Diagnosi clinica e radiologica della fibrosi polmonare idiopatica

Sergio Harari
U.O. di Pneumologia e UTIR
Ospedale San Giuseppe
Milano

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

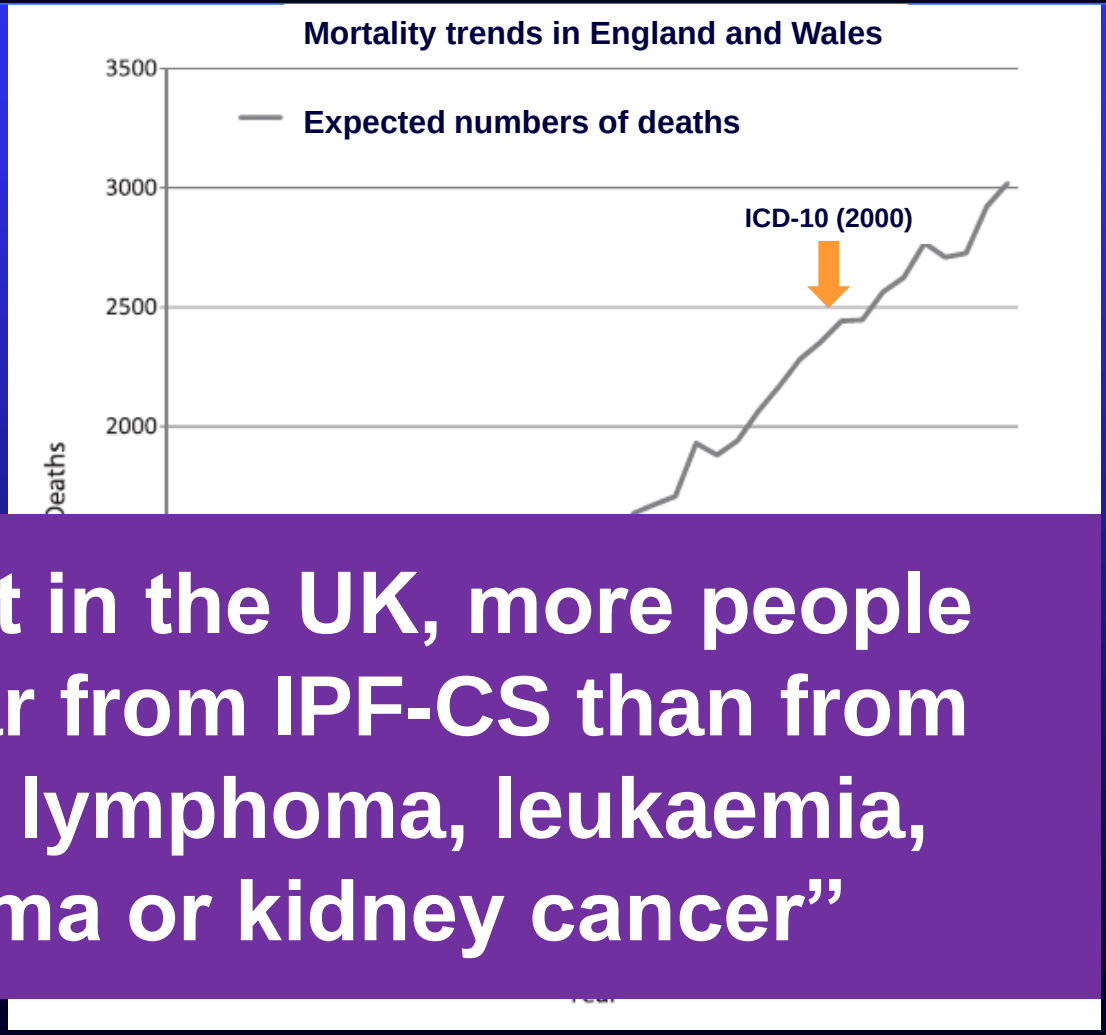
Other:
- Sarcoidosis
- Vasculitis/DAH
- LCH
- LAM
- PAP
- Eosinophilic pneumonia
- Neurofibromatosis
- Chronic aspiration
- Inflammatory bowel disease

Desquamative interstitial pneumonia	Respiratory bronchiolitis interstitial lung disease
Acute interstitial pneumonia	Cryptogenic organising pneumonia
Non-specific interstitial pneumonia	Lymphocytic interstitial pneumonia

The rising incidence of idiopathic pulmonary fibrosis in UK

Navaratnam V et al. Thorax 2011;66:462

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



"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"

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)

ATS/ERS Consensus Statement. *Am J Respir Crit Care Med*. 2002;165:277-304

ATS/ERS Consensus Statement. *Am J Respir Crit Care Med*. 2000;161:646-664

Diagnostic criteria for IPF without surgical lung biopsy

Major Criteria
Exclusion of other known causes of ILD
Evidence of restriction and/or impaired gas exchange
HRCT: bibasilar reticular abnormalities with minimal ground-glass opacities (Honeycombing is characteristic[1)]
TBB or BAL that does not support an alternative diagnosis

Minor Criteria
Age > 50 years
Insidious onset of otherwise unexplained dyspnea on exertion
Duration of illness > 3 months
Bibasilar, inspiratory, Velcro® crackles

All major criteria and at least 3 minor criteria must be present to increase the likelihood of an IPF diagnosis

1. Not included in current guidelines

ATS/ERS. *Am J Respir Crit Care Med.* 2000;161:646-664.

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)

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

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

Delayed access and survival in Idiopathic Pulmonary Fibrosis
A Cohort study

Lamas DJ et al. Am J Respir Crit Care Med 2011; 184: 842

- Our results suggest that the recognition (or suspicion) of IPF should prompt early referral to a

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

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

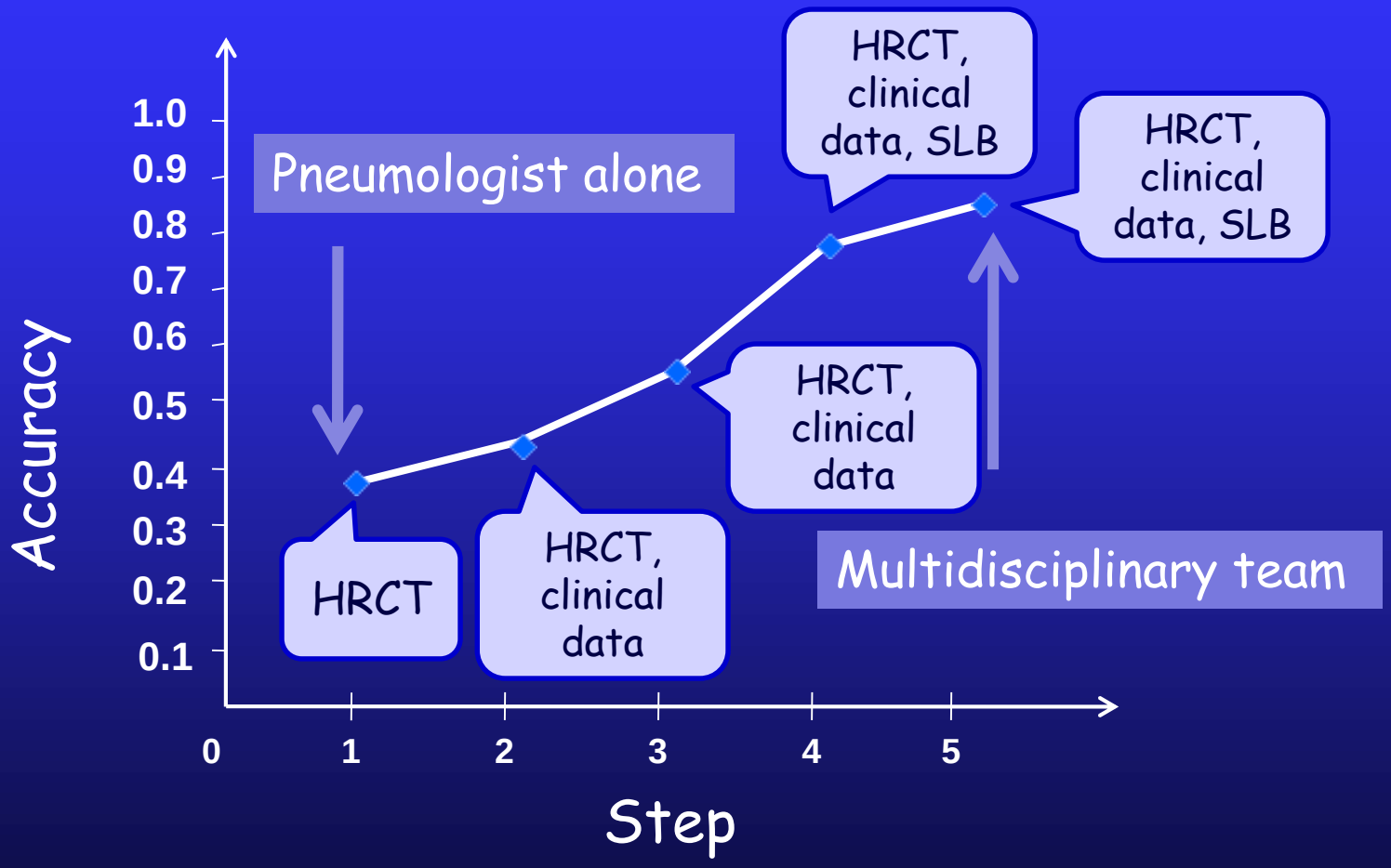
Clinical	*Radiology*	*Pathology*
• History • Physical • Laboratory • PFTs	• Chest X-ray • HRCT	• Surgical lung biopsy
Primary care physicians	Pulmonologists	Radiologists	Pathologists

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

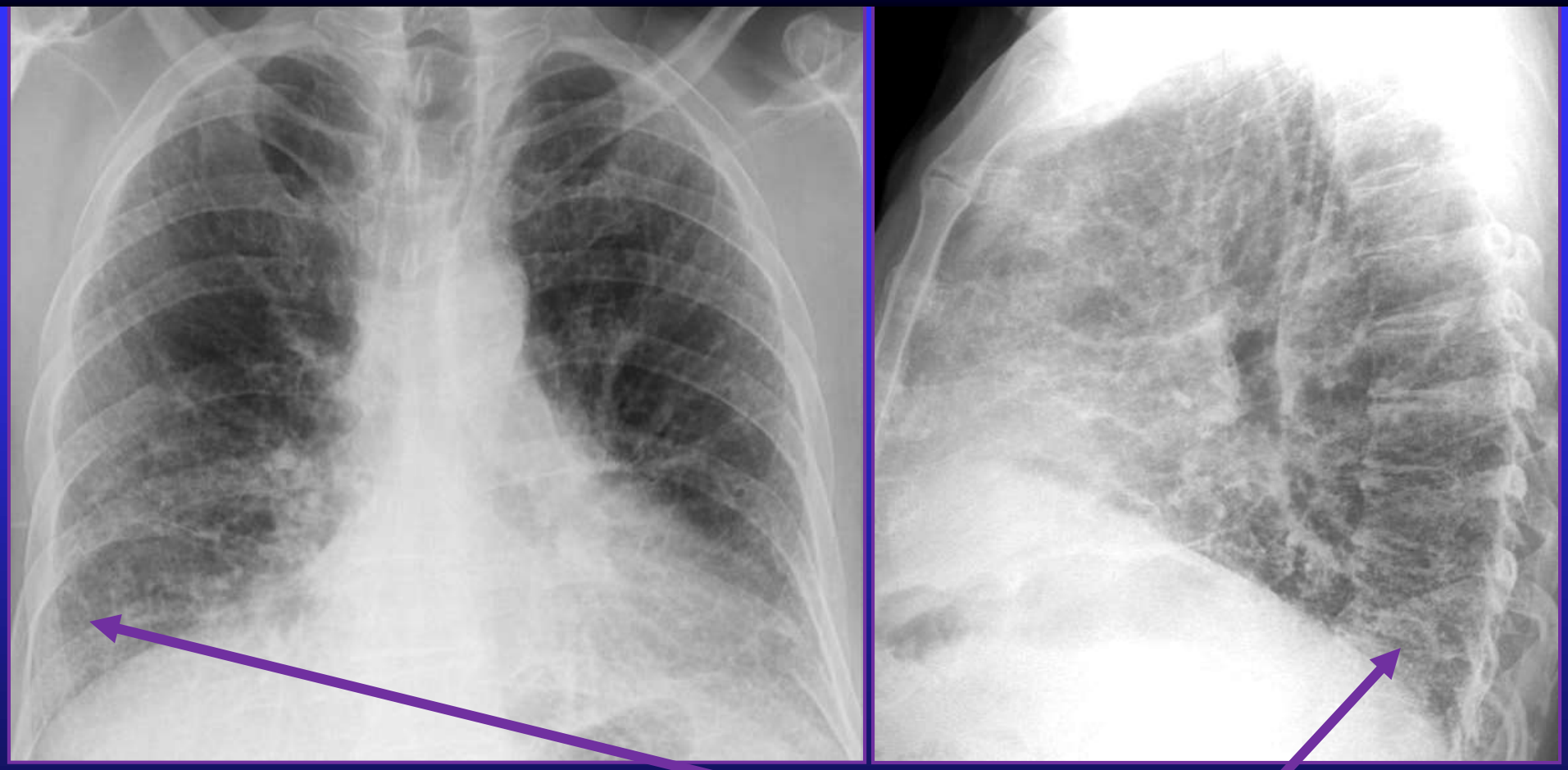
a) the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy

a) specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy"

The major and minor criteria proposed in the 2000 ATS/ERS Consensus Statement have been eliminated

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

Chest radiograph in IPF



A normal chest x-ray does not exclude IPF

Demystifying Idiopathic Interstitial Pneumonia

Harold R. Collard, MD; Talmadge E. King, Jr, MD *Arch Intern Med. 2003;163:17-29*

exercise Pa_{O_2}). The most useful clinical tool for distinguishing between subclasses is high-resolution computed tomography (HRCT) of the chest. The diagnostic utility of HRCT

Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis

Cordier JF, Cottin V Eur Respir J 2013; in press

- IPF is a relatively recent disease linked to the tobacco epidemics
- IPF is a disease of ageing
- Earlier diagnosis of IPF could be obtained by recognizing the value of velcro crackles

  and
- by promoting the screening for IPF as a by-product of low-dose CT screening for lung cancer

Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis

Cordier JF, Cottin V Eur Respir J 2013; in press

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.

fibrosis, suggesting that the development of ILD may result from an interaction between age, smoking and genetic factors.

Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis

Cordier JF, Cottin V Eur Respir J 2013; in press

- 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

Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis

Cordier JF, Cottin V Eur Respir J 2013; in press

The mean duration between first symptoms and referral to a tertiary care center is longer than 2 years and is associated with a higher risk of death independent of disease severity.

Lamas DJ et al. Am J Respir Crit Care Med 2011; 184: 842

effective drug therapy, it has become relevant since recent studies that demonstrated a reduction in the rate of decline of FVC using pirfenidone and nintedanib

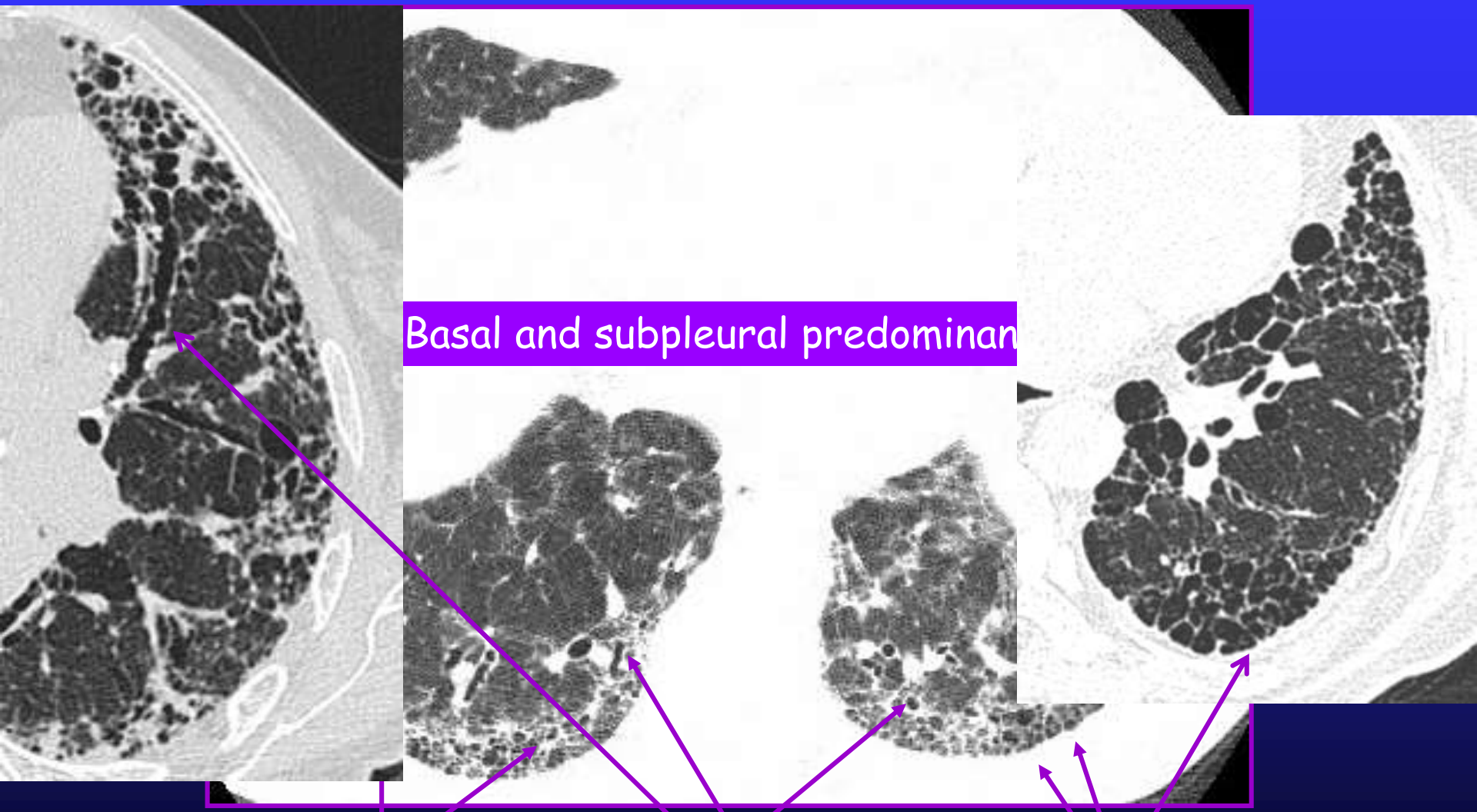
Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis

Cordier JF, Cottin V Eur Respir J 2013; in press

We consider that presently only two approaches could realistically allow an earlier diagnosis of IPF:

Crackles are almost constant in patients with IPF. Although found in other ILDs and not specific for IPF, velcro crackles must prompt a thorough diagnostic process, including HRCT

Classic IPF HRCT



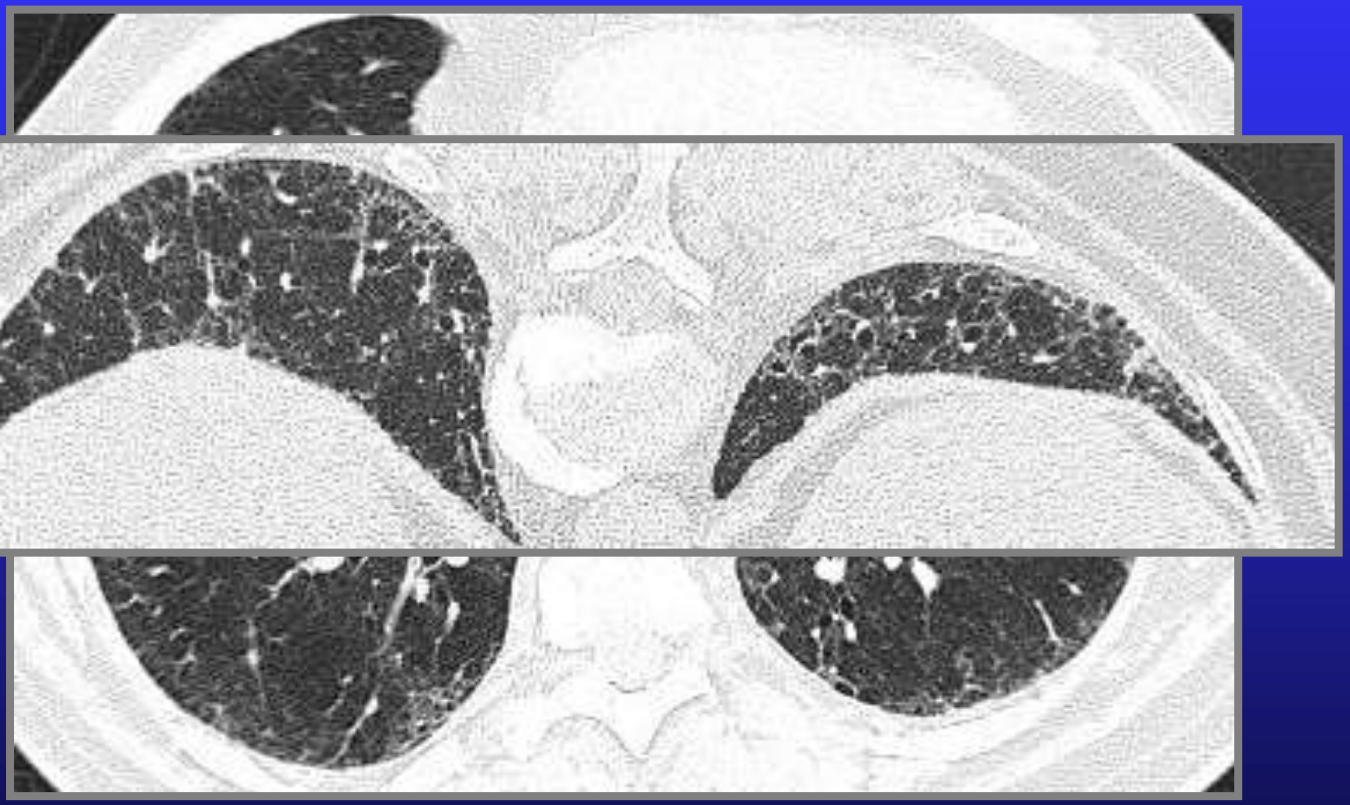
HRCT diagnosis of IPF

IPF Findings	Consider Alternate Diagnosis
UIP pattern (all four): Sub-pleural, basal predominance Reticular abnormality Honeycombing with or without traction bronchiectasis Absence of features listen as inconsistent with UIP	*Possible UIP pattern (all three):* Subpleural, basal predominance Reticular abnormality Absence of features listen as inconsistent with UIP

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

ATS/ERS. *Am J Respir Crit Care Med*. 2000;161:646-664.

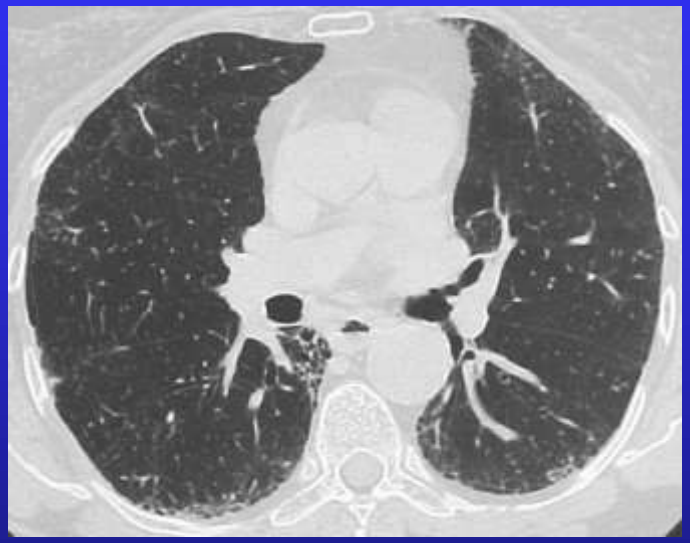
Use of prone Imaging



UIP: progression of fibrosis on CT

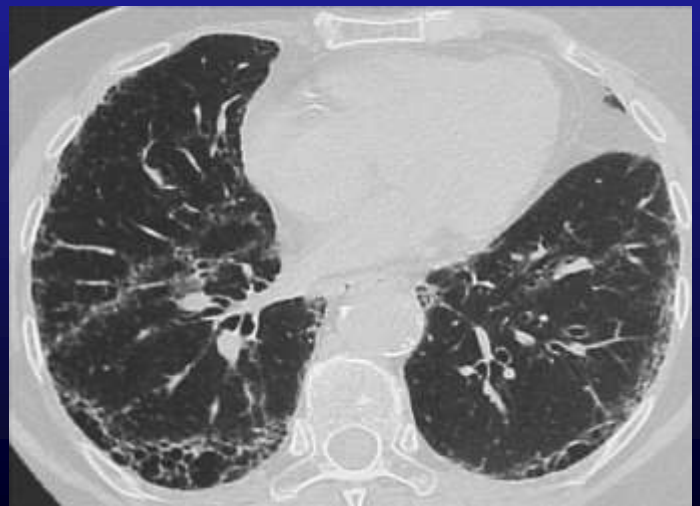
Early:

Reticular



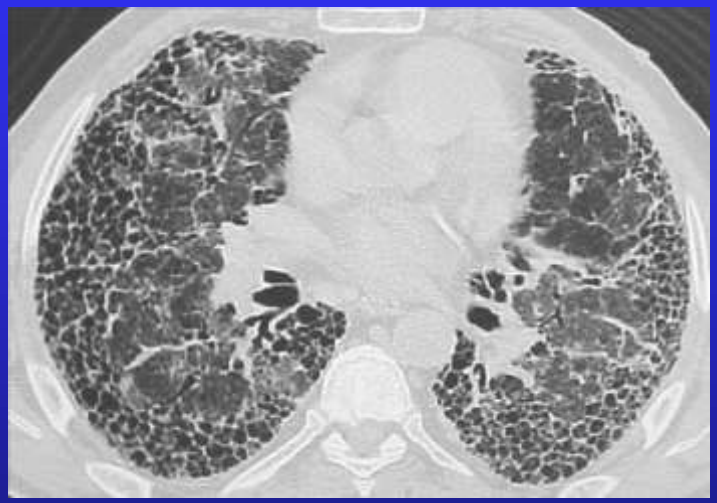
Midcourse:

Subpleural honeycombing



Late:

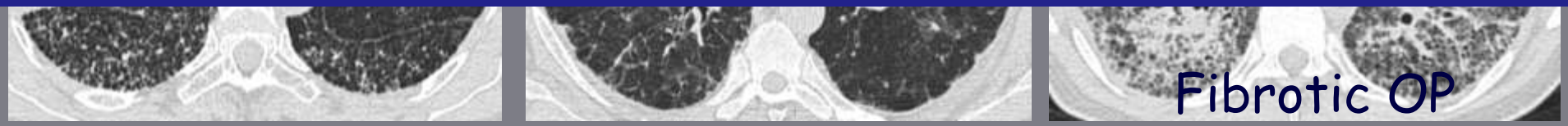
Diffuse honeycombing



Inconsistent with UIP pattern (any of the seven):

- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive groud 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**



Key conclusion

- 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

Atypical HRCT appearances in IPF

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

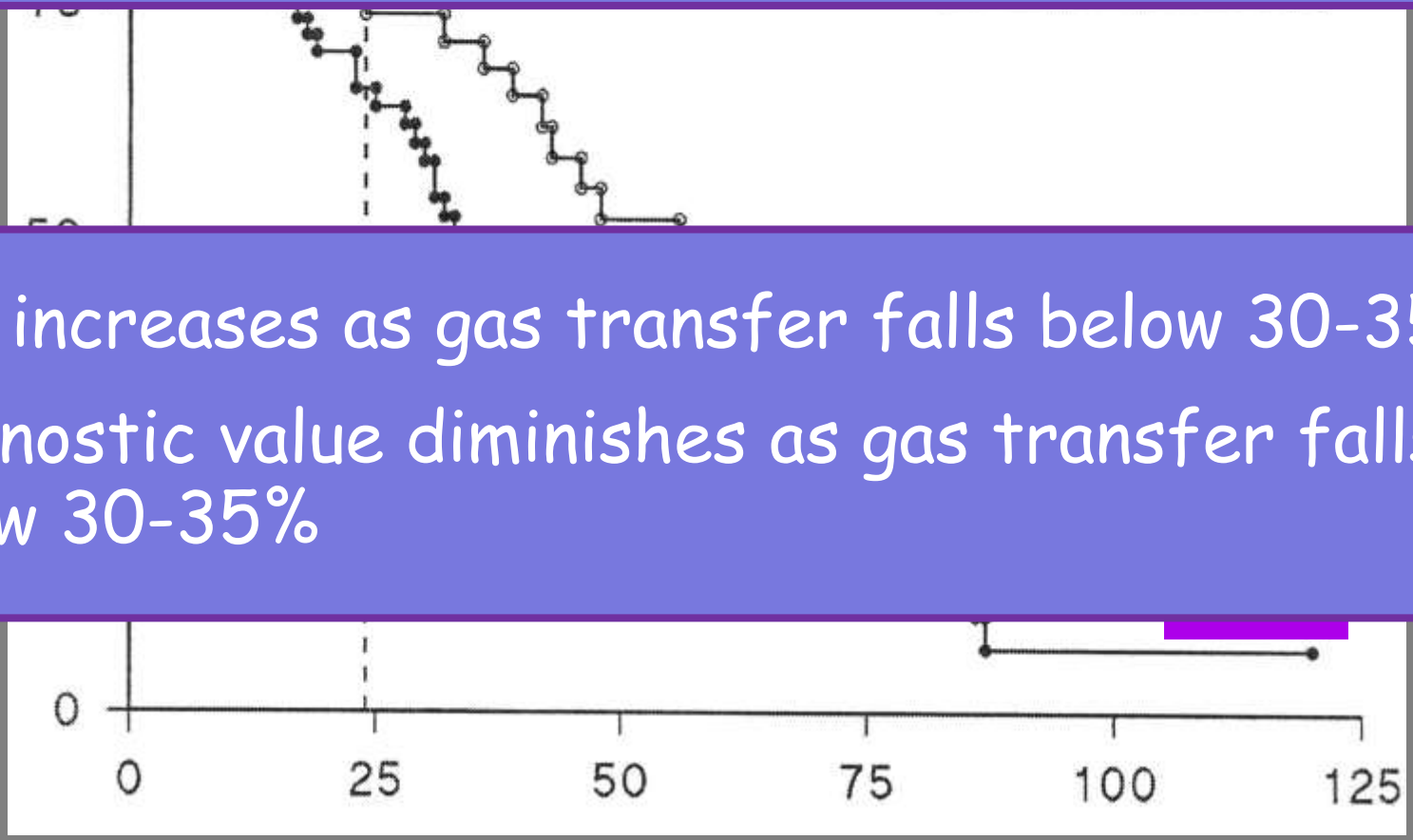
***Am J Respir Crit Care Med* 2011; 183: 788-824**

Probable UIP pattern	Possible UIP pattern (All three criteria)	Not UIP pattern (any of the six criteria)
❖Evidence of marked fibrosis/architectural distortion, ± honeycombing	❖Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation	❖ Hyaline membranes
		❖ Organizing pneumonia
❖ Absence of either patchy involvement or fibroblastic foci, but not both	❖Absence of other criteria for UIP	❖ Granulomas
		❖ Marked interstitial inflammatory cell infiltrate away from honeycombing
❖ Absence of features against a diagnosis of UIP suggesting an alternate diagnosis OR	❖Absence of features against a diagnosis of UIP suggesting an alternate diagnosis	❖ Predominant airways centered changes
		❖ Other features suggestive of an alternate diagnosis
❖ Honeycomb changes only		

Risks of biopsy

- 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%

Latsi PI et al. *Am J Respir Crit Care Med* 2003; 168: 531

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 chonic HP; prominent lymphocitosis (>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)

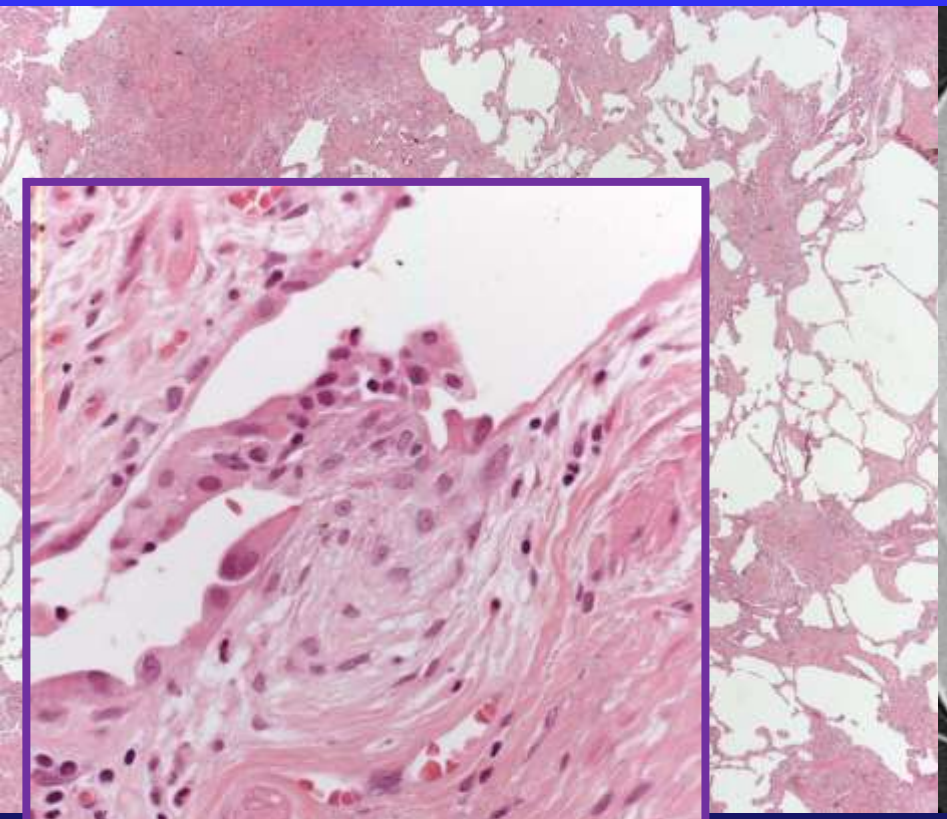
***Am J Respir Crit Care Med* 2011; 183: 788-824**

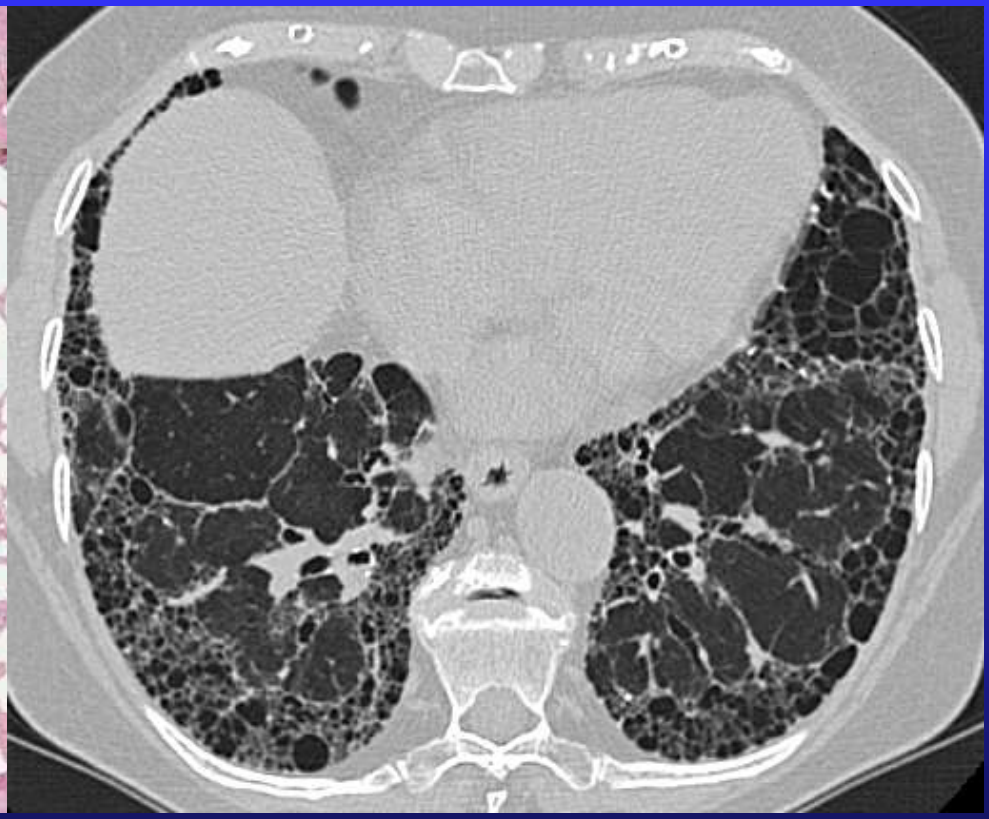
Should TBB be used in the evaluation of suspected IPF?

In cases requiring histopathology, the specifity 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**

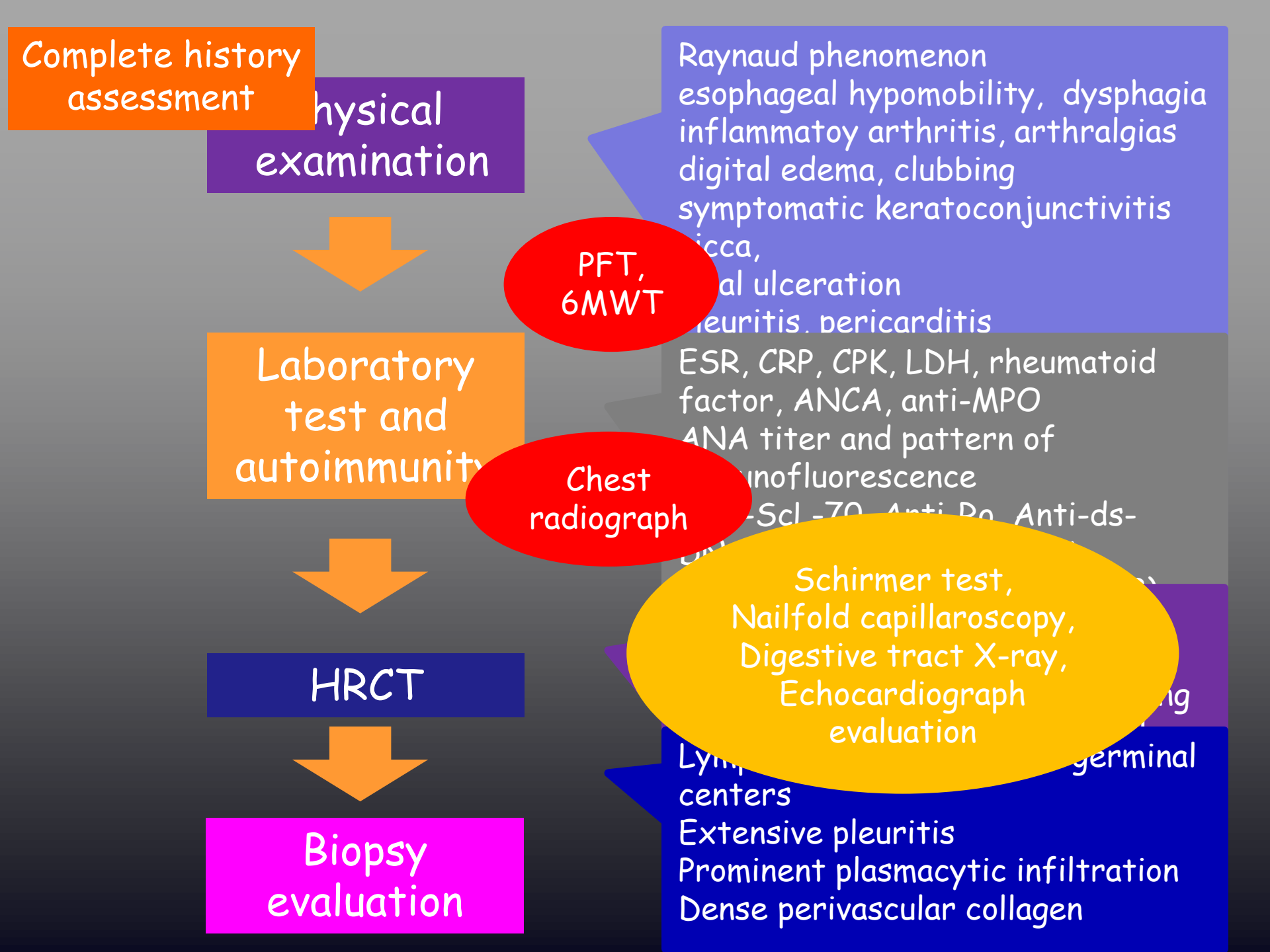
Serologic tests can help exclude other conditions

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
hysical examination
Laboratory test and autoimmunity
HRCT
Biopsy evaluation
PFT, 6MWT
Chest radiograph
Schirmer test, Nailfold capillaroscopy, Digestive tract X-ray, Echocardiograph evaluation
Raynaud phenomenon
esophageal hypomobility, dysphagia
inflammatoy arthritis, arthralgias
digital edema, clubbing
symptomatic keratoconjunctivitis
icca,
al ulceration
leuritis, pericarditis
ESR, CRP, CPK, LDH, rheumatoid factor, ANCA, anti-MPO
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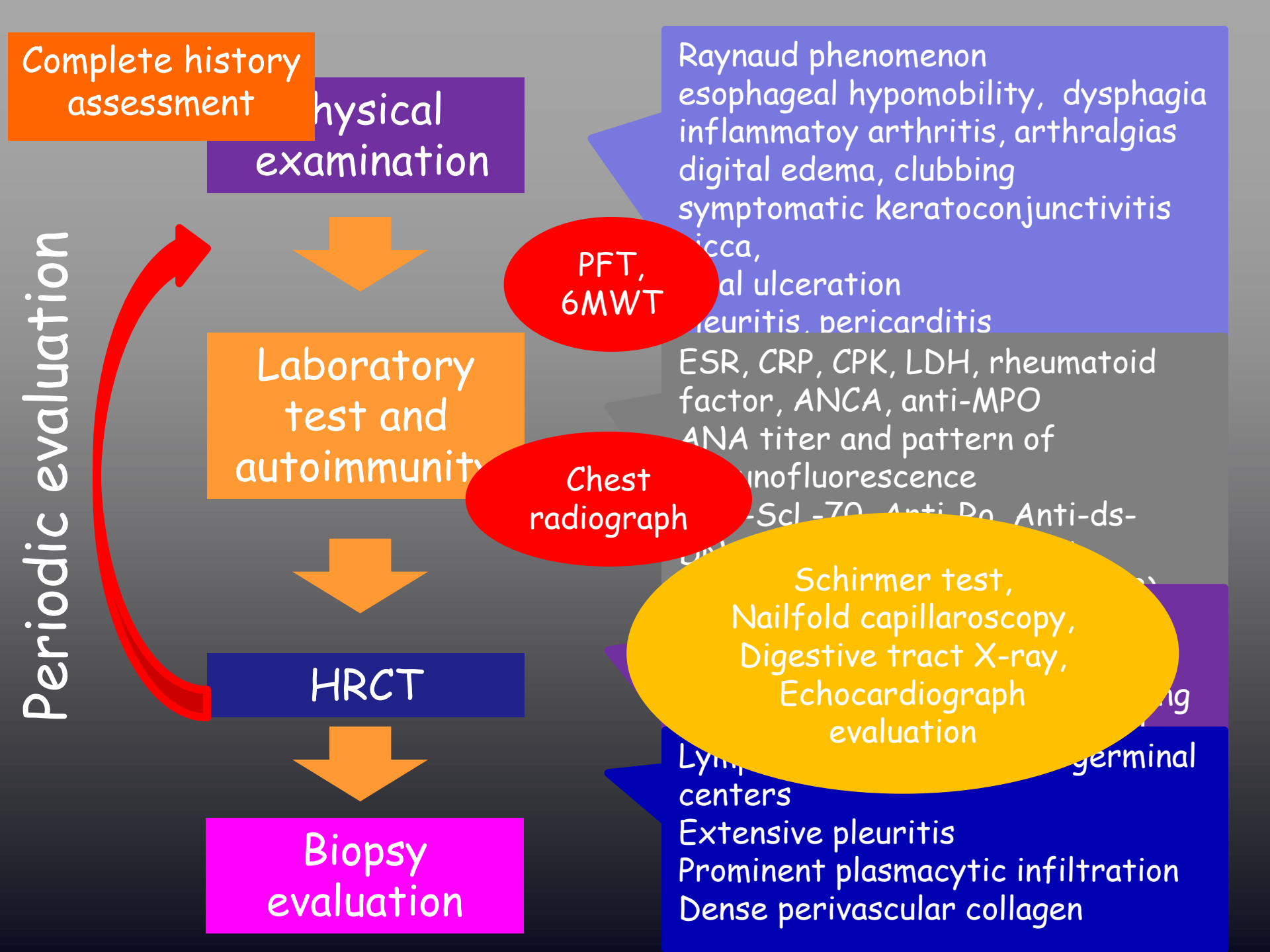
ng
germinal centers
Extensive pleuritis
Prominent plasmacytic infiltration
Dense perivascular collagen

What's the problem?

- 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?


Complete history assessment
hysical examination
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HRCT
Biopsy evaluation
Periodic evaluation
PFT, 6MWT
Chest radiograph
Schirmer test, Nailfold capillaroscopy, Digestive tract X-ray, Echocardiograph evaluation
Raynaud phenomenon
esophageal hypomobility, dysphagia
inflammatoy arthritis, arthralgias
digital edema, clubbing
symptomatic keratoconjunctivitis
icca,
al ulceration
leuritis, pericarditis
ESR, CRP, CPK, LDH, rheumatoid factor, ANCA, anti-MPO
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Extensive pleuritis
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Chronic EAA

Churg A et al. Am J Surg Pathol 2006;30:201-8

- Traditionally divided on clinical grounds into acute, subacute, and chronic stages. Most biopsy specimens come from patients in the subacute stage.

- **Pathologic features in chronic, ie, fibrotic stage (n=13) showed 3 patterns:**

  1) predominantly peripheral fibrosis in a patchy pattern with architectural distortion and fibroblast foci resembling, microscopically UIP;

  2) relatively homogeneous linear fibrosis resembling fibrotic NSIP;

  3) irregular predominantly peribronchiolar fibrosis. In some instances, mixtures of the UIP-like and peribronchiolar patterns were found.

Chronic EAA

Churg A et al. Am J Surg Pathol 2006;30:201-8

- The presence of isolated giant cells, poorly formed granulomas, or Schaumann bodies is crucial to arriving at the correct diagnosis, and the finding of peribronchiolar fibrosis may be helpful.
- Despite the presence of extensive fibrosis, some patients responded to removal from exposure and steroid therapy

Chronic hypersensitivity pneumonitis: differentiation from UIP and NSIP using thin-section CT

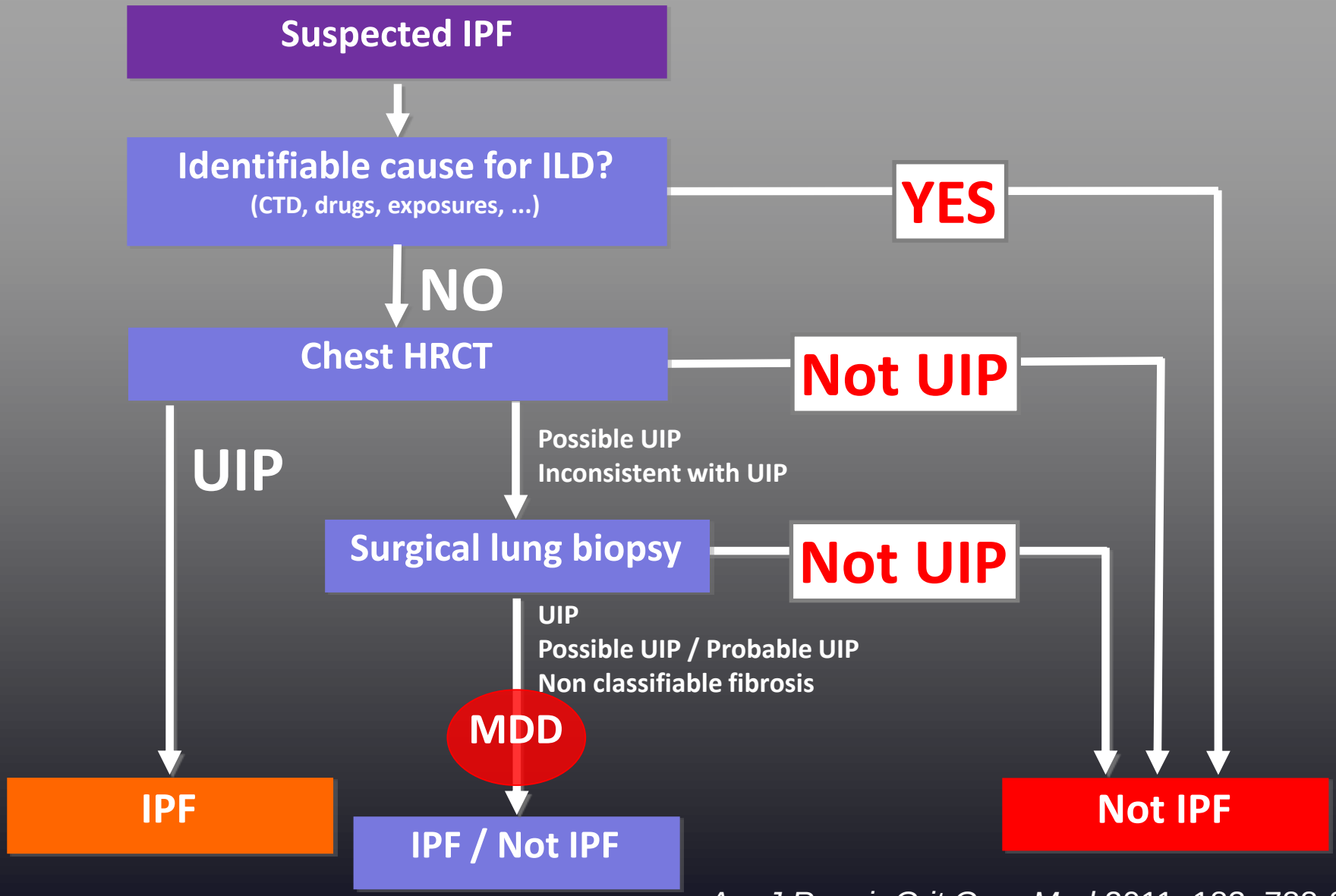
Silva C. Radiology 2008; 246: 288

HRCT findings allow confident distinction of chronic HP from IPF and NSIP approximately 50% of the time

Diagnosis of HP at CT prompts a thorough clinical history to determine inciting antigens and removal of the pt from the source

The HRCT findings most helpful in differentiating chronic HP from IPF and NSIP are lobular areas with decreased attenuation and vascularity, centrilobular nodules and lack of lower zone predominance of abnormalities

Diagnostic algorithm for IPF



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

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

Conclusions

- 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!