Centre de Référence de l'Histiocytose Langerhansienne

MaRIH
Filière de santé Maladies Rares ImmunoHématologiques

Inserm

Les PID des connectivites
Le point de vue du pneumologue

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Les PID des connectivites
Généralités

- Causes fréquentes de PID
  - PIA
  - PID subaigües ou chroniques

- La connectivite est connue:
  - Éliminer: infections, médicaments, cœur…
  - Atteinte spécifique

- La PID est le mode de découverte de la connectivite
  - Importance de sa reconnaissance
    - ✓ Pronostic
    - ✓ Prise en charge spécifique

- Situation particulière
  - PID « pauci-immune/connectivite indifférenciée »= IPAF

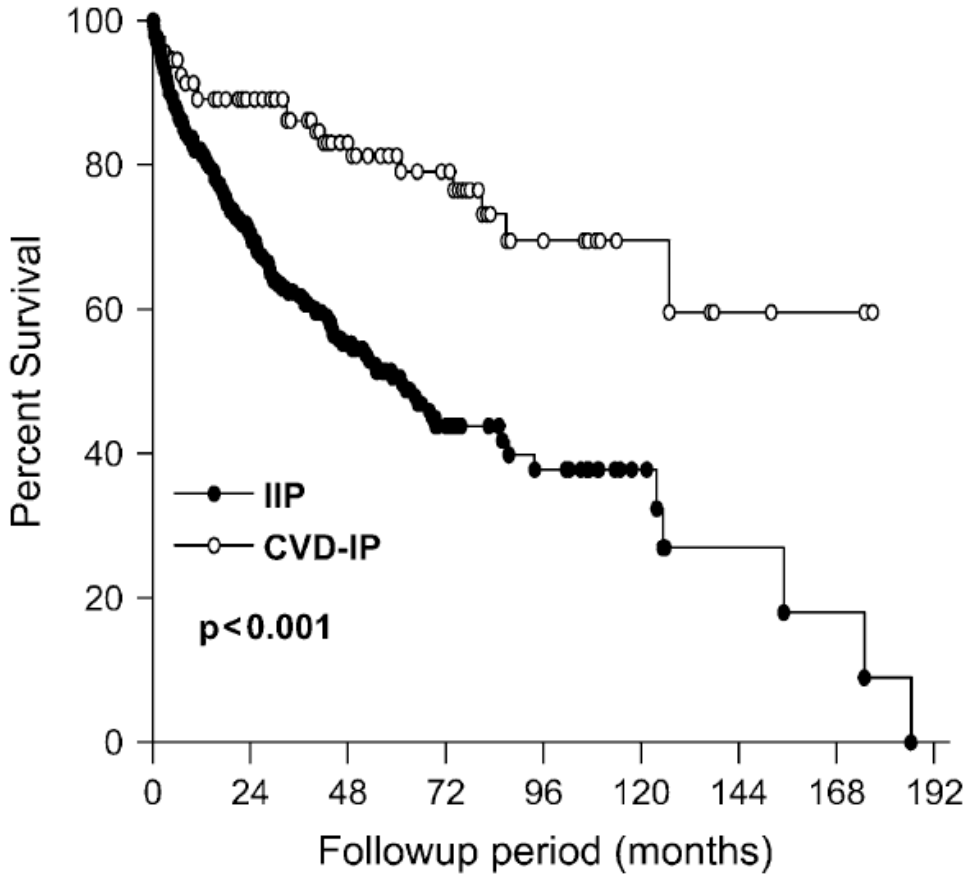


Figure 1. Survival of total subjects with idiopathic interstitial pneumonia (IIP) and interstitial pneumonia associated with collagen vascular disease (CVD-IP).

Park et al. AJRCCM 2007

Atteintes pulmonaires des connectivites

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjögren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

Fischer and du Bois Lancet 2012

Fréquence des PID au cours des connectivites

Table 1. Interstitial lung diseases associated with connective tissue diseases

Rheumatic disease	Frequency of ILD (%)	Comment
Systemic sclerosis	45 (clinically significant)	More common in diffuse disease; topoisomerase-1 antibodies
Rheumatoid arthritis	20 to 30	Increased risk with cigarette smoking
Polymyositis/dermatomyositis	20 to 50[a]	More common with anti-synthetase antibodies
Sjögren's syndrome	Up to 25	–
Systemic lupus erythematosus	2 to 8	Usually in patients with multisystem disease
Mixed connective tissue disease	20 to 60	–

ILD, interstitial lung disease. [a]Frequency may be higher based on recent studies.

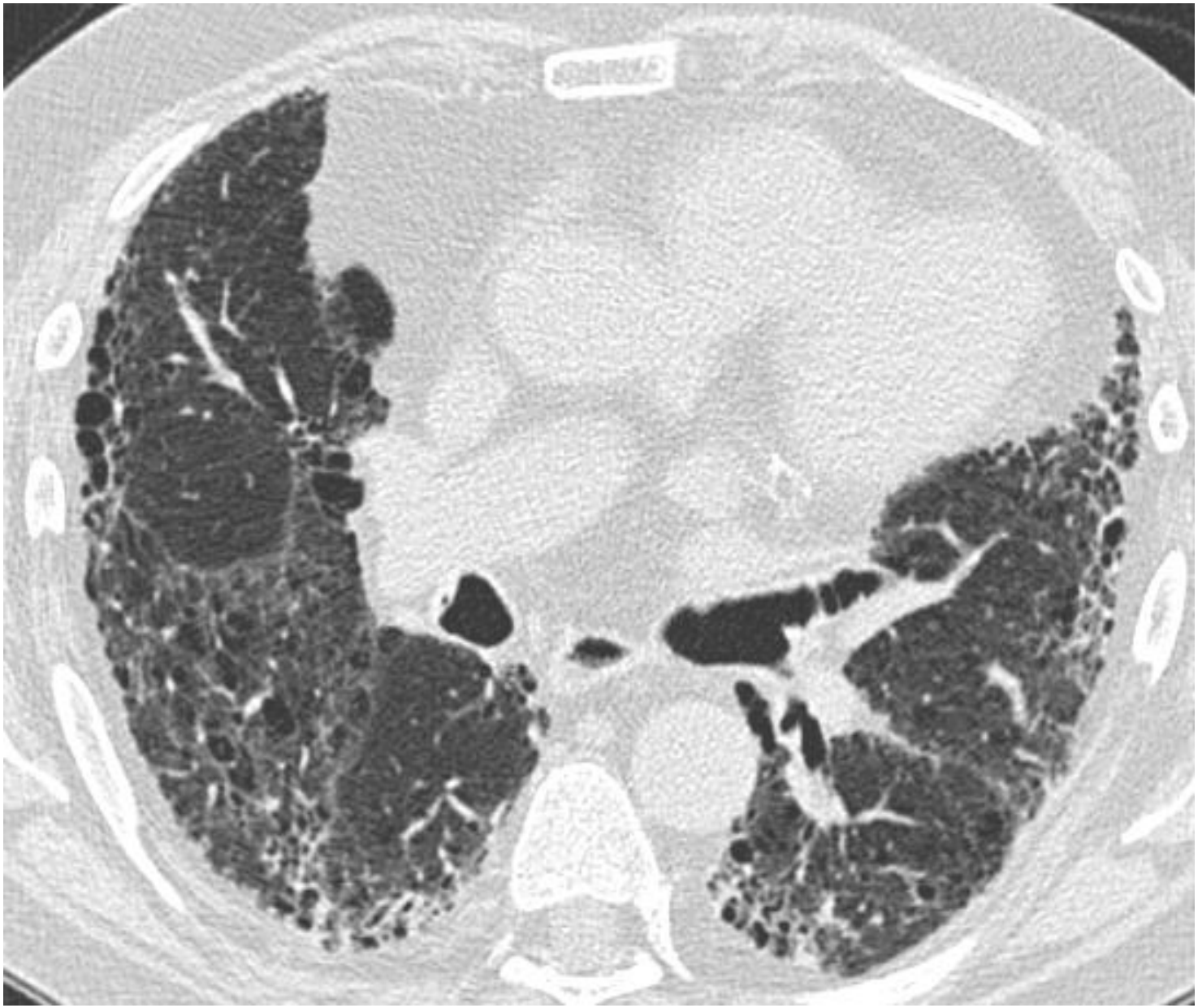
Castelino and Varga

Arthritis Research & Therapy 2010, **12**:213

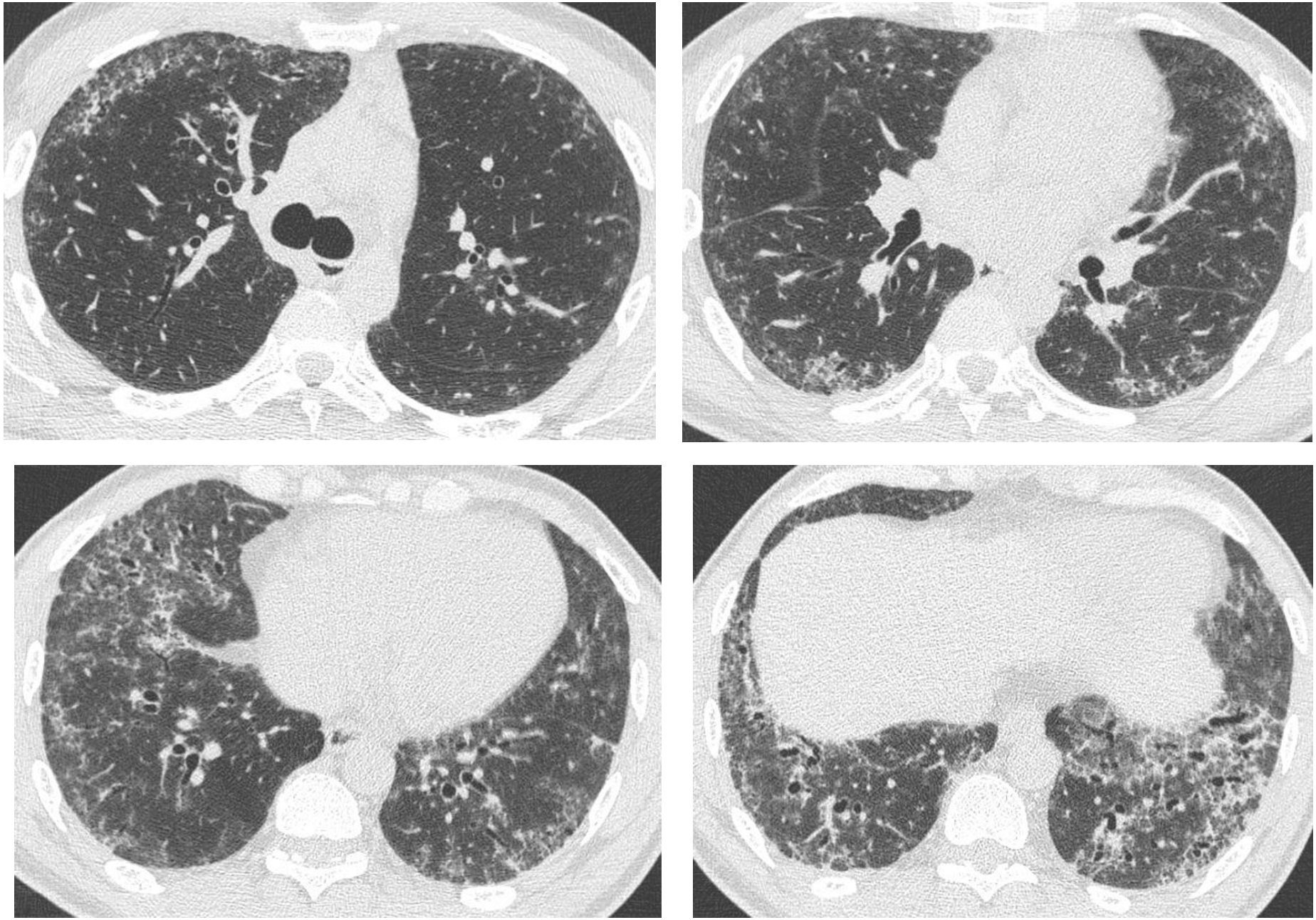
Classification des PID idiopathiques

Aspect histologique	Entité clinique
PI commune (UIP)	Fibrose pulmonaire idiopathique
PI non spécifique	PI non spécifique
P organisée	PI organisée cryptogénique
Dommage alvéolaire diffus	PI aiguë
Bronchiolite respiratoire	Bronchiolite respiratoire avec PI
PI desquamative	PI desquamative
PI lymphocytaire	PI lymphocytaire

ATS/ERS 2002/2013

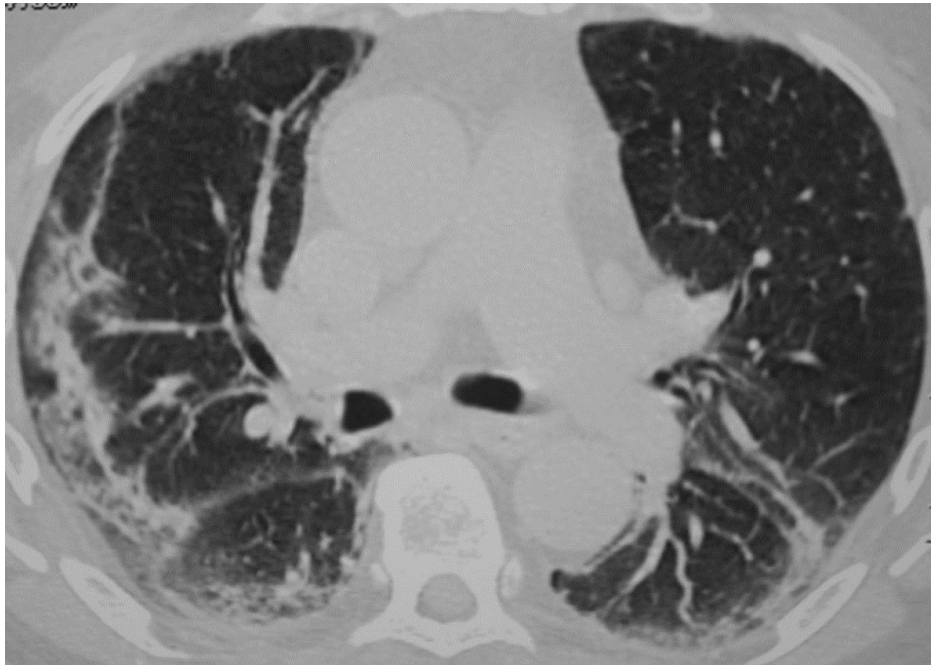


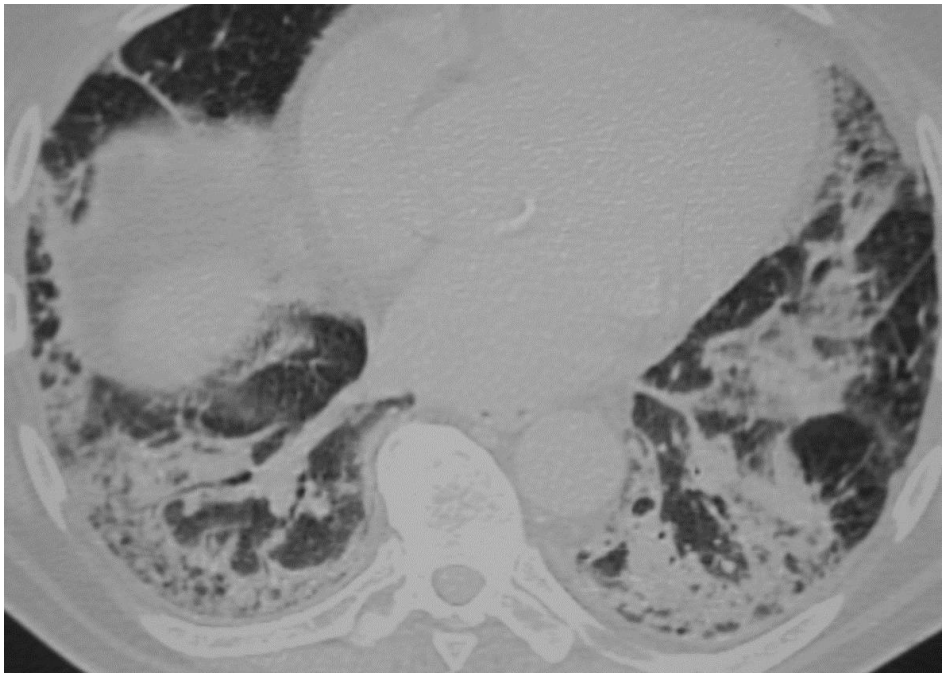
PIC/UIP



PINS/NSIP

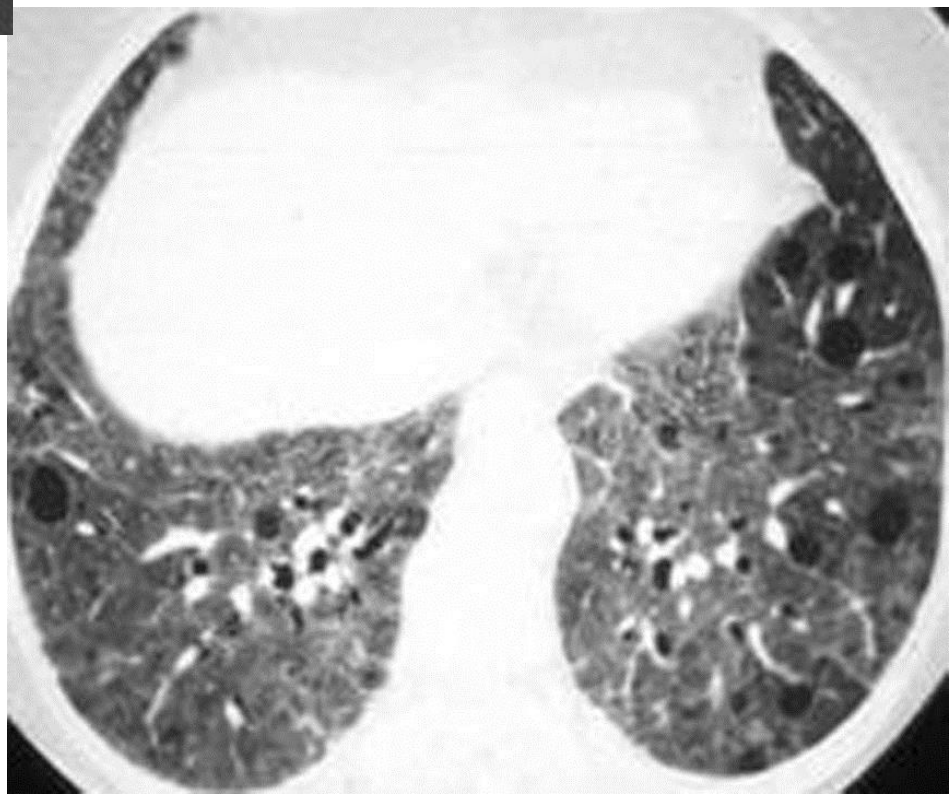
PO/OP





PO/PINS

PIL/LIP



PID et connectivites
Entités nosologiques

Disease association	Characteristic histopathologic pattern
Idiopathic pulmonary fibrosis	Usual interstitial pneumonia
Systemic sclerosis	Nonspecific interstitial pneumonia
	Usual interstitial pneumonia
Rheumatoid arthritis	Usual interstitial pneumonia
	Nonspecific interstitial pneumonia
Polymyositis/dermatomyositis	Nonspecific interstitial pneumonia
	Usual interstitial pneumonia
	Cryptogenic organizing pneumonia
	Diffuse alveolar damage
Sjögren's syndrome	Nonspecific interstitial pneumonia
	Lymphocytic interstitial pneumonia
Systemic lupus erythematosus	Acute interstitial pneumonia
Mixed connective tissue disease	Nonspecific interstitial pneumonia

Castelino and Varga

Arthritis Research & Therapy 2010, **12**:213

PIA et connectivites

- Connectivites
  - LEAD
  - Myosites inflammatoires
  - Connectivites mixtes

- Complication spécifique
  - Différents aspects nosologiques: *DAD, HIA, Pneumonie organisée aigue, Exacerbation de PID…*

- Rechercher de principe
  - Infection opportuniste ++
  - Atteinte cardiaque ++
  - Toxicité médicamenteuse

Feuillet et Tazi Rev Mal Respir 2011

Recherche d'une connectivite devant une PID subaigüe/chronique

- Démographie
  - Femme < 50 ans
    - (PR, homme)
  - Ethnie?
- Clinique +++
- Imagerie
- Biologie usuelle
- LBA
- Immunologie
- Histopathologie pulmonaire

Symptômes et signes d'examen extra respiratoires en faveur d'une connectivite devant une PID

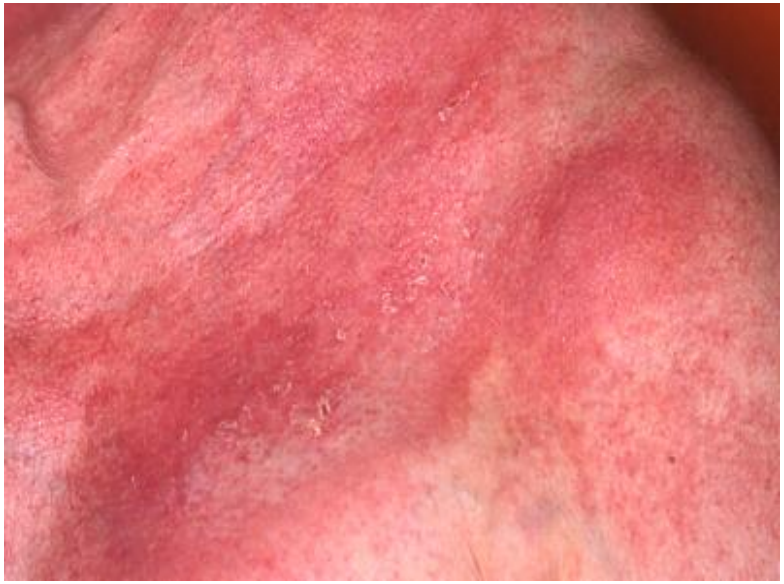
Organ	Main manifestations to be evaluated[#]
Peripheral circulation	Raynaud's phenomenon
Skin	Sclerodactily
	Digital ulcerations or scars
	Telangiectasia
	Violaceous erythematous rash over the interphalangeal joints, knuckles, elbows and knees (Gottron's sign)
	Lilaceous rash of the eyelids
	Rash of the neck and upper chest and shoulders (heliotrope rash, *e.g.* photosensitivity)
	Mechanics' hand
Joints	Joint pain or swelling (arthritis, arthralgia)
	Morning stiffness
Muscle	Muscle pain and muscle weakness
Mouth and eyes	Dry mouth and dry eyes (sicca syndrome)

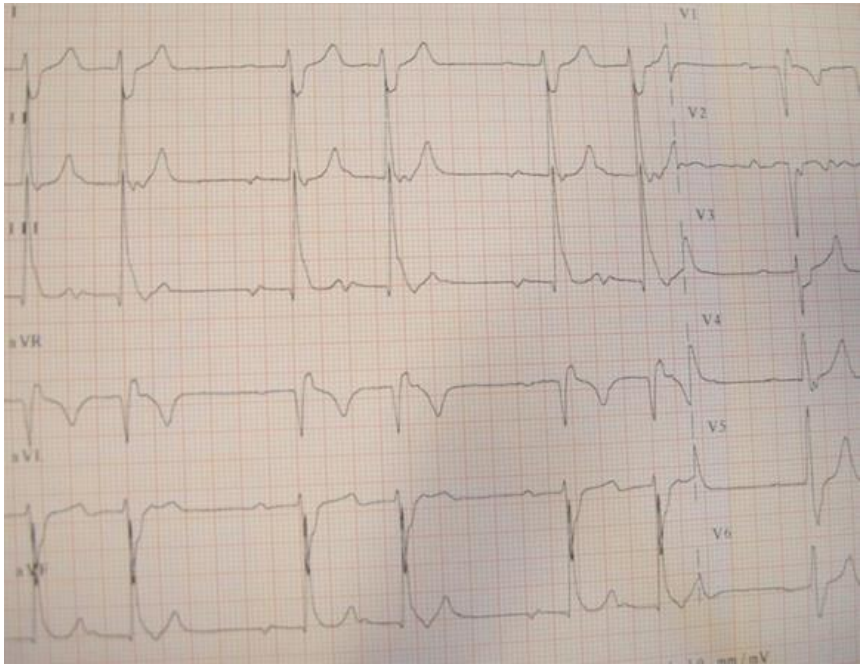
[#]: this list is not exhaustive.

Cottin ERR 2013

Signe du V

Signe du châle




V1
V2
V3
V4
V5
V6
aVR
aVL

Recherche d'une connectivite devant une PID subaigüe/chronique

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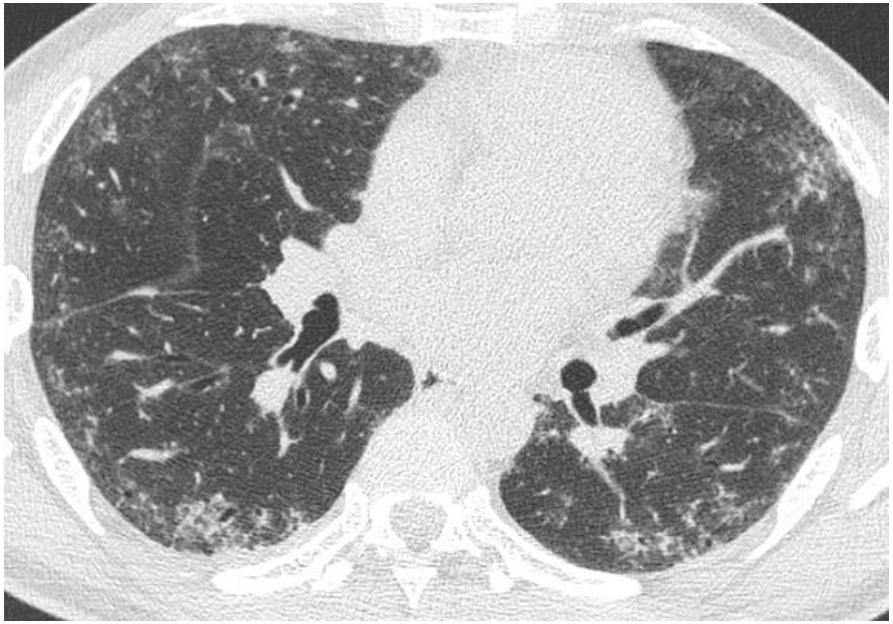
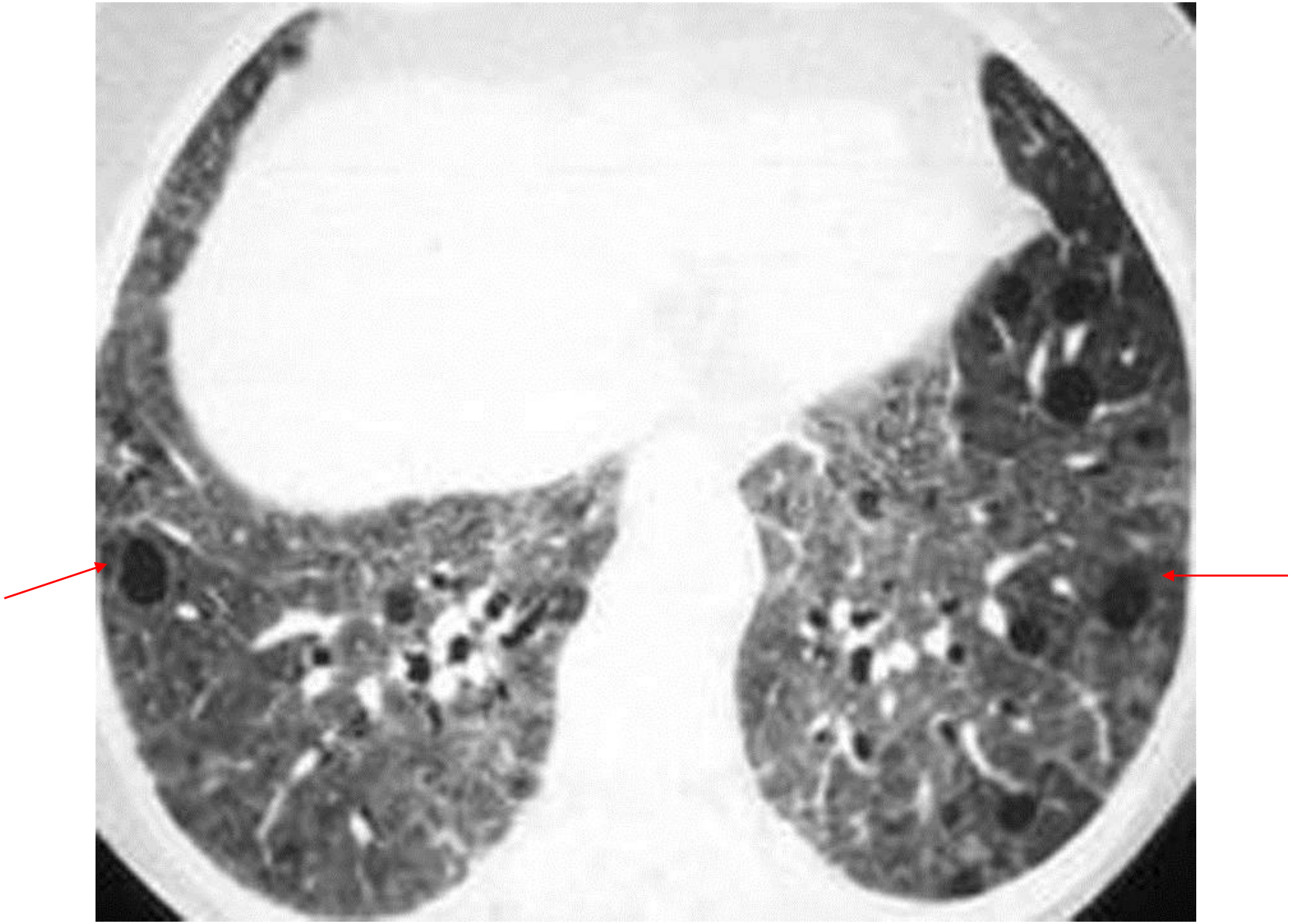
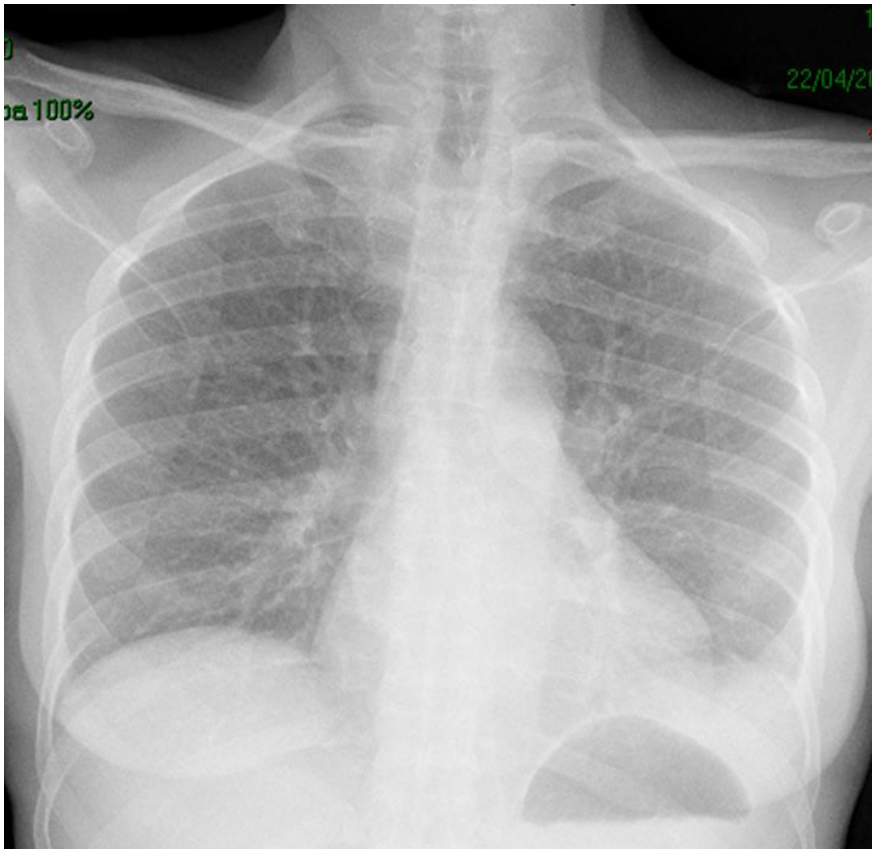
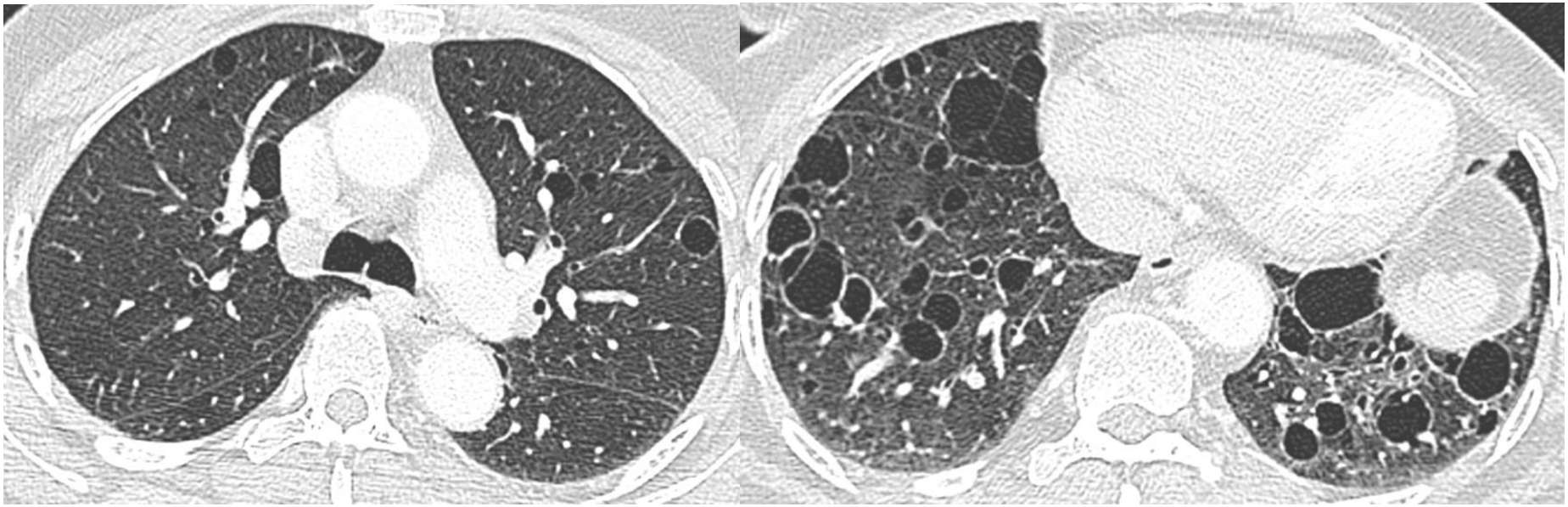
PO/OP



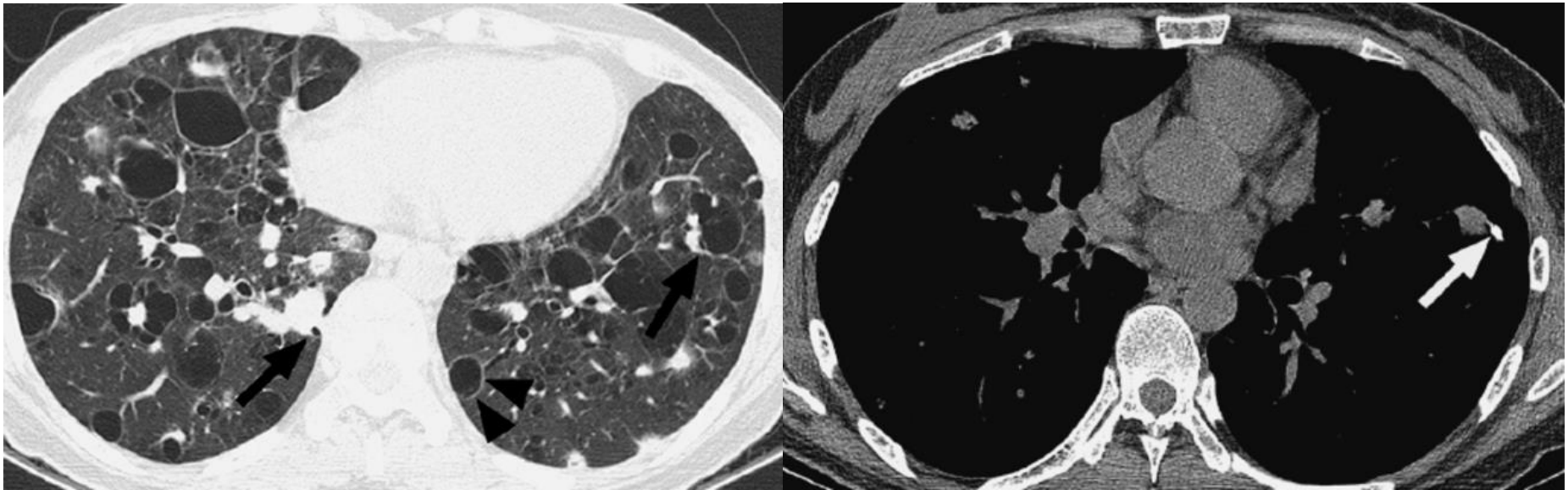


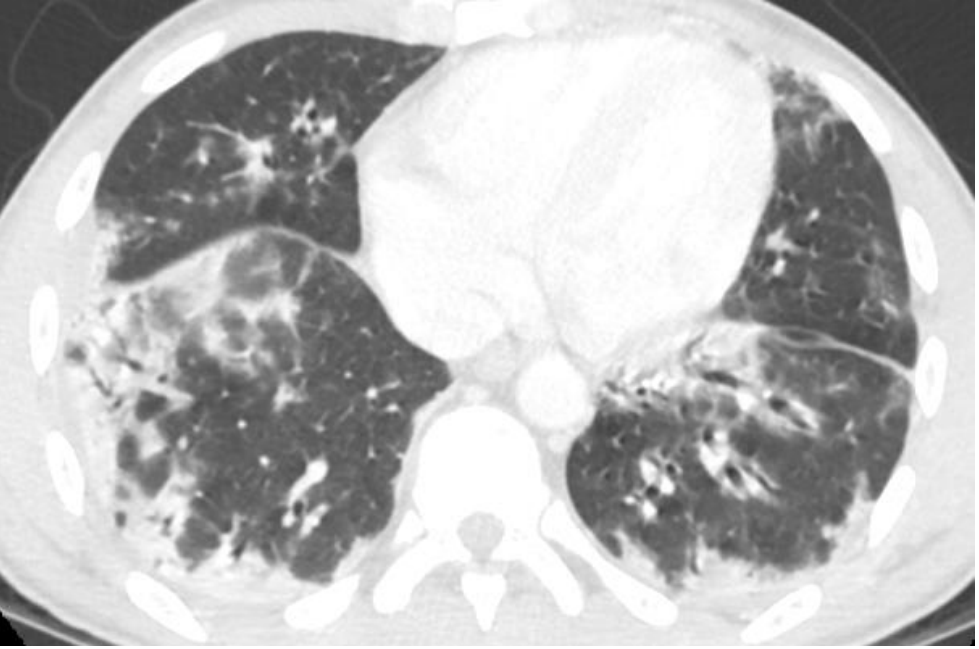

100%

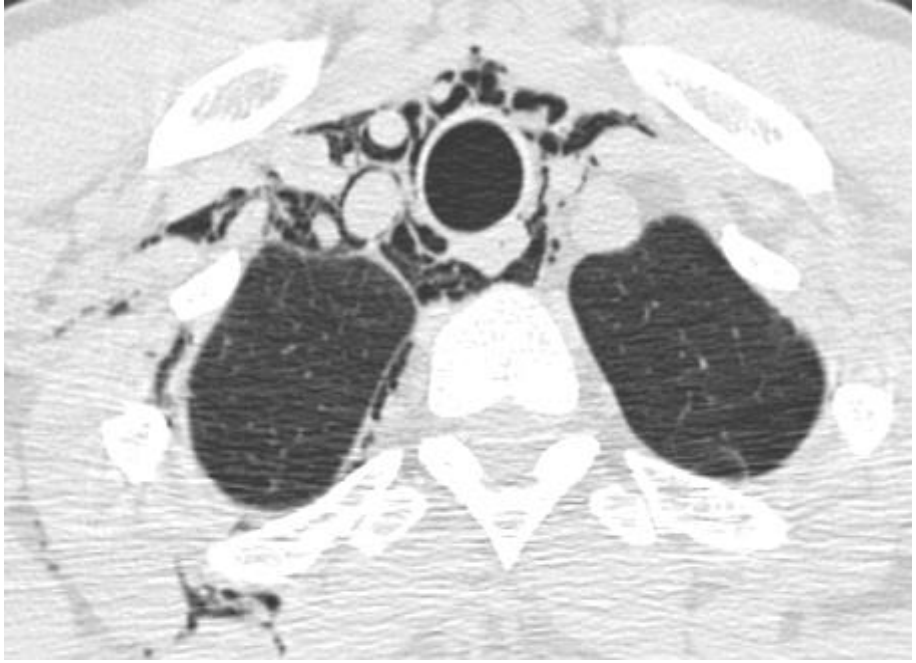
Sjogren + LIP kystique pure

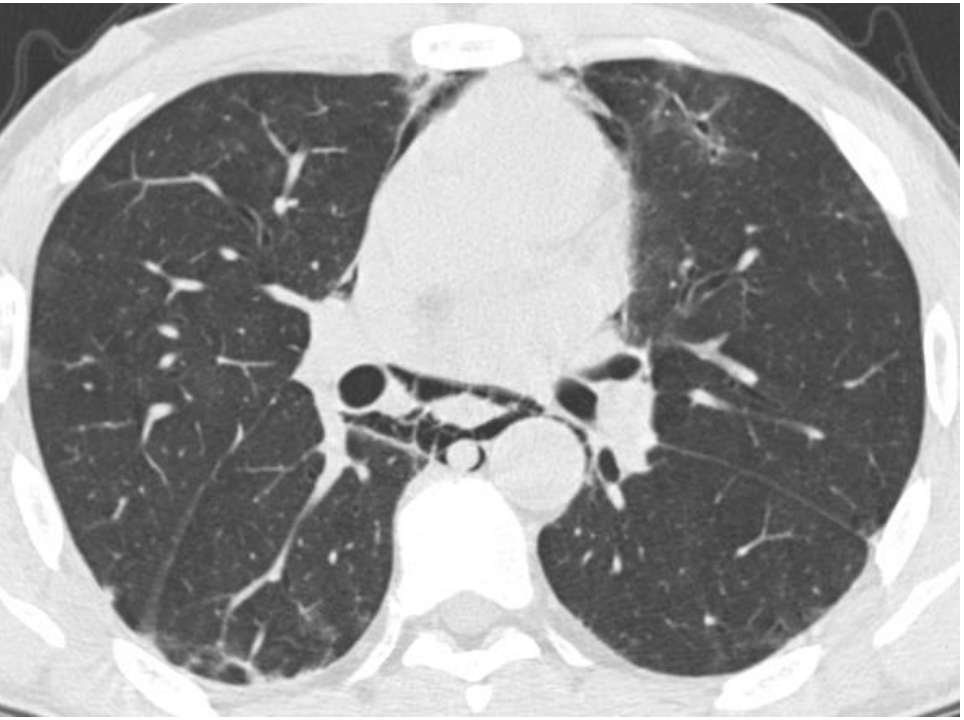


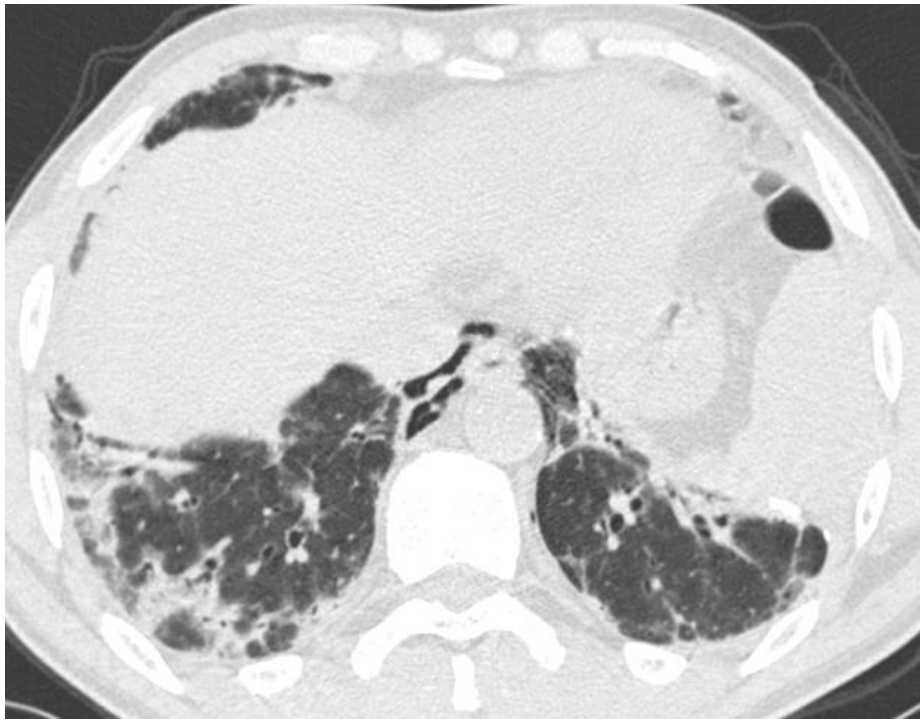
Sjogren + LIP + amylose + prolifération lymphoïde

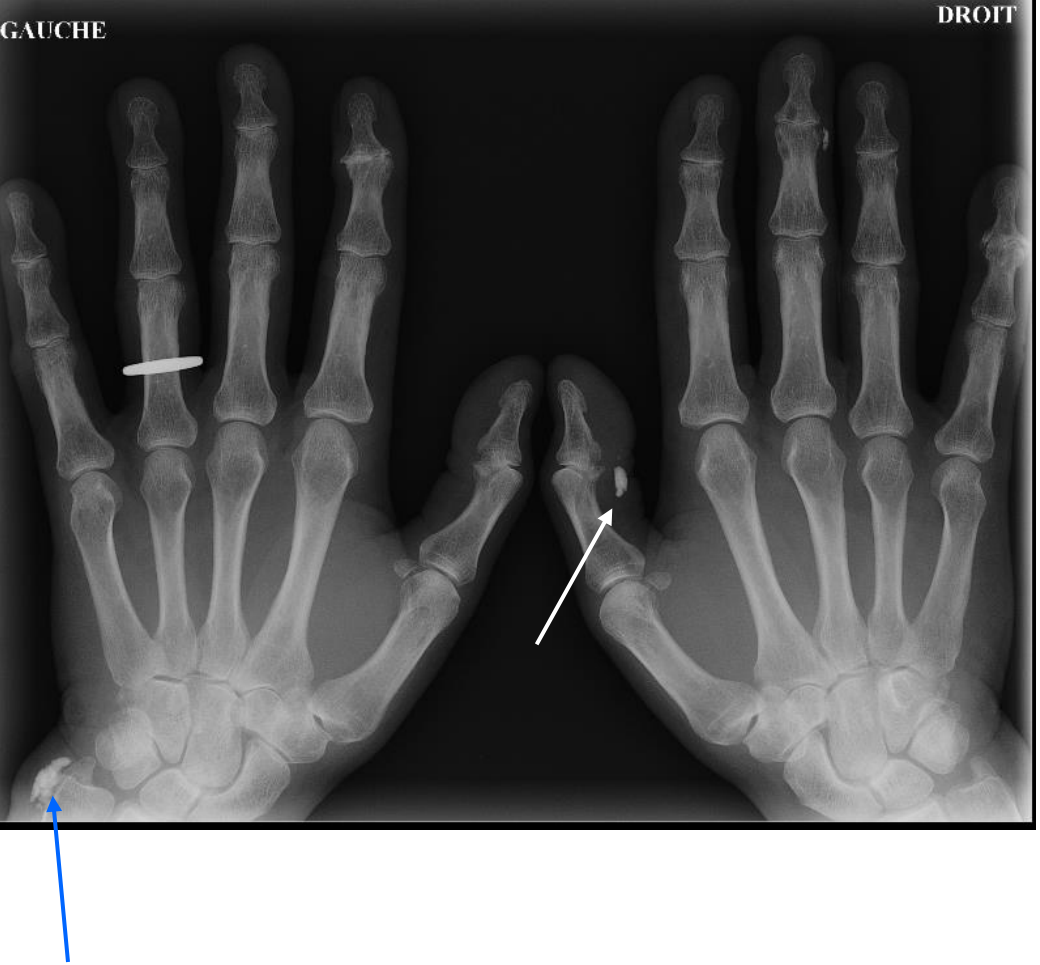











GAUCHE
DROIT

Recherche d'une connectivite devant une PID subaigüe/chronique

- Démographie
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  - Ethnie?
- Clinique +++
- Imagerie
- Biologie usuelle
- LBA
- Immunologie
- Histopathologie pulmonaire

Biologie usuelle

- Cytopénies (lymphocytes)
- Hyperγglobulinémie
- Cholestase/cytolyse hépatique
- CPK (aldolase), (CRP)
- Fonction rénale, sédiment urinaire

LBA

- Peu d'éléments d'orientation
- Lymphocytose alvéolaire
- Eliminer infections+++

Recherche d'une connectivite devant une PID subaigüe/chronique

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- Immunologie : auto-immunité
- Histopathologie pulmonaire

Table 3 Useful antibodies for CTD-ILD assessment[2]

Autoantibody	Commonly associated CTD
High titer ANA (≥ 1:320 titer)	Many
High titer RF (≥ 60 IU/mL)	RA, Sjögren disease, SLE
Anti-CCP	RA
Anti-centromere	Systemic sclerosis
Anti-nucleolar-ANA	Systemic sclerosis
Anti-Ro (SS-A)	Many
Anti-La (SS-B)	SLE, Sjögren disease
Anti-Smith	SLE
Anti-ribonucleoprotein	SLE, MCTD
Anti-dsDNA	SLE
Anti-topoisomerase (Scl-70)	Systemic sclerosis
Anti-tRNA synthetase antibodies	Polymyositis/ dermatomyositis (antisynthetase syndrome)
Anti-PM-Scl	Systemic sclerosis / myositis overlap
Anti-Th/To	Systemic sclerosis
Anti-U3 ribonucleoprotein	Systemic sclerosis
Anti-MDA-5 (CADM)	Clinical amyopathic dermatomyositis

Fischer and Richeldi
Sem.Resp.Crit.Care Med. 2014

Identification of Citrullinated Hsp90 Isoforms as Novel Autoantigens in Rheumatoid Arthritis–Associated Interstitial Lung Disease

Harlow et al. Arthritis & Rheumatism 2012

Table 1 Myositis-specific antibodies

Myositis-associated antibodies	Target antigen	Prevalence in IIM[17–19,27,37–39,44,48,93]	Clinical features[17,27,37–39,42,54–57,59]
Anti-Ro52	Extractable nuclear antigen Ro52	13–26%	Associated with more severe ILD
Anti-MDA-5	MDA-5 RNA helicase	20–25%[a]	Skin ulceration; CADM; rapidly progressing/ acute interstitial pneumonitis
Anti-155/140	155/140-kDa polypeptides	7–16%	Highest risk of malignancy, lower risk of ILD
Anti-SRP	Cytoplasmic signal recognition particle	5–6%	Severe myopathy and weakness; risk of ILD is not increased
Anti-Mi-2	Nuclear helicase protein	14%	Milder myopathy and classic DM findings; risk of ILD is not increased

Table 2 Antisynthetase antibodies

Antisynthetase antibodies (ARS)	Target antigen	Prevalence in IIM[18,31,48,78,93]	% of ARS antibodies detected[14,20,23,26,31,50,79,93]	Clinical features[34,77,79]
Anti-Jo-1	Histidyl-tRNA synthetase	8–18%	36–88%	Classic DM, ILD
Anti-EJ	Glycyl-tRNA synthetase	5–10%	7–23%	Classic DM and CADM, ILD
Anti-PL-7	Threonyl-tRNA synthetase	5%	9–25%	Classic DM, ILD
Anti-OJ	Isoleucyl-tRNA synthetase	3%	5–8%	Isolated ILD
Anti-PL-12	Alanyl-tRNA synthetase	1%	2–11%	Isolated ILD, CADM
Anti-KS	Asparaginyl-tRNA synthetase	1%	4–8%	Isolated ILD
Anti-Zo	Phenylalanyl-tRNA synthetase	< 1%	< 1%	
Anti-YRS	Tyrosyl-tRNA synthetase	< 1%	< 1%	

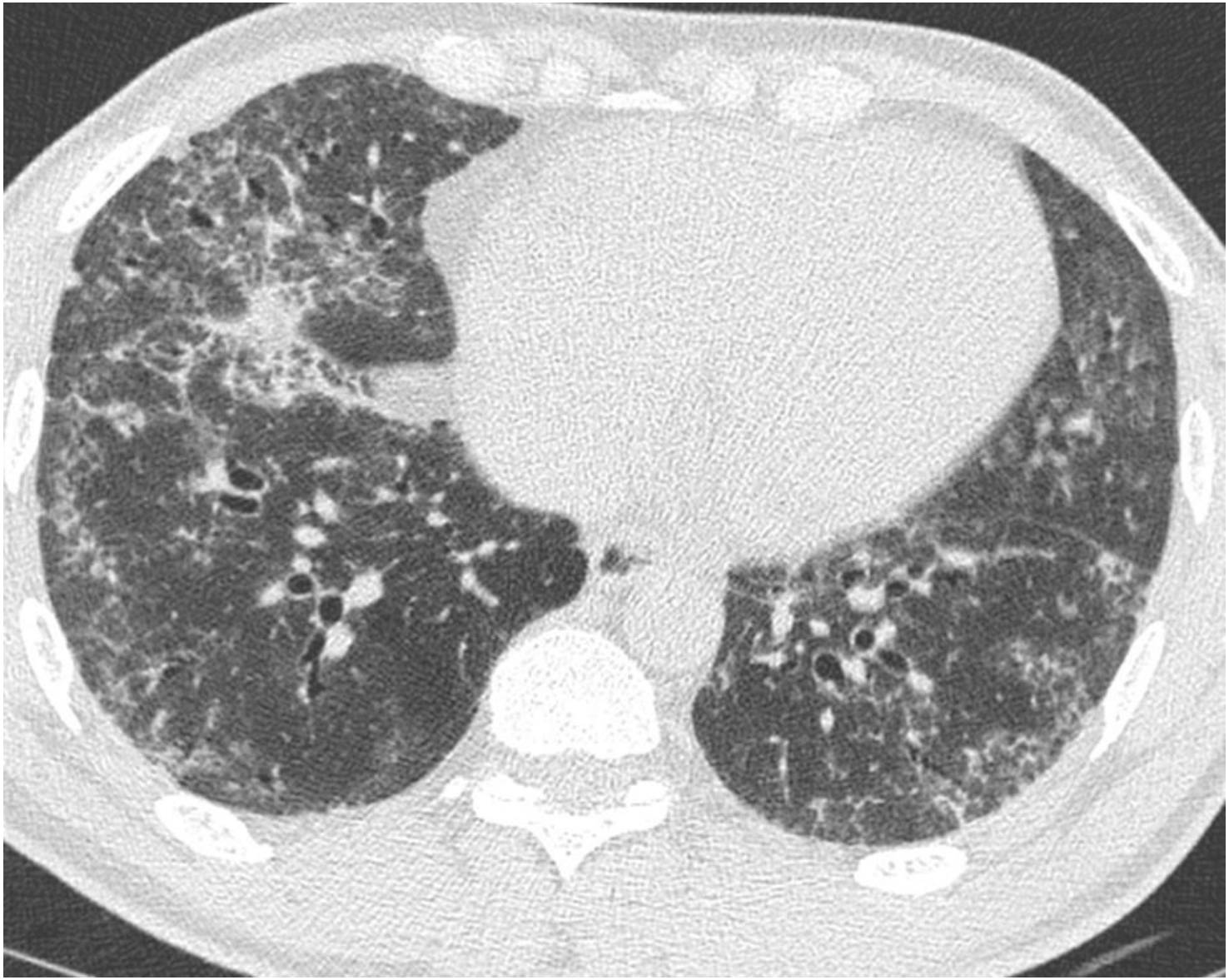
Hallowell et al. Sem.Resp.Crit.Care Med. 2014

Un homme de 40 ans est adressé pour une PID d'installation progressive associée à un amaigrissement de 6 kg en 9 mois

- Patient sénégalais en France depuis 1988 (dernier séjour au Sénégal 2008)
- Sevrage tabagique depuis 14 ans
- Responsable administratif RATP (exposition amiante minime avant)
- Pas d'animal, ne prend pas de médicament
- Pas de PID familiale

- <u>Janvier 2009:</u>
  - Toux sèche et dyspnée d'effort progressive
  - Amaigrissement de 6 kg en 9 mois

- <u>Octobre 2009:</u>
  - Toux sèche, DE 2-3 étages
  - Syndrome sec buccal depuis 3 mois
  - Hippocratisme digital ancien
  - Petites tâches purpuriques de la pulpe des doigts
  - Alopécie en plaques
  - Crépitants discrets des bases pulmonaires
  - Discret syndrome inflammatoire, éosinophiles 600/mm^3



Hypothèse

PINS avec probable syndrome de Sjögren

Possible vascularite cutanée associée

- EFR
  - CPT 4210 ml (56%)
  - CV 2770 ml (51%)
  - VR 1440 ml (70%)
  - VEMS/CVF 88%
  - DLCO (27%)

- LBA
  - 686 000 cell/ml
  - MA 65%, LY 13%, PNN 12%, PNE 10%
  - Pas de germe

- BGSA stade IV de Chisholm
- Biopsie du scalp: alopécie cicatricielle incomplète non spécifique

- Immunologie
  - FAN 1/1600 de type anti-synthétases
  - SSA (52 kD) positifs, SSB positifs
  - Anti-PL-12 positifs

Recherche d'une connectivite devant une PID subaigüe/chronique

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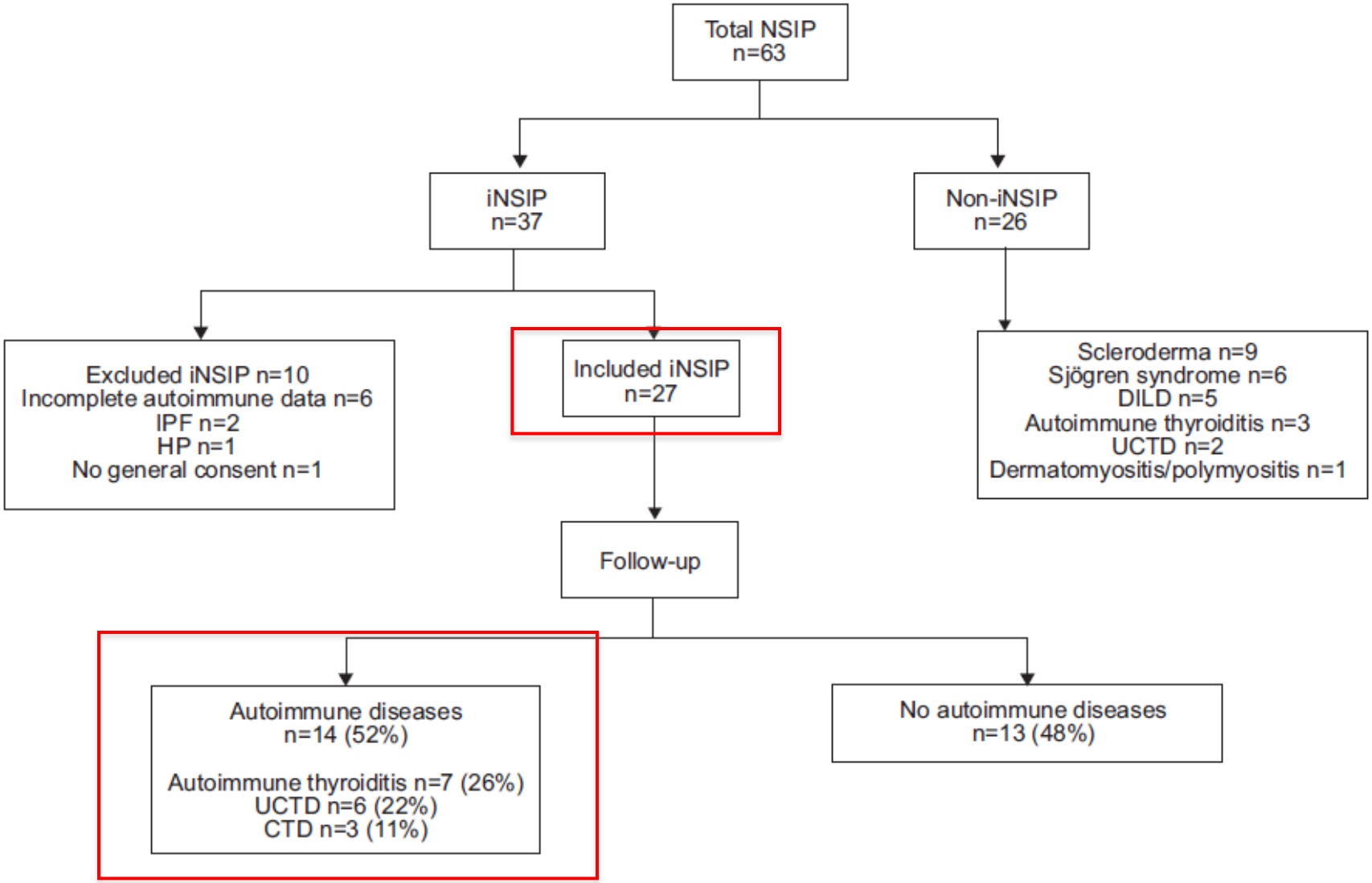
Idiopathic nonspecific interstitial pneumonia: an interstitial lung disease associated with autoimmune disorders?

Romagnoli et al. ERJ 2011

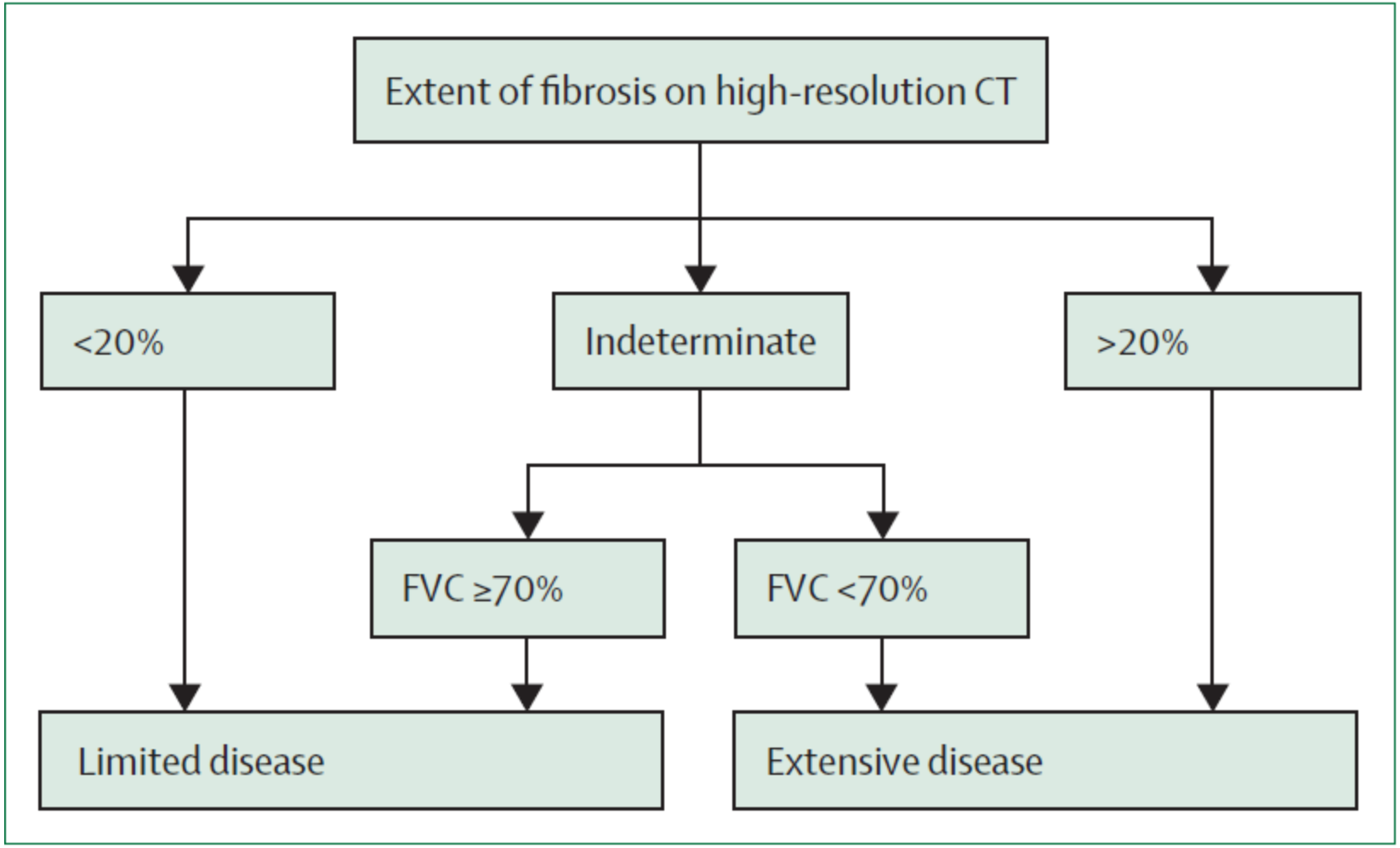


Particularités histo-pathologiques

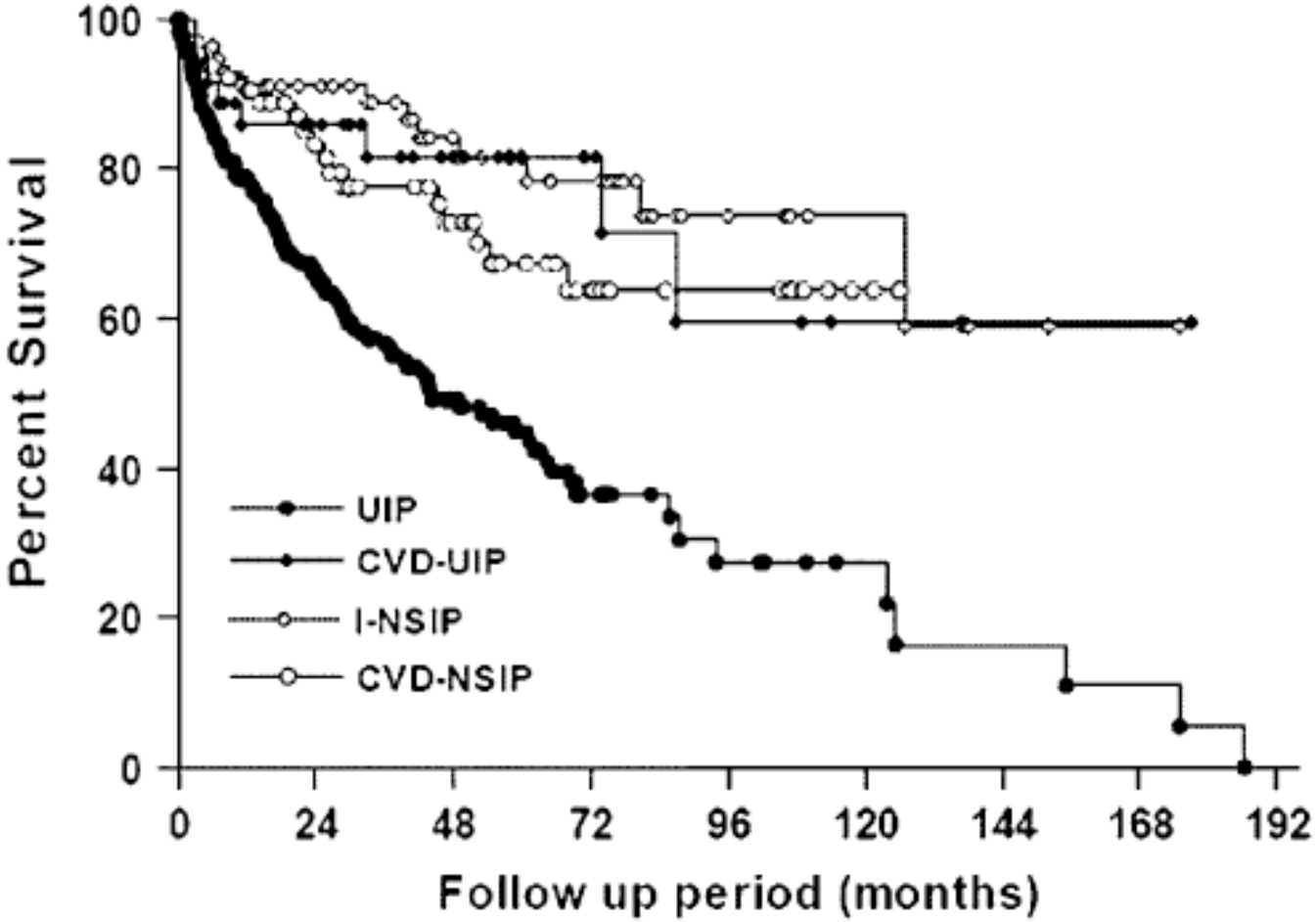
- Nodules lymphoïdes avec centres germinatifs
- Atteinte pleurale (étendue)
- Infiltration plasmocytaire importante
- Dépôts collagènes denses péri-vasculaires

Pronostic des PID des connectivites

Pronostic PID de la sclérodermie



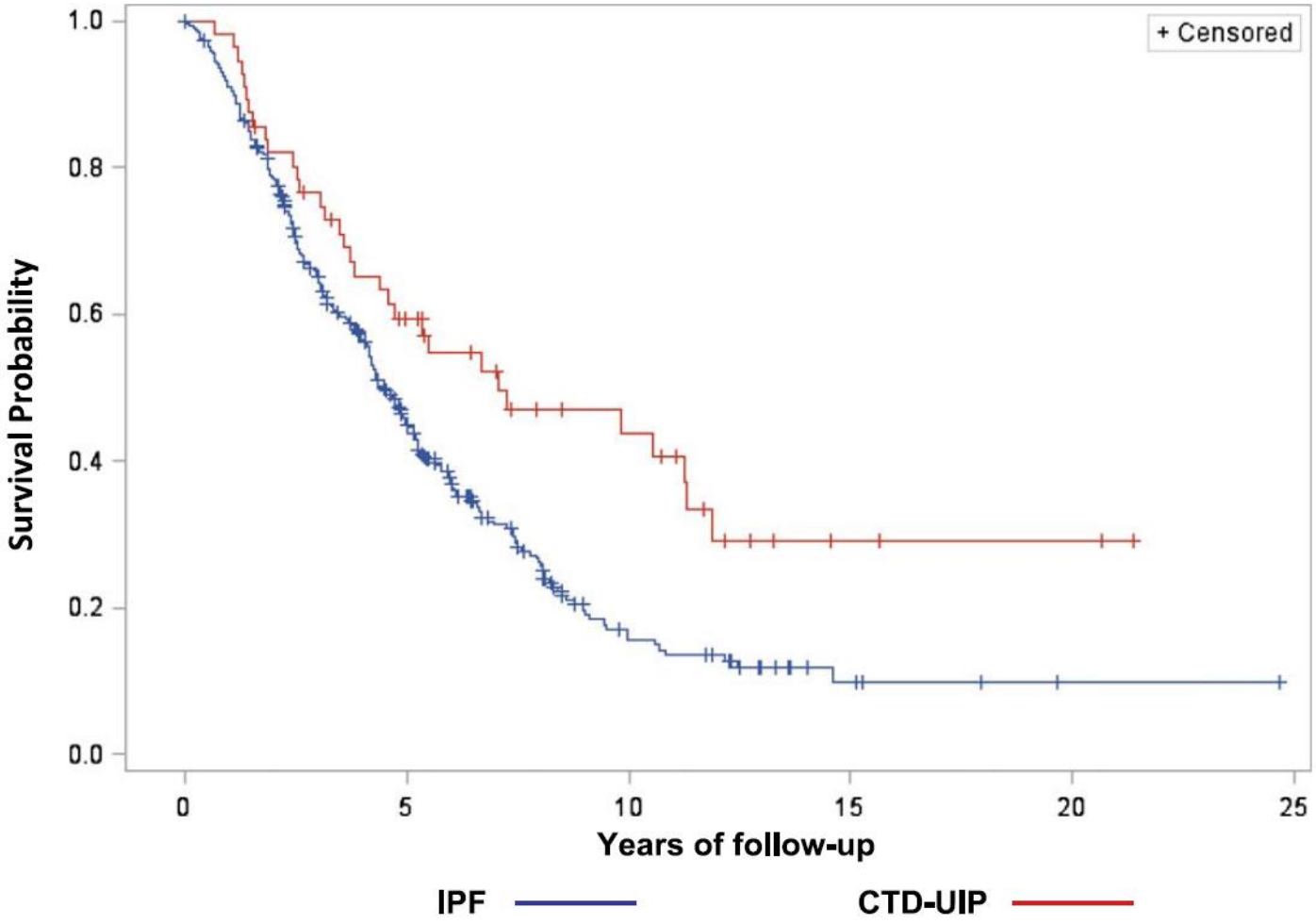
Fischer and du Bois Lancet 2012



Park et al. AJRCCM 2007

Pulmonary Function and Survival in Idiopathic vs Secondary Usual Interstitial Pneumonia

Strand et al. Chest 2014



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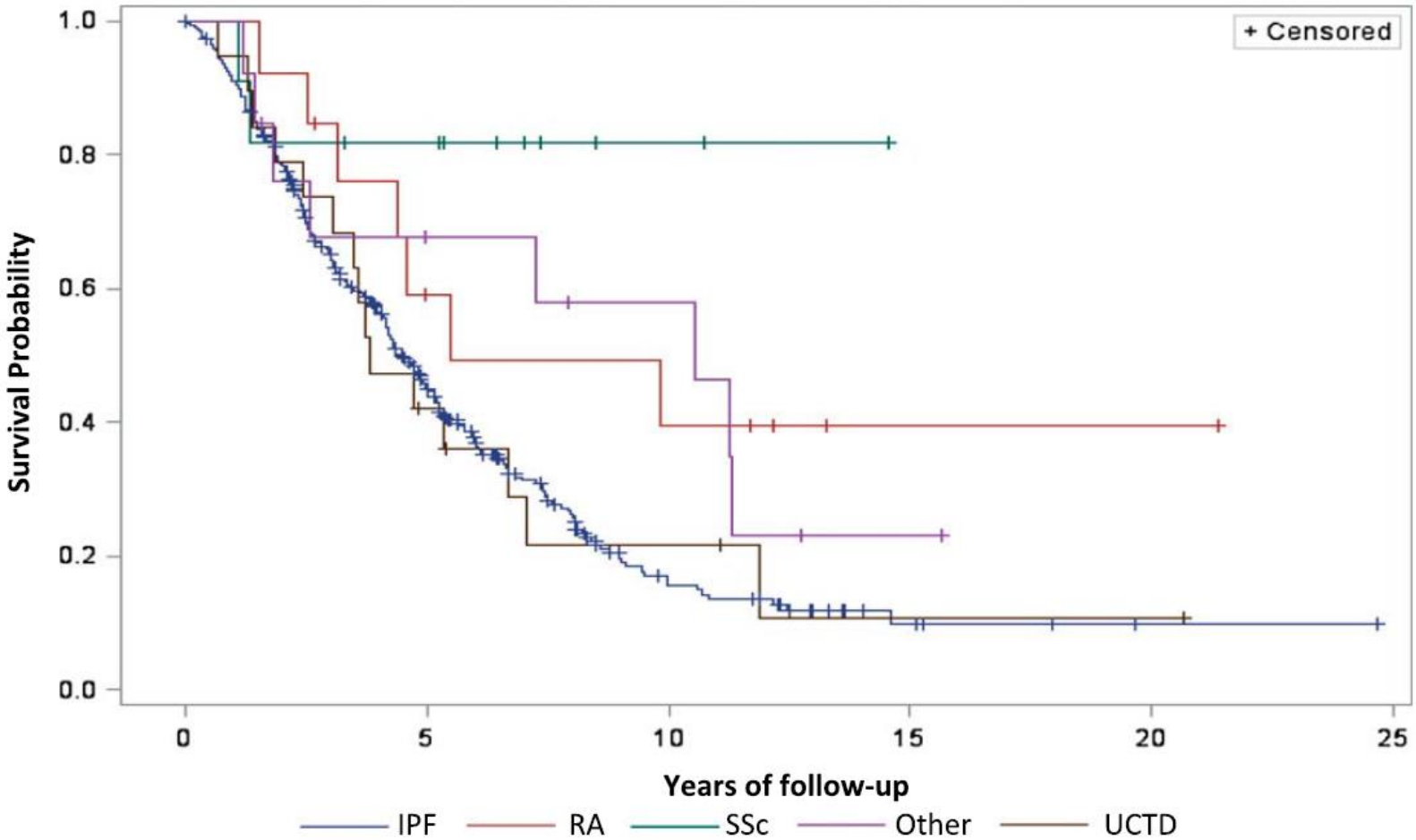
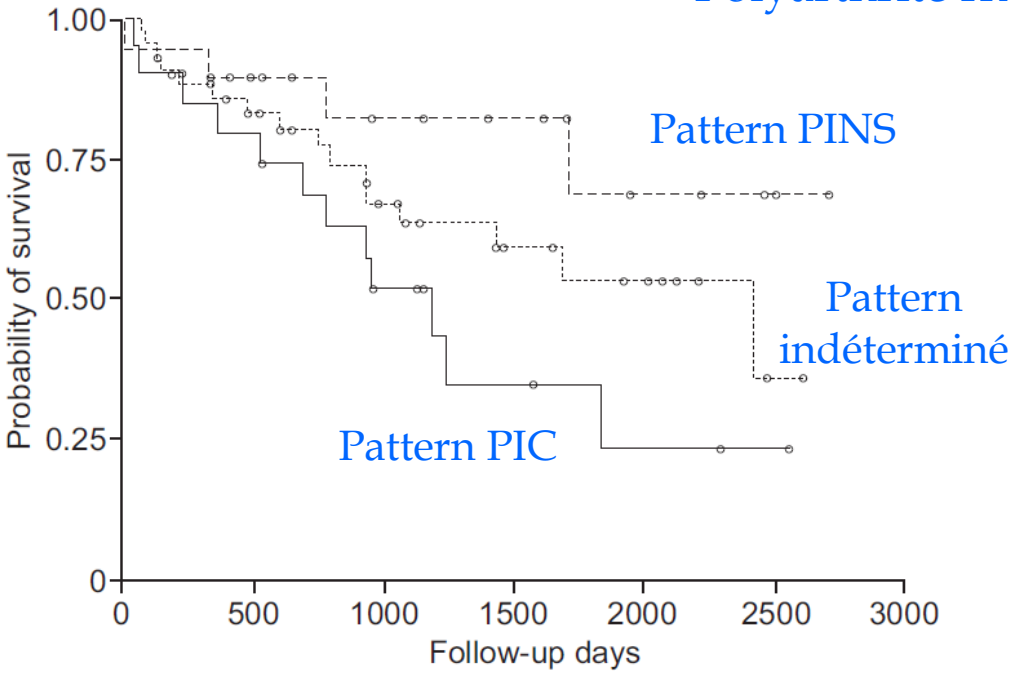
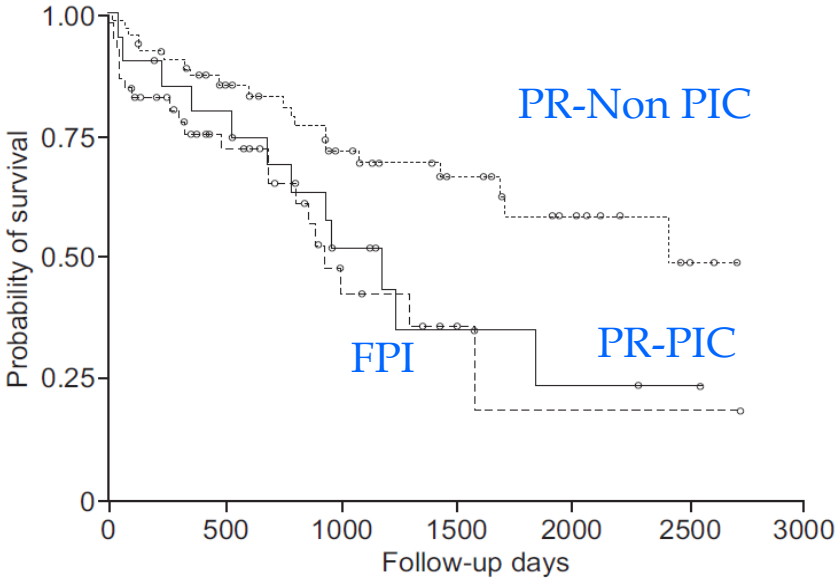
Strand et al. Chest 2014



Polyarthrite rhumatoïde





Kim et al. ERJ 2010

TABLE 2 Predictors of survival time in patients with rheumatoid arthritis-associated interstitial lung disease

	Bivariate		Multivariate	
	Hazard ratio	p-value	Hazard ratio	p-value
Female sex	0.55	0.10	0.30	0.008
Baseline FVC (% pred)	0.98	0.01		
Baseline $D_{L,CO}$ (% pred)	0.97	0.002	0.96	0.003
Definite UIP pattern#	2.09	0.04	2.34	0.05

Combined Pulmonary Fibrosis and Emphysema Syndrome in Connective Tissue Disease

Cottin et al.

Table 1. Classification of connective tissue diseases in the 34 study patients*

Rheumatoid arthritis	18 (53)
Systemic sclerosis	10 (29)
Diffuse cutaneous	3 (9)
Limited cutaneous	7 (20)
Mixed connective tissue disease	2 (6)
Overlapping connective tissue disease	2 (6)
Sjögren's syndrome	1 (3)
Polymyositis	1 (3)

* Values are the number (%) of patients.

Tabagisme

ARTHRITIS & RHEUMATISM
Vol. 63, No. 1, January 2011, pp 295–304

PID « pauci-immune »
« connectivite indifférenciée »
IPAF

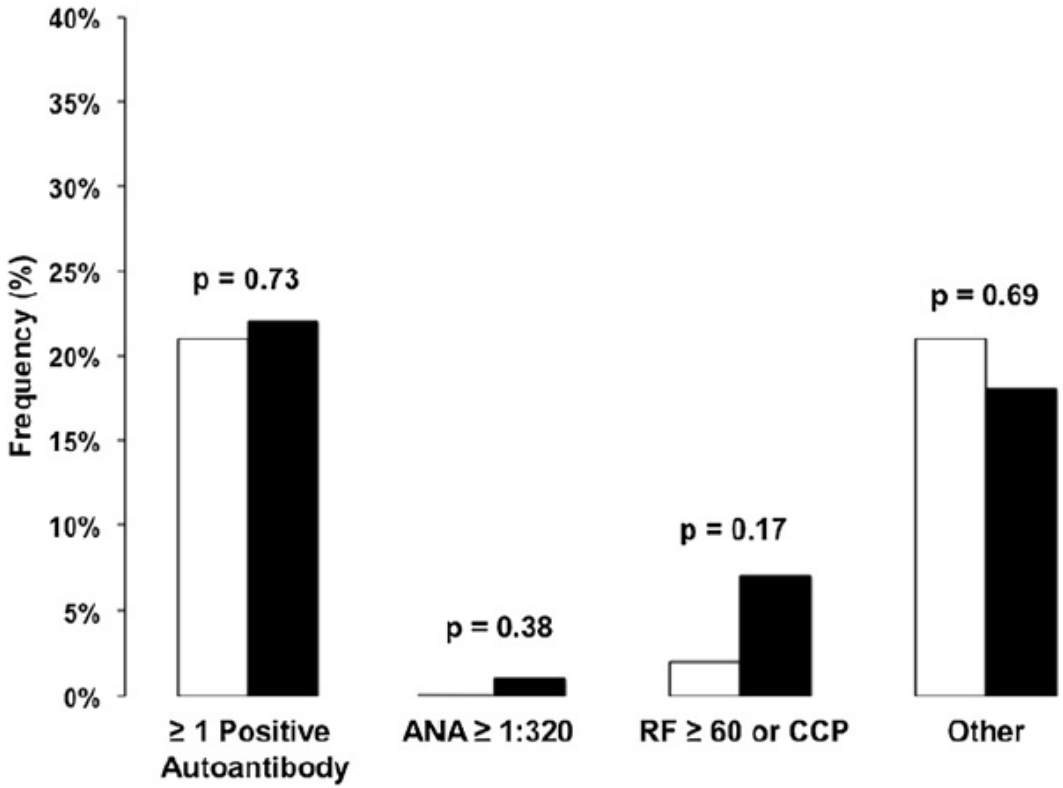
Connective Tissue Disease-Associated Interstitial Lung Disease

A Call for Clarification *Fischer et al. Chest 2010*

1. NSIP, UIP, LIP, OP, and DAD (or DIP if no smoking history), as determined by surgical lung biopsy specimen or suggested by high-resolution CT *and*
2. Insufficient extrathoracic features of a definite CTD to allow a specific CTD designation *and*
3. No identifiable alternative etiology for IP *and*
4. Any *one* of the following autoantibodies or *at least two* of the histopathology features:

Autoantibodies	Histopathology features
a. High-titer ANA (>1:320) or RF (>60 IU/mL)	(a) Lymphoid aggregates with germinal centers
b. Nucleolar-ANA	(b) Extensive pleuritis
c. Anti-CCP	(c) Prominent plasmacytic infiltration
d. Anti-Scl-70	(d) Dense perivascular collagen
e. Anti-Ro	
f. Anti-La	
g. Anti-dsDNA	
h. Anti-Smith	
i. Anti-RNP	
j. Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12, and others)	
k. Anti-PM-Scl	
l. Anticentromere	

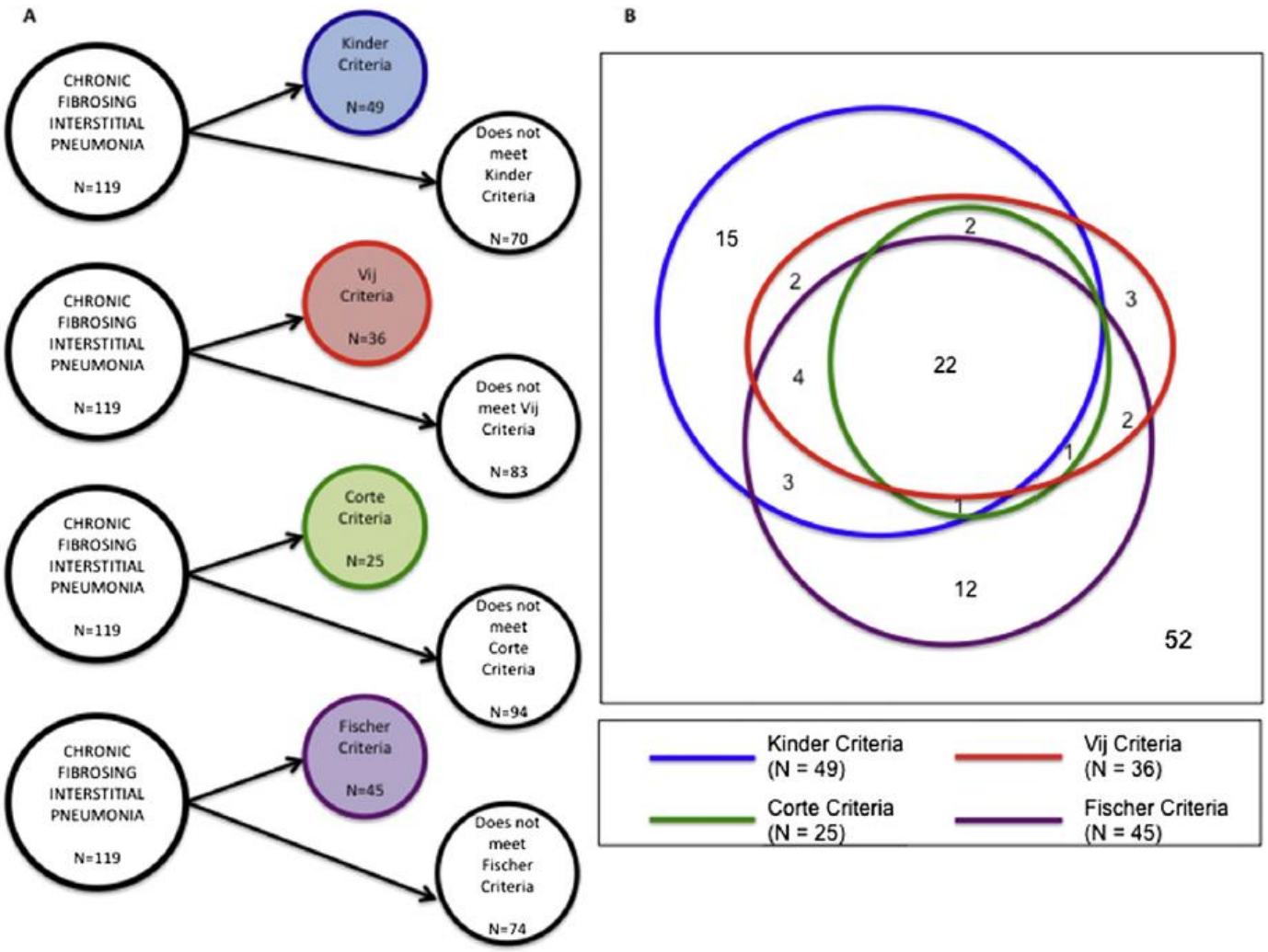
Prevalence and clinical significance of circulating autoantibodies in idiopathic pulmonary fibrosis



Lee et al. Respir Med 2013

Survival in interstitial pneumonia with features of autoimmune disease: A comparison of proposed criteria

Assayag et al. Res Med 2015



Survival in interstitial pneumonia with features of autoimmune disease: A comparison of proposed criteria *Assayag et al. Res Med 2015*

Unadjusted and adjusted hazard ratios for mortality associated with each of the criteria.

	Hazard ratio (95% CI) p-value	
	Unadjusted	Adjusted for GAP score [12]
Kinder criteria	0.55 (0.30–1.03) 0.06	0.66 (0.35–1.26) 0.21
Vij criteria	0.45 (0.22–0.92) 0.03	0.50 (0.22–1.11) 0.09
Corte criteria	0.45 (0.19–1.06) 0.07	0.35 (0.13–0.97) 0.04
Fischer criteria	0.60 (0.33–1.10) 0.10	0.60 (0.31–1.18) 0.14

Abbreviations: GAP, Gender-Age-Physiology.

An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

Fischer et al. Eur Respir J 2015

TABLE 1 Classification criteria for "interstitial pneumonia with autoimmune features"

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

A. Clinical domain

1. Distal digital fissuring (*i.e.* "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud's phenomenon
6. Unexplained digital oedema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

B. Serologic domain

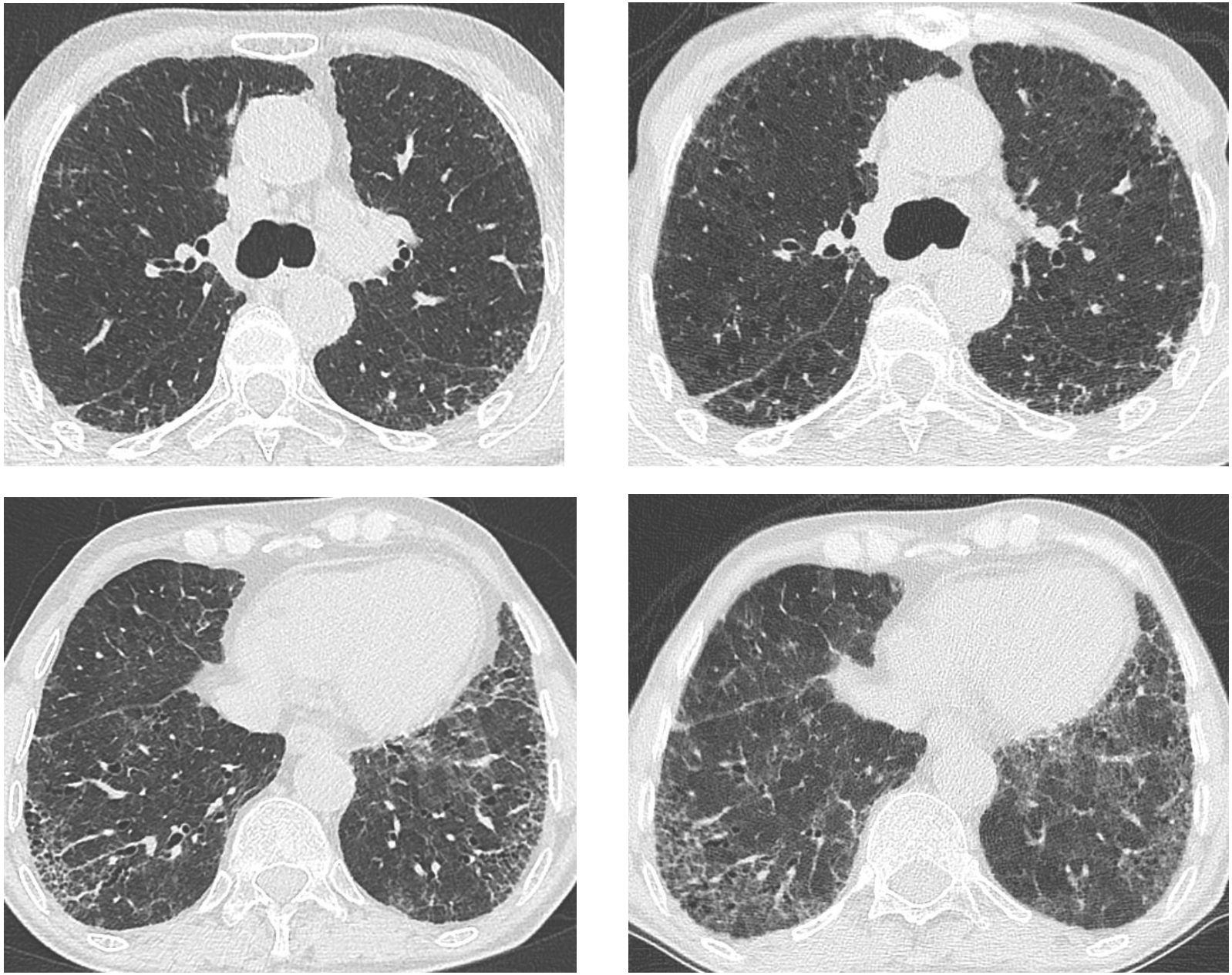
1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titre) *or*
   b. ANA centromere pattern (any titre)
2. Rheumatoid factor ⩾2× upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

C. Morphologic domain

1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates with germinal centres
   f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multi-compartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease[#] (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy

Une PID fibrosante chez un homme de 78 ans

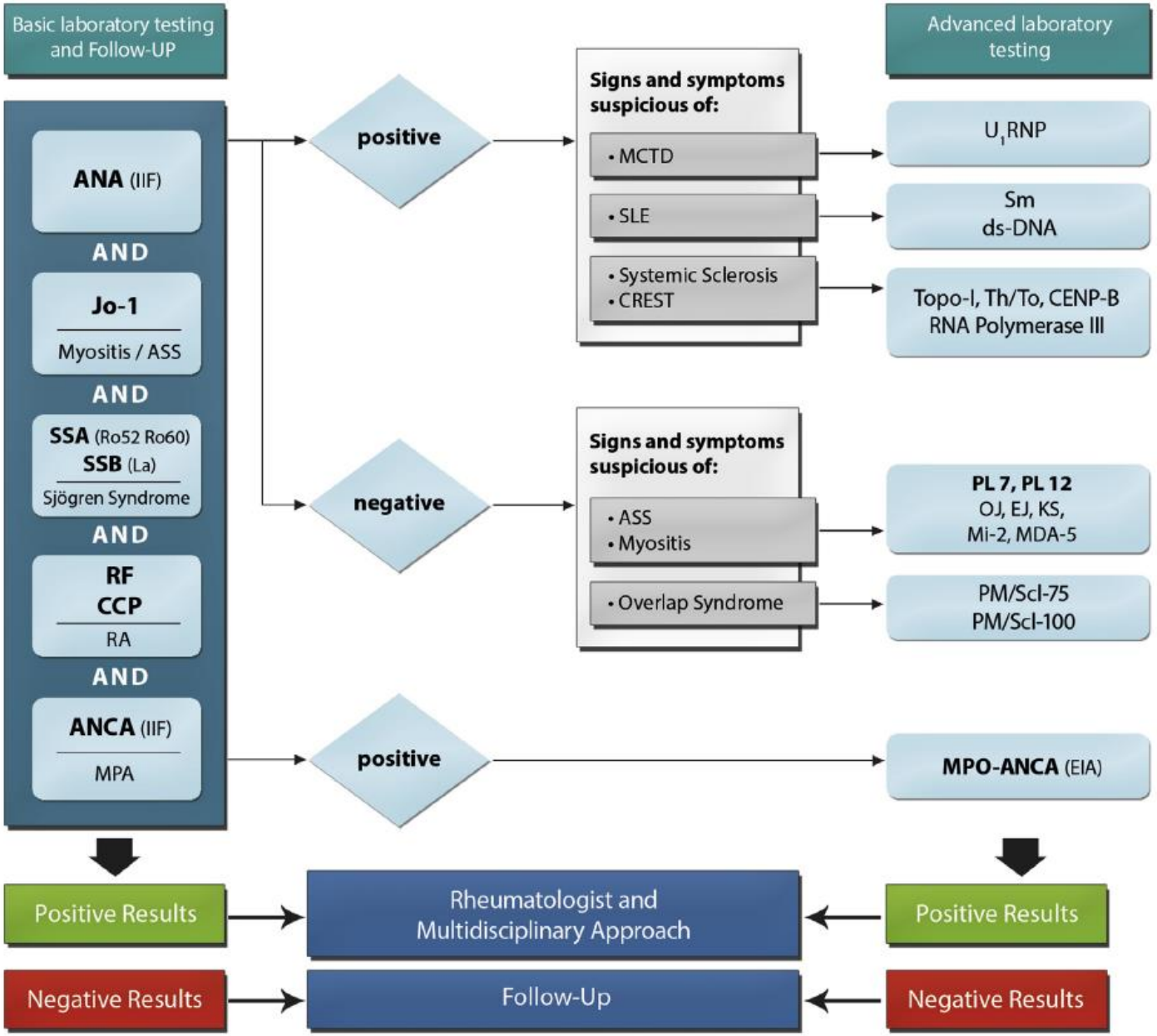
- Mars 2015, en Algérie, dyspnée rapidement progressive, asthénie, PaO_2 53 mmHg
- Traitement empirique Médrol 30 mg/j amélioration
- Déc 2015: Médrol 4 mg/j
  - CPT 57%, CV 61%, DLCO 30%
  - PaO_2 80 mmHg $PaCO_2$ 39 mmHg, T6mn 582 m (115%); SpO_2 99% à 86%
- Oct 2016: dyspnée 2 étages, pas de signe extrathoracique
  - CPT 57% CV 55%, DLCO 27%
  - PaO_2 75 mmHg, T6mn 503 m (99%) SPO_2 98% à 85%
- Echo cœur: FEVG 66%; PAPs 48 mmHg



Décembre 2015 Octobre 2016

- Biologie usuelle normale y compris EPP et CPK
- FAN 1/1600 d'aspect « anti-synthétases »
- Anti-JO1 négatifs
- Anti-PL-12 positifs

The use of auto-antibody testing in the evaluation of interstitial lung disease (ILD) – A practical approach for the pulmonologist *Bahmer et al. Res. Med 2016*



Conclusion

- Diversité des présentations
  - des PID
  - des différentes connectivites
- Démarche rigoureuse, préciser au mieux le type de connectivite
  - Approche multidisciplinaire++
  - Diagnostics différentiels: infections, cœur, médicaments
- Impact pronostique et thérapeutique
- IPAF
  - Définition consensuelle
  - Evaluation impact pronostiquez