physical examination

Laboratory test and autoimmunity

HRCT

Biopsy evaluation

PFT, 6MWT

Chest radiograph

Raynaud phenomenon, esophageal hypomobility, dysphagia inflammatory arthritis, arthralgias, digital edema, clubbing, symptomatic keratoconjunctivitis sicca, oral ulceration, pleuritis, pericarditis

ESR, CRP, CPK, LDH, rheumatoid factor, ANCA, anti-MPO

ANA titer and pattern of immunofluorescence

Anti-Scl-70, Anti-Ro, Anti-ds-DNA, anti-CCP

Anti-PM-Scl, anticentromere

Schirmer test, Nailfold capillaroscopy, Digestive tract X-ray, Echocardiograph evaluation

Lymphoid aggregates with germinal centers

Extensive pleuritis

Prominent plasmacytic infiltration

Dense perivascular collagen
It is not uncommon for pulmonologist to find patients with IP who are supposed to have a systemic autoimmune disease. Within current classification schemes, many of these patients are labeled as idiopathic by default. Despite the recognition that IP may be the *forme fruste* presentation of CTD, current classification criteria do not allow a CTD designation for ILD alone.
Why is important to discover an occult CTD?

- For disease prognosis
- For appropriate therapeutic approach
- For a search of additional system involvement or underlying malignancy
- For specific complications
- Is lung biopsy indicated?
Physical examination

Raynaud phenomenon
esophageal hypomobility, dysphagia
inflammatory arthritis, arthralgias
digital edema, clubbing
symptomatic keratoconjunctivitis sicca,
sialoadenitis, oral ulceration
polyarthritis, pericarditis

Laboratory test and autoimmunity

ESR, CRP, CPK, LDH, rheumatoid factor, ANCA, anti-MPO
ANA titer and pattern of
immunofluorescence
Scl-70, Anti- Ro, Anti-ds- DNA, Anti- CCP
anti- PM-Scl, anticentromere
anti- Jo-1, PL- 7, PL- 12,

HRCT, PFT, 6MWT

Chest radiograph

Schirmer test, Nailfold capillaroscopy, Digestive tract X-ray, Echocardiograph evaluation

Biopsy evaluation

Lymphoid aggregates with germinal centers
Extensive pleuritis
Prominent plasmacytic infiltration
Dense perivascular collagen

Complete history assessment

Periodic evaluation
Diagnostic algorithm for IPF

Suspected IPF

Identifiable cause for ILD?
(CTD, drugs, exposures, ...)

YES

Chest HRCT

Not UIP

UIP

Possible UIP
Inconsistent with UIP

Surgical lung biopsy

Not UIP

MDD

IPF

IPF / Not IPF

Not UIP

Not IPF

MDD

UIP

Possible UIP / Probable UIP
Non classifiable fibrosis

Am J Respir Crit Care Med 2011; 183: 788-824
Ospedale San Giuseppe
Rare lung diseases (2001-2014)
Tot 1076 pts

- IPF 395
- Sarcoidosis
- LAM
- Pulmonary hypertension
- Others IIP
- BOOP
- PLCH
- Vasculitides
Should a multi-disciplinary discussion be used in the evaluation of suspected IPF?

The diagnosis of IPF is, by definition, multidisciplinary. Proper communication between the various disciplines involved in the diagnosis of IPF (pulmonary, radiology, pathology) has been shown to improve inter-observer agreement among experienced clinical experts as to the ultimate diagnosis.

Recommendation: we recommend that a multi-disciplinary discussion should be used in the evaluation of IPF (strong recommendation, low-quality evidence).

Timely referral to ILD experts is encouraged.

Am J Respir Crit Care Med 2011; 183: 788-824
Conclusions

- The early recognition of IPF starts with a high level of clinical suspicion.
- The approach to the diagnosis of IPF requires a multi-disciplinary effort (pulmonologist, radiologist, and pathologist).
- Differentiating IPF from other ILDs can direct the management and predict the prognosis of these patients.
In some patients, lung involvement precedes other systemic manifestations, making the distinction between IIP and lung involvement of CTD impossible.

An association of IIP with CTD should be vigorously searched, not only at time of diagnosis but also during follow-up.
Conclusions

♦ It is important to look for additional minor/minimal abnormalities (clinical, radiological, histological) that may help in diagnosis of occult CTD or chronic HP

♦ IPF can be diagnosed on HRCT in the majority of cases but a crucial sub-group have very atypical HRCT appearances

♦ Perform an accurate diagnosis of ILD and IPF is very difficult and complex!