Challenge du diagnostic de FPI et autres PII

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Disclosure of interests

Member of European and French Advisory boards on IPF (supported by Intermune)

Member of International and French Advisory boards on IPF (supported by Bohringer-Ingelheim)

Investigator (BIBF, CAPACITY, BUILD 1 and 3, MUSIC etc…) or member of steering committes on IPF trials (INSPIRE, CAPACITY, BUILD3)

2 essential forewords

Lead-in

To be or not to be IPF*?

Is there anything in between?

*William Shakespeare is among my top four writers (with Homere; Dante Aligheri and Marcel Proust)

Summary

Objective of guidelines

Emblematic clinical situations to cope with

Some statistics about guidelines

→ experience with multidisciplinary diagnosis in Avicenne hospital

Impact of treatment recent knowledge on « IPF diagnosis paradigm »

New questions

Introduction

Despite or thanks to their limitations (mind to ban any *revisionism*!), IPF guidelines* have highlighted many practical interrogations. Even errors led to further advances

Thus, this presentation is not an indictment directed against IPF guidelines* but rather an implementation and a try to foresee what will happen next in a still ongoing long history

Our inspiration stemmed from the excellent paper from Xaubet et al**, some national guidelines and … some personal experience

Raghu AJRCCM 2011; Xaubet SVDLD 2013***

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Review of idiopathic pulmonary fibrosis diagnosis and management recommendations in Europe

A. Xaubet[1], J. Behr[2], E. Bendstrup[3], V. Cottin[4], N. Hirani[5], C. M. Kähler[6], C.M. Sköld[7]

SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2013; 30; 249-261

An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

William D. Travis, Ulrich Costabel, David M. Hansell, Talmadge E. King, Jr., David A. Lynch, Andrew G. Nicholson, Christopher J. Ryerson, Jay H. Ryu, Moise´s Selman, Athol U. Wells, Jurgen Behr, Demosthenes Bouros, Kevin K. Brown, Thomas V. Colby, Harold R. Collard, Carlos Robalo Cordeiro, Vincent Cottin, Bruno Crestani, Marjolein Drent, Rosalind F. Dudden, Jim Egan, Kevin Flaherty, Cory Hogaboam, Yoshikazu Inoue, Takeshi Johkoh, Dong Soon Kim, Masanori Kitaichi, James Loyd, Fernando J. Martinez, Jeffrey Myers, Shandra Protzko, Ganesh Raghu, Luca Richeldi, Nicola Sverzellati, Jeffrey Swigris, and Dominique Valeyre
on behalf of the ATS/ERS
Committee on Idiopathic Interstitial Pneumonias

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS
APPROVED BY THE ATS BOARD OF DIRECTORS, JUNE 2013, AND BY THE ERS STEERING COMMITTEE, MARCH 2013

Am J Respir Crit Care Med Vol 188, Iss. 6, pp 733–748, Sep 15, 2013

Philosophie générale des modifications

- Conforte les grandes innovations de 2002
- Renforce la possibilité de diagnostic sans recourir à la biopsie pulmonaire
- 3 cadres:
  - les grands cadres de 2002 (FPI; PNIS etc…)
  - Les PII rares (FEPP, LIP)
  - Les PII inclassables
- Soulève la question des PII difficiles à classées

  → intérêt de la classification comportementale

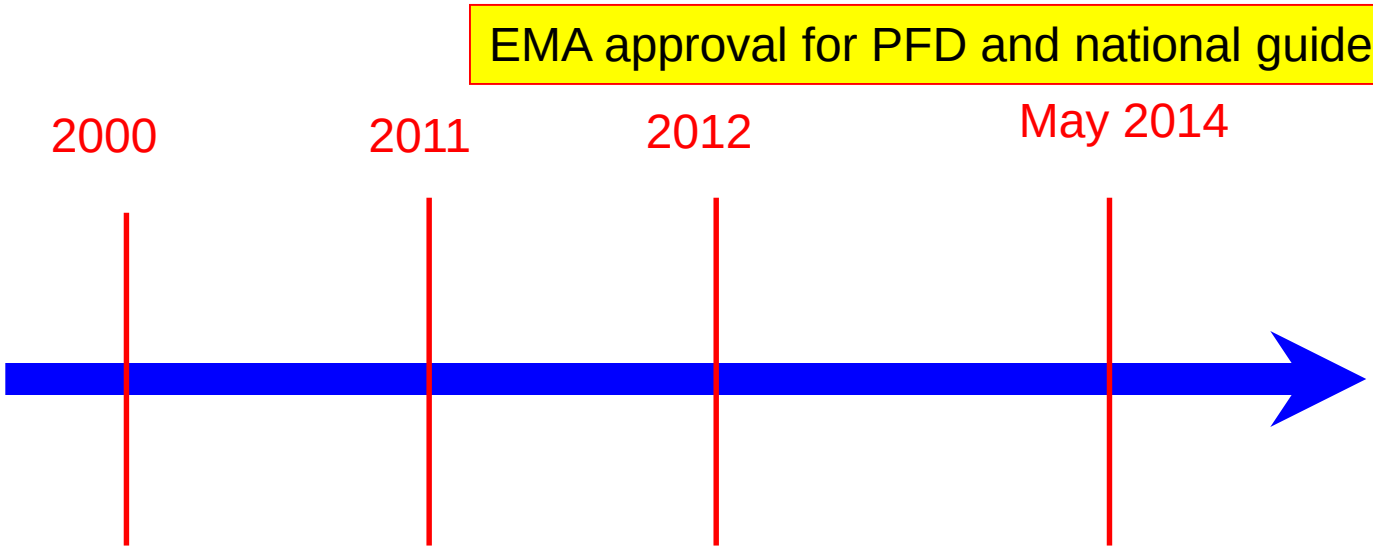
Modifications de la classification 2013

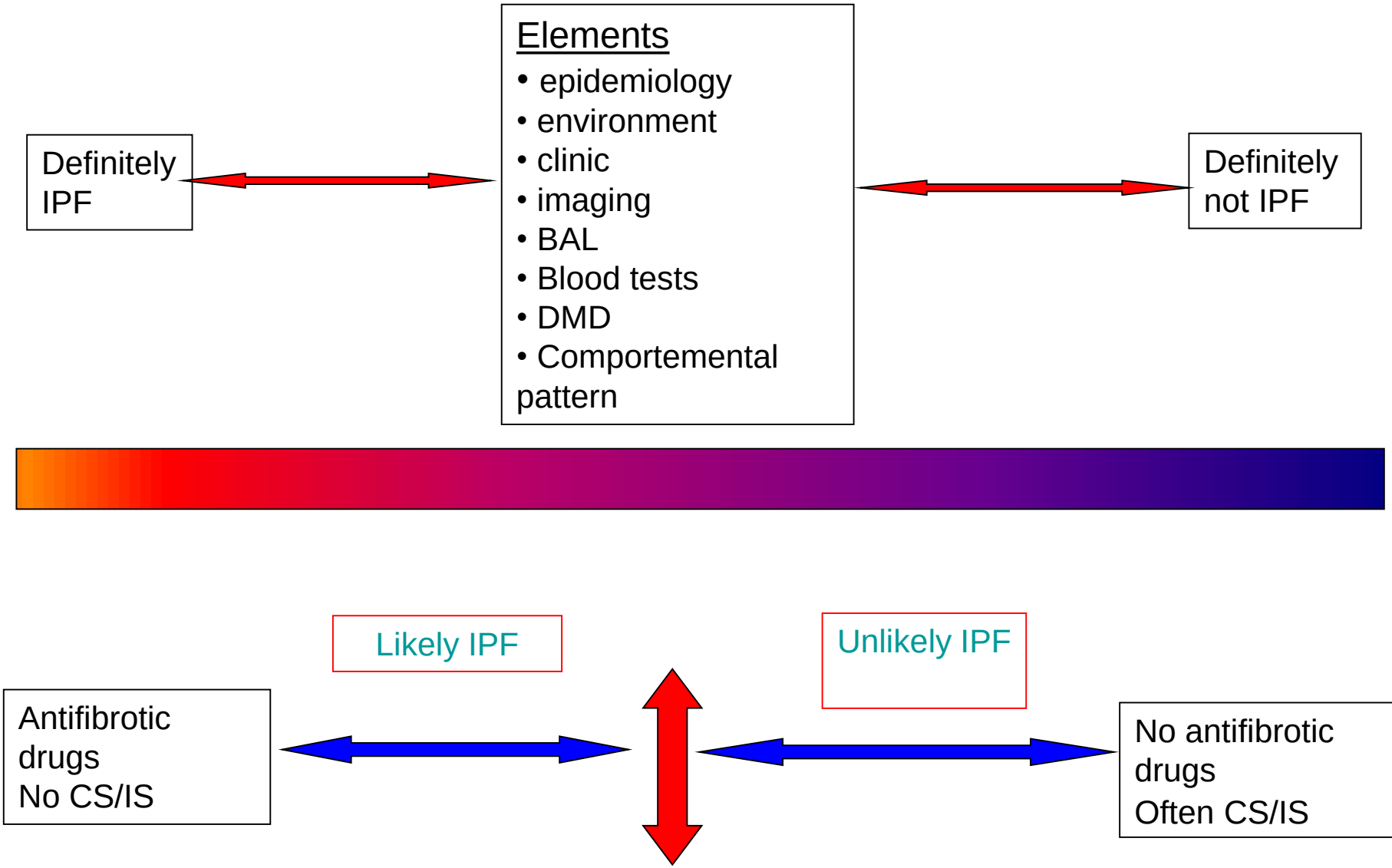
- Idiopathic NSIP→ entité à part entière (plus provisoire)
- BR-ILD → diagnostic clinique non invasif
- EA des PII (FPI et PINS) mieux définie
- PII non classables (certaines=combinaisons de x patterns)
- PII rares:
  - Fibro-elastose pleuro-pulmonaire
  - LIP
  - PO fibrineuses aigues
  - PII bronchocentrées
- Nouvelles classifications
  - Chroniques fibrosantes/liées au tabac/aigues-subaigues
  - Selon le comportement évolutif clinique

Grandes catégories de PII

Catégories	Diagnostic C-R-P	Pattern morphologique
PII chronique fibrosante	FPI NSPI*i*	UIP NSIP
PII liée au tabac	RB-ILD DIP	BR DIP
PII (sub)aiguës	COP AIP	OP DAD

Impact of treatment recent knowledge on IPF diagnosis paradigm





D Valeyre ERR 2016

Diagnostic Criteria

The diagnosis of IPF requires the following:

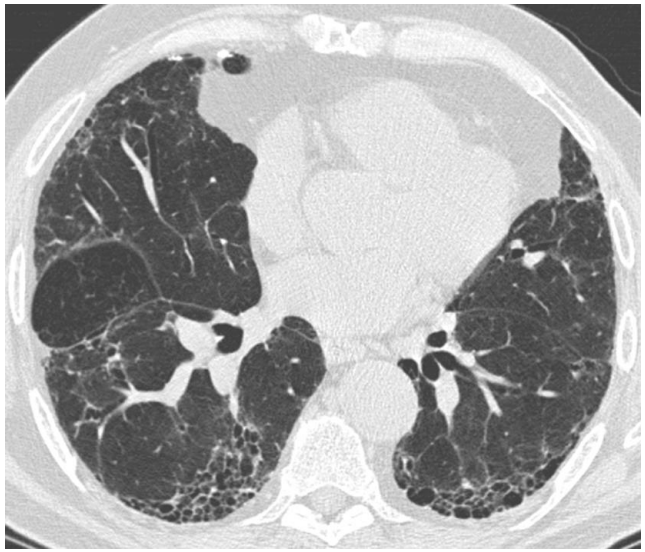
1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (*see* Table 4).
3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy (*see* Tables 5 and 6).

Raghu AJRCCM 2011

TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• 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)

Definition of abbreviation: UIP = usual interstitial pneumonia.



Courtesy Pr Michel Brauner

Raghu AJRCCM 2011

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

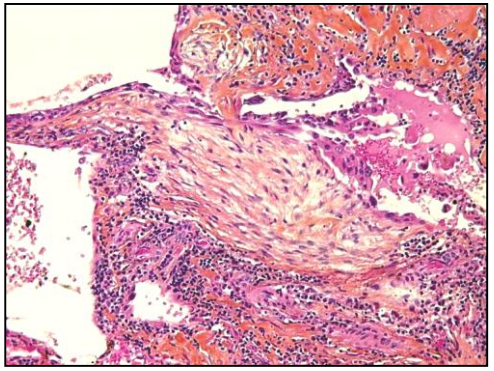
UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

Definition of abbreviations: HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.

* Can be associated with acute exacerbation of idiopathic pumonary fibrosis.

† An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.

‡ This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.



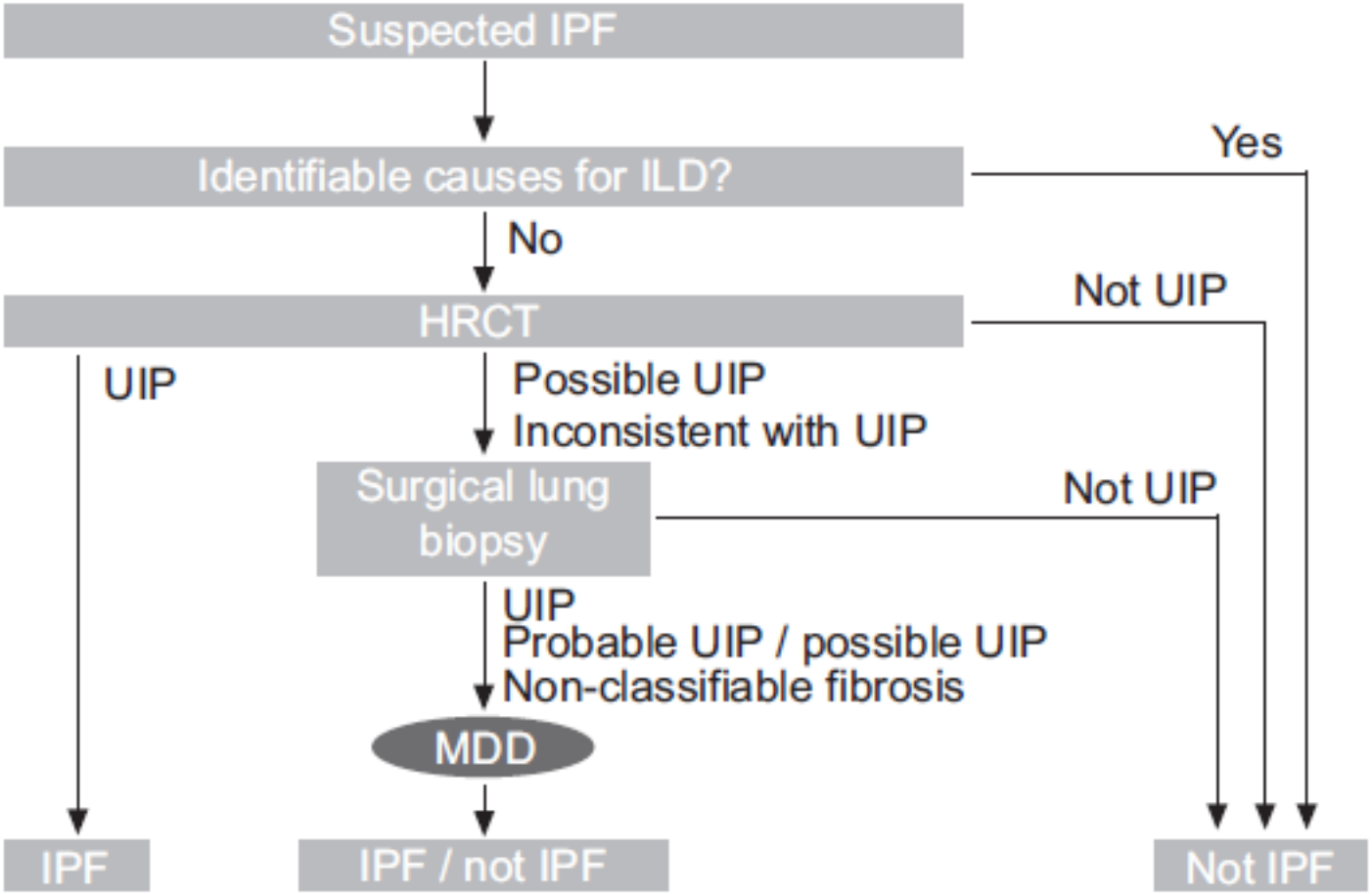
Courtesy Dr Marianne Kambouchner

Raghu AJRCCM 2011

TABLE 6. COMBINATION OF HIGH-RESOLUTION COMPUTED TOMOGRAPHY AND SURGICAL LUNG BIOPSY FOR THE DIAGNOSIS OF IPF (REQUIRES MULTIDISCIPLINARY DISCUSSION)

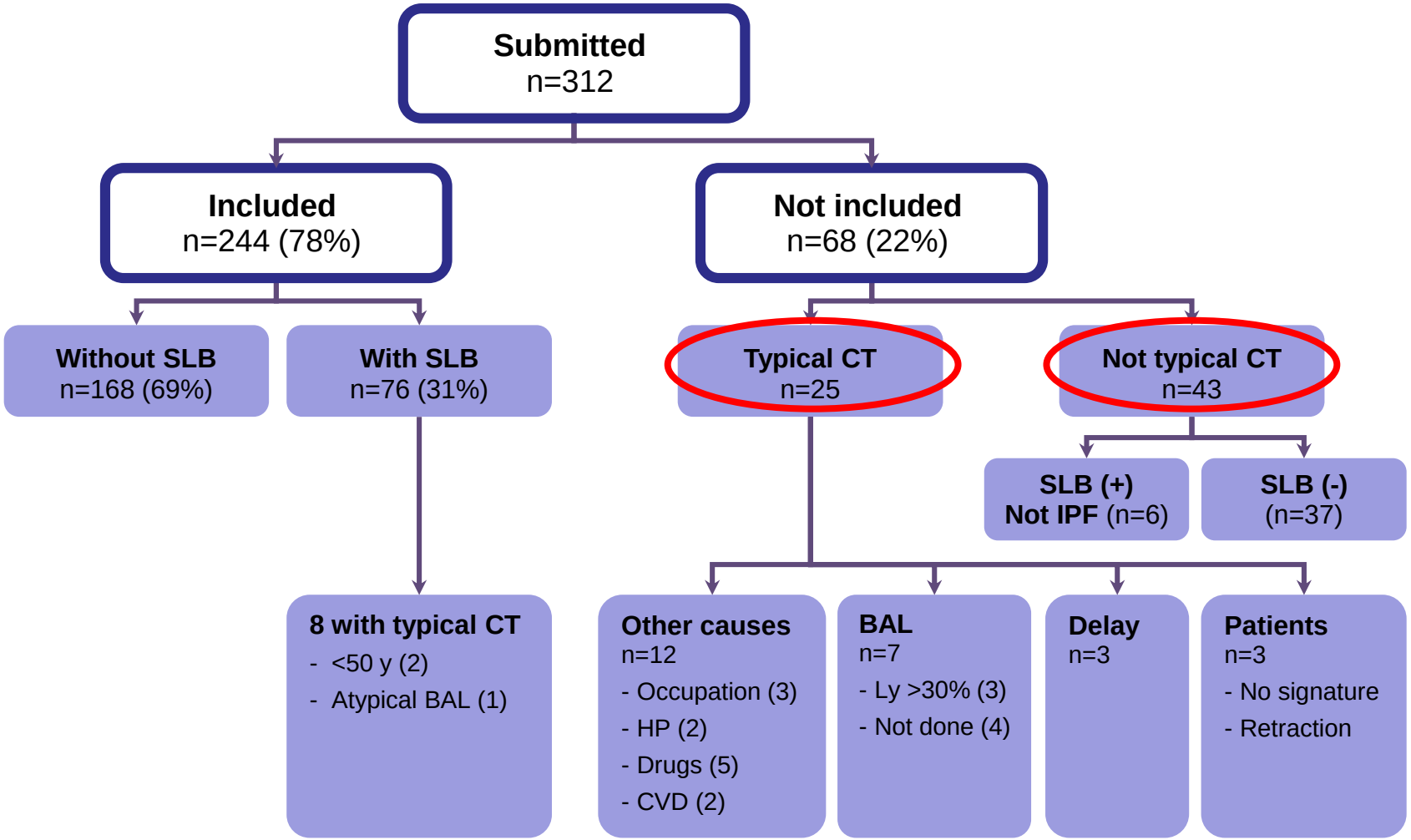
HRCT Pattern*	Surgical Lung Biopsy Pattern* (When Performed)	Diagnosis of IPF?†
UIP	**UIP** **Probable UIP** **Possible UIP** **Nonclassifiable fibrosis**‡	**YES**
	Not UIP	No
Possible UIP	**UIP** **Probable UIP**	**YES**
	Possible UIP Nonclassifiable fibrosis	Probable§
	Not UIP	No
Inconsistent with UIP	UIP	Possible§
	Probable UIP Possible UIP Nonclassifiable fibrosis Not UIP	No

Raghu AJRCCM 2011



Raghu AJRCCM 2011 revised by AU Wells ERR 2013

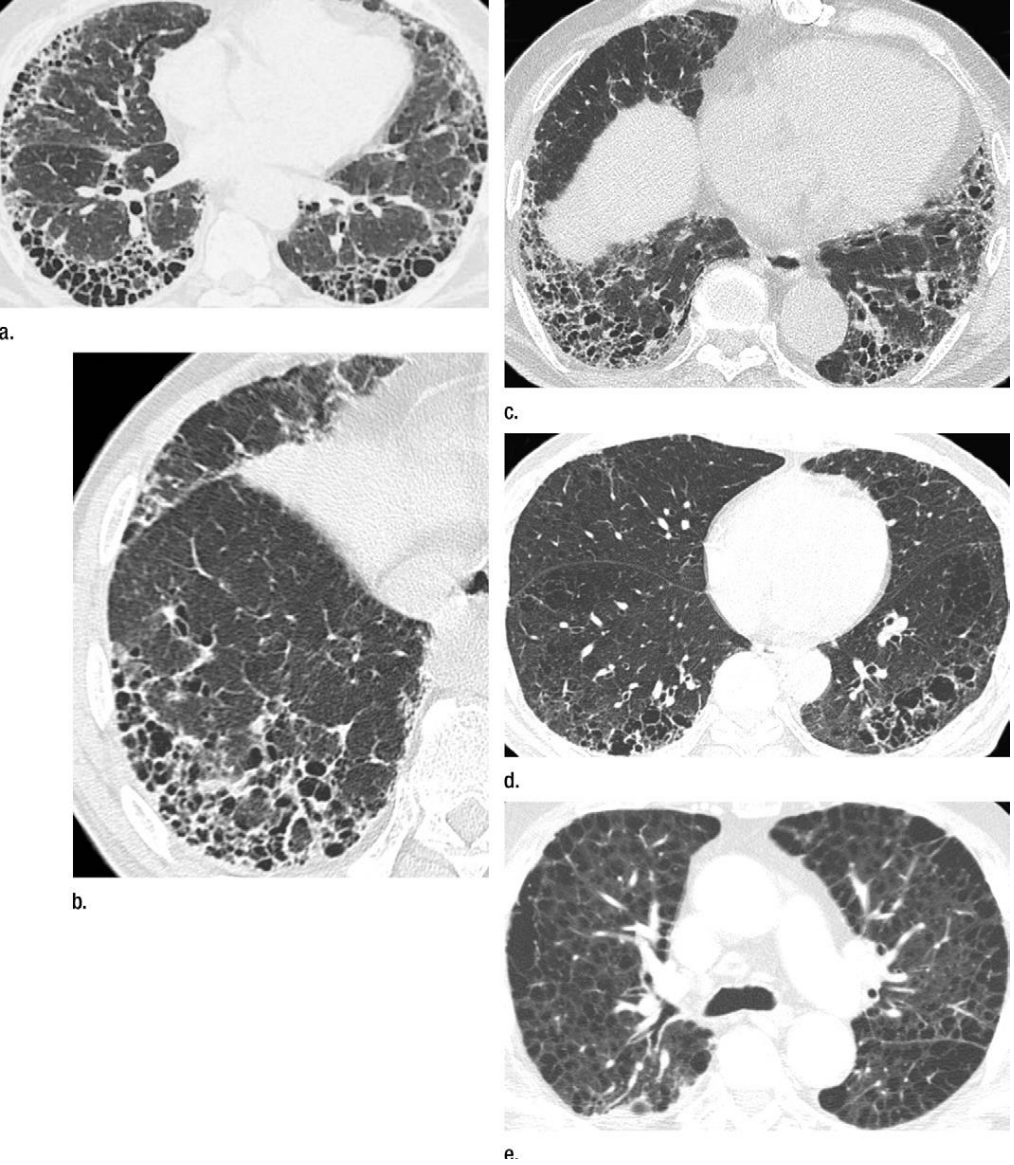
COFI – Inclusions



FPI vs asbestose vs FPI chez exposé à l'amiante

- Asbestose typique*
- Véritable FPI chez travailleurs exposés**
- FPI impactée par exposition à l'amiante***

Roggli 2010; Gaensler 1991; Lee 2015



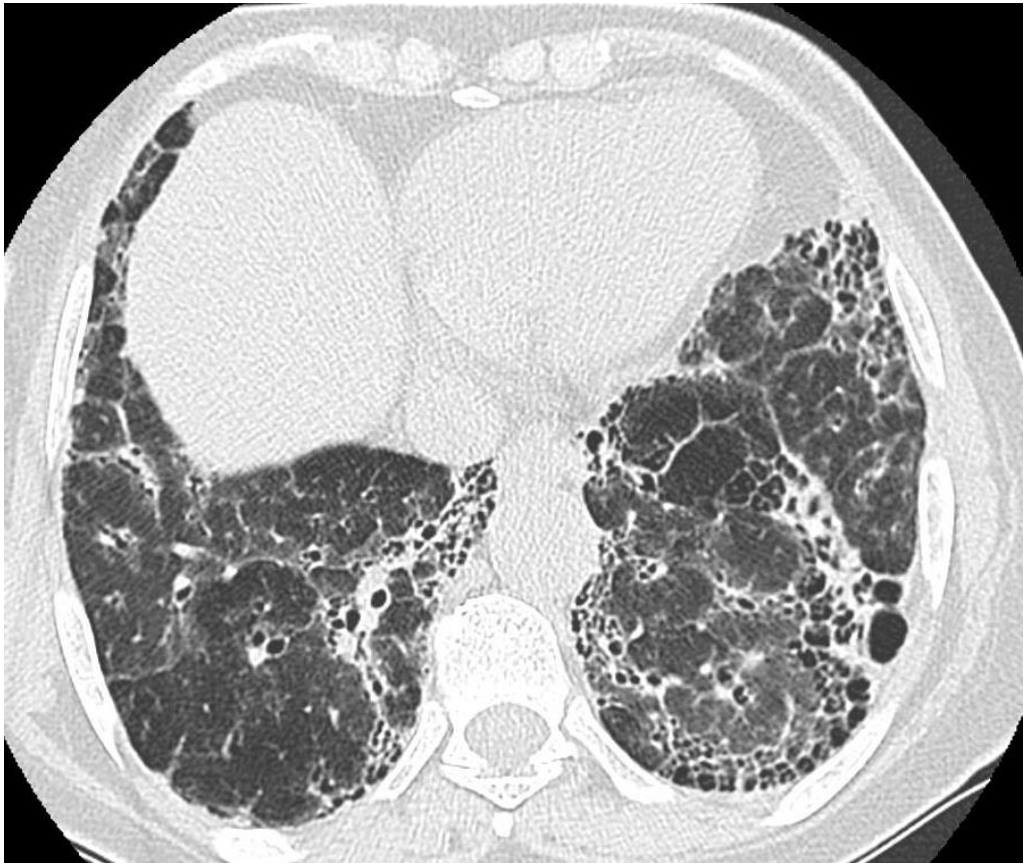
Identification of HC at CT is subjective and disagreement is largely caused by conditions that mimic HC

Watadani T. ***Radiology:*** Volume 266: Number 3—March 2013

Figure 1: Thin-section CT images of representative reference standard cases of honeycombing. (a) Score of 5: Clustered cysts with relatively thick walls in the subpleural regions. This image was scored as a 5 by 39 (91%) of 43 observers in reading sessions. (b) Score of 4: Clustered cysts in both subpleural and peribronchovascular distribution. This image was scored as a 4 in 25 (58%) of 43 reading sessions. (c) Score of 3: Traction bronchiectasis and small areas of honeycomblike multicystic space in bilateral subpleural regions. (d) Score of 2: Clustered thin-walled cysts apart from the chest wall suggest complicated emphysema, but CT images in the upper lungs were unavailable. This image was scored as a 3 in 27 (63%) of 43 reading sessions. (e) Score of 1: This image was scored as a 1 by 41 (95%) 43 observers in reading sessions.

Risk for overdiagnosis of IPF

Male, 65, ex-smoker
Possible exposure to domestic molds
No precipitins
CT: UIP pattern vs inconsistent with UIP pattern
BAL: 15% lymphocytes, CD4/8=1
Surgical biopsy: HP-UIP



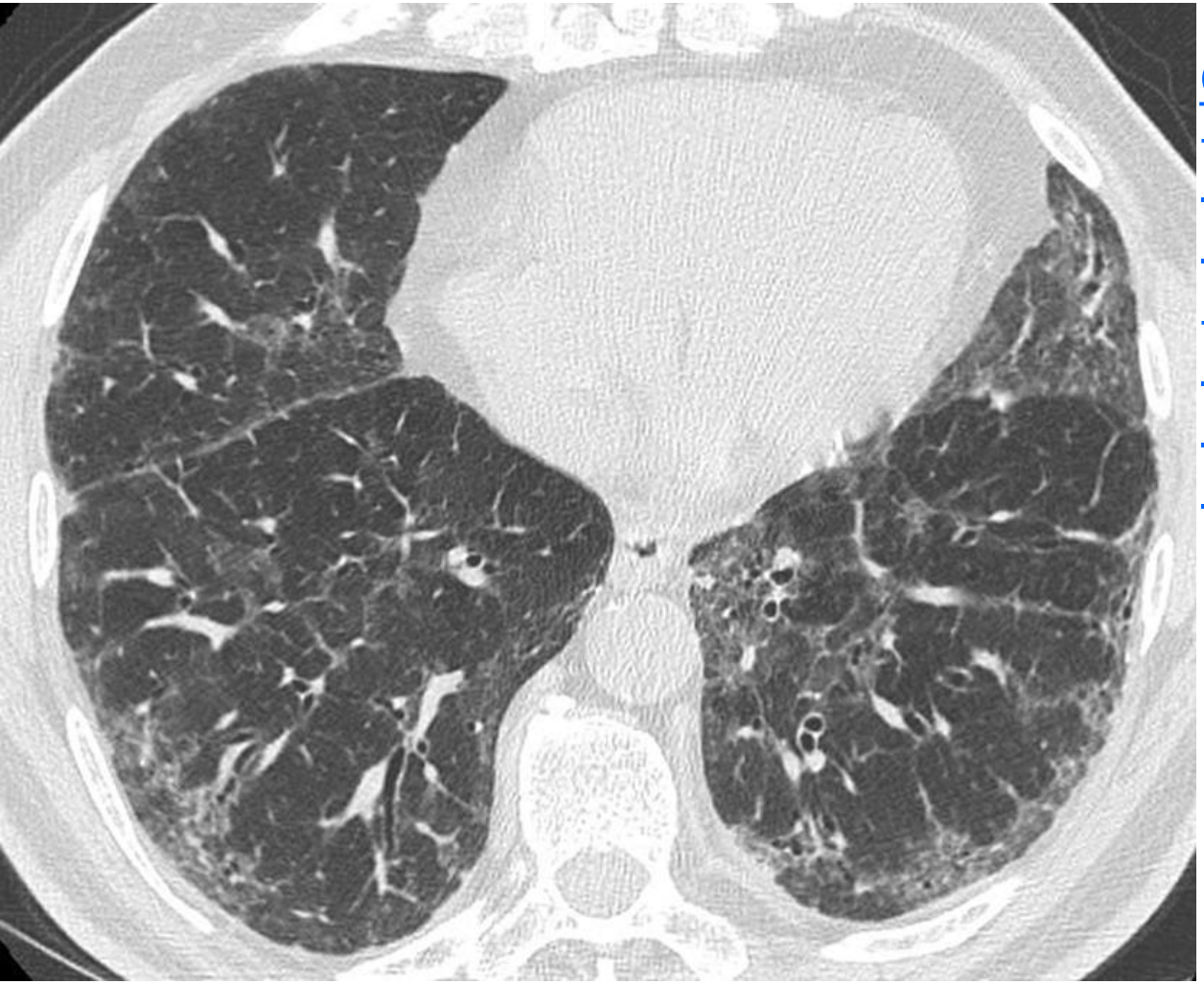
Diagnosis
MDD: fibrosing HP of unknown origin

- Need for search of precipitins and BAL in case of doubt according to exposures or CT
- Need search of CVD at presentation and during follow up (up to10% of UIP with CVD at 5 yr)

Morell Lancet RM 2013; Kono PLOS ONE 2014; Morris JCTS 2014

Risk of underdiagnostic:

how to cope with possible UIP at CT?



Clinical context

- Fortuitous discovery
- Male, 75, ex smoker
- no exposure
- no systemic disease
- FVC=80%; DLCO=70%
- no SLB
- Progression 12 mo later

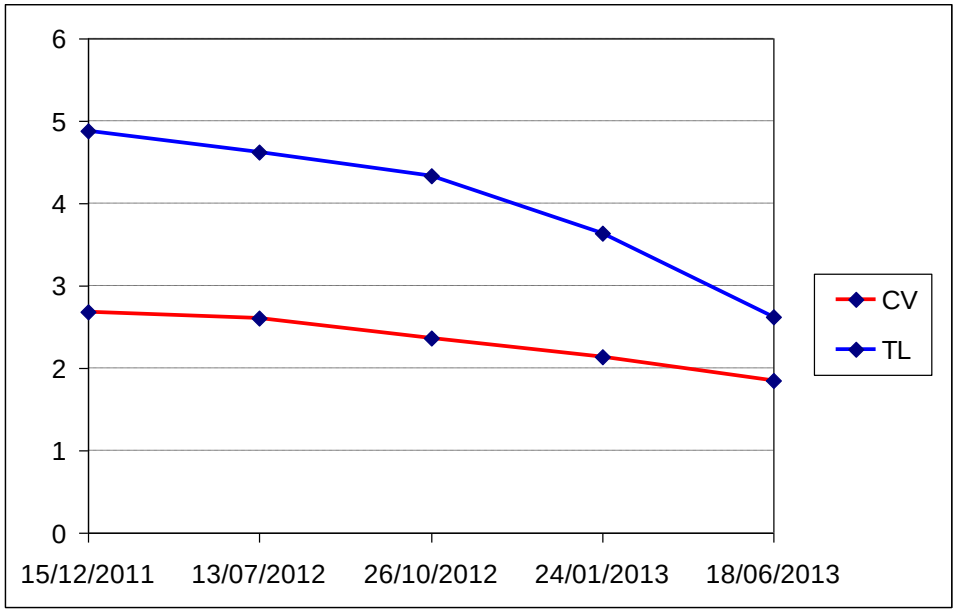
Diagnosis:

- possible IPF (guidelines)*
- MDD : IPF?

Raghu AJRCCM 2011; Fells AJRCCM 2008**; Raghu Lancet RM 2014; Johansson Lancet RM 2014*

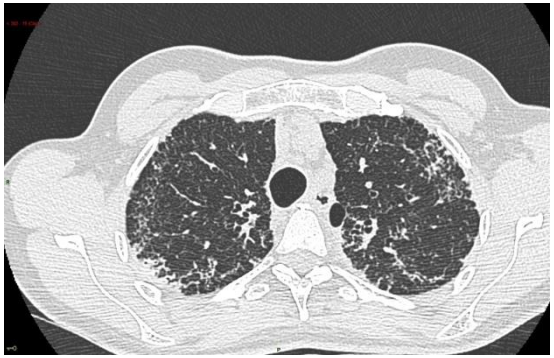
Case record (1)

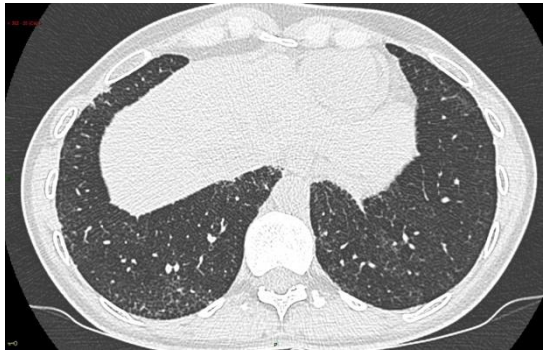
- Female, 41 years-old, never-smoker
- No cause, no familial history
- No systemic disease
- Rapidly progressive IIP
- Onset in summer, 2 yrs before lung surgery
- Pathology: UIP pattern x 2 (surgery + lung explant 2 yrs later)*
- TERT mutation (isoleucine $\rightarrow$ threonine position 720

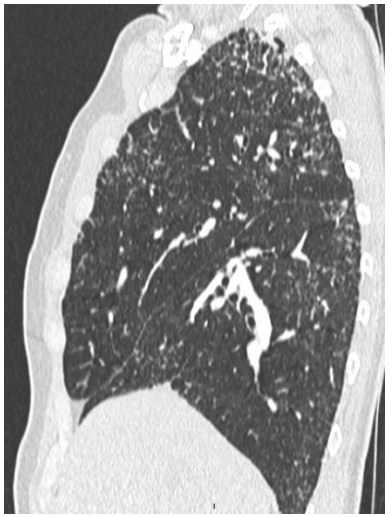


Reviewed by M Kambouchner and C Danel

Case record (2)







IPF guidelines diagnosis:

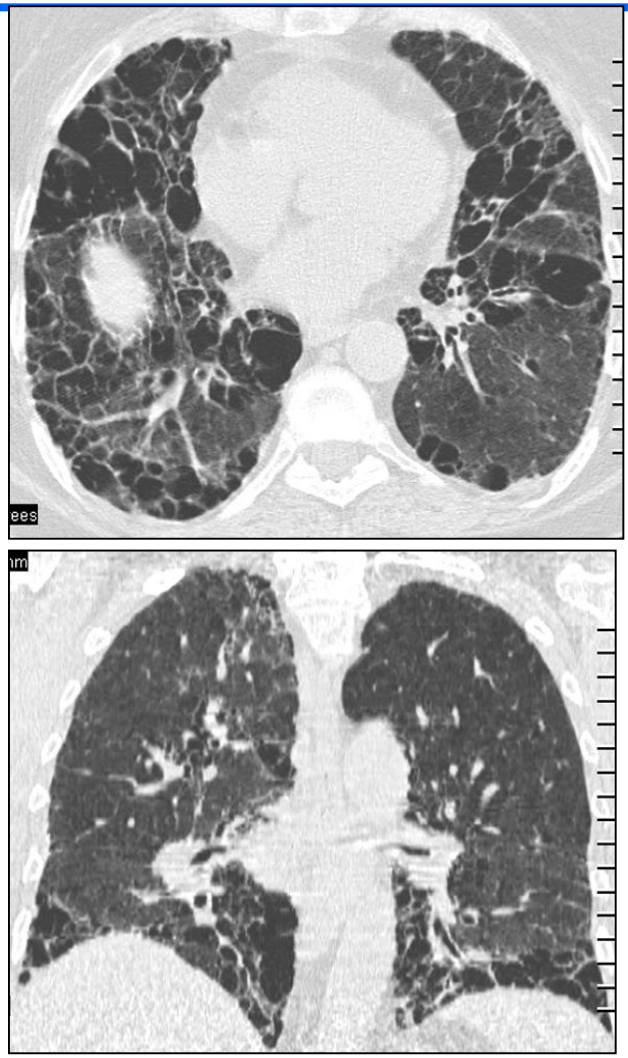
- Inconsistent with UIP pattern at CT +
  UIP pattern at histopathology = possible IPF → recommendation to review CT!

Our diagnosis hypothesis:

- TERT mutation-linked pulmonary fibrosis
- Index case of future familial PF
- Definite TERT mutation-linked IPF (why not???)
- Eligible for anti IPF therapy

Case record

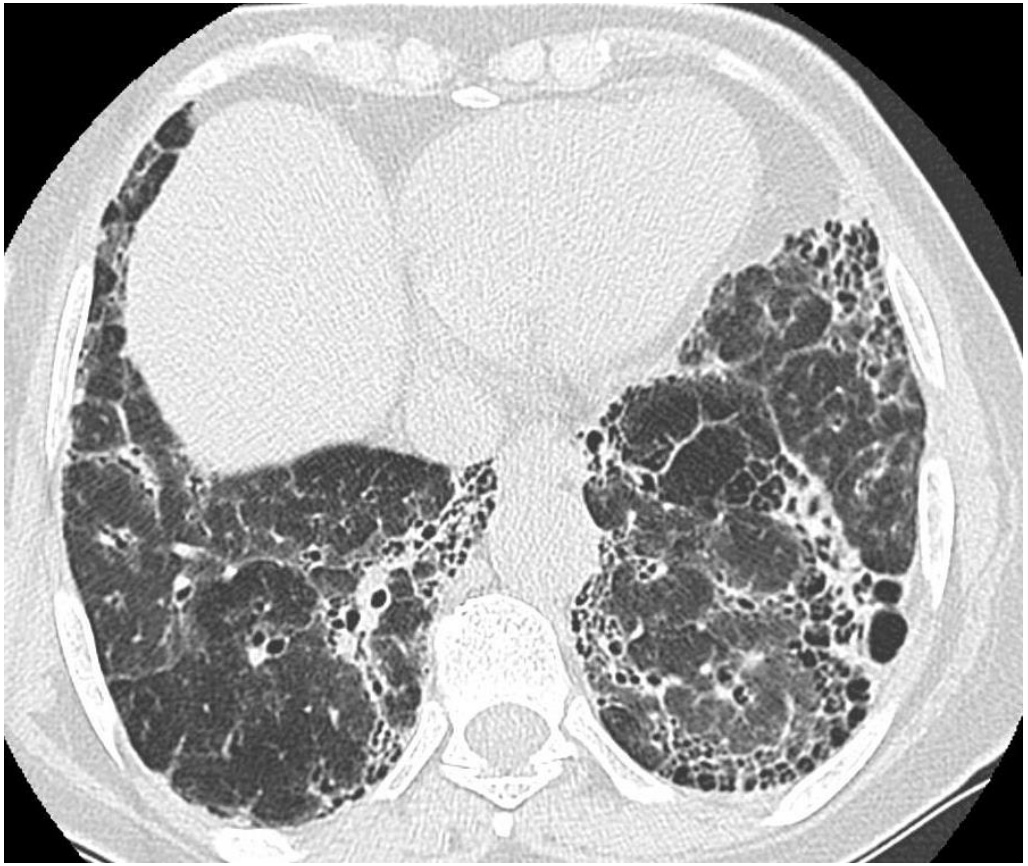
- Male 70, smoker, no risk factor, no systemic disease, with CT UIP pattern
- Screened in an E-rare academic study based on BAL biological research
- Screen failure face to >30% BAL lymphocytes
- Investigation for alternative hypothesis
- Evidence of typical granulomas on multiple bronchial biopsies
- No modification in next 2 yrs
- Conclusions
  - IPF guidelines: typical UIP eligible for anti IPF therapy
  - versus « end-stage advanced pulmonary sarcoidosis »* (often a burnt out process without progression)



Absehra AJR 2000, Xu Am J Surg Pathol 2013, Shigemitsu ERJ 2010; Tachibana Intern Med2012; Stock Thorax 2013

Case record

Male, 6, ex-smoker
No significant exposure
No precipitins including against moistures
BAL: 15% lymphocytes, CD4/8=1
Surgical biopsy: PH-UIP



Diagnosis
Guidelines diagnosis: definite IPF
MDD: fibrosing HP of unknown origin

Comments:
-Often as severe as IPF
-If progressive, anti IPF drugs???

SLB or not

- No prospective study specifying the contra-indications of SLB according to:
  - Age
  - PFT
  - Co-morbidities
  - Therapeutic consequences
- Unknown agreement concerning indications of SLB between medical centres
- Need for more consensus and …studies
- Lung cryobiopsy?

Morris JCTS 2014; Tomasseti AJRCCM 2016

BAL

- No indication if UIP pattern without any doubt for any alternative diagnosis
- Often recommended in situations where other diagnosis than IPF may be considered and/or a SLB is considered:
  - Particularly: inconsistent with UIP CT pattern

Multidisciplinary discussion

Thus, the accuracy of diagnosis of IPF increases with clinical, radiologic, and histopathologic correlation and can be accomplished with a multidisciplinary discussion among experienced clinical experts in the field of ILDs (111). This is particularly relevant in cases in which the radiologic and histopathologic patterns are discordant (e.g., HRCT is inconsistent with UIP and histopathology is UIP).

Raghu AJRCCM 2011

Agreement for MDD between centres?
Sometimes, need for some exemples
(kind of jurisprudence)

Multidisciplinary diagnosis in Avicenne hospital

- Registration of cases by one of us (Y Uzunhan) since a short laps of time
- Weekly meeting on ILD
- Discussion of ~20 selected cases/week at presentation or follow up
  - from our team (~400 new ILD/yr, ~ 80 new IIP/yr)
  - files from other centres
  - Diagnosis considered; probabilities; behavioural diagnosis; decision for surgery; therapeutic decision; inclusions in studies
- People present
  - Pneumologists (often all present): H Nunes, Y Uzunhan, D Bouvry, O Freynet, D Sadoun, B Duchemann, F Jeny, D Valeyre + pneumologists from other universitary or general hospitals; from Paris area or others
  - Radiologists: (at least one) PY Brillet or M Brauner or D Piver
  - Pathologists: JF Bernaudin and/or M Kambouchner

Suspected IPF diagnosis distribution in Avicenne hospital ILD meeting

Study of 30 last cases for which IPF could be considered
16/30 (47%) → definite or probable IPF (with CT or CT + pathology)
12/30 (40%) → possible UIP at CT but no surgery (for age or comorbdity)
4/30 (13%) → inconsistent UIP CT pattern, surgery not possible, no evident alternative diagnosis

With IPF guidelines:

→ Almost as many « possible UIP pattern » in older patients (high prevalence of IPF) as in patients with definite IPF pattern

→ Half IPF diagnosis are missed

PII inclassables

- Un certain nombre de patients, y compris après biopsie pulmonaire ne rentrent dans aucune catégorie
- Souvent combinaison de manifestations appartenant à plusieurs « *patterns* »
- ~10% des cas

Diagnostic de iPINS

→ PII + histo

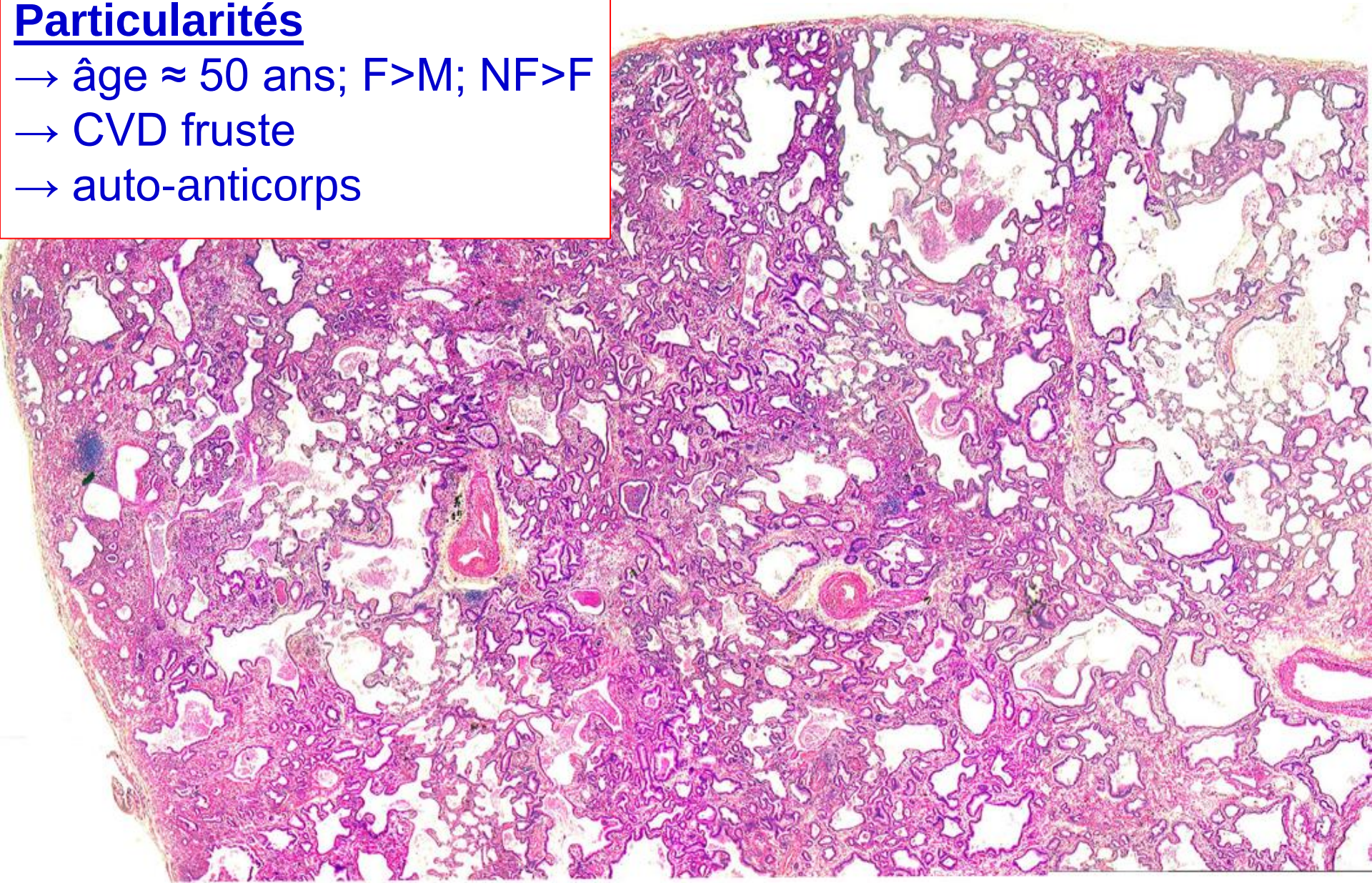
Particularités

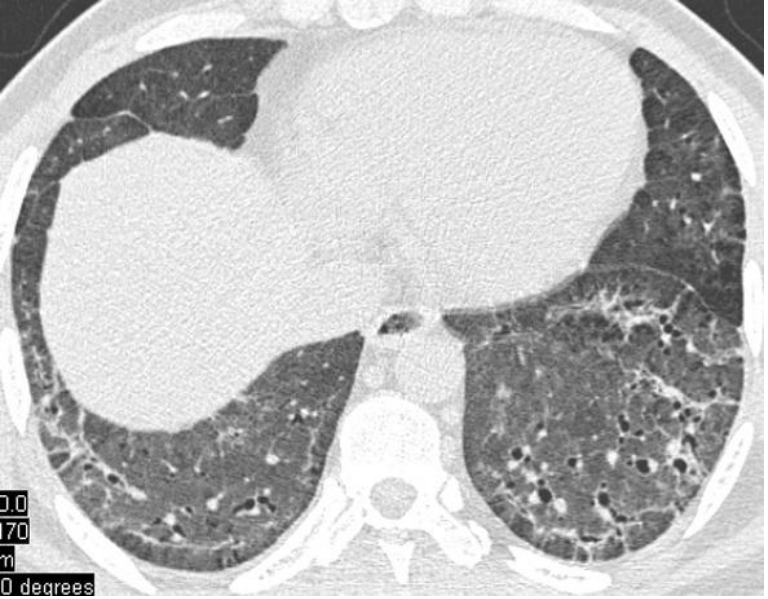
→ âge ≈ 50 ans; F>M; NF>F

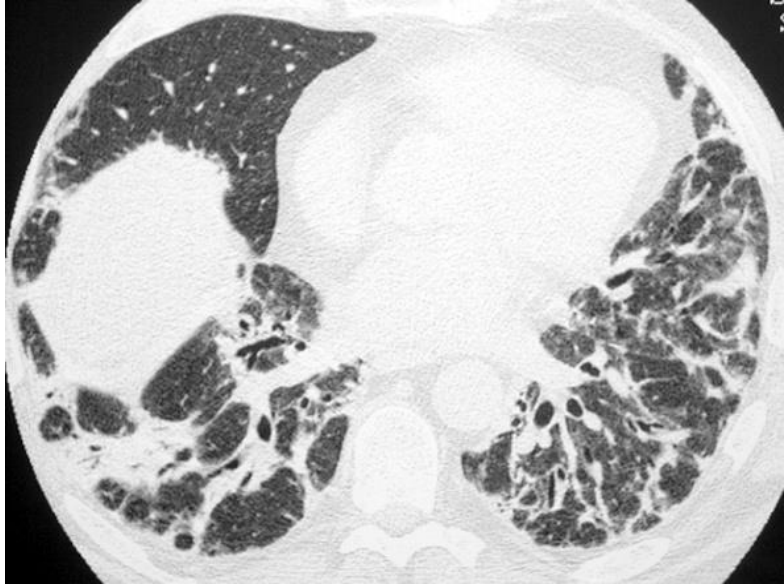
→ CVD fruste

→ auto-anticorps

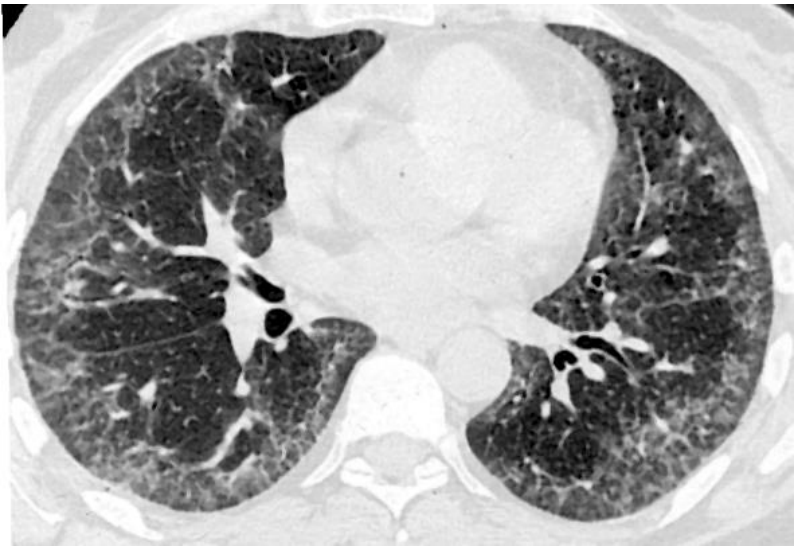
Courtesy M Kambouchner

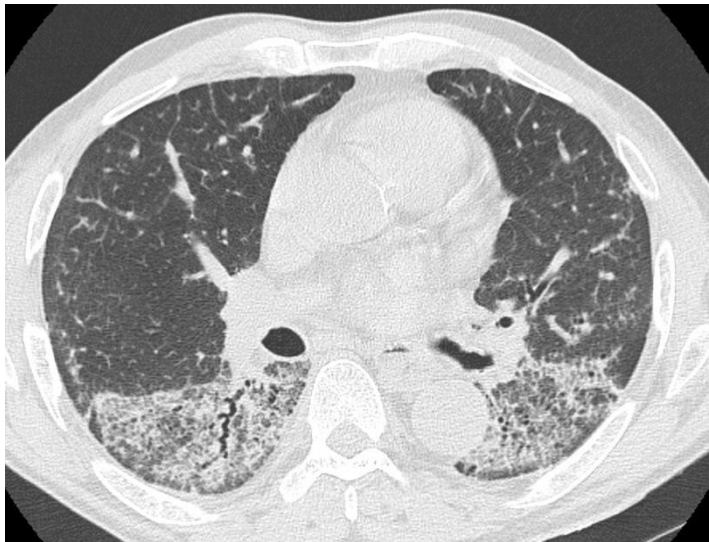




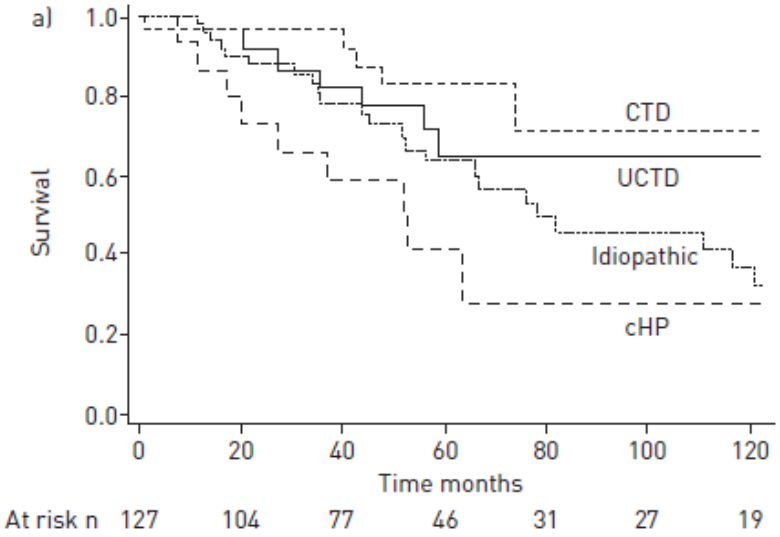


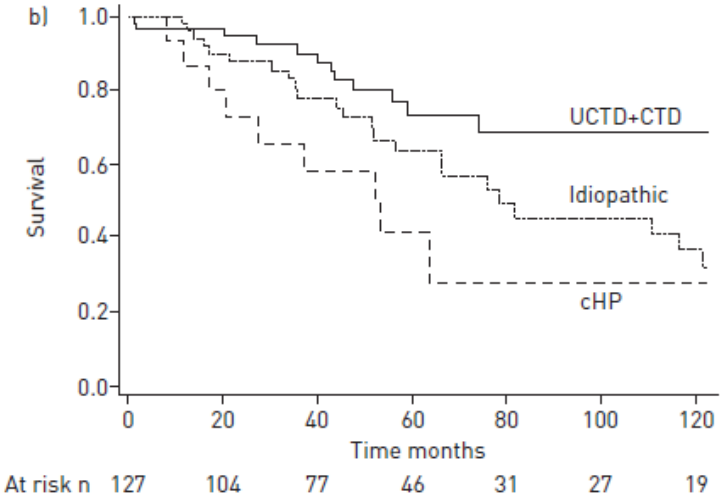
PINS (courtesy M Brauner et PY Brillet)





Patient survival according to aetiological group





Nunes ERJ 2015

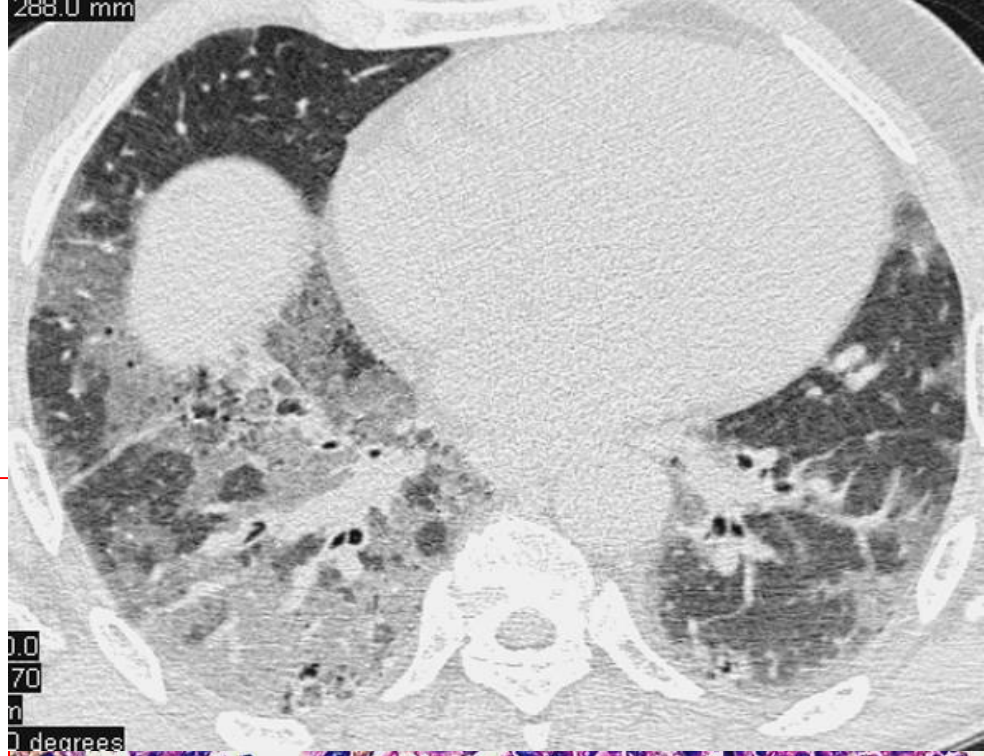
Diagnostic de DIP

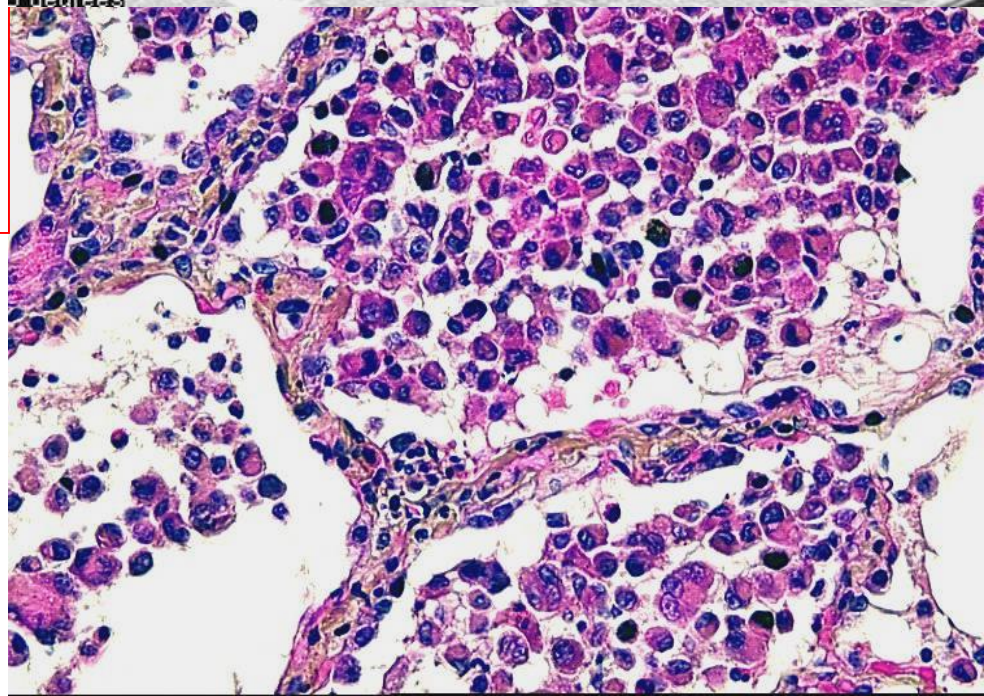
→ PII + histo

Particularités

→ tabac

→ VD sans RM





Diagnostic de POC

→ PII

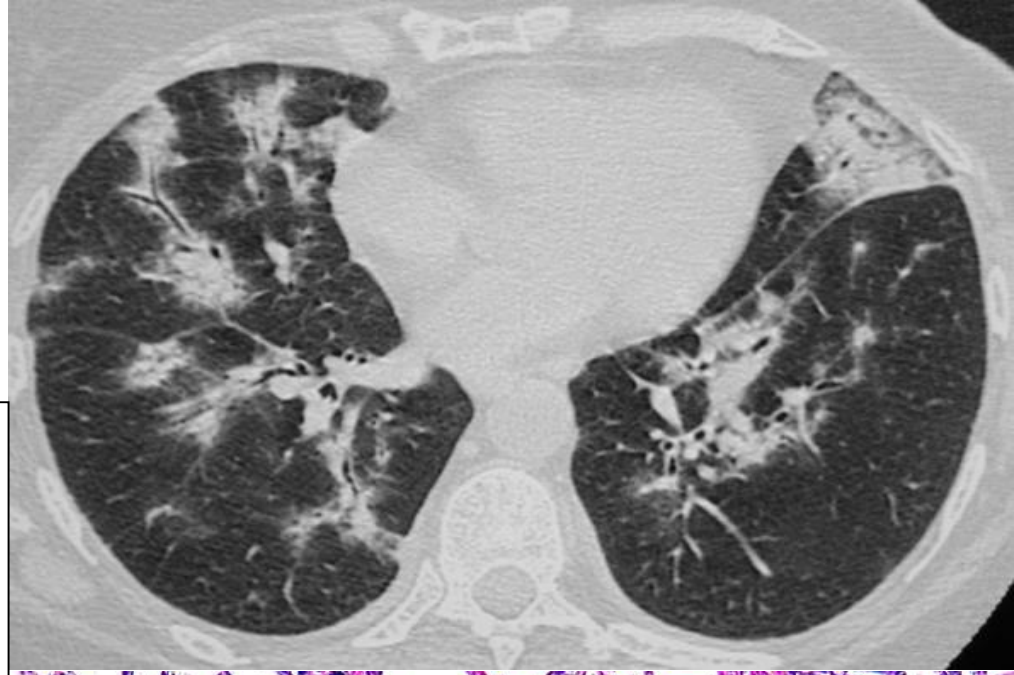
→ histologie

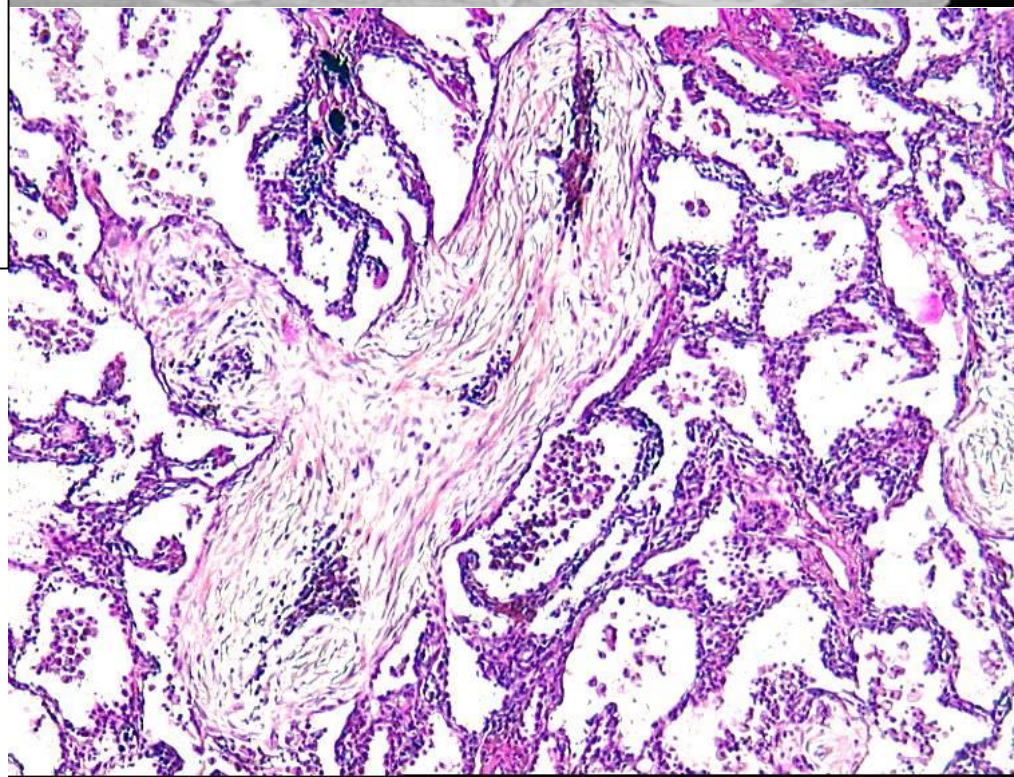
Particularités

→ éliminer autres causes

→ imagerie évocatrice

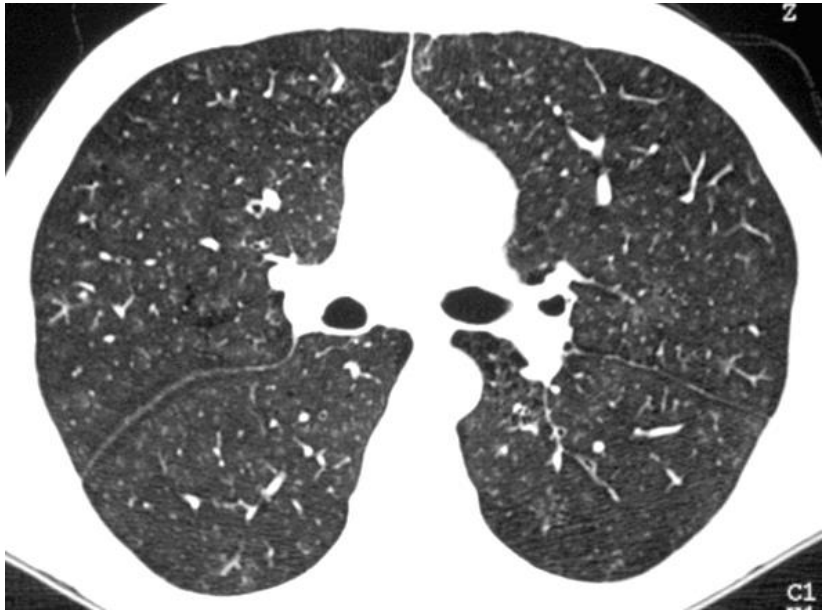
→ BTB

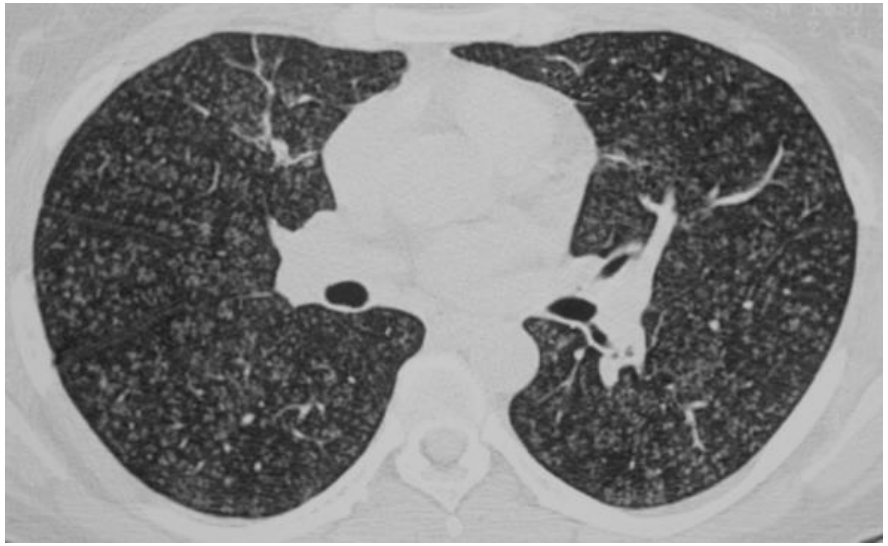




Courtesy M Kambouchner and M Brauner

Bronchiolite respiratoire/BR-PID





Diagnostic possible en dehors d’une biopsie pulmonaire

Les PII « rares »

Pneumonie interstitielle lymphocytaire

- Réponse immune anormale
- Devenue très rare: reclassement fréquent en NSIP
- Verre dépoli 100%
- Kystes à paroi fine 50%
- Autres signes inconstants
  - ✓Rayon de miel périvasculaire
  - ✓Micronodules
  - ✓Epaississements septaux et péribronchovasculaires

Fibroélastose pleuro-pulmonaire

- Entité récente bien distincte des autres (pathologie; aussi, présentation)
- Contexte
  - Formes familiales
  - ATCD carcinologiques; greffe de moelle osseuse
  - Infections répétées
  - Auto-immunité?
- Imagerie
- Evolution: inéxorablement progressive
- Pathogénie: « rejet » chronique du poumon?
- Traitement
  - transplantation

Azoulay ERJ 1999; Frankel Chest 2004; Maher ERJ 2012; Poletti 2011

Conclusions (1)

IPF guidelines 2011

- Improvements
  - Grading probabilities of diagnosis
  - MDD
- Limitations/failures
  - HC: no specification of the probability level; Insufficient place for BAL
  - Lack of management guidance in probable or possible IPF (a lot of patients)
  - Lack of jurisprudence for MDD decisions (how to cope with ≠ CT/pathogy patterns + clinical presentation)

Proposal

- More subtle analysis of CT (particularly for HC)
- Scores to determine IPF probability based on CT, age, PF evolution trend for patients with possible IPF for which surgery is dangerous
- Specify when MDD may upgrade IPF diagnosis to definite IPF
- Organize webbs associating reference and less experienced centres
- Qualités des DMD et des participants (Clinicien +++, Radiologue, pathologiste)

Conclusion (2)

Now, this is not the end.

It is not even the beginning of the end.

But it is perhaps the end of the beginning…

Sir Winston Churchill

Thanks to « my faithful team »

Avicenne hospital

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- Pathologists: M Kambouchner
- Physiologists: C Planès, C Lamberto, T Gille, F Lhuissier

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