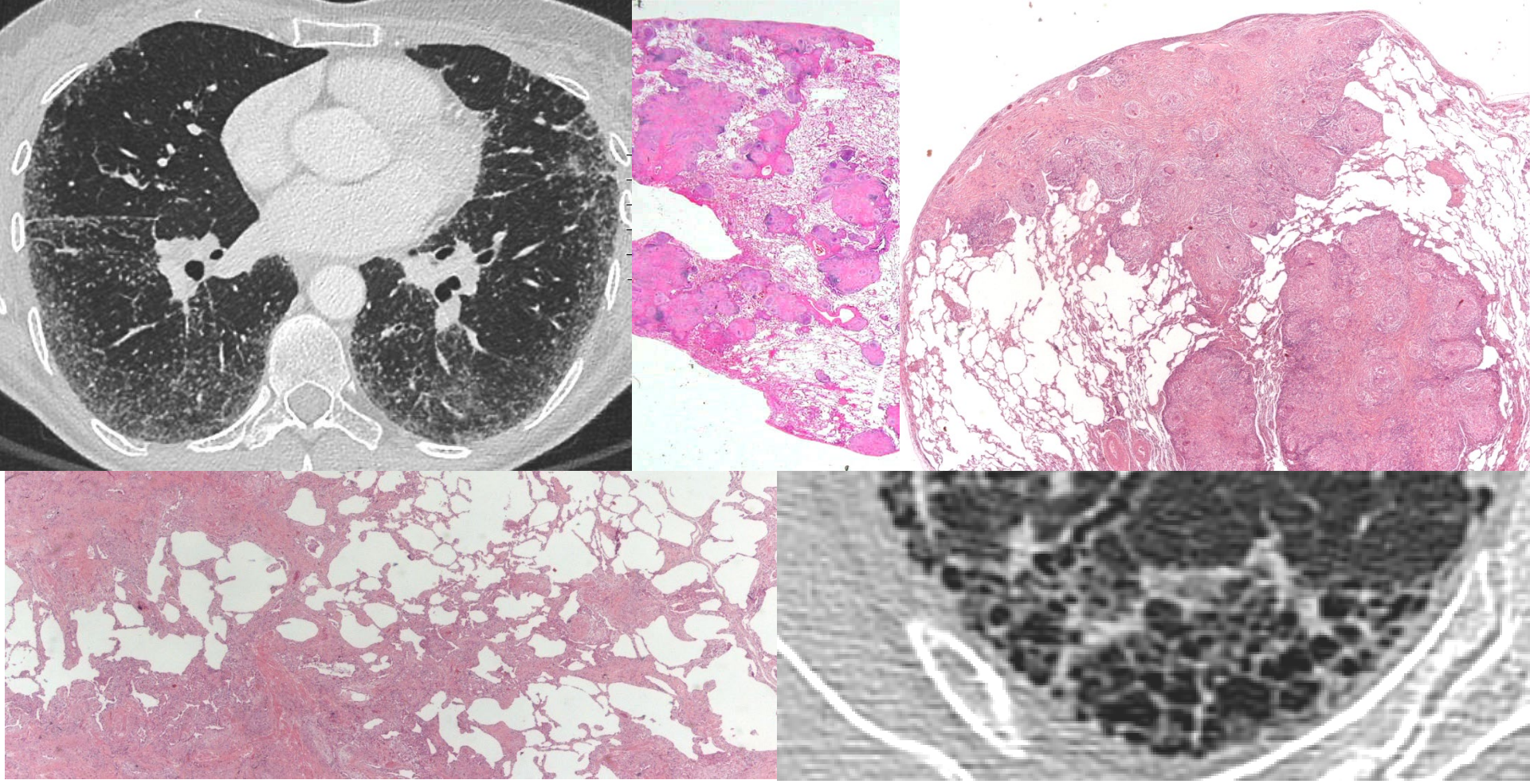

Le malattie polmonari rare e il MMG

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What is a "rare disease"?

- *Europe:* a disease is considered as *rare* when it affects 1 person per 2,000 (Prevalence <0.05%)

- *USA:* a disease is considered as *rare* when it has a prevalence of fewer than 200,000 affected individuals in the United States (Certain diseases with 200,000 or more affected individuals may be included in this list if certain subpopulations of people who have the disease are equal to the prevalence standard for rare diseases)

What is an "orphan disease"?

The term "orphan" denotes diseases that either because of their rarity or paucity of therapeutic options are less well understood by patients and their caregivers

Du Bois RM . Am J Respir Crit Care Med 2002; 166: 1157

ILDs represent a very large group of more than 200 different entities, many of which are rare or "orphan“ diseases

- Much remains unknown or debatable for many of these ILDs, notably issues of prevalence, incidence and mortality rates

Demedts et al. Eur Respir J 2001; 18: 2-16S

AREAS OF MEDICINE WHICH ARE NOT FINANCIALLY REWARDING BECOME ORPHAN

- RARE DISEASES

6.000 RARE DISEASES

10 % OF PATIENTS WITH SEVERE DISEASE

DRUGS FOR RARE DISEASES ARE ORPHANS BECAUSE

- FEW ANIMAL MODELS AVAILABLE

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- LONG TIME AND HIGH COST OF DRUG DEVELOPMENT

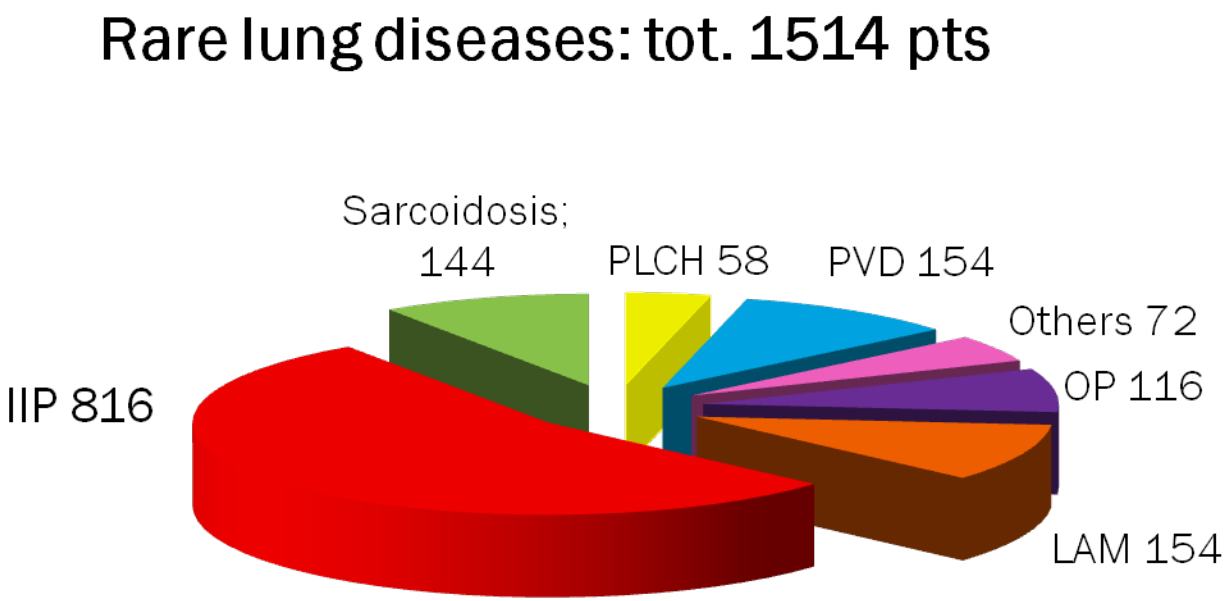
DRUGS FOR RARE DISEASES ARE ORPHANS BECAUSE

- FEW ANIMAL MODELS AVAILABLE
- DIFFICULTIES TO RECRUTE PATIENTS
- LONG TIME AND HIGH COST OF DRUG DEVELOPMENT
- LACK OF FINANCIAL SUPPORT

ORPHAN DRUG PROGRAM

	USA	JAPAN	EUROPE
BEGINNING	1987	1993	1999
PATIENTS	< 220.000	< 50.000	< 200.000
EXCLUSIVITY	10 yrs	10 yrs	10 yrs
GRANTS	yes	yes	no
DETAXATION	yes	yes	no
AGENCY	FDA	PMDA	EMEA

Ospedale S. Giuseppe Milan, Italy: 1999 – July 2018



- ILDs represent a very large group of more than 200 different entities, many of which are rare or "orphan“ diseases
- Much remains unknown or debatable for many of these ILDs, notably issues of prevalence, incidence and mortality rates

Demedts et al. Eur Respir J 2001; 18: 2-16S

Are interstitial lung diseases still orphan diseases?

Although the prevalence of ILDs is rather rare (67.5/100.000 for females and 80.9/100.000 for males), very many more patients die each year as a result of ILDs than other more diffuse respiratory diseases

Clinical Classification

Diffuse parenchimal lung diseases

Exposure-related:
- occupational
- environmental
- medication

55-60%

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

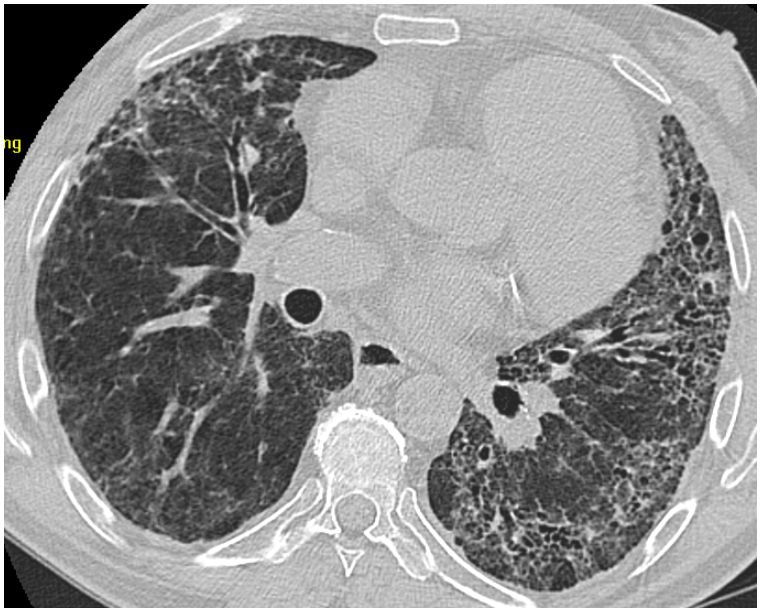
Cryptogenic organising pneumonia

Non-specific interstitial pneumonia

Lymphocytic interstitial pneumonia

Idiopathic diseases

Collagen vascular diseases



Infectious diseases

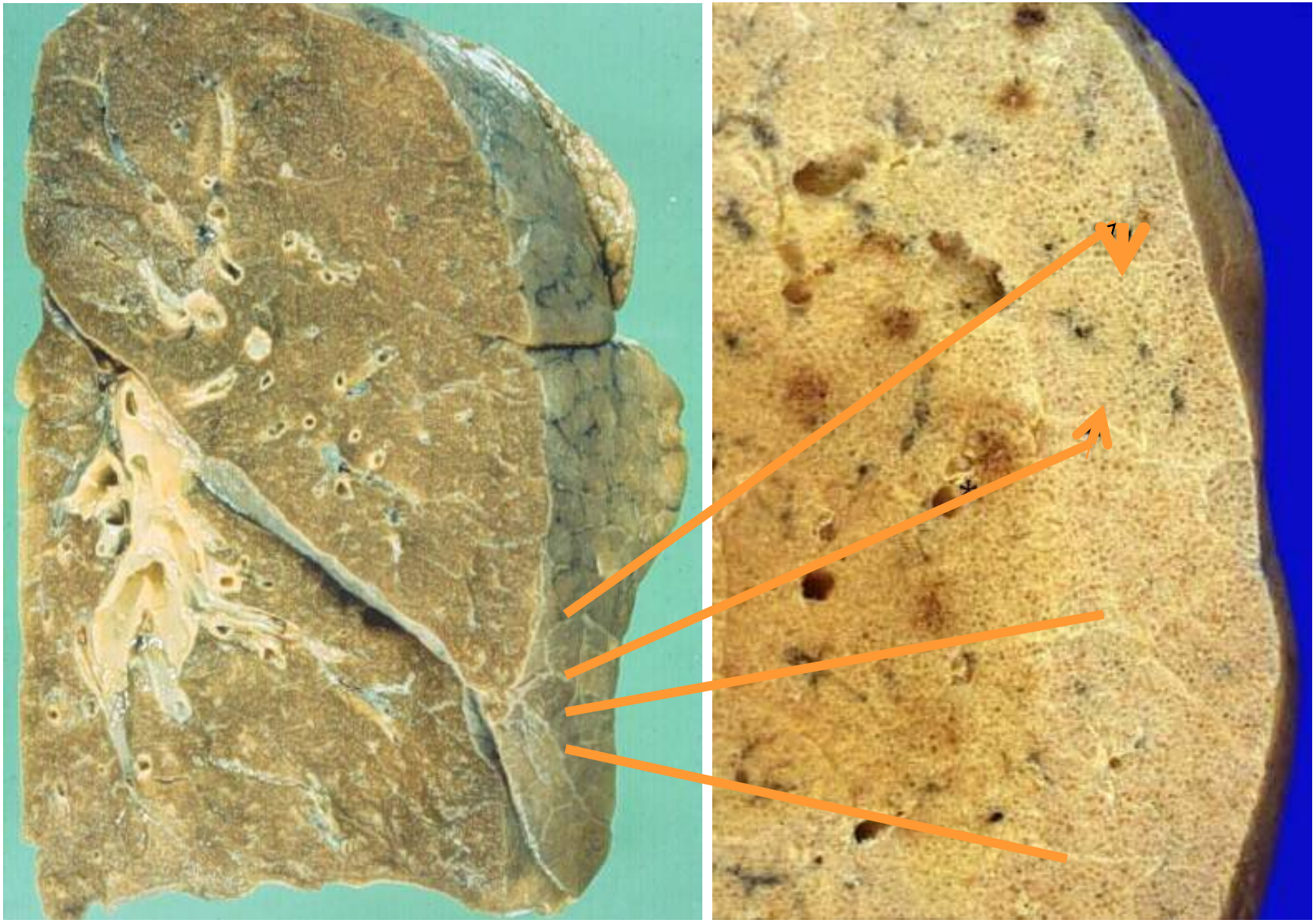
Gastro-intestinal disorders

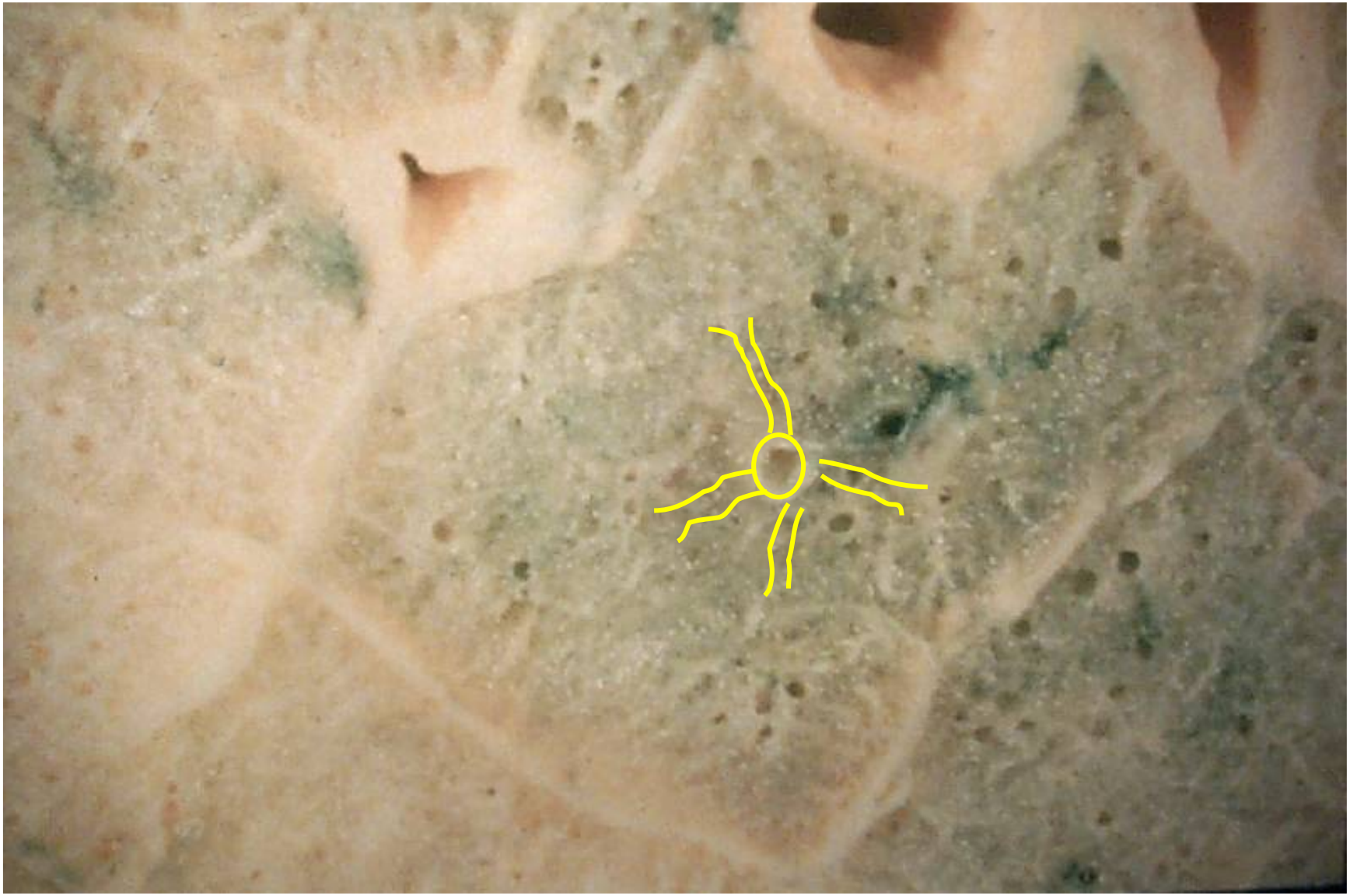
Neoplastic diseases

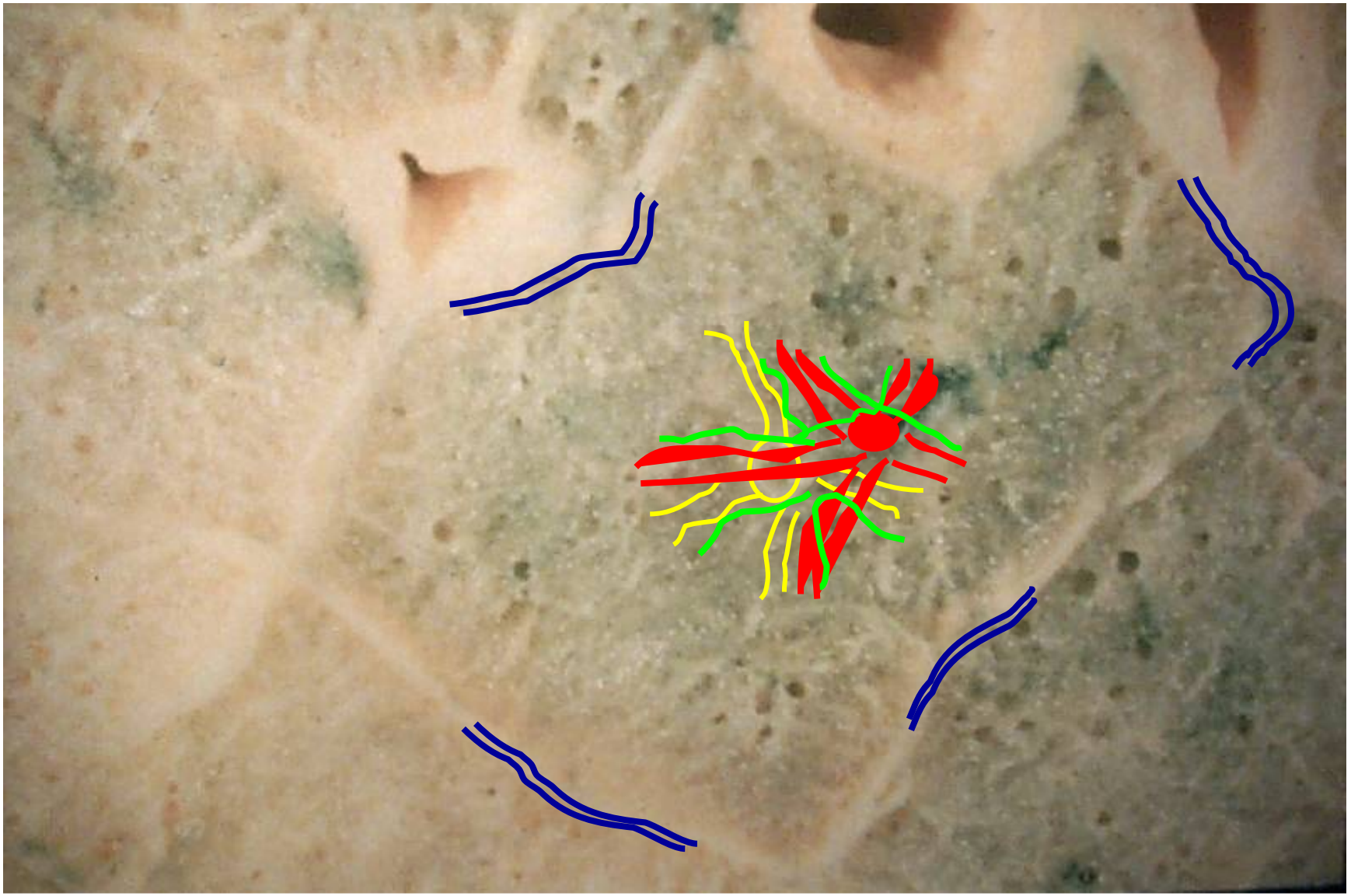
Drug toxicity

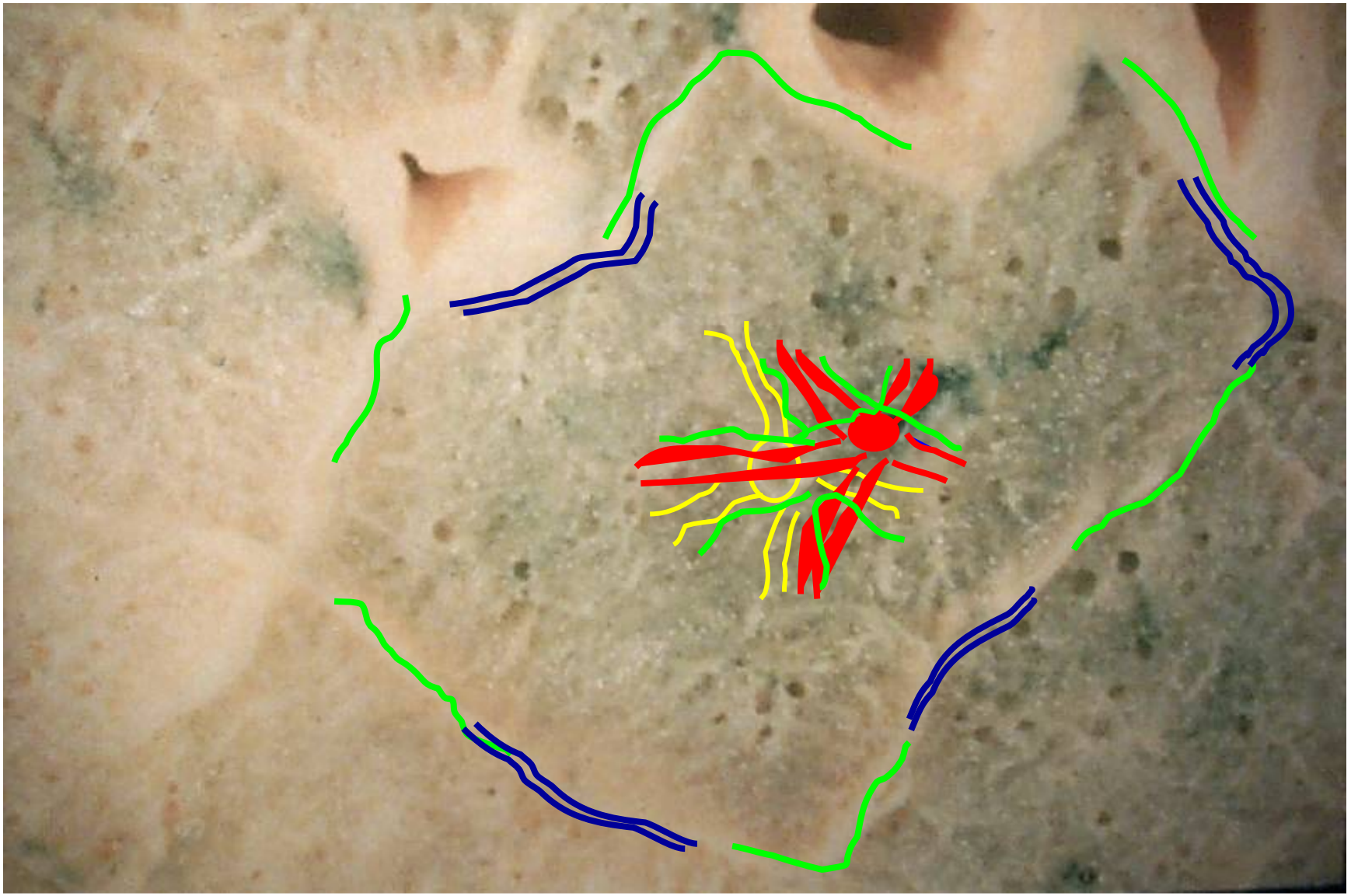
Occupational diseases

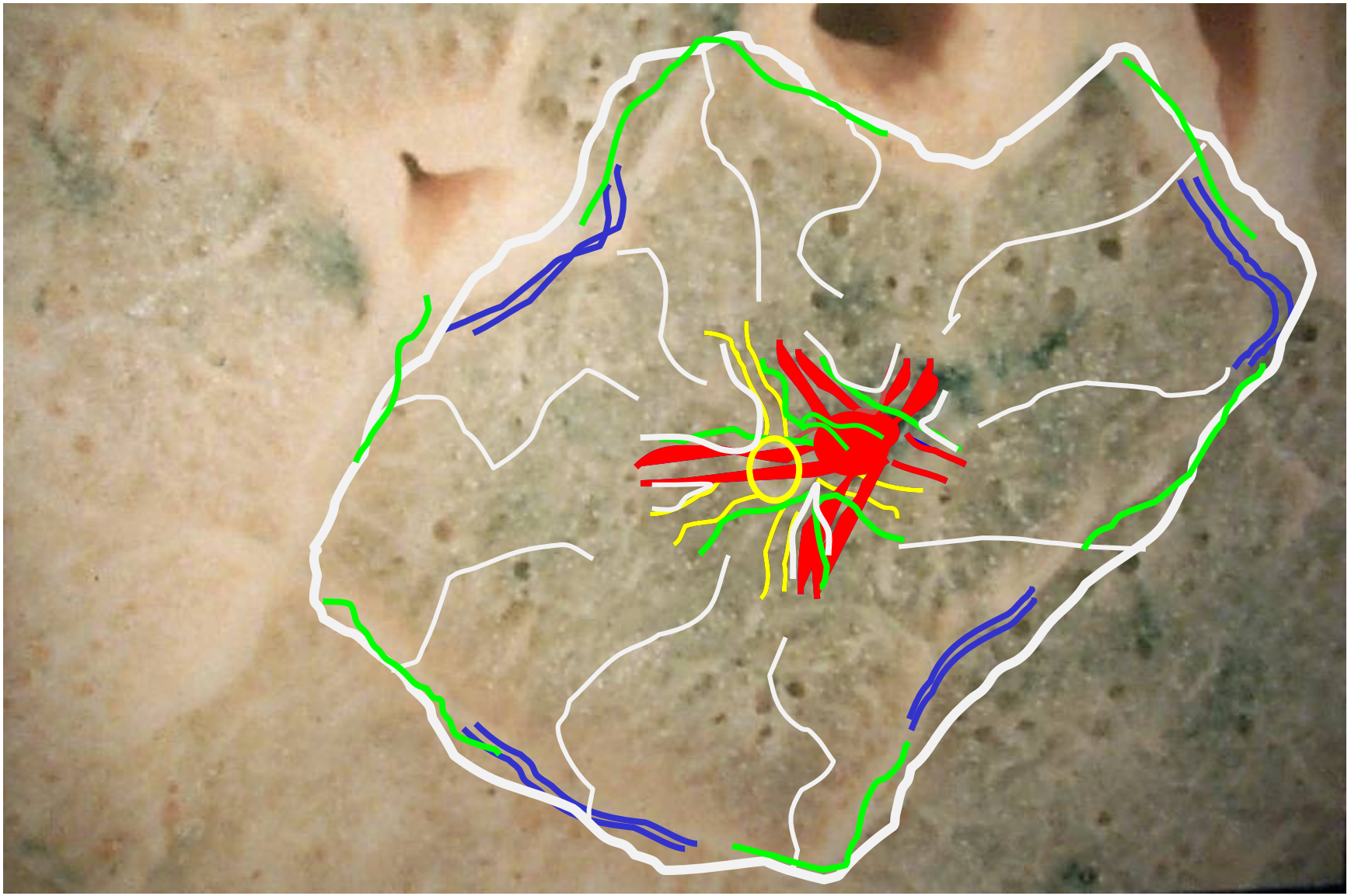
Secondary pulmonary lobule

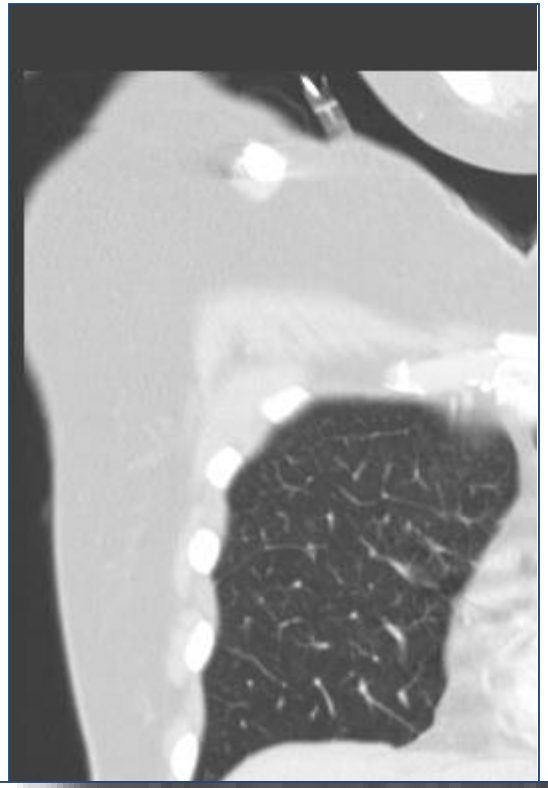


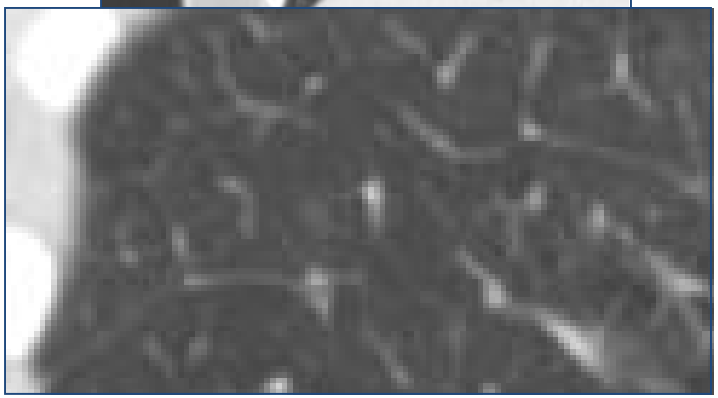


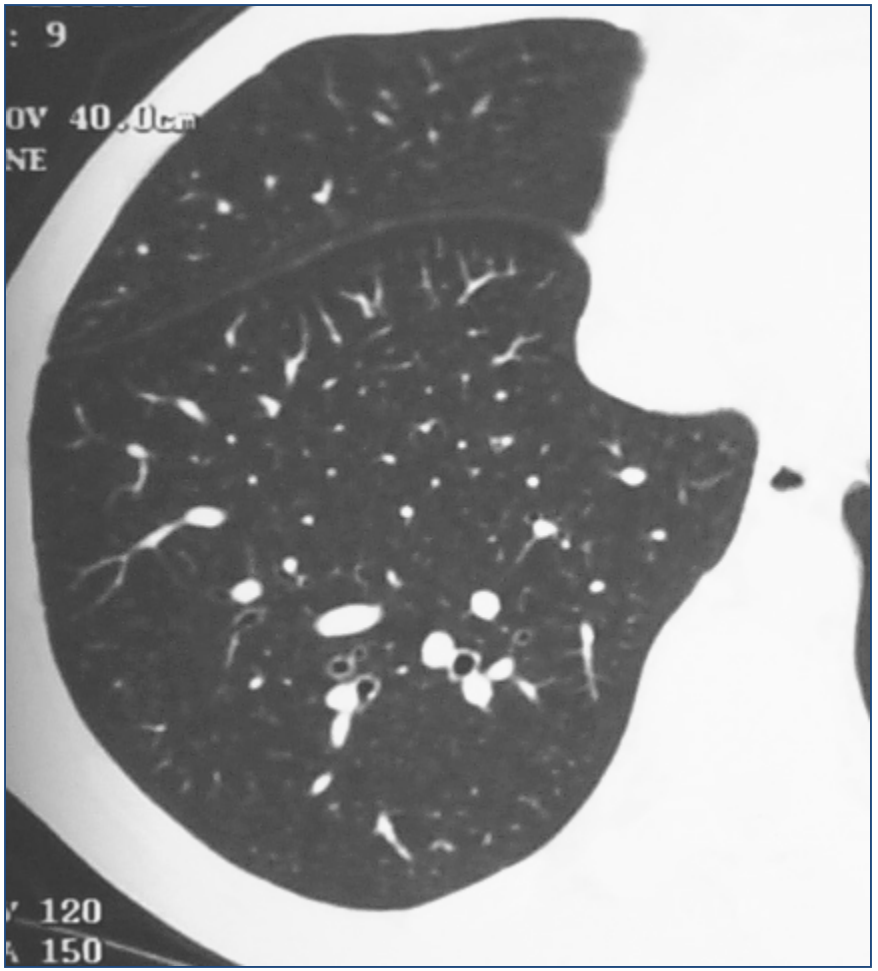








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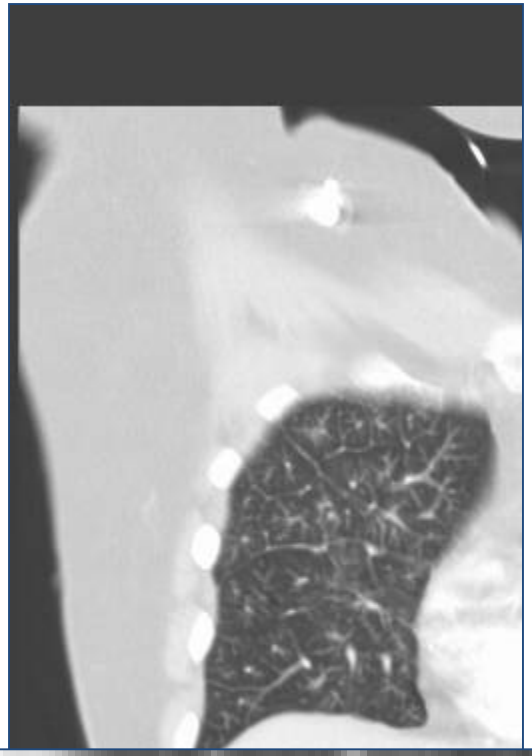
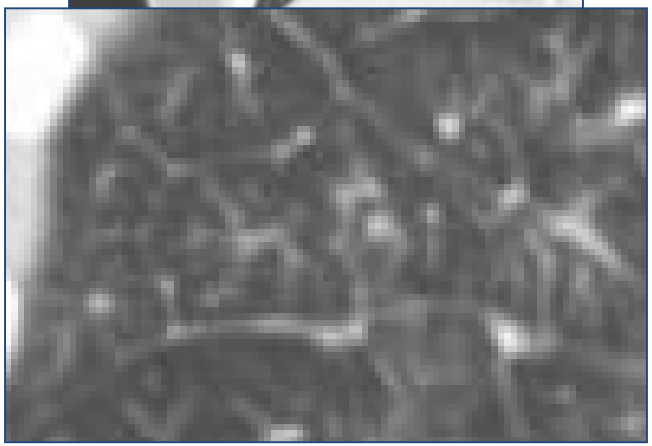
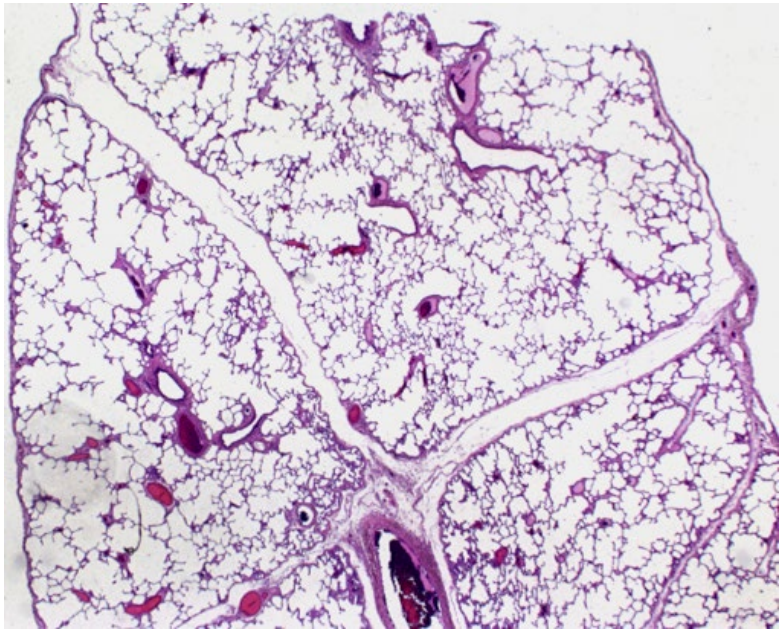
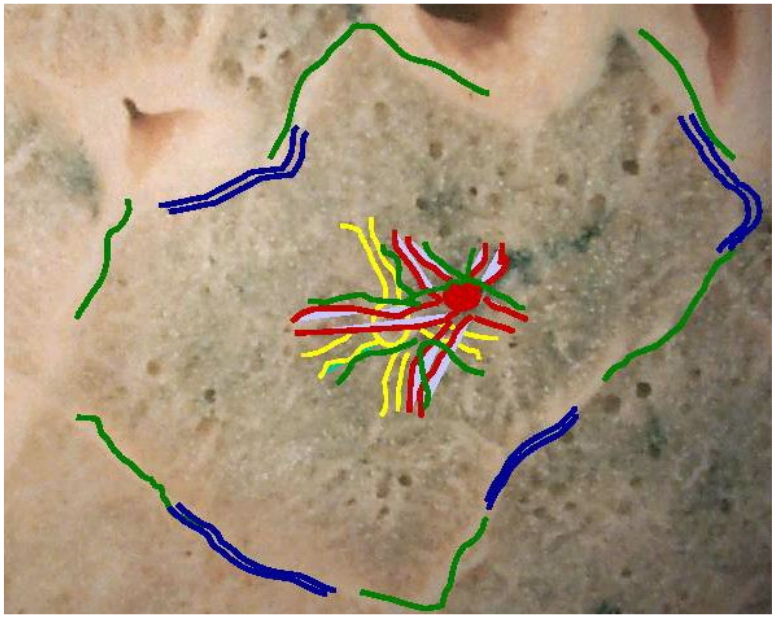


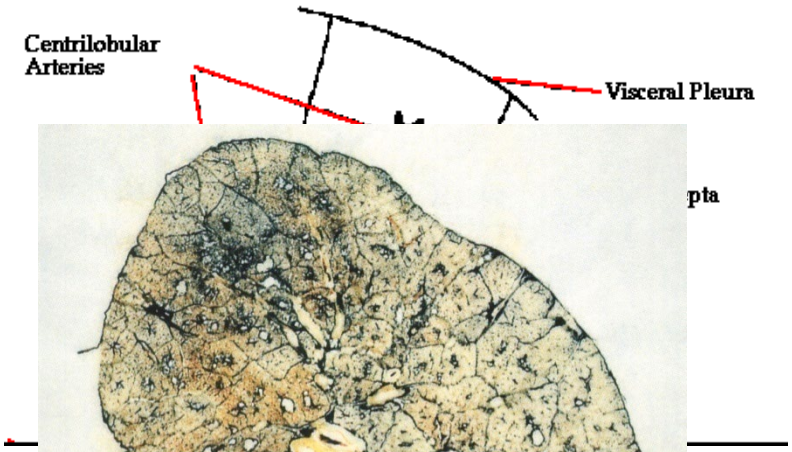


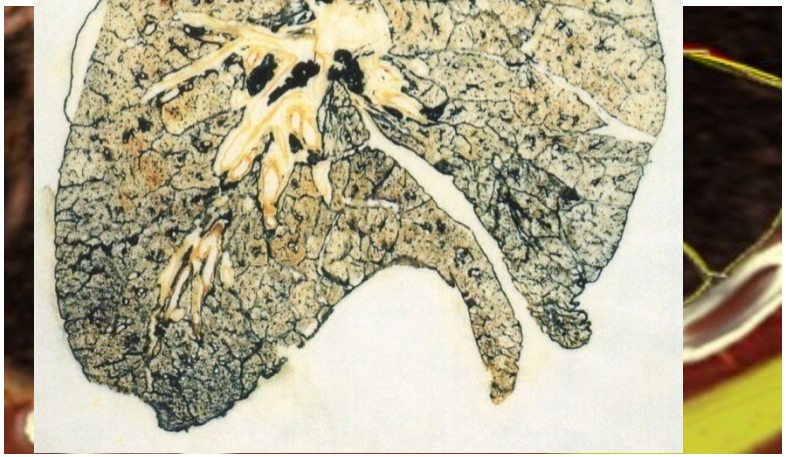


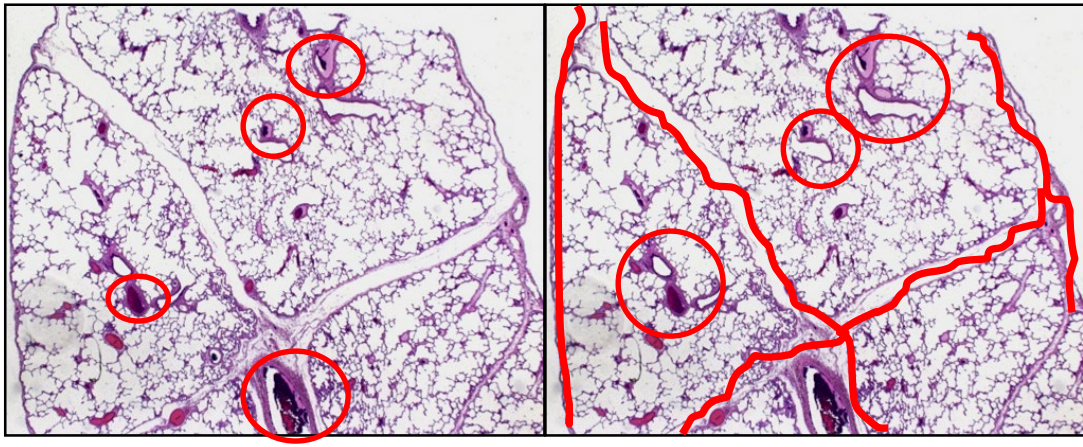


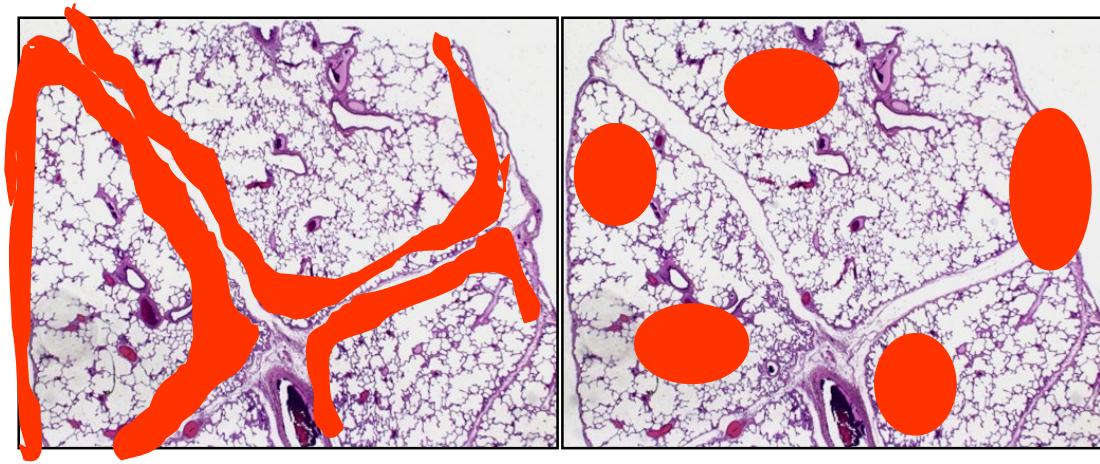
Pneumopatie infiltrative diffuse

Coinvolgono il lobulo polmonare secondario



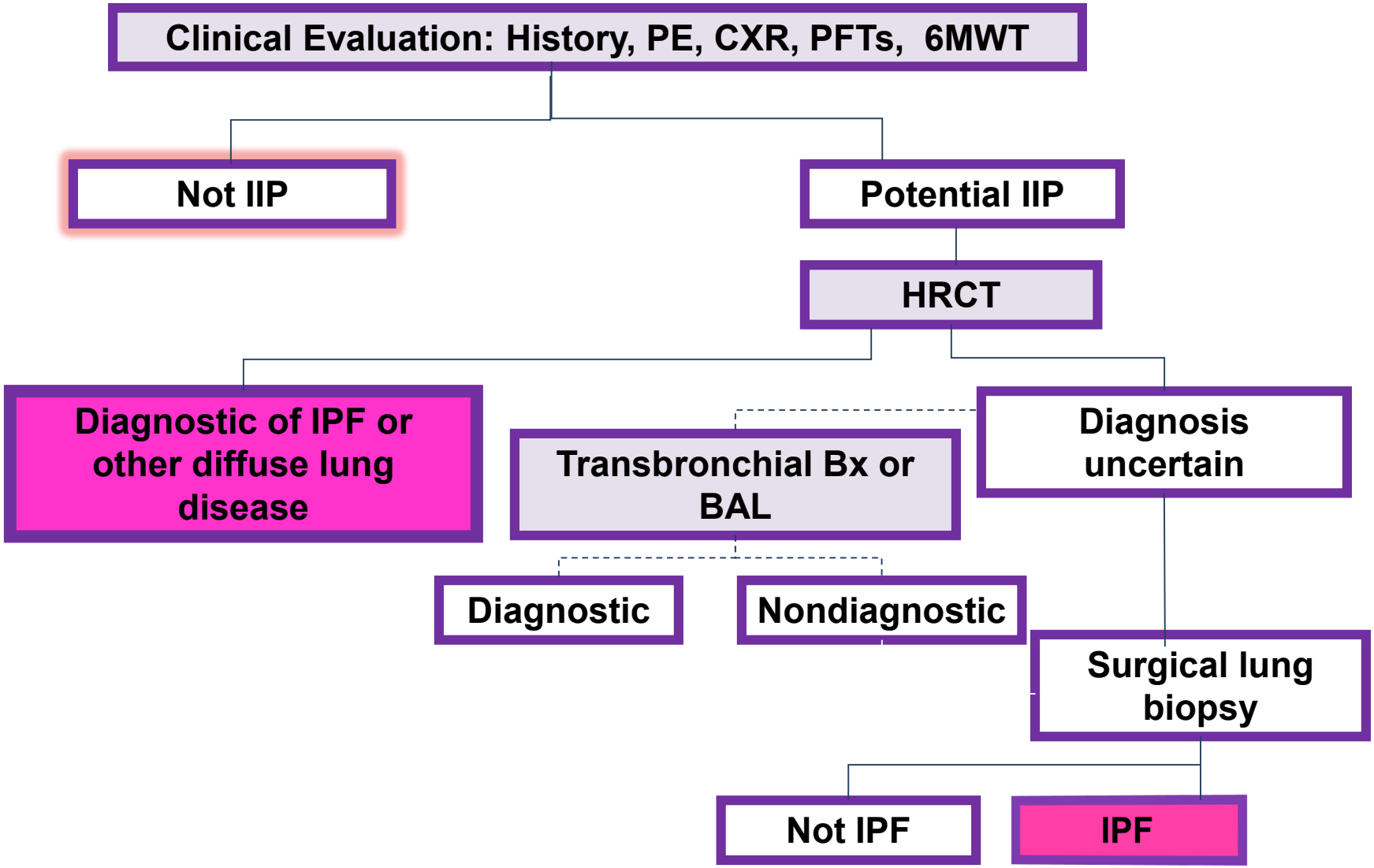


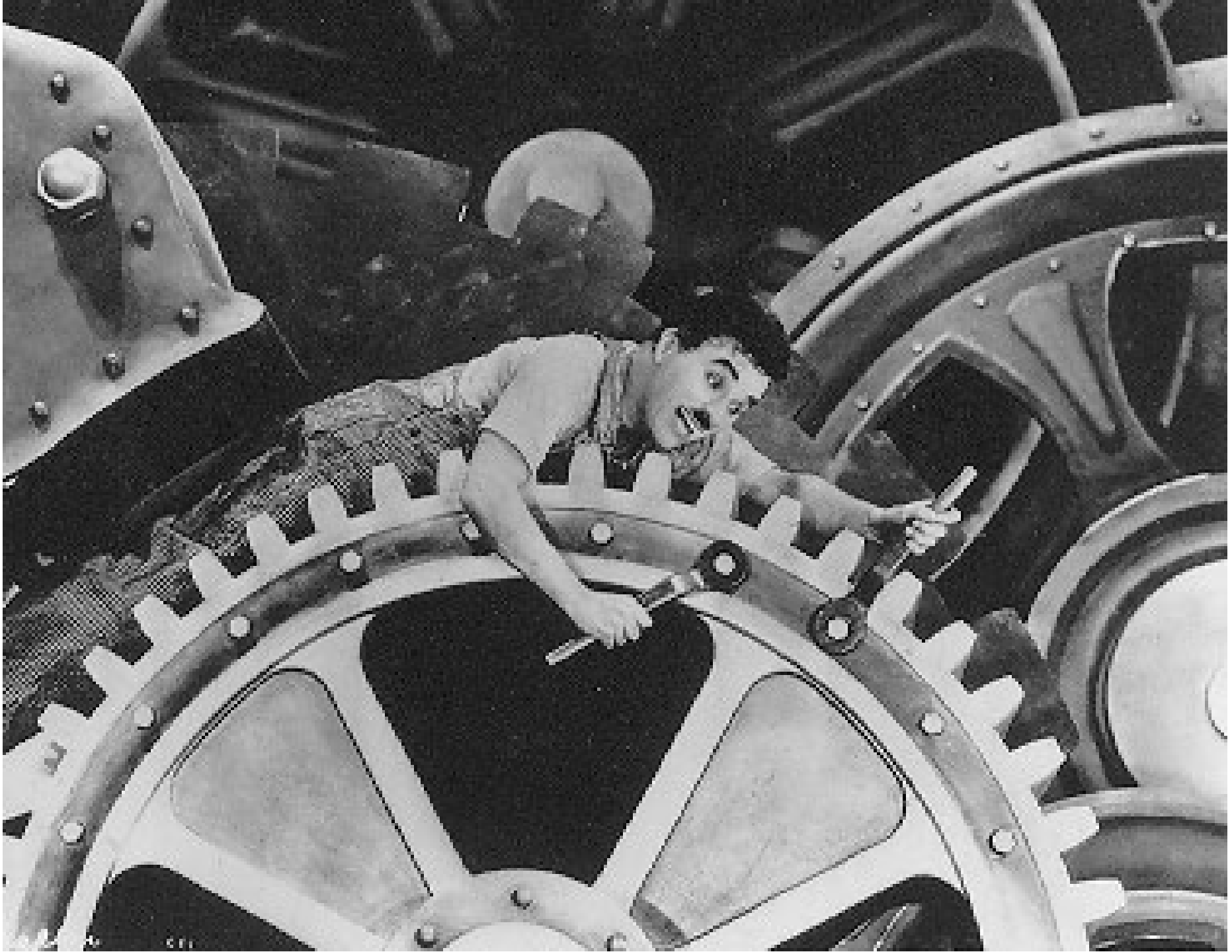




Approach to Diagnosing

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

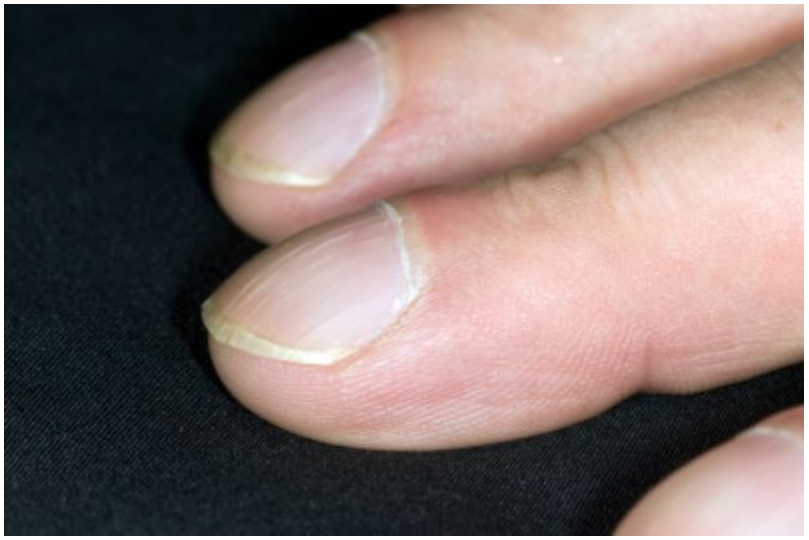




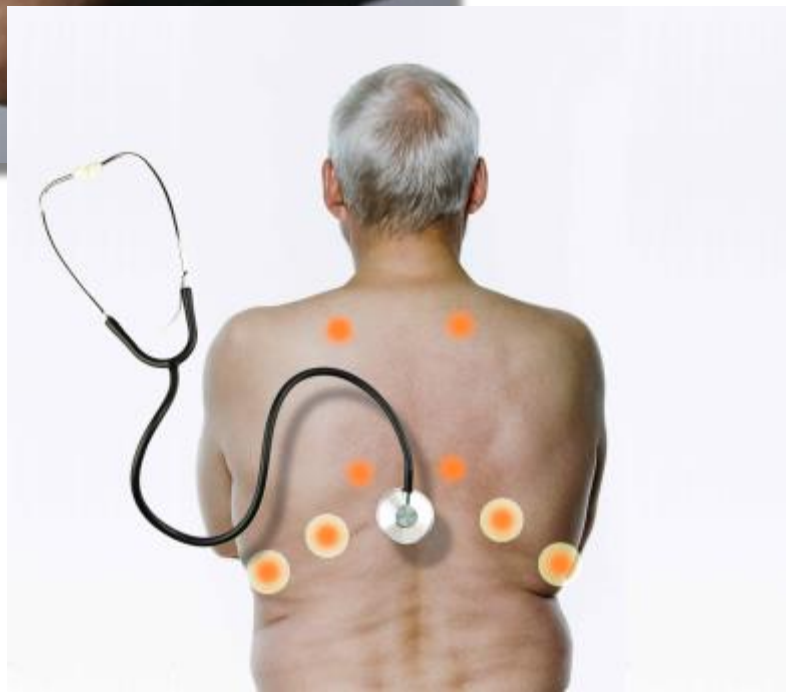
Clinical features of IPF

- Age >45 years at presentation
- Non-productive cough
- Progressive exertional dyspnoea
- Dry, inspiratory bibasilar "Velcro®-like" crackles
- Abnormal pulmonary function test results - evidence of restriction and impaired gas exchange
- Clubbing of fingers

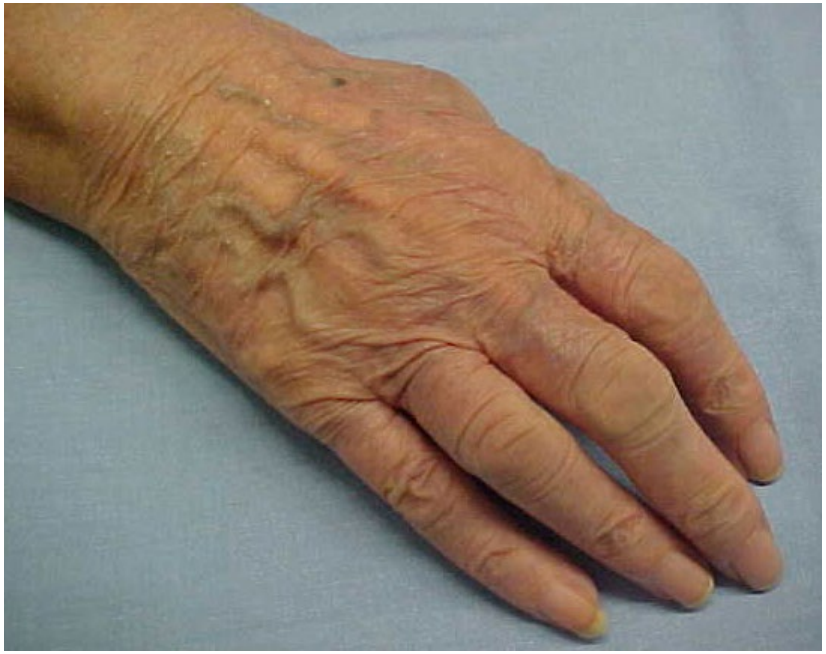
Clubbing of the fingers develops in 25–50% of patients with IPF

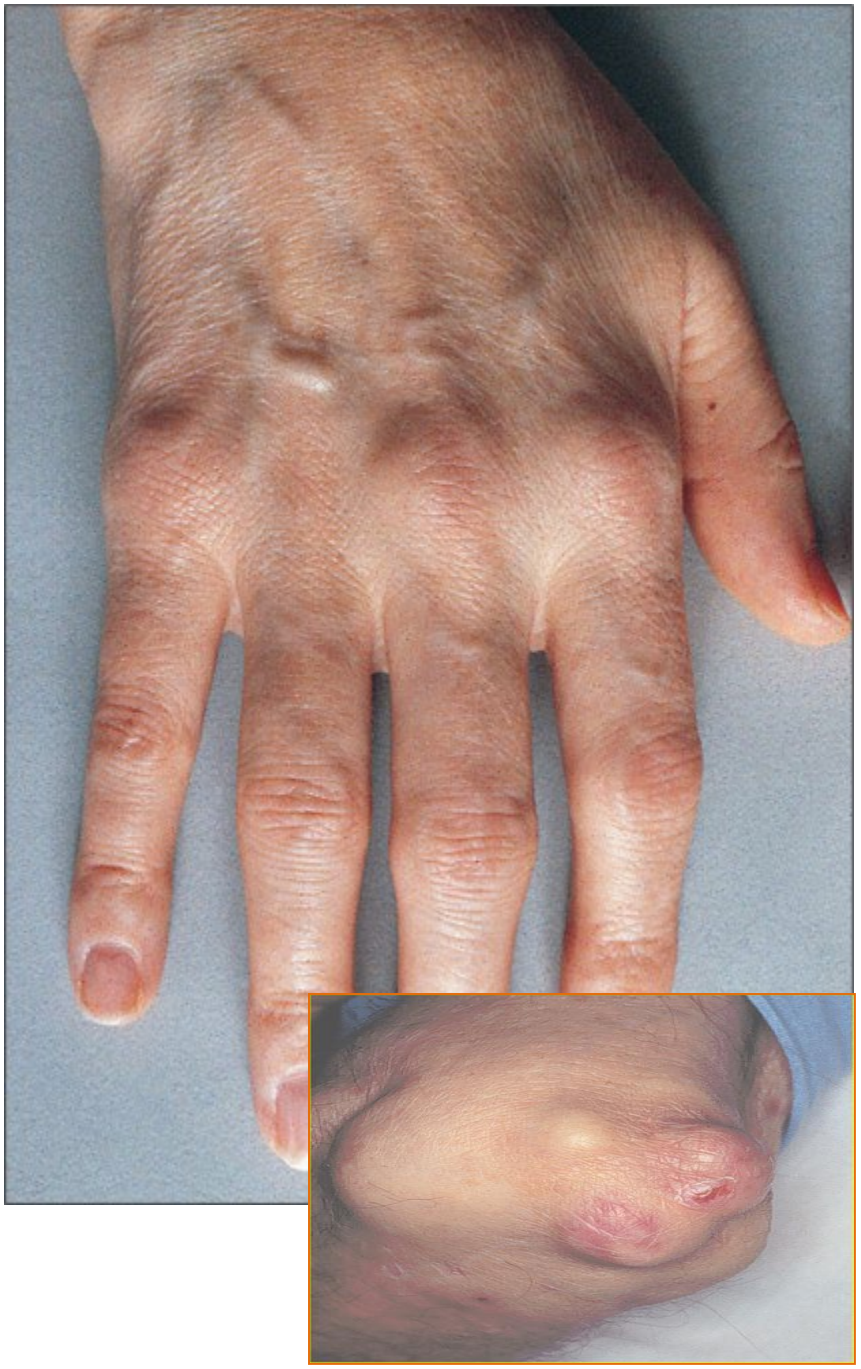


- Other clinical features may be evident in the later phases of disease
  - *e.g.* cyanosis, cor pulmonale, accentuated pulmonic second sound and peripheral oedema



AR iniziale: tumefazione delle IFP e delle MCP rigidità mattutina, riduzione della forza, incapacità a fare il pugno

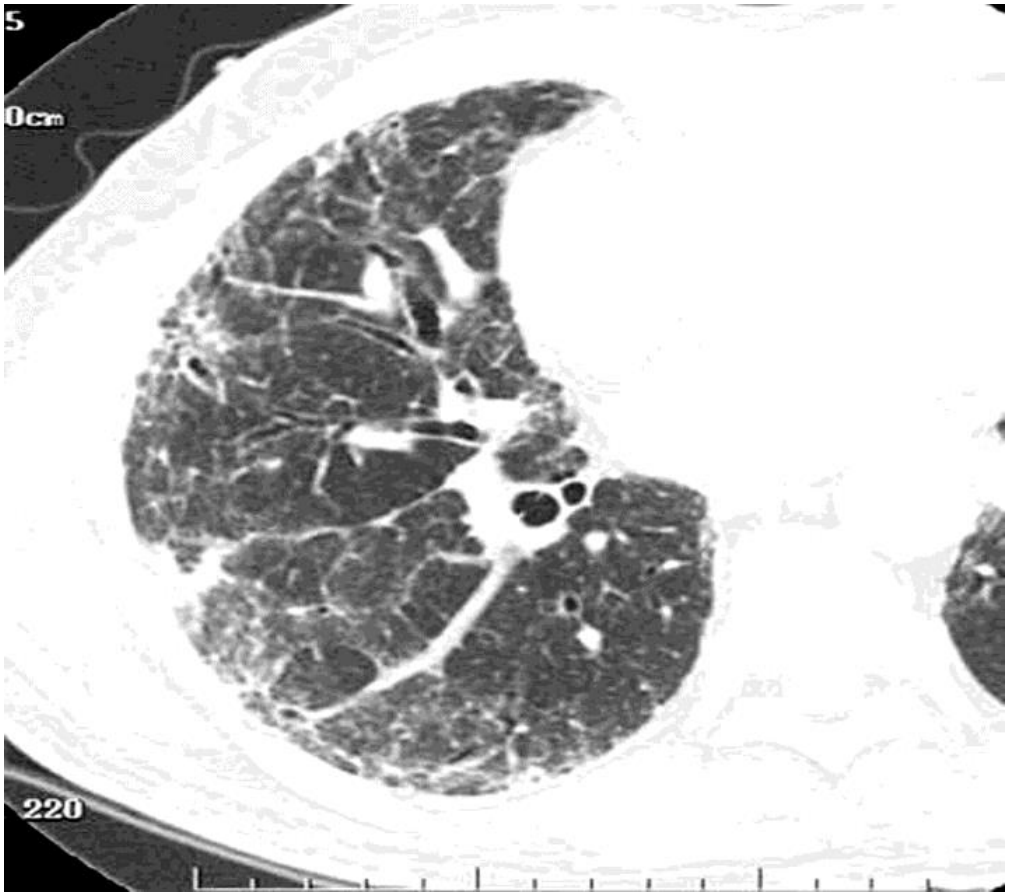




Interstitial lung disease in RA

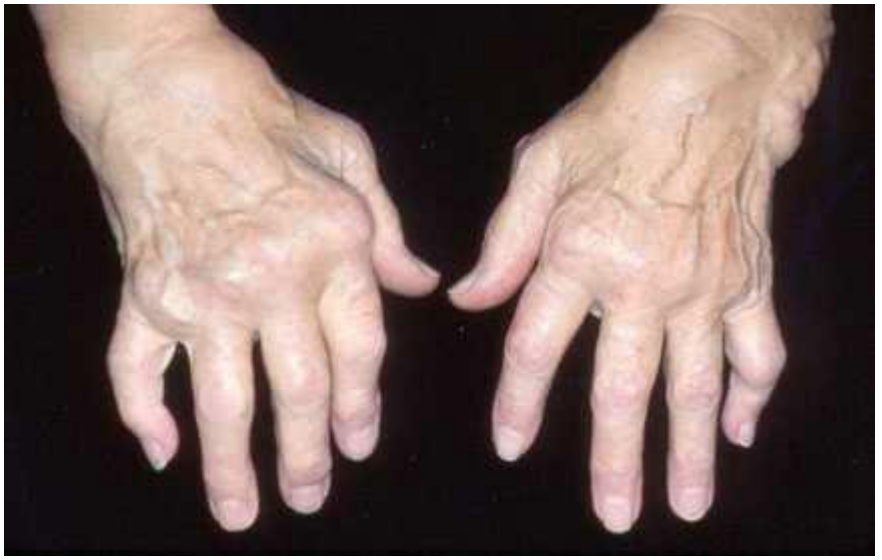
ILD is the most common lung manifestation of RA

- Varied presentation
- UIP is the most common pattern
  - –Can also see NSIP, OP, LIP, DAD
- Accounts for 7% of all RA-associated deaths
- Risk of death is 3x higher than for RA without ILD



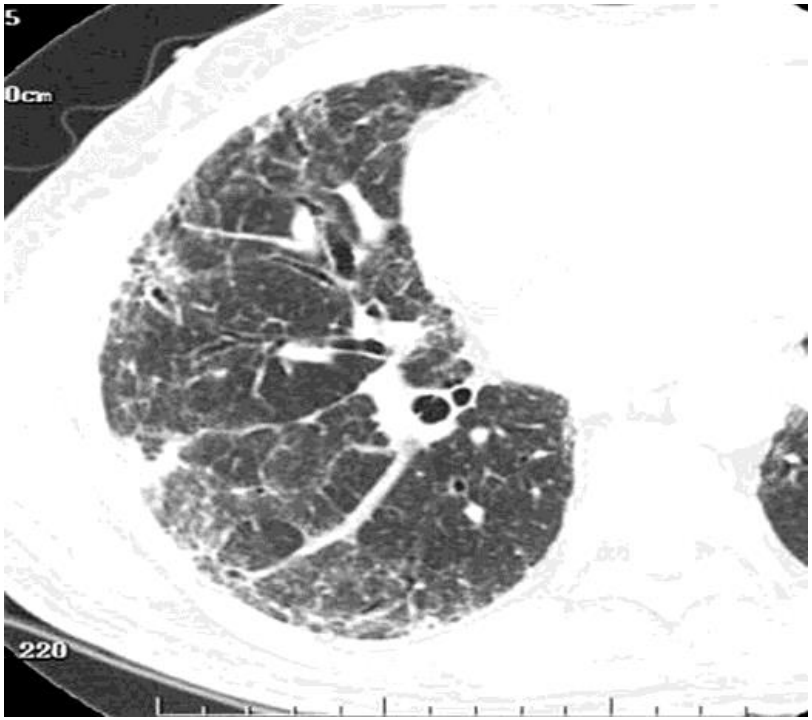
K Brown Proc Am Thor Soc 2007, Doyle CHEST 2013, Olson AJRCCM 2011

Patients are surprised to learn that their “arthritis has attacked” their lungs

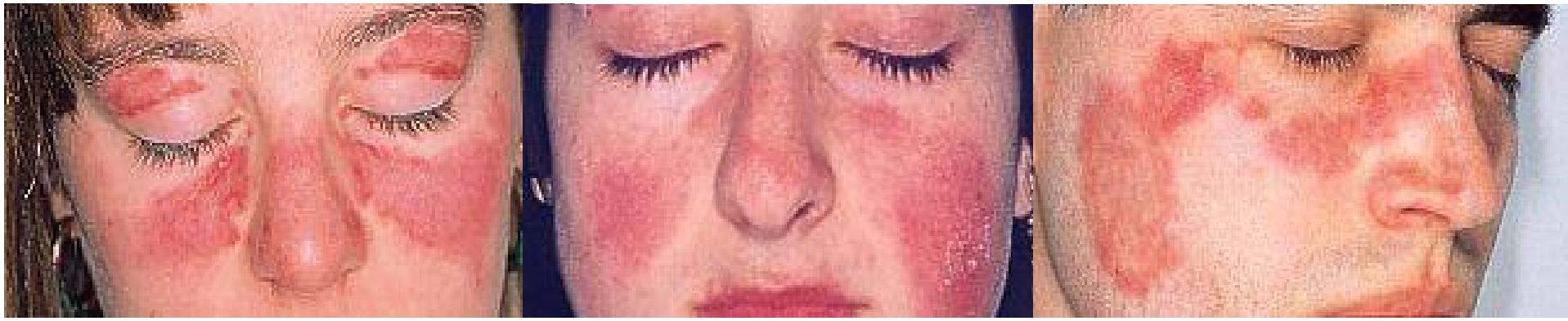


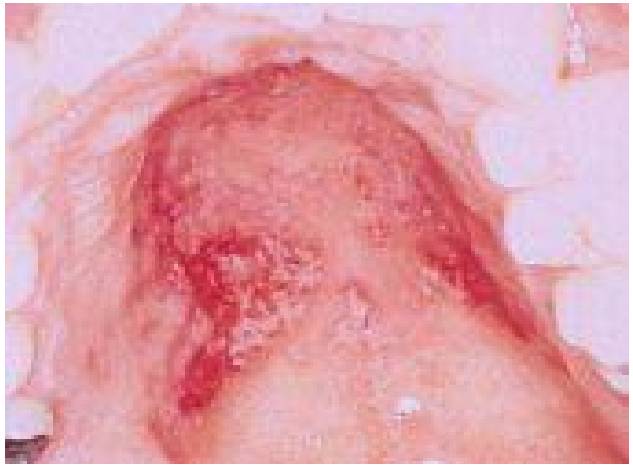
Lung disease in RA is common yet:

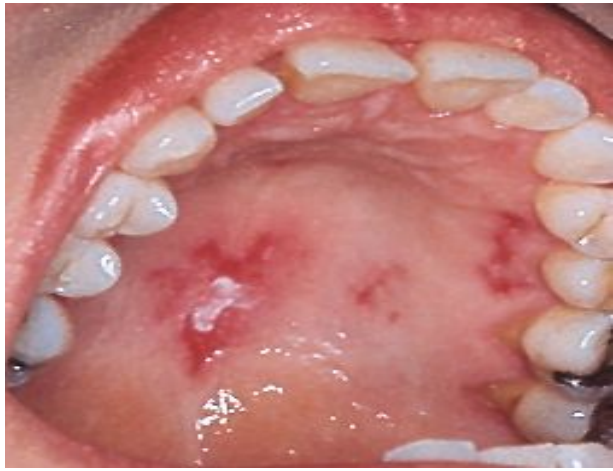
- poorly understood
- under-appreciated
- under-recognized
- of uncertain pathogenesis
- without proven treatment

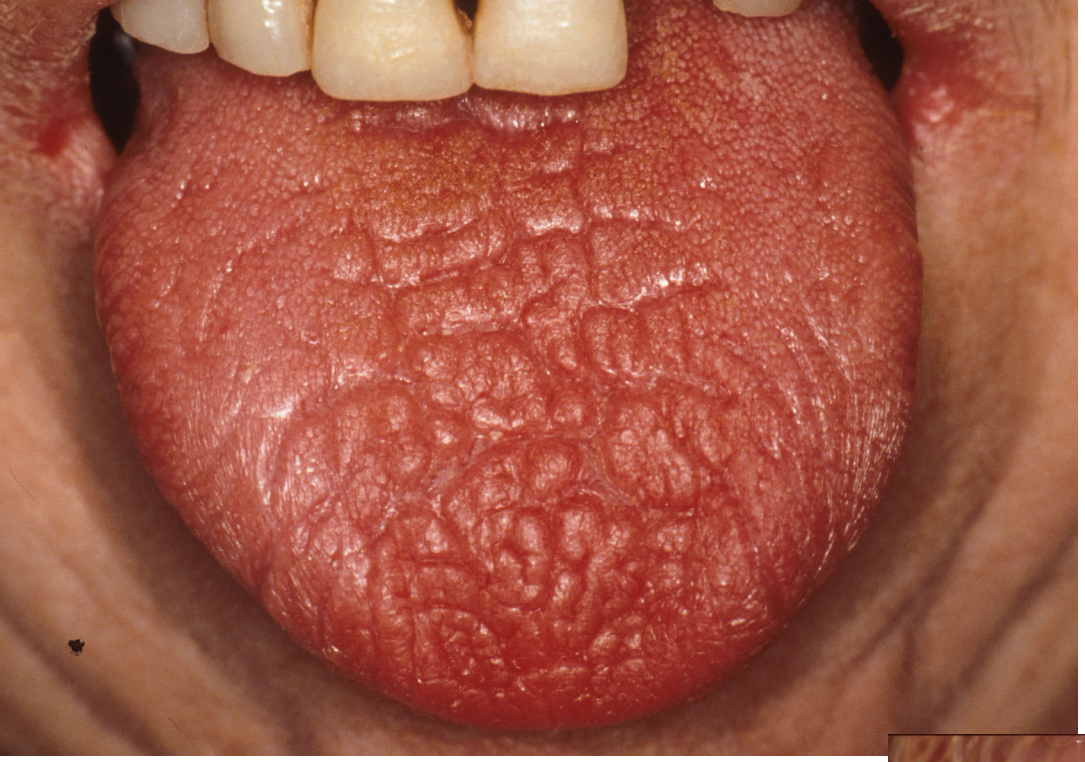


Systemic Lupus Erythematosus



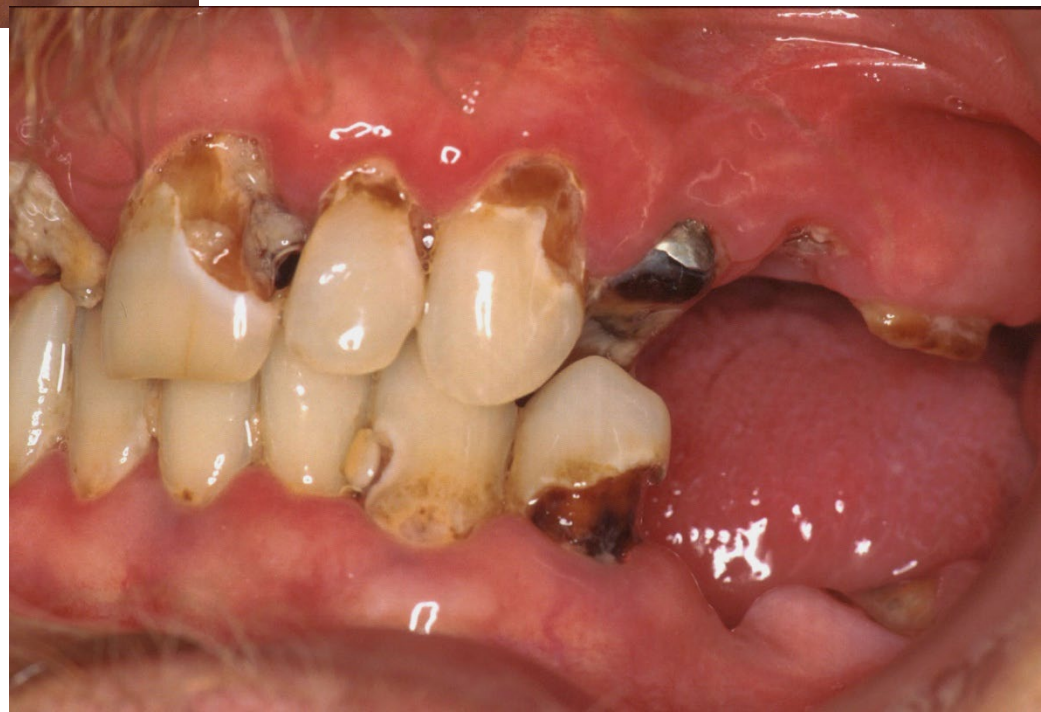


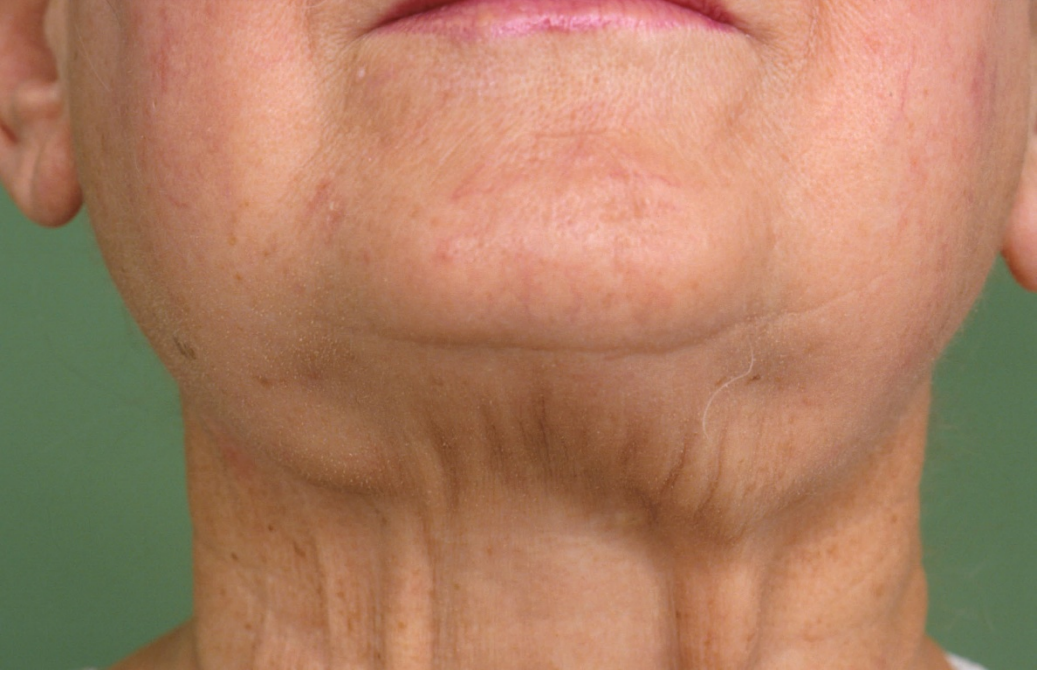




Severe xerostomia with dry tongue

Sjogren's Syndrome- Cervical Dental Caries

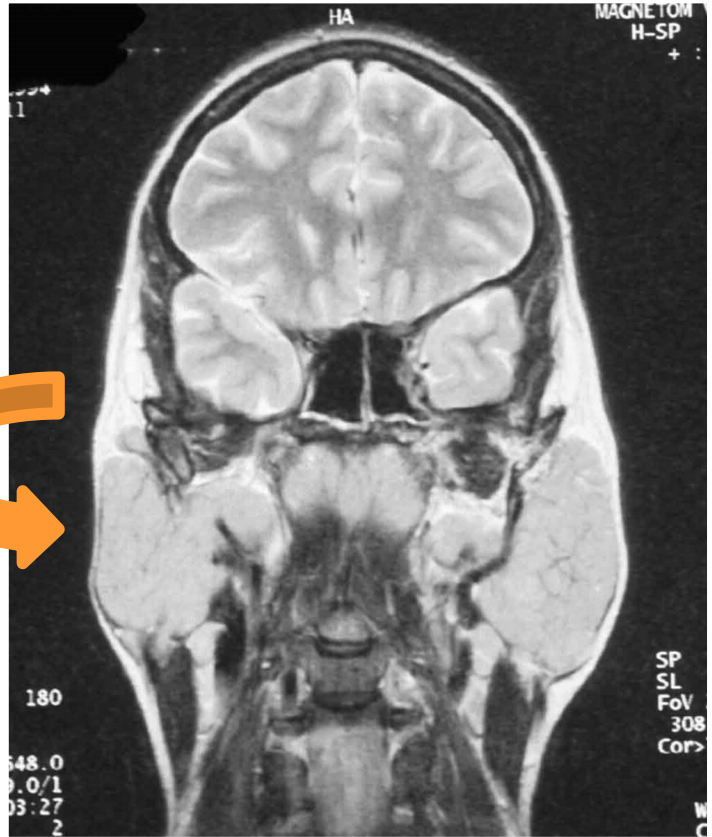




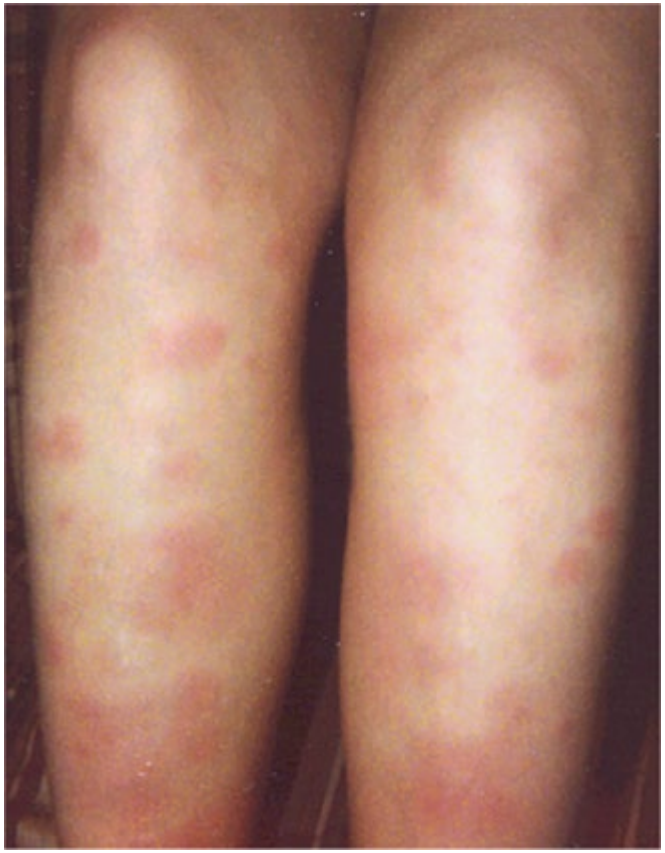
Sjogren's Syndrome - Diffuse Submandibular Salivary Gland Enlargement

Sjogren's Syndrome - Investigations

MRI



Clinical factors of prognostic value

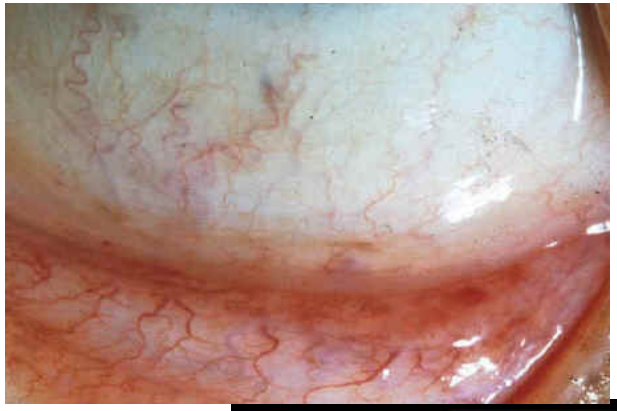


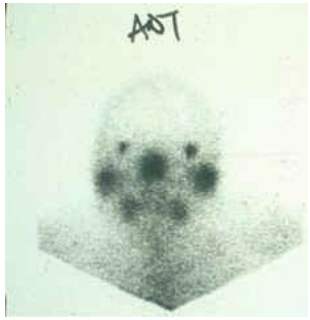
Good prognosis:

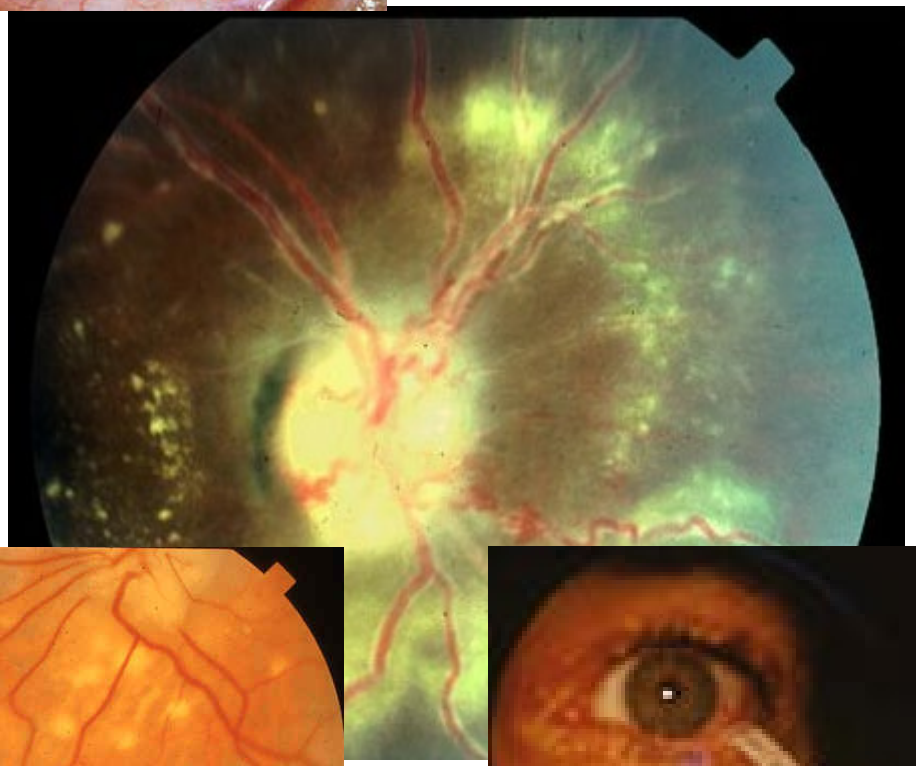
- Erythema nodosum and acute inflammatory manifestations: *e.g.* fever, polyarthritis
- race and certain HLA type (HLA-DR17+)
- Löfgren's syndrome

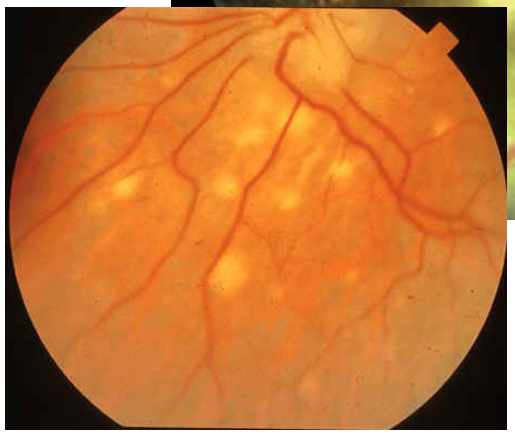
Manifestazioni Cliniche della Sarcoidosi

Aspetti	%
Intratoracica	88
Oculare	**27**
Cutanea	15-34
Parotidi	6
Milza	10
Linfonodi	27
Osso	3-4
Cuore	3-5
Rene	1
S. Nervoso	4-5

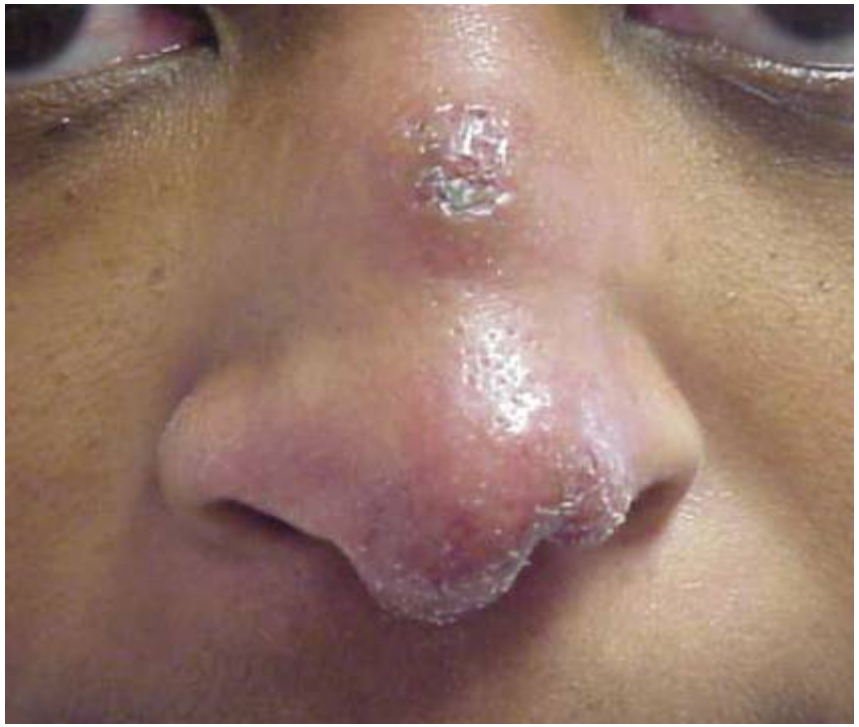


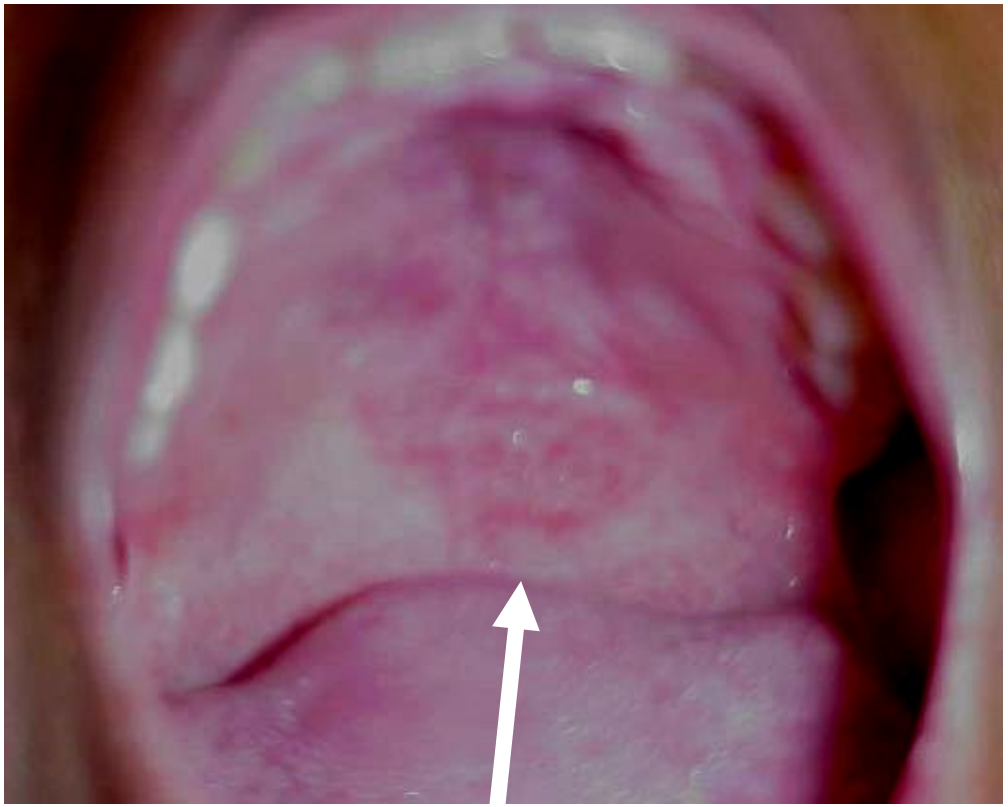






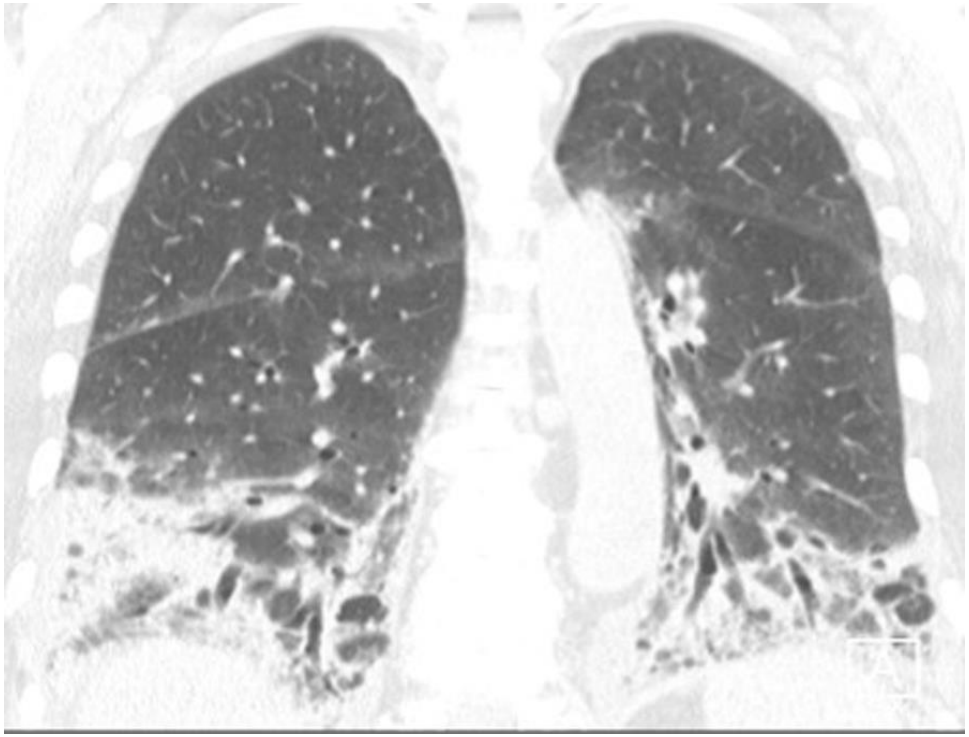
Lupus pernio with associated lesion destroying hard palate





Lesion in hard palate

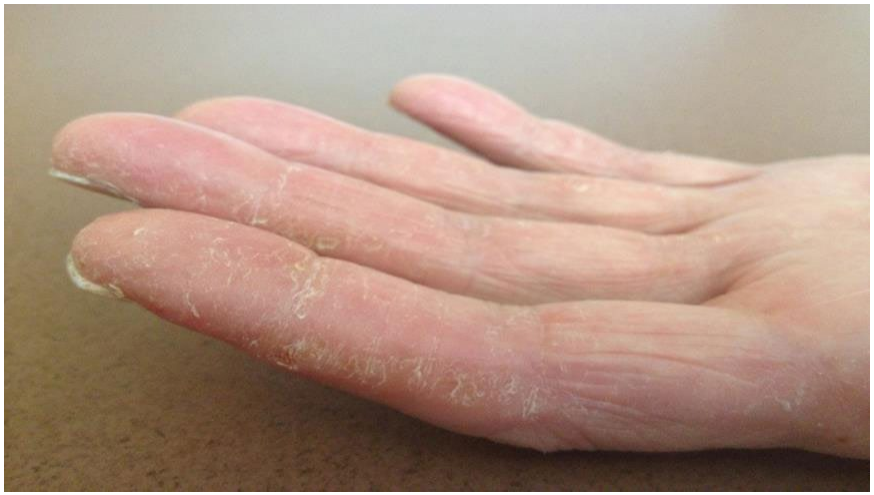
screening for CTD-ILD with an ANA, ANA profile, RF, CCP, and Scl-70, misses the anti-synthetase syndrome

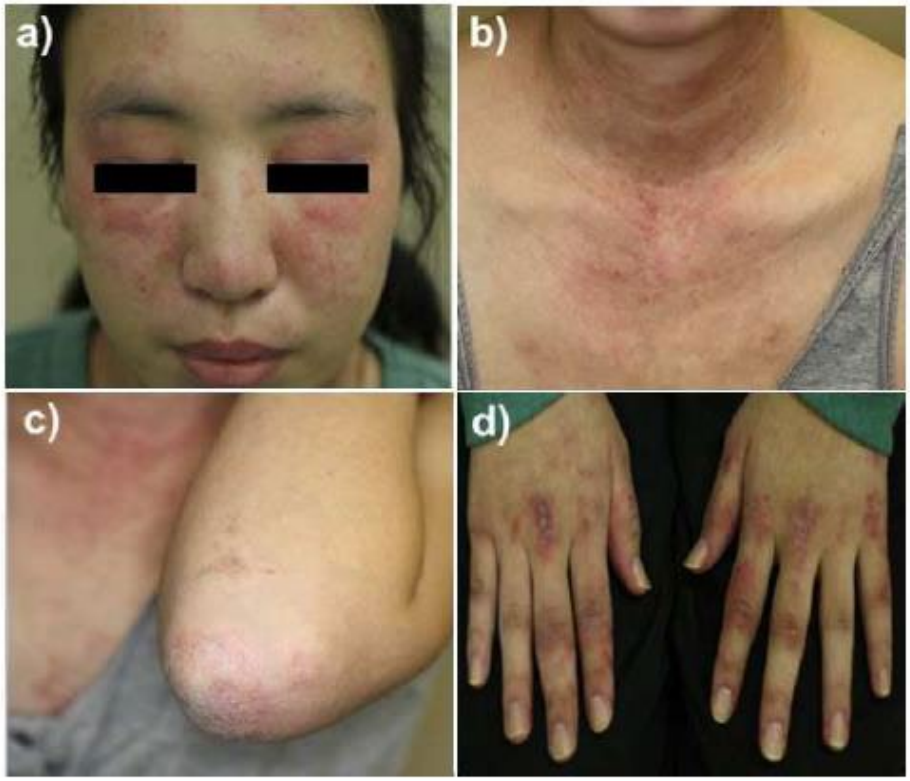


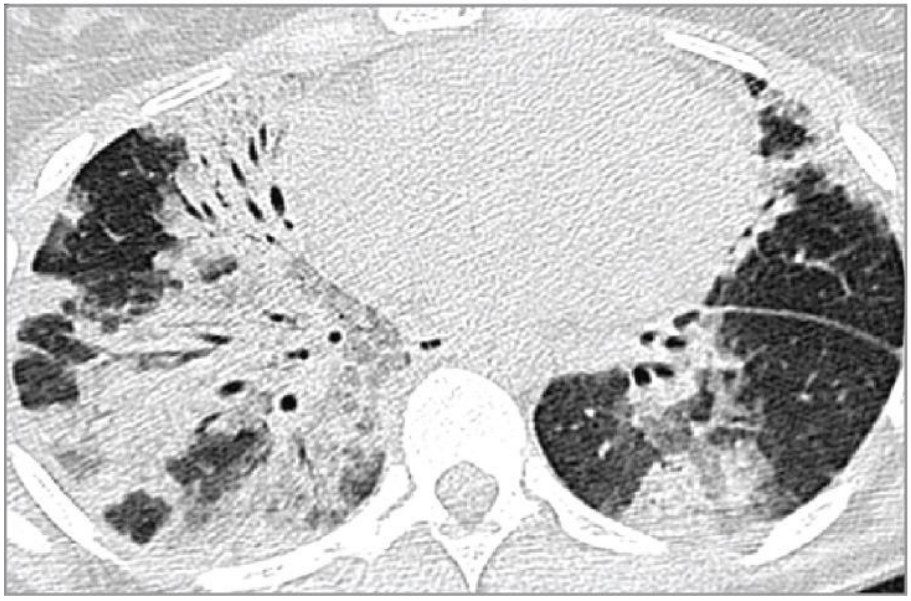
many of these patients do NOT have myositis

Chartrand et al J Rheumatol 2016

mechanic hands







MDA-5 Ab-associated ILD

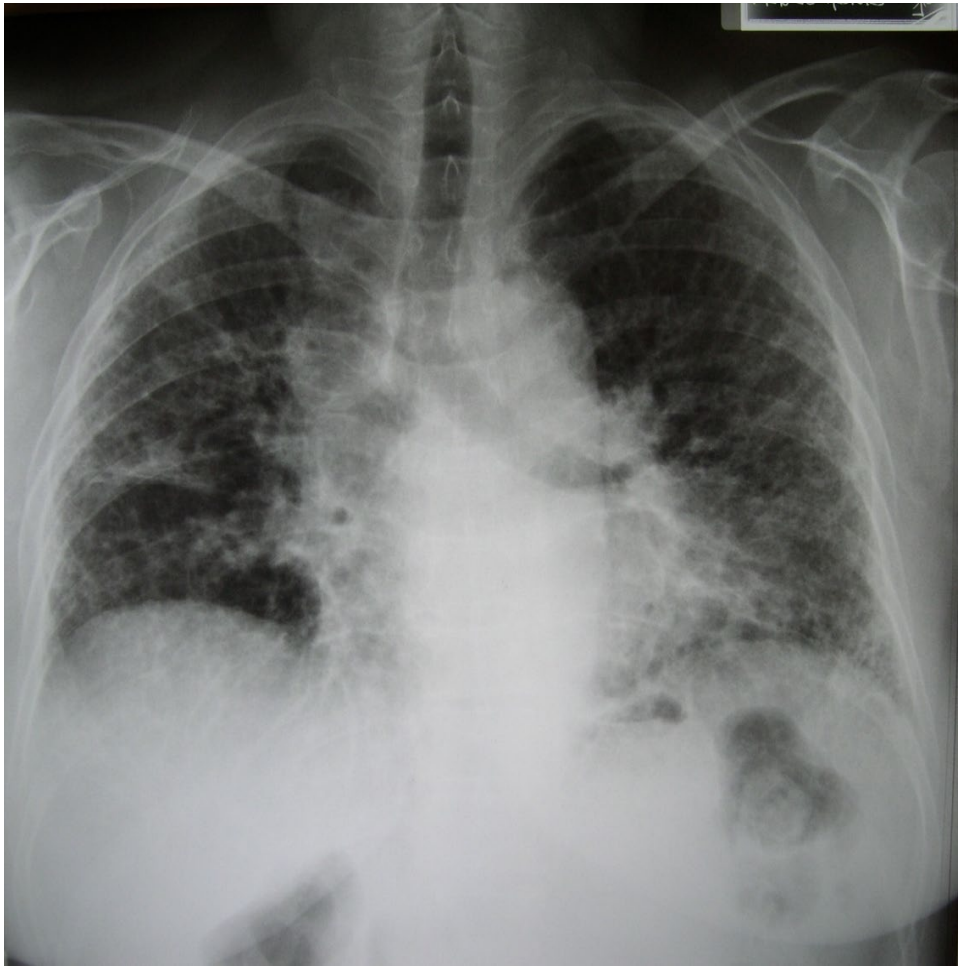
Clinical amyopathic dermatomyositis (CADM)

- Often mimics the anti-synthetase syndrome
  - Deep cutaneous ulcerations
  - Painful palmar papules
- Initial reports with rapidly progressive, fulminant ILD
  - (e.g. DAD)
- Recent cases suggest more of a spectrum

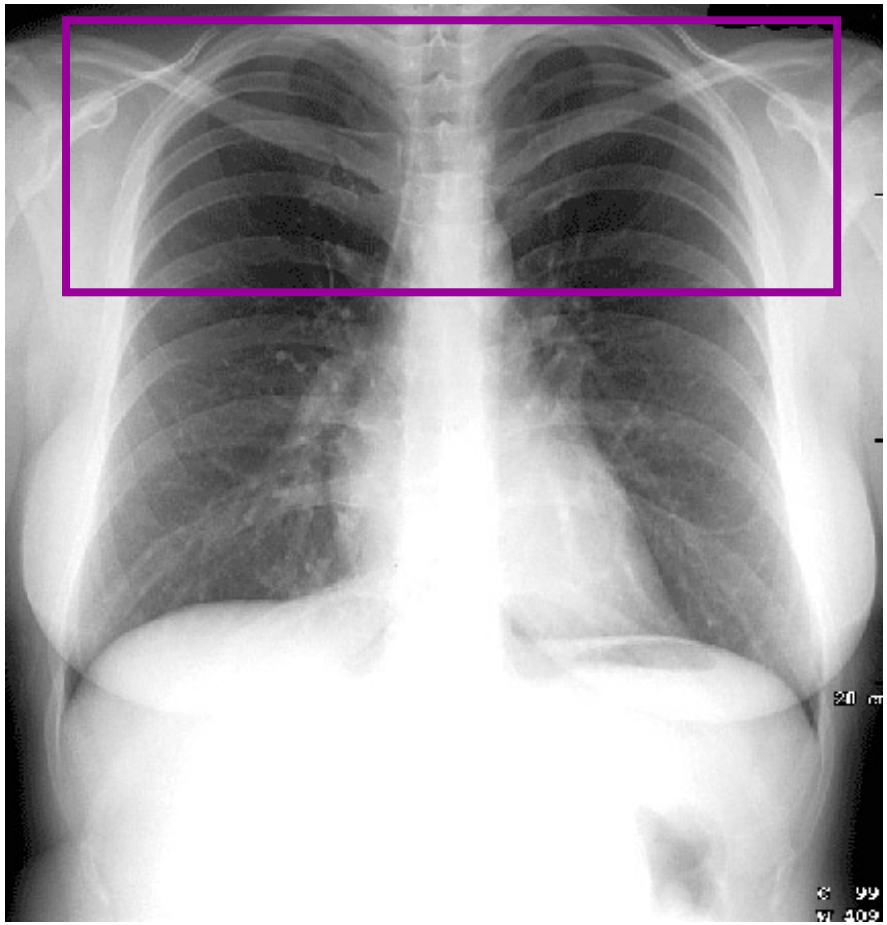
Sato et al Arthritis Rheum 2005, Hallowell and Danoff Curr Rheum Rep 2014, Suzuki et al Resp Med Case Reports 2016

Radiografia standard del torace

La radiografia standard del torace è un momento importante nella valutazione di un paziente con pneumopatia infiltrativa diffusa, tuttavia la sensibilità della metodica è bassa e la specificità scarsa



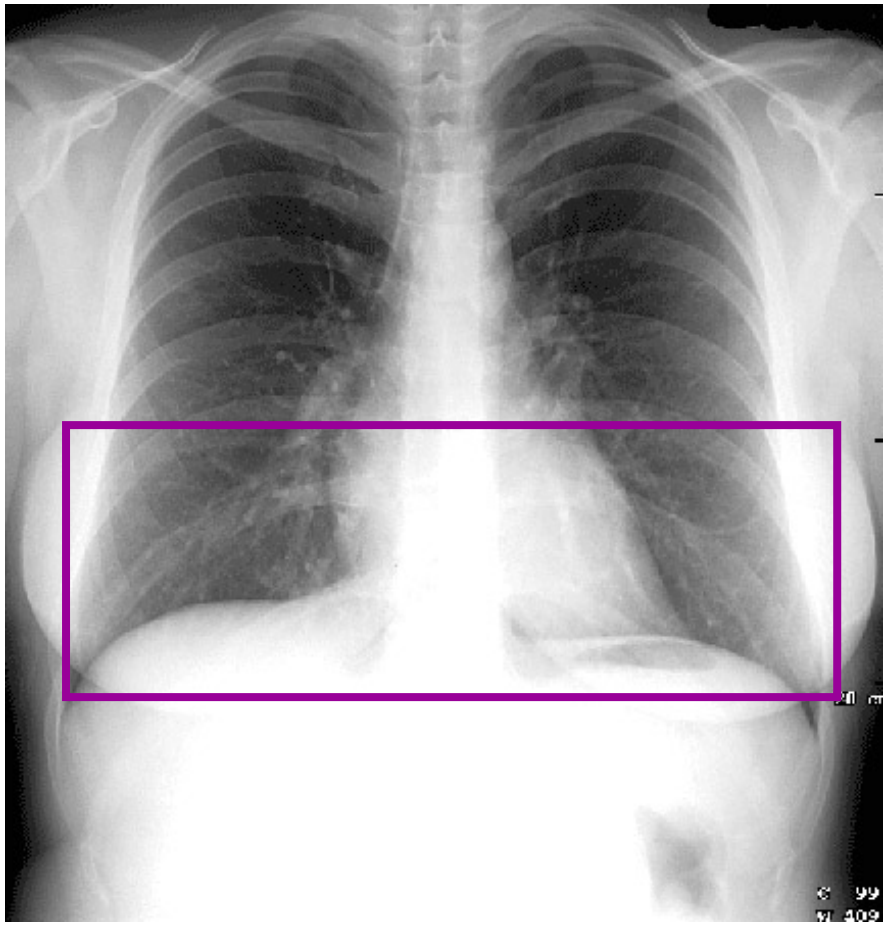
Radiografia standard del Torace



Predominanza Zone Superiori

- Sarcoidosi
- Istiocitosi X
- Silicosi
- Polmoniti da ipersensibilità
- Polmonite eosinofila cronica
- Farmaci

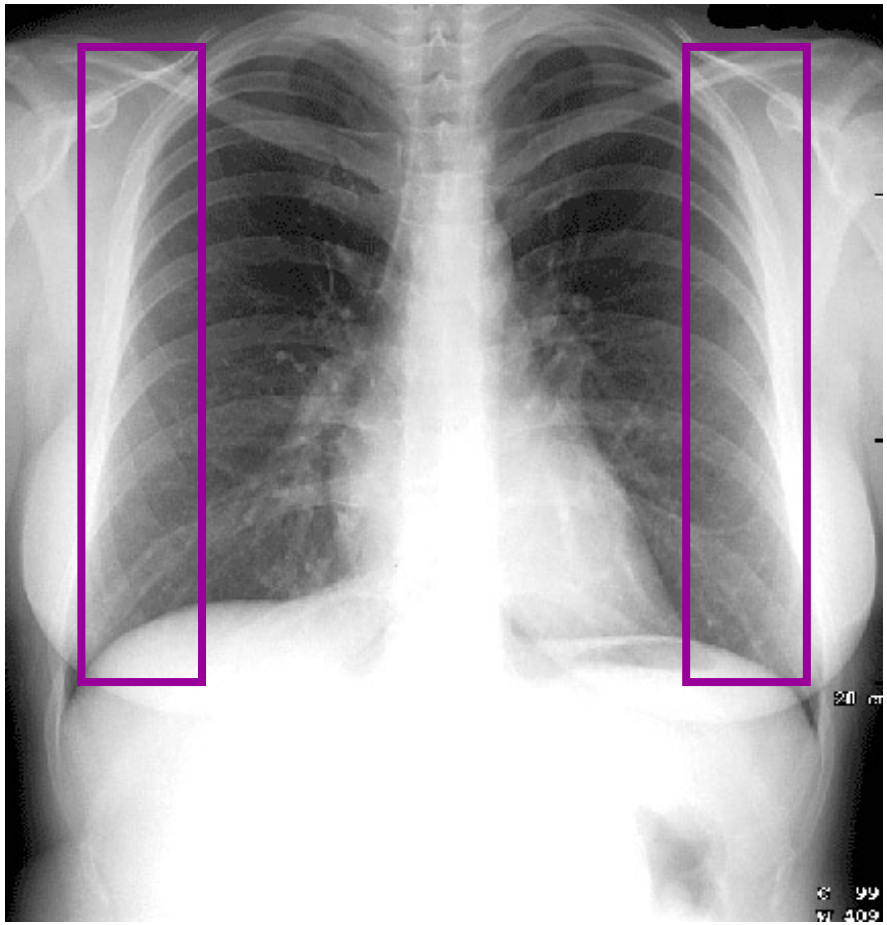
Radiografia standard del Torace



Predominanza Zone Inferiori

- Fibrosi Polmonare Idiopatica
- Asbestosi
- Connettiviti

Radiografia standard del Torace



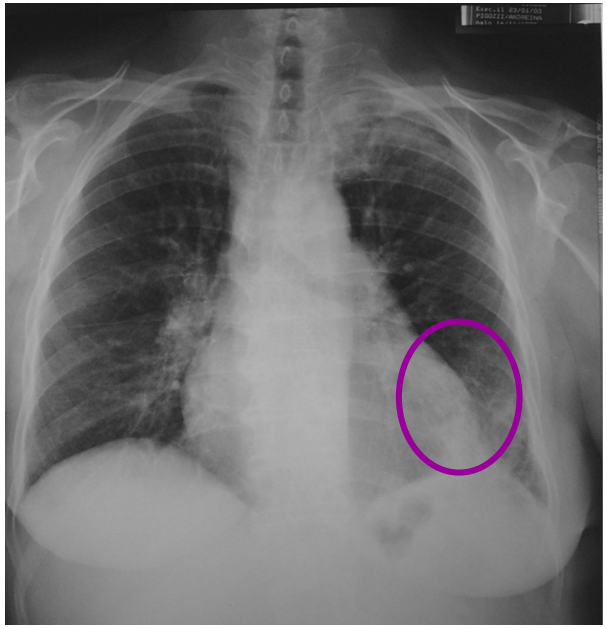
Predominanza Zone Periferiche

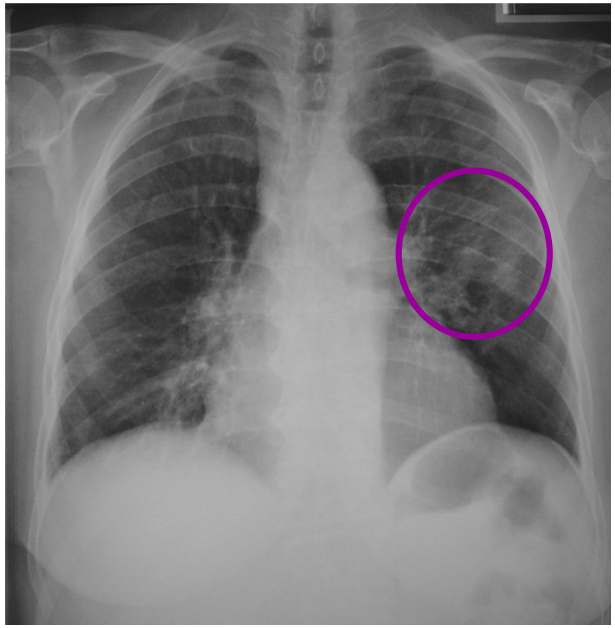
- Polmonite Eosinofila Cronica
- Polmonite Organizzativa Idiopatica

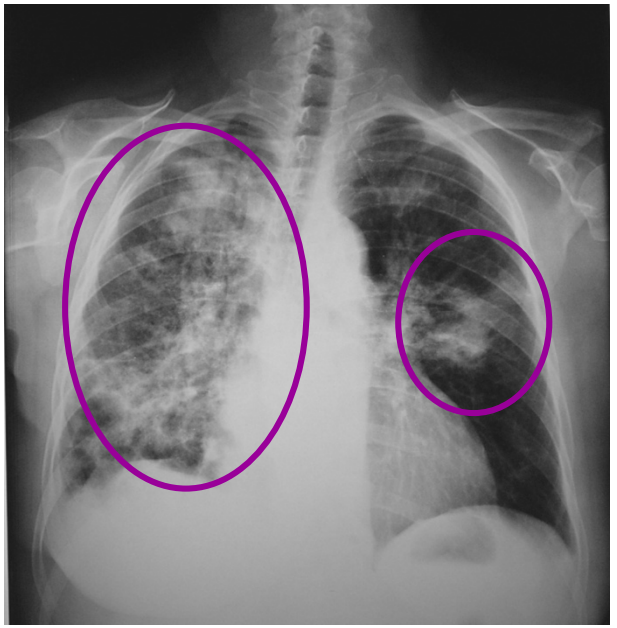
Radiografia standard del Torace

Infiltrati Migranti

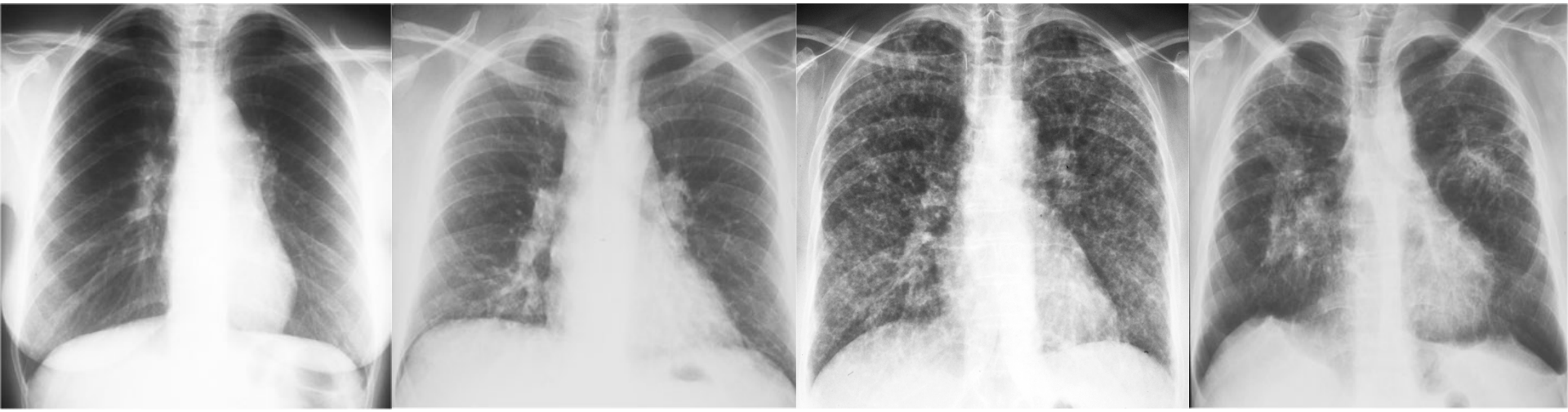
- Polmonite Eosinofila Cronica
- Polmonite Organizzativa Idiopatica
- Farmaci







Chest radiographic stages in sarcoidosis



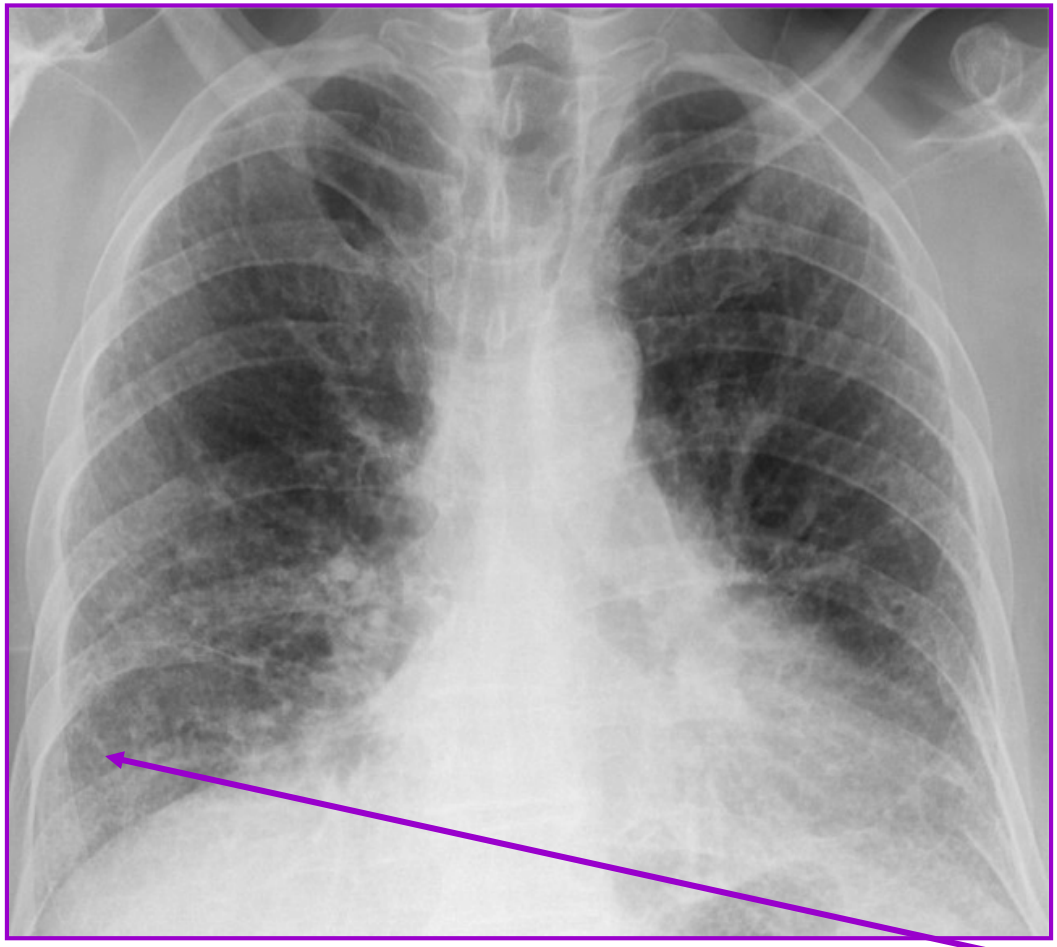
stage I

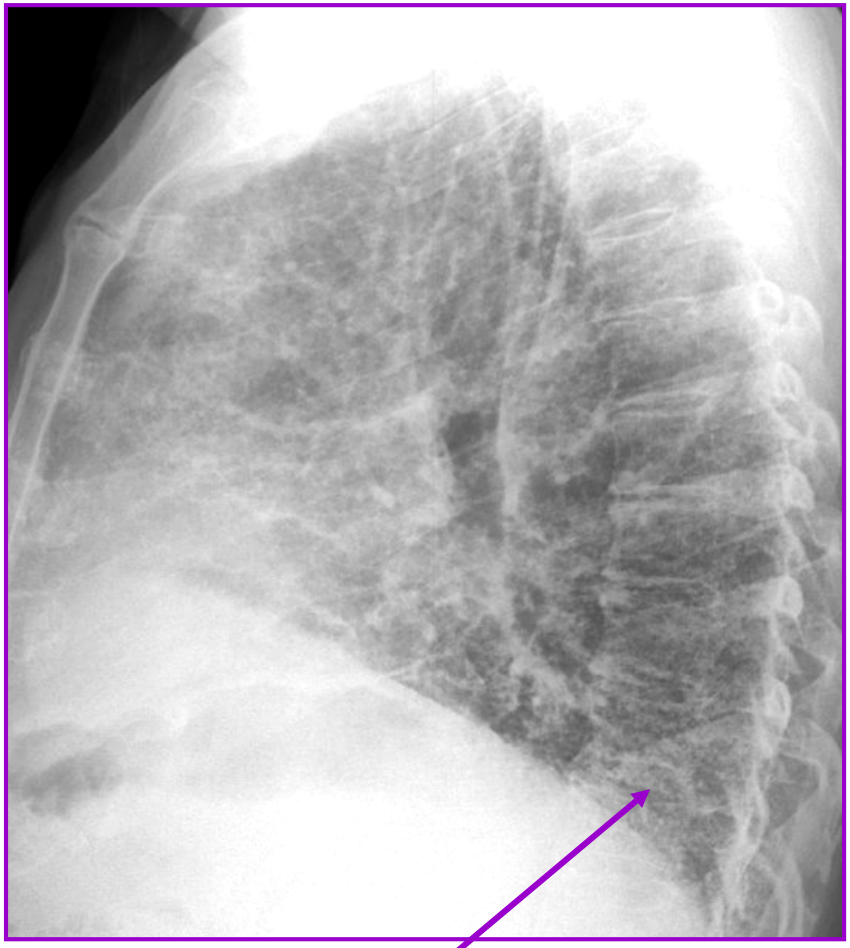
stage II

stage III

stage IV

Chest Radiograph in IPF





Reduced lung volume

Basal and peripheral reticulation

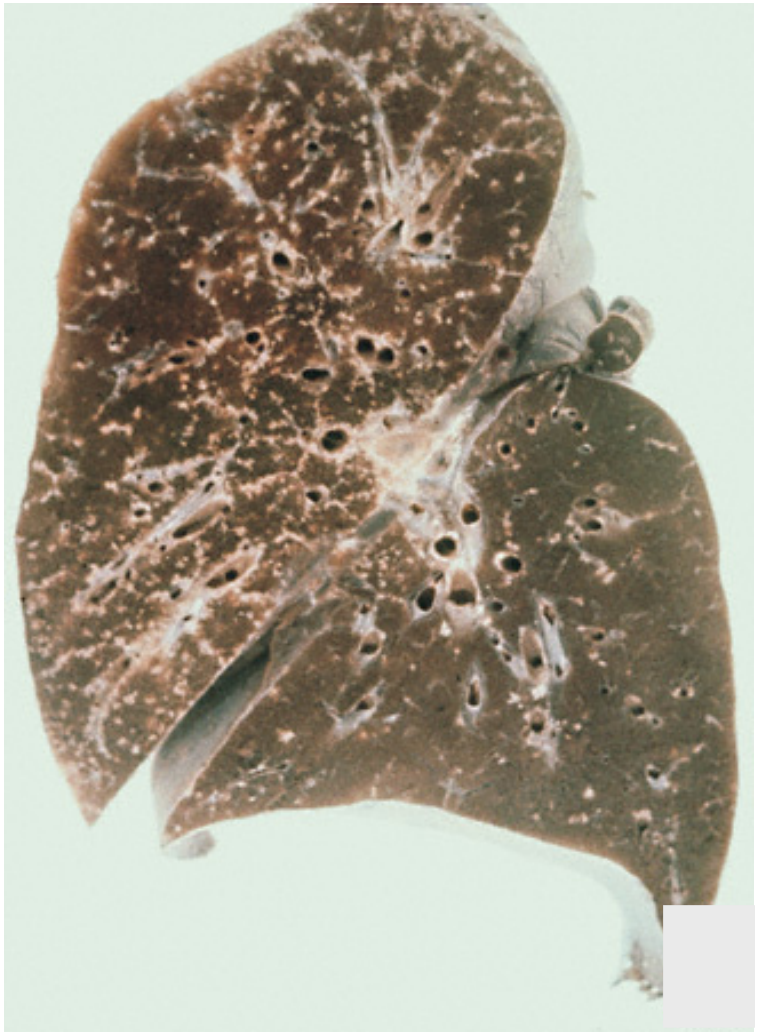
Demystifying Idiopathic Interstitial Pneumonia

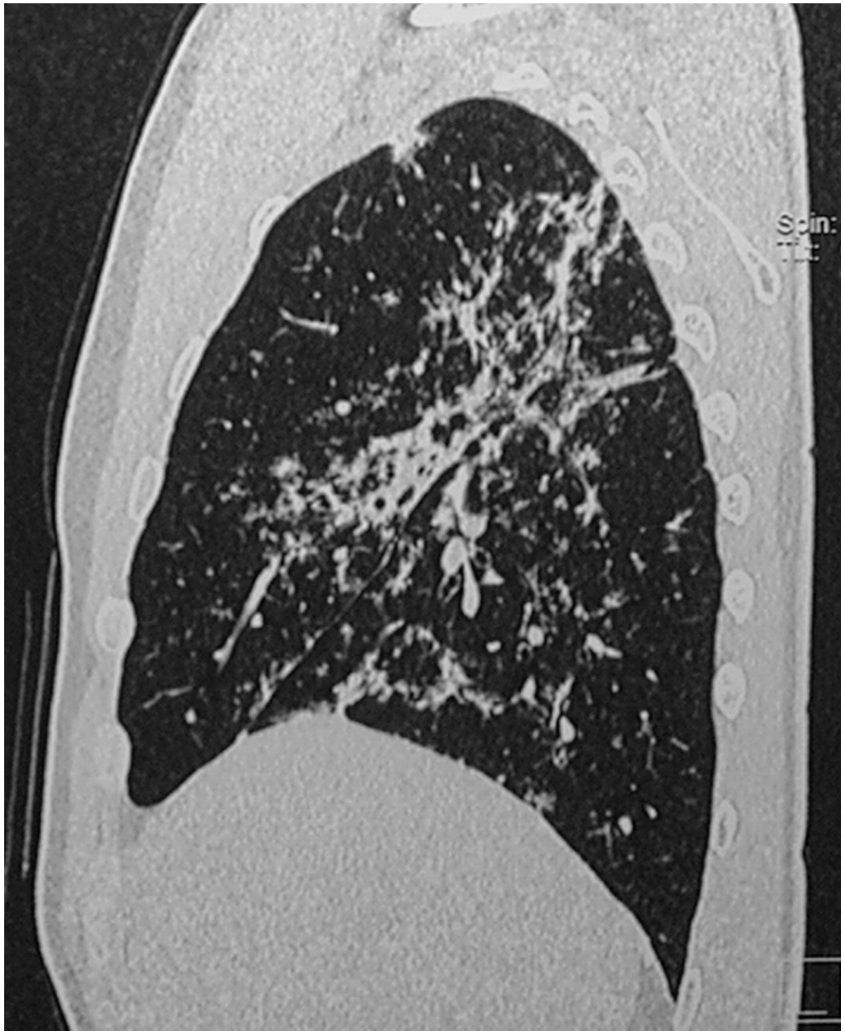
Harold R. Collard, MD; Talmadge E. King, Jr, MD *Arch Intern Med. 2003;163:17-29*

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

HRCT e Polmone

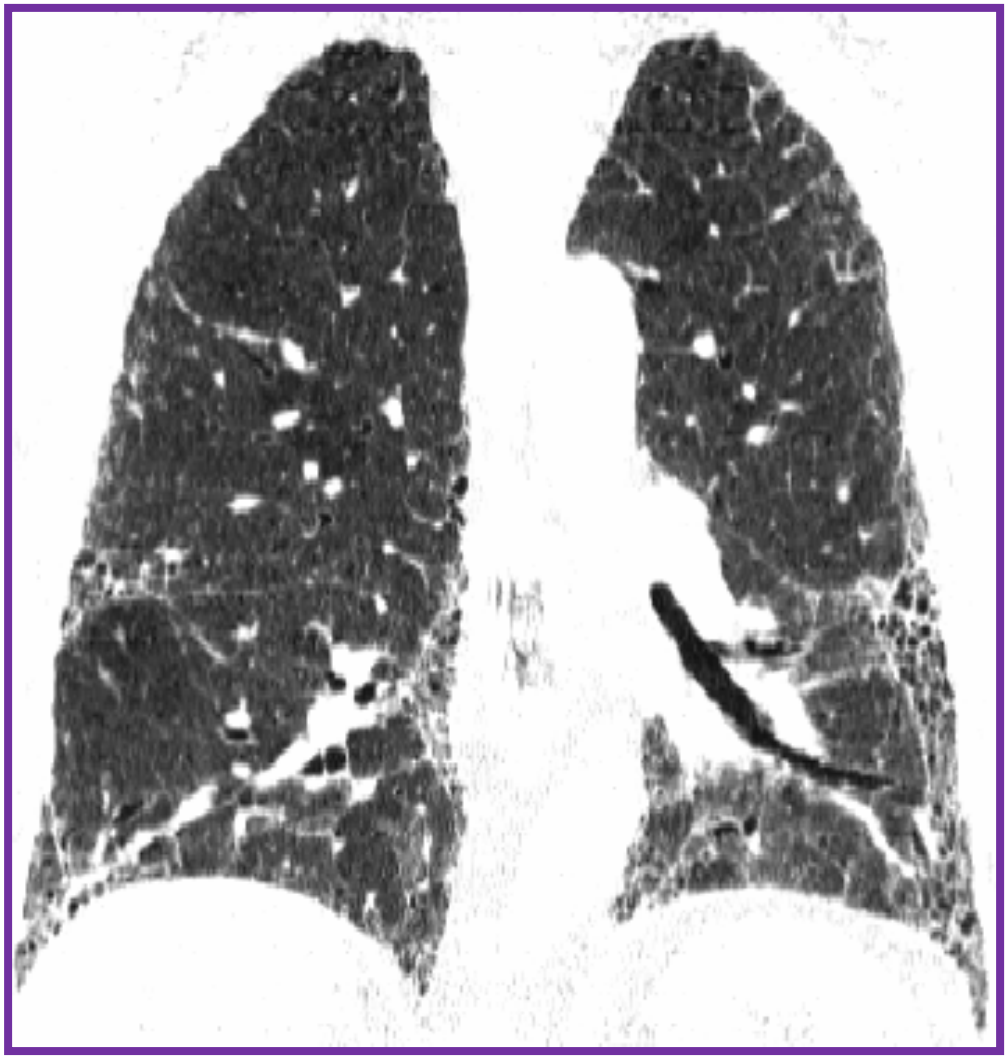
Sarcoidosi

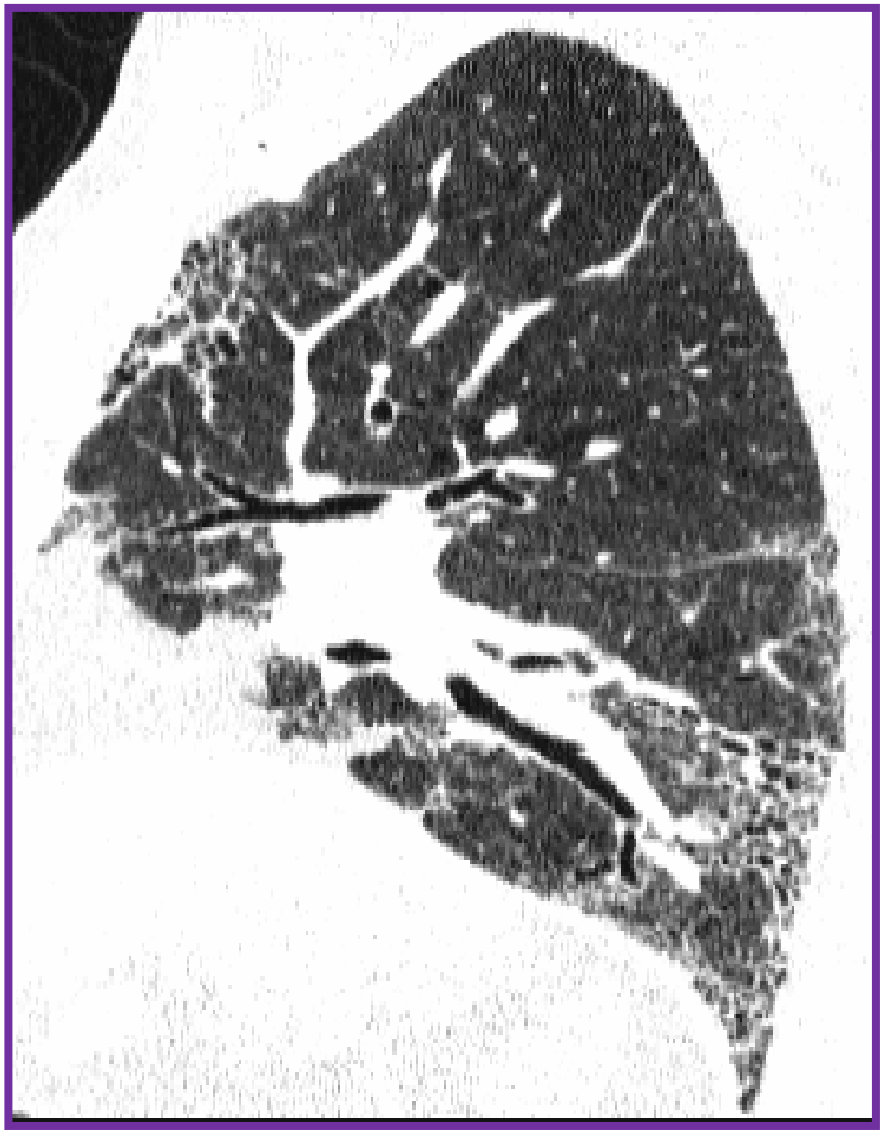




HRCT e Polmone

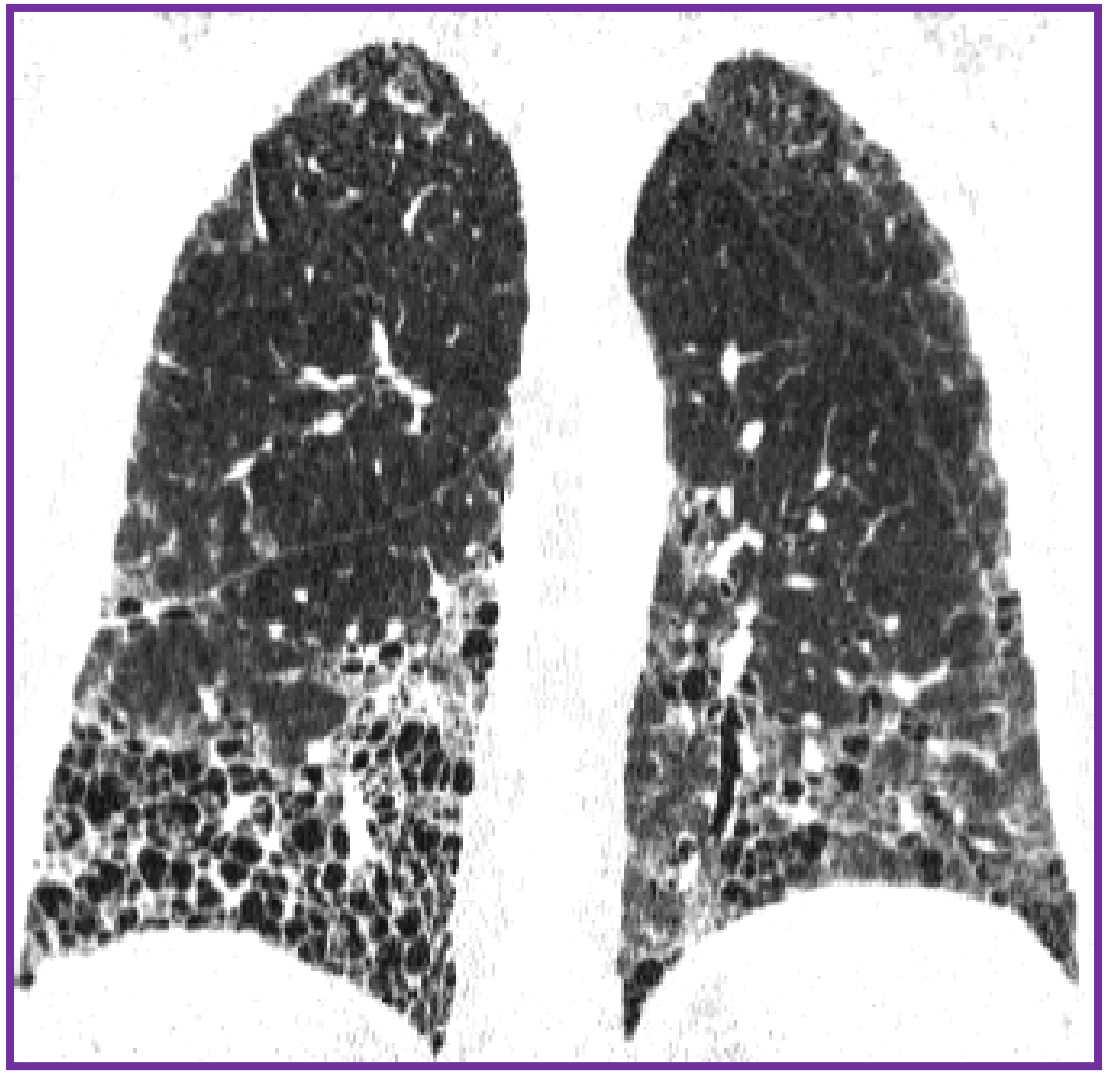
Usual Interstitial Pneumonia

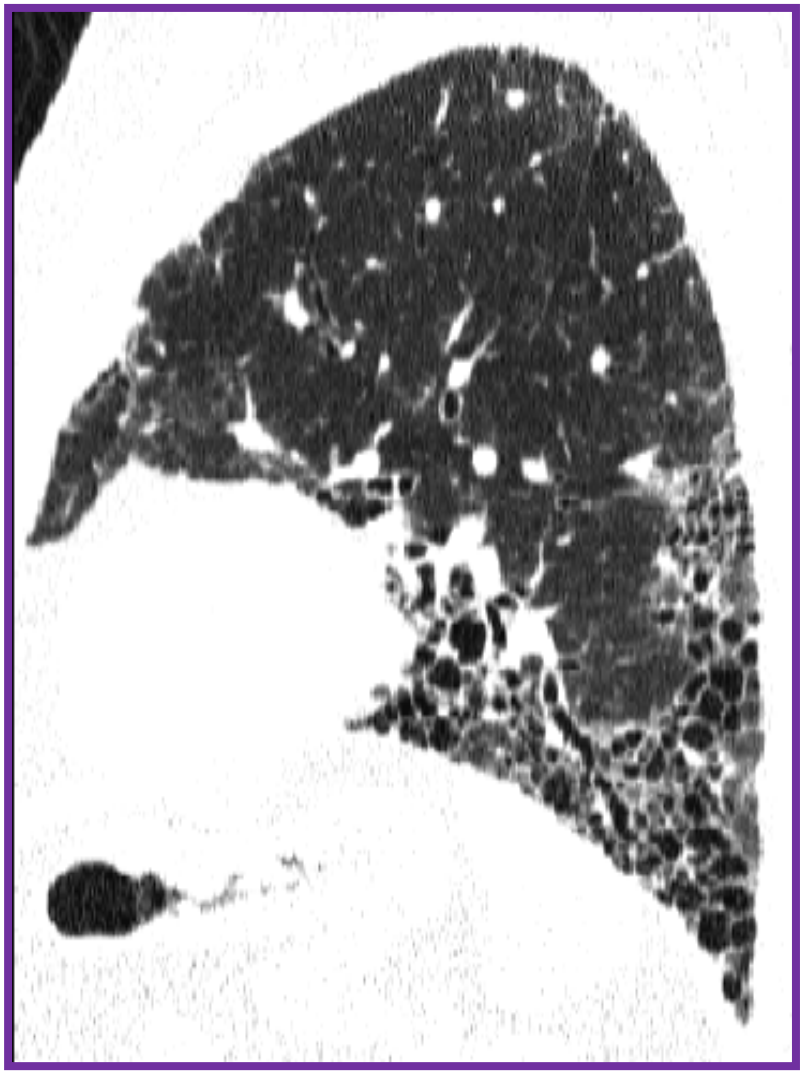




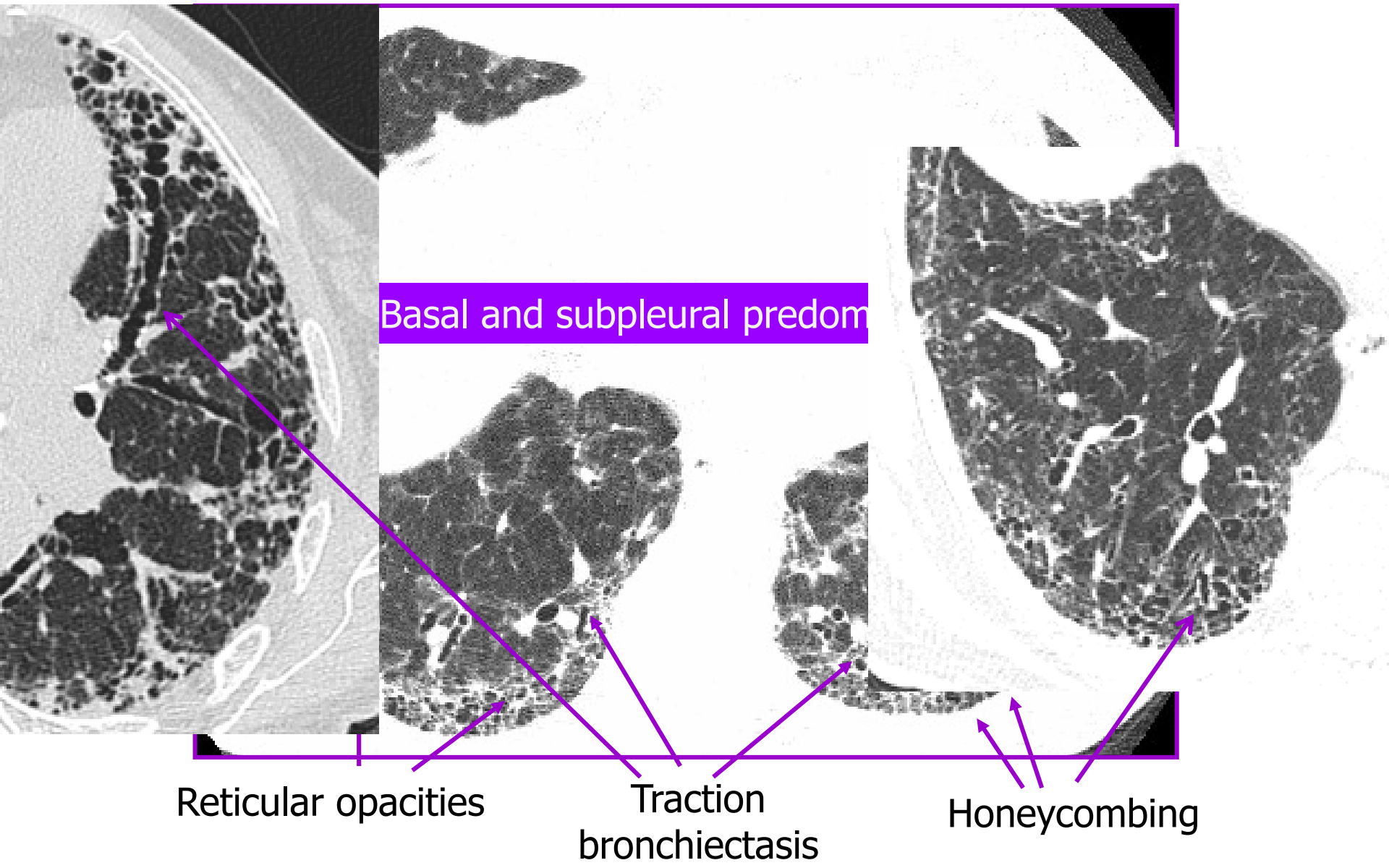
HRCT e Polmone

Usual Interstitial Pneumonia

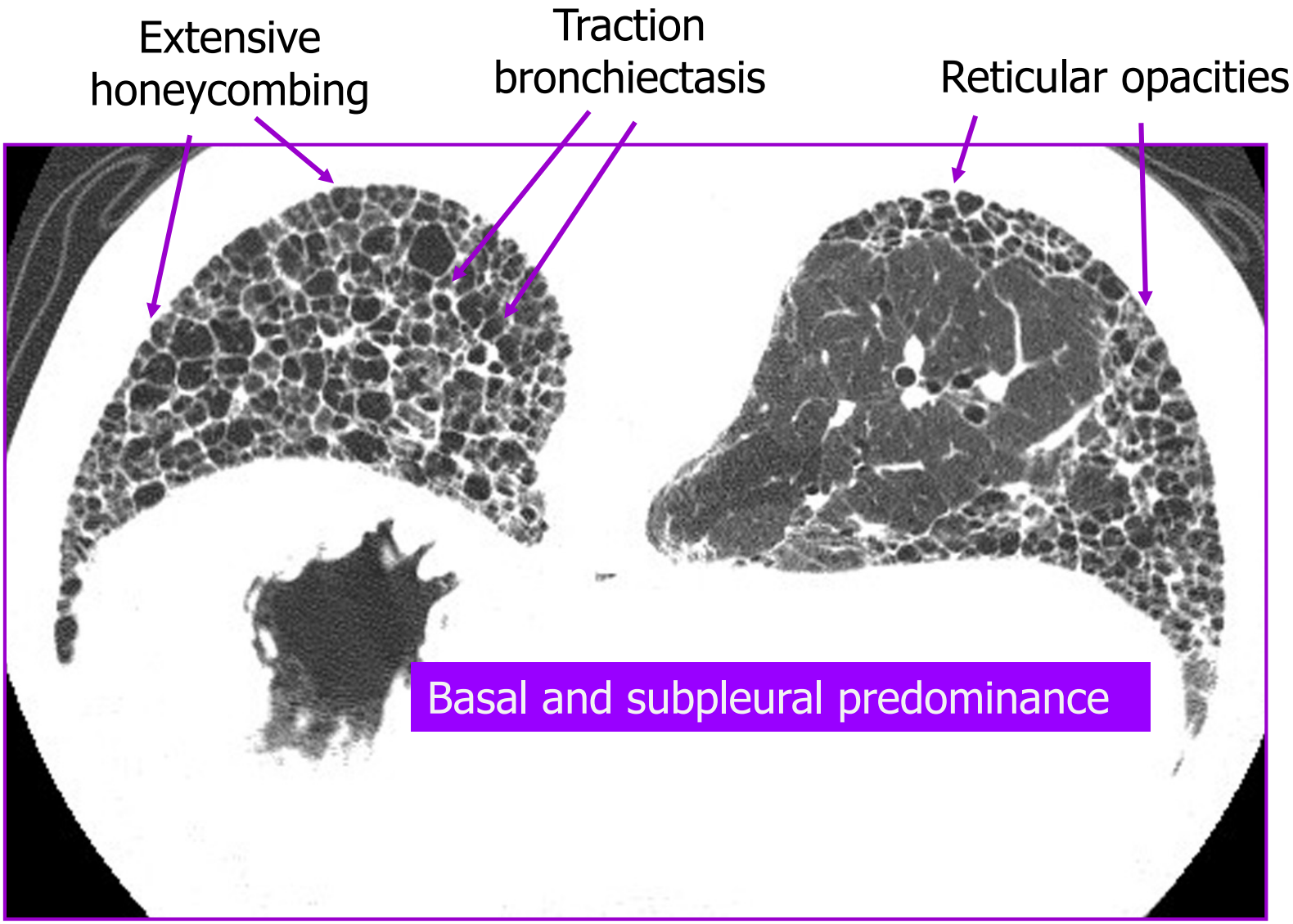




Classic IPF HRCT

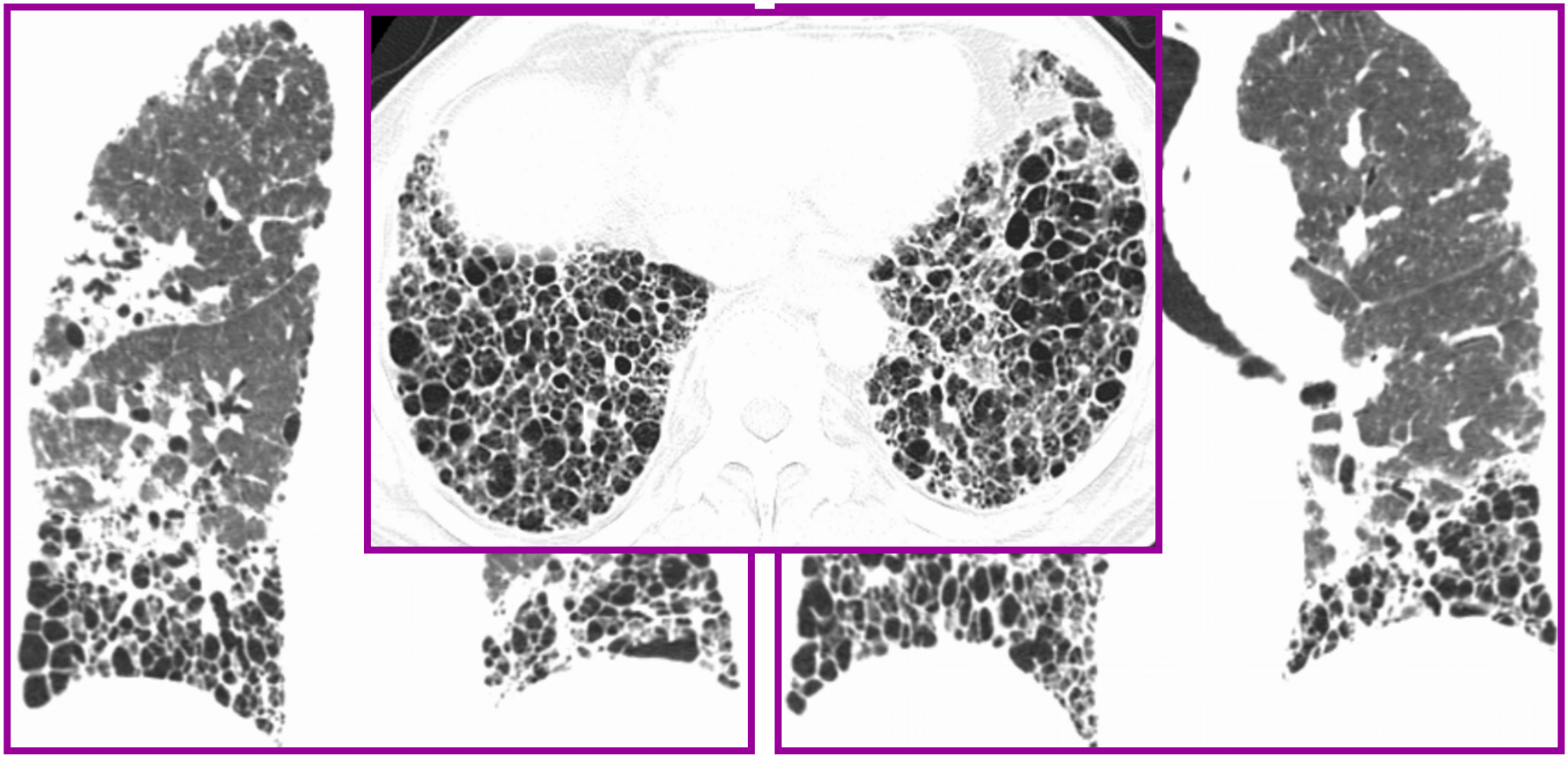


Advanced IPF HRCT



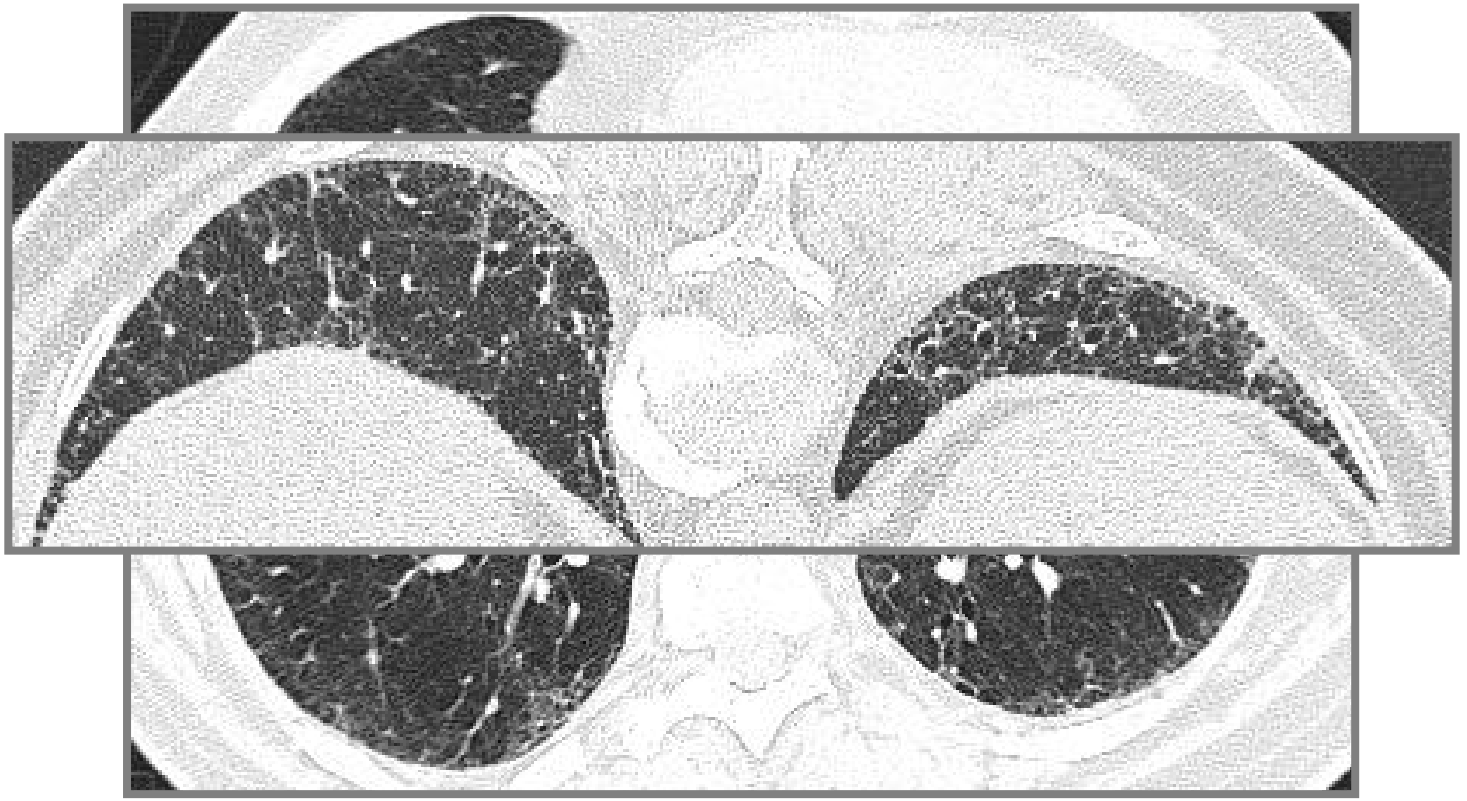
HRCT and lung

Honeycombing



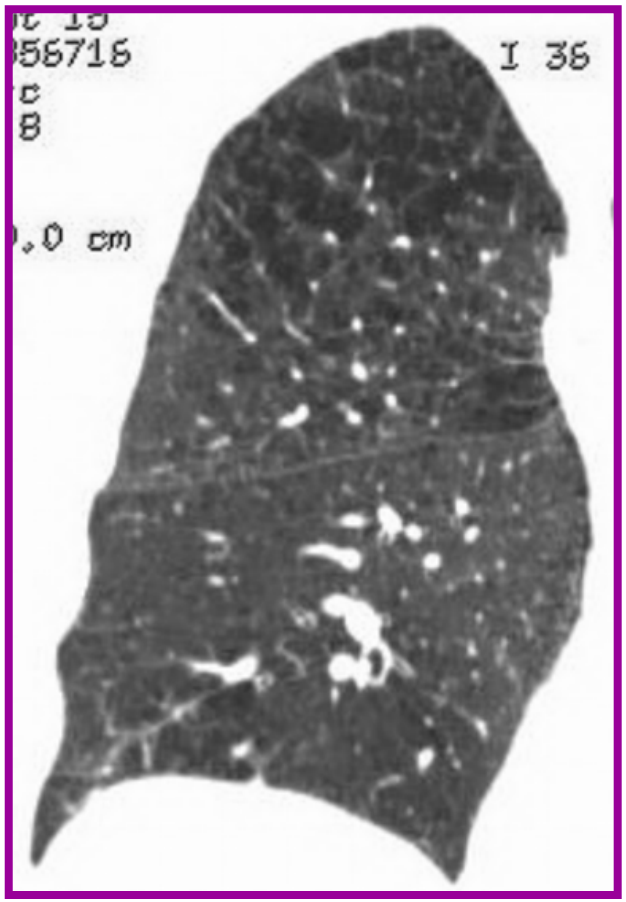
Apico-basilar gradient

Use of prone Imaging

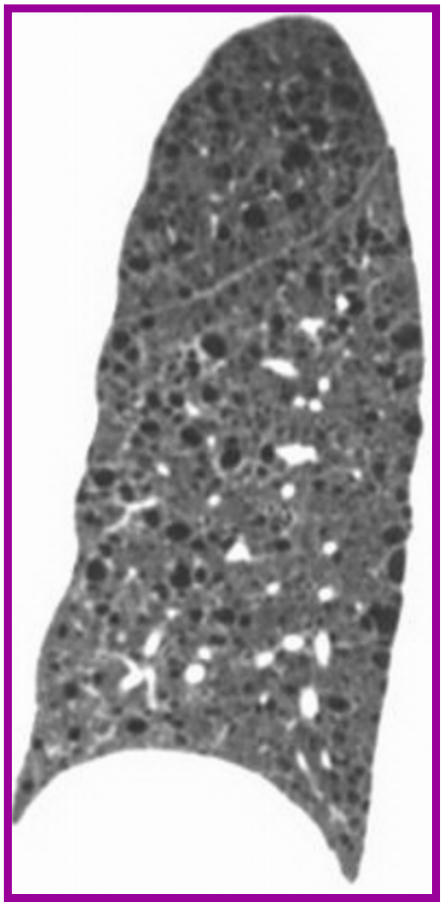


HRCT e Polmone

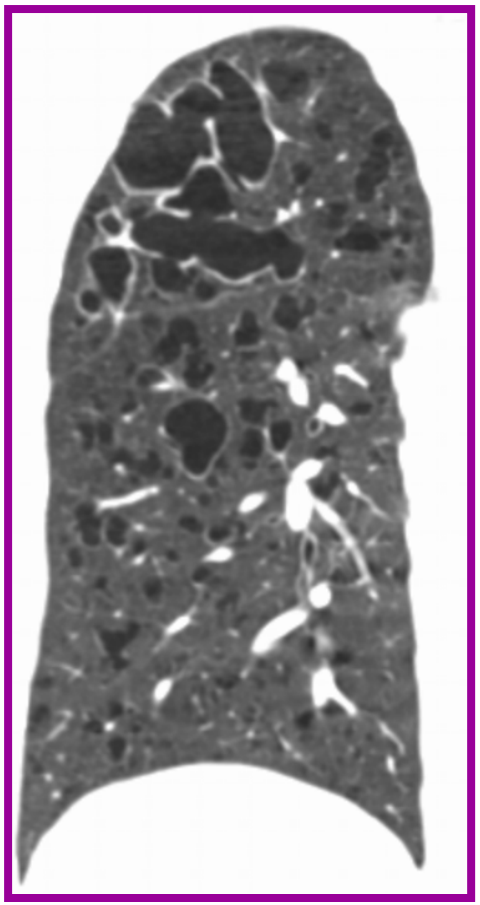
Cystic Lung Disease Summary



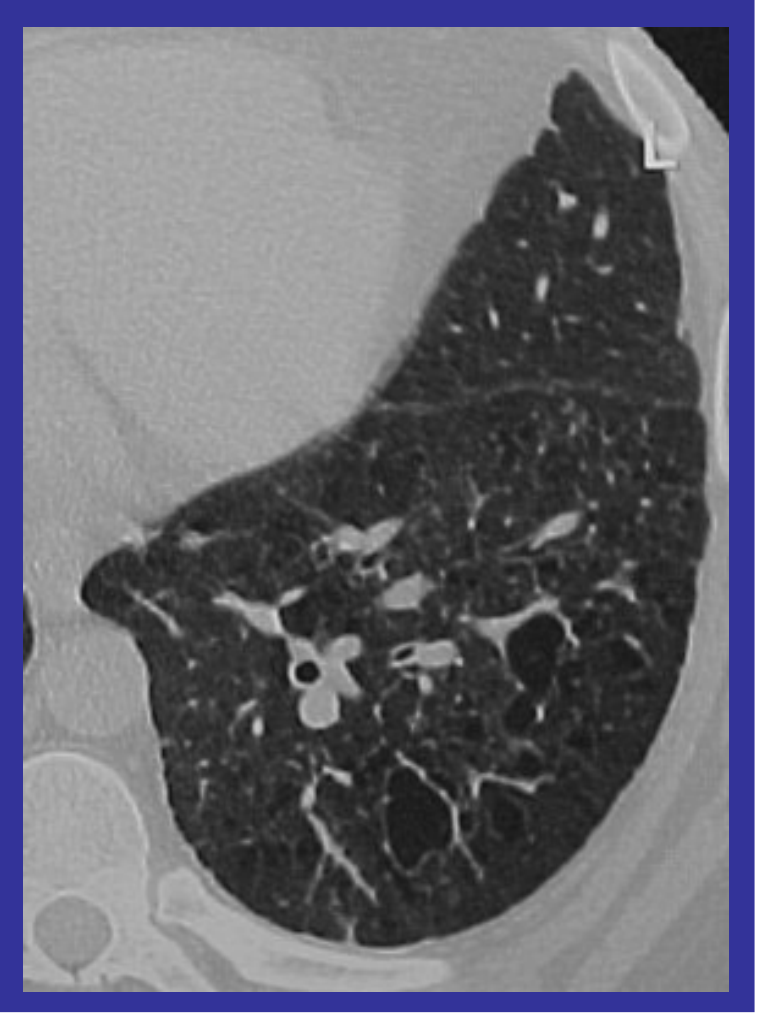
Emphysema



LAM



PLCH

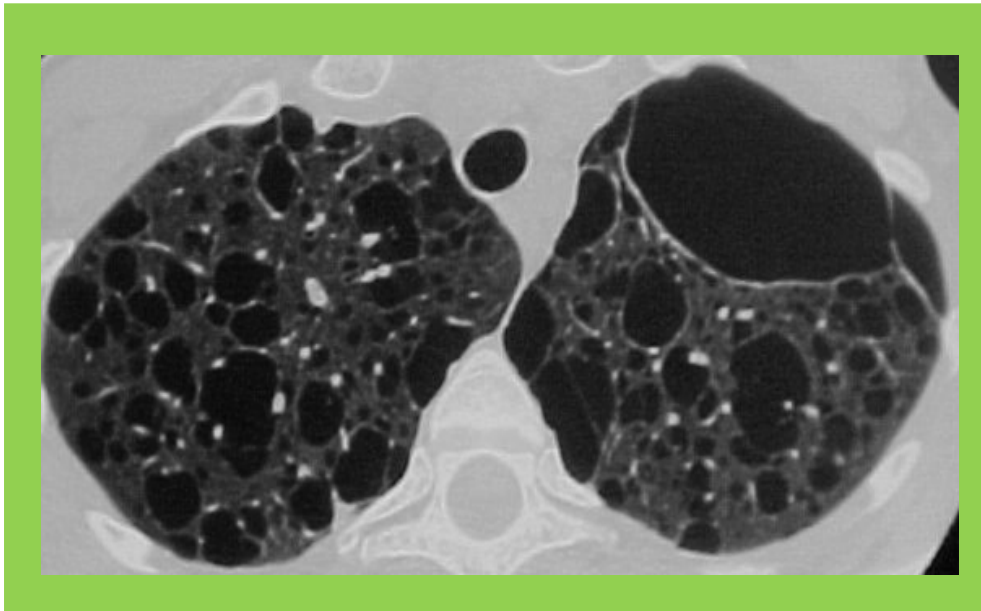


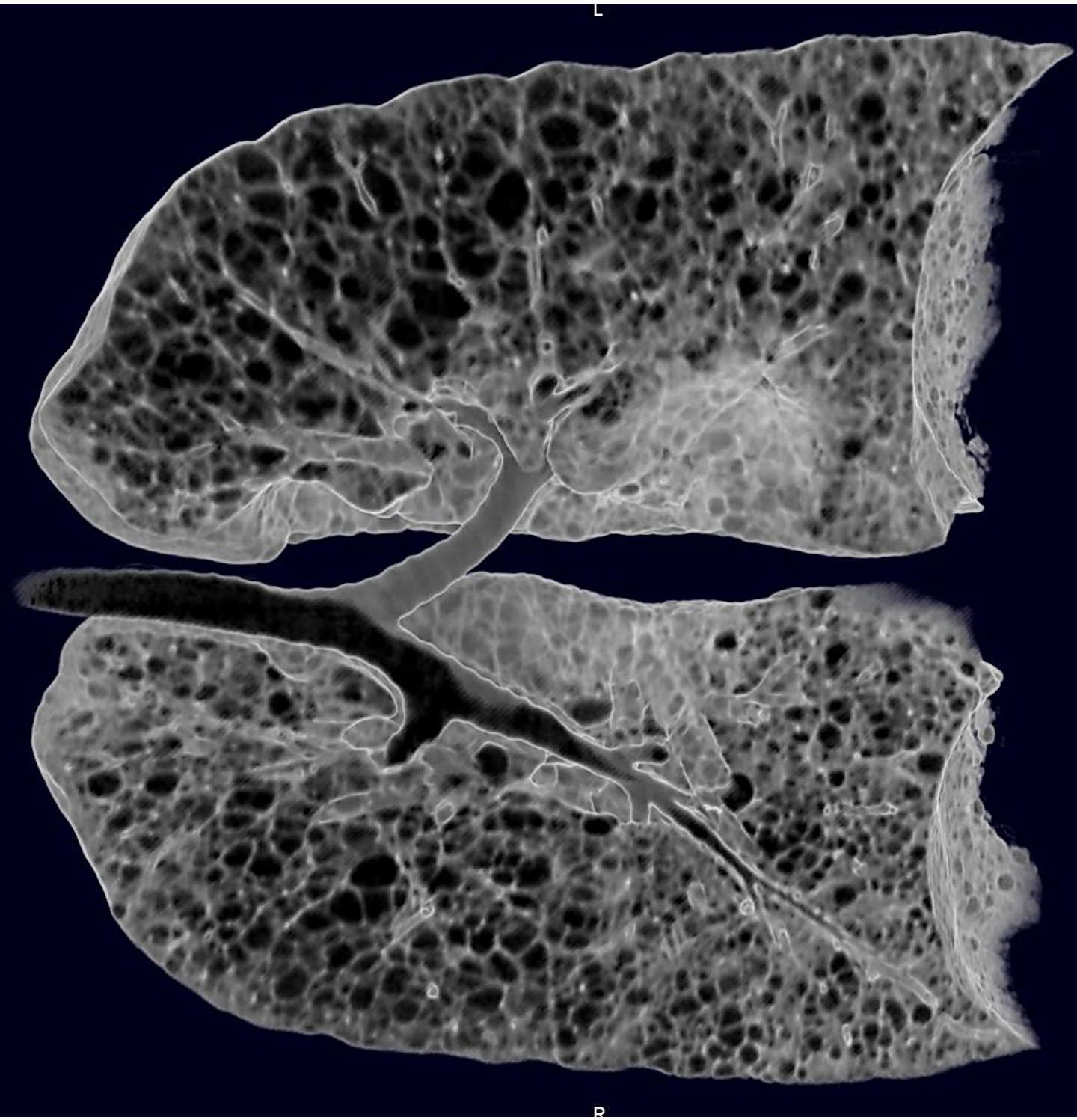
PLCH

- Estimated prevalence =3.2%

LAM

- Estimated prevalence = 0.1/100000
- 800 reported cases
- Incidence: from 0.23 to 0.31/million women/per year and did not change significantly over time (P = 0.89).

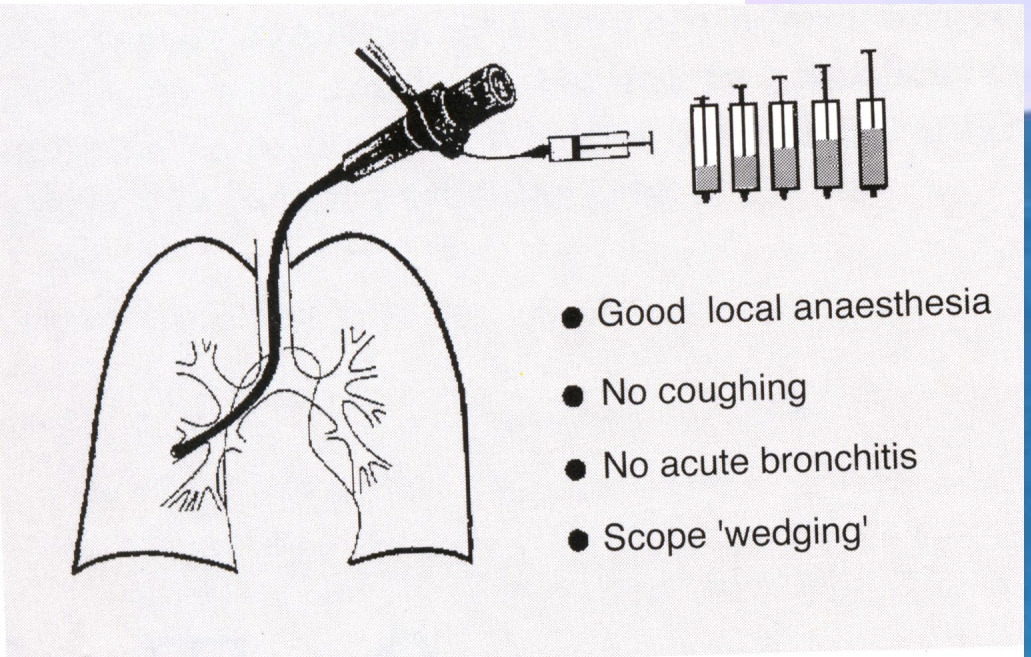


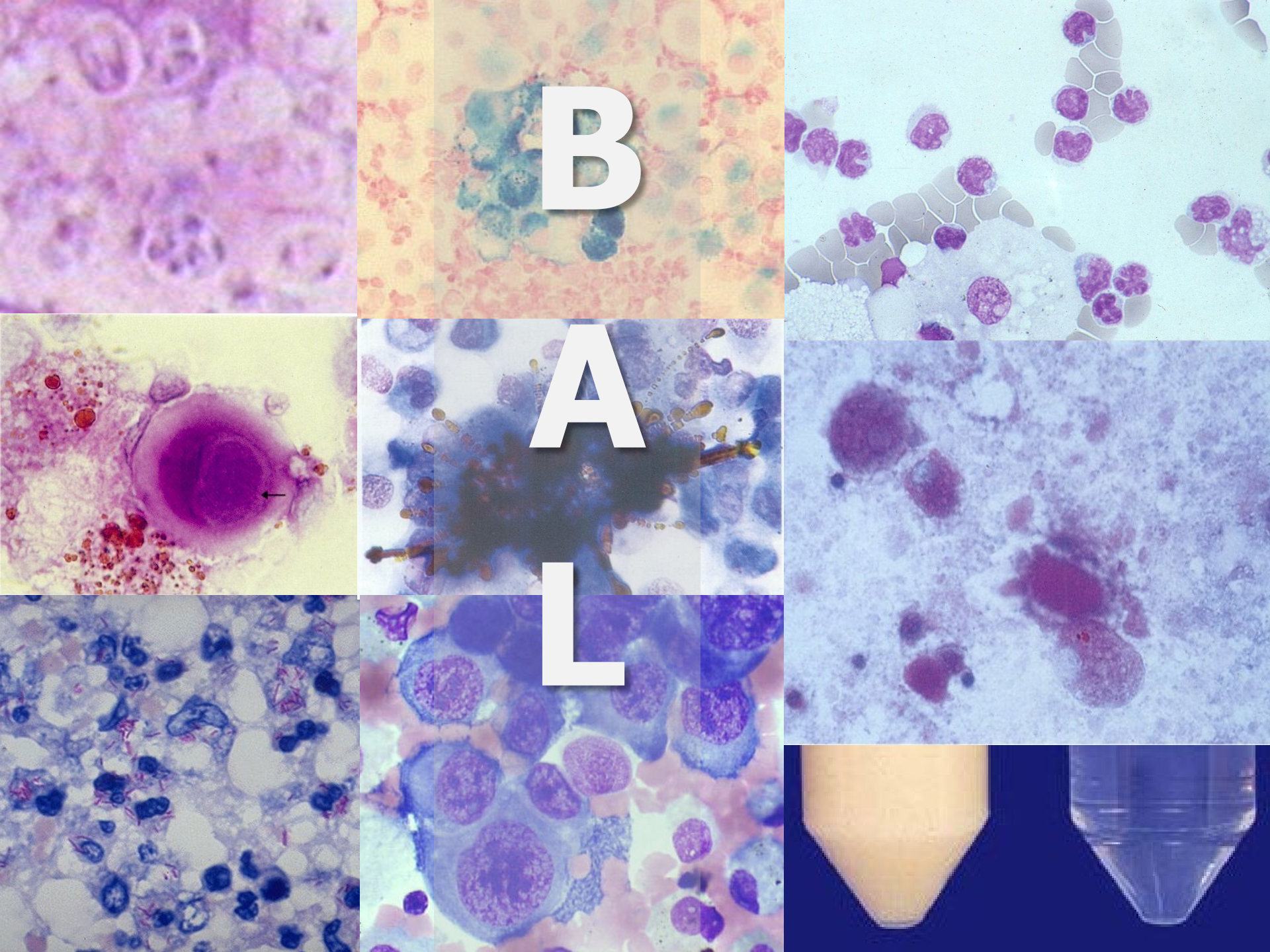

L
R

BronchoAlveolar Lavage

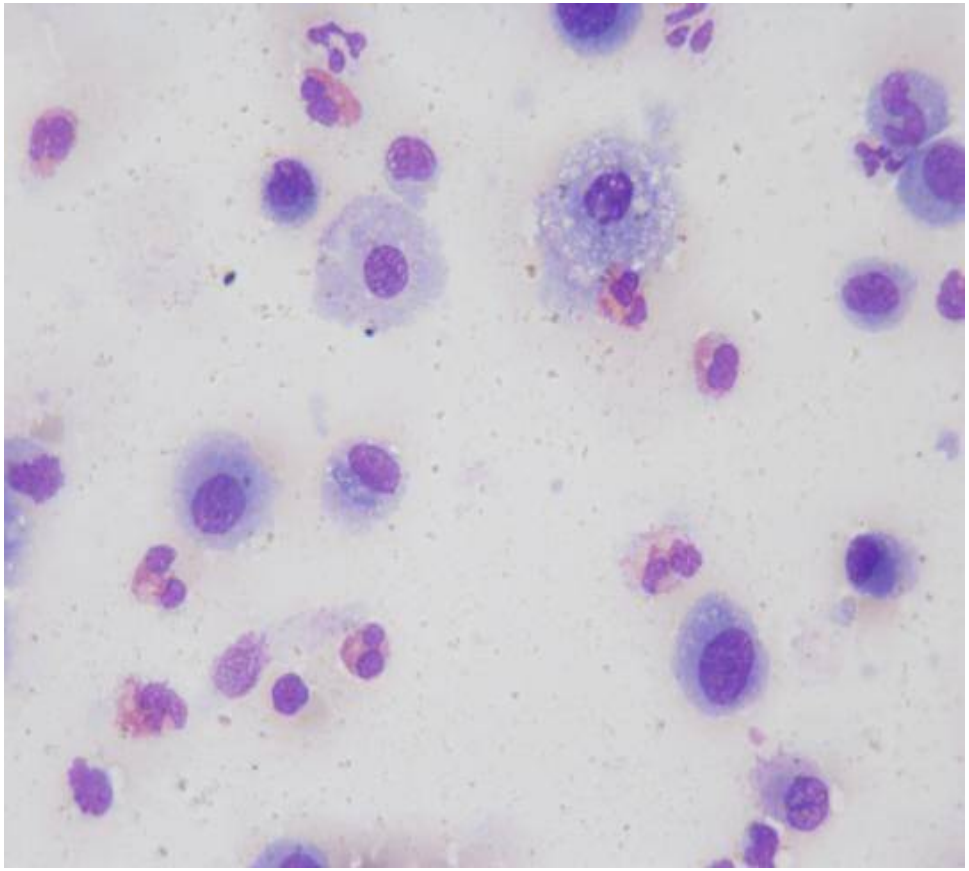
(BAL)

Instillazione di 120-200 cc di soluzione fisiologica.




B
A
L

Bronchoalveolar lavage in ILD



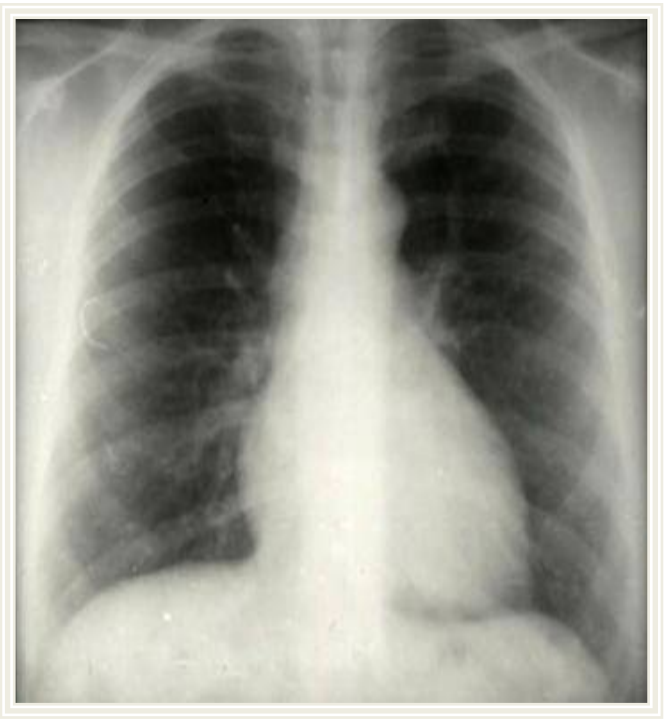
HPC, female, 80 years-old
Eosinophilic lung disease

Cellularity	12 x 10^4/ml
Macrophages	52%
Lymphocites	14%
Neutrophils	6%
Eosinophils	28%
CD4/CD8	1.28

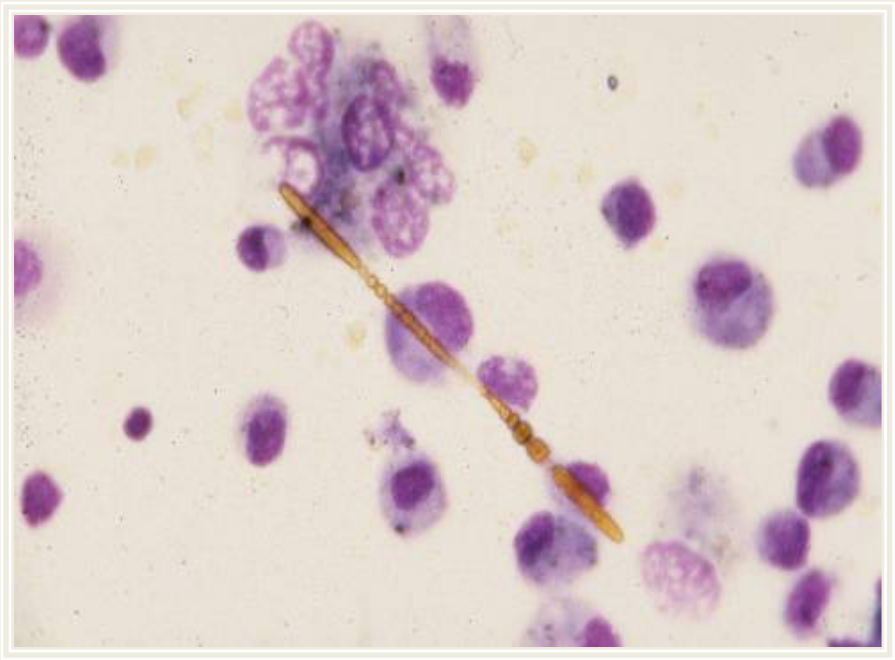
Occupational Diseases

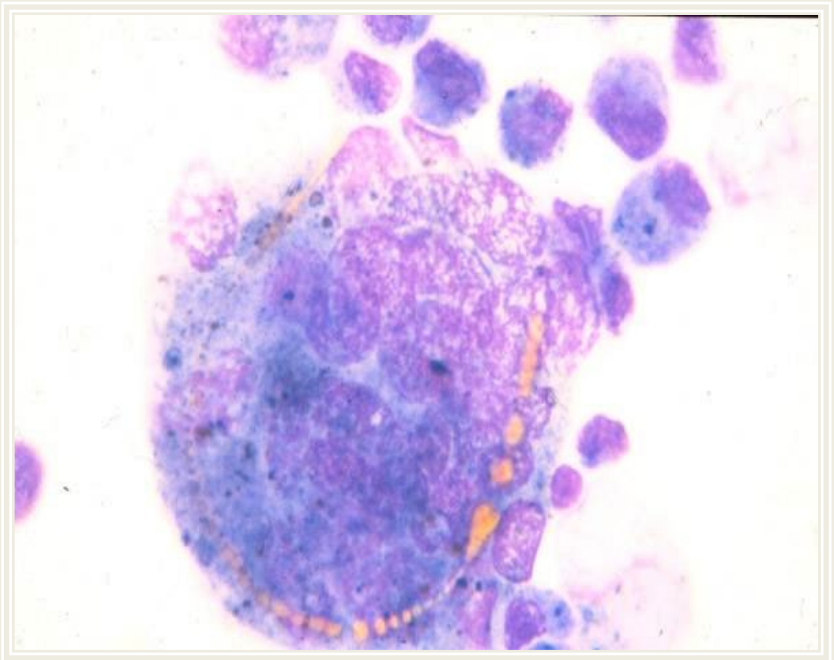
J. C. S., male, 62 years-old
Progressive dyspnea and fatigue
Restrictive ventilatory defect

Professional contact with Asbestos



Occupational Diseases

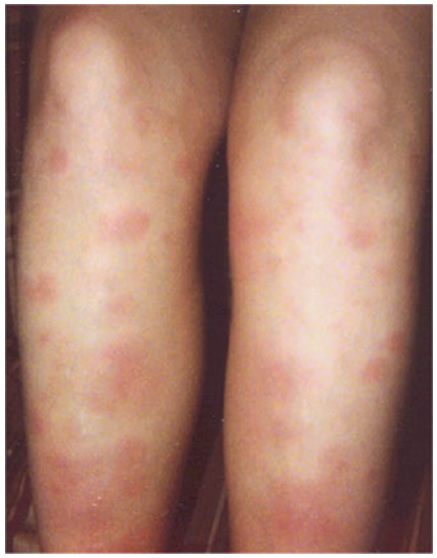


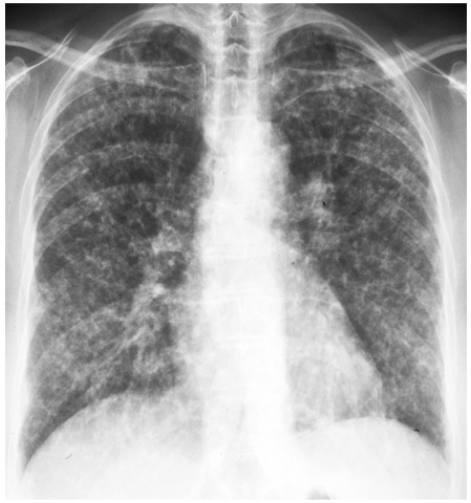


Identification of asbestos bodies > 1/ml

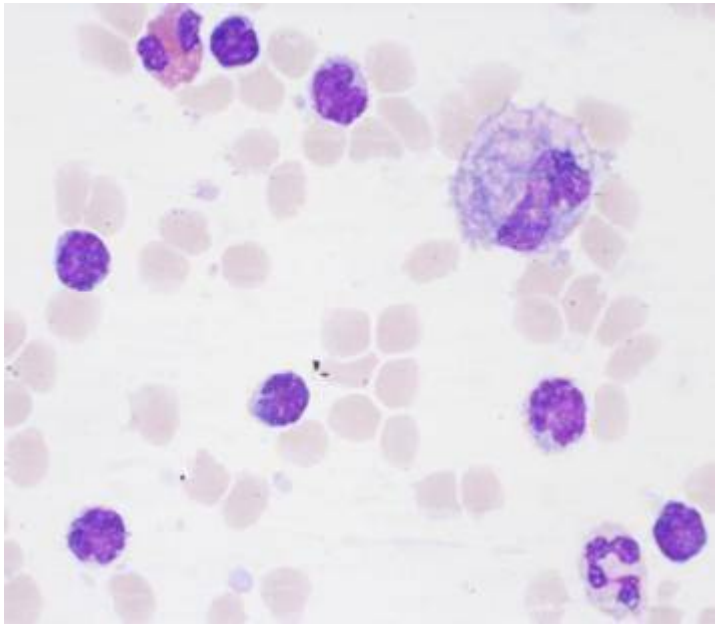
C Robalo Cordeiro et al. Sem Respir Crit Care Med 2007, 28 : 504-513

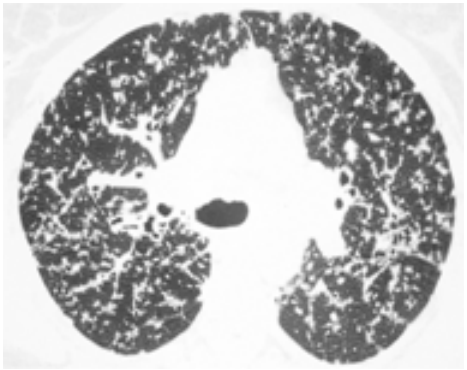
Sarcoidosis





CD4/CD8 > 3.5	
Sensitivity	53%
Specificity	94%

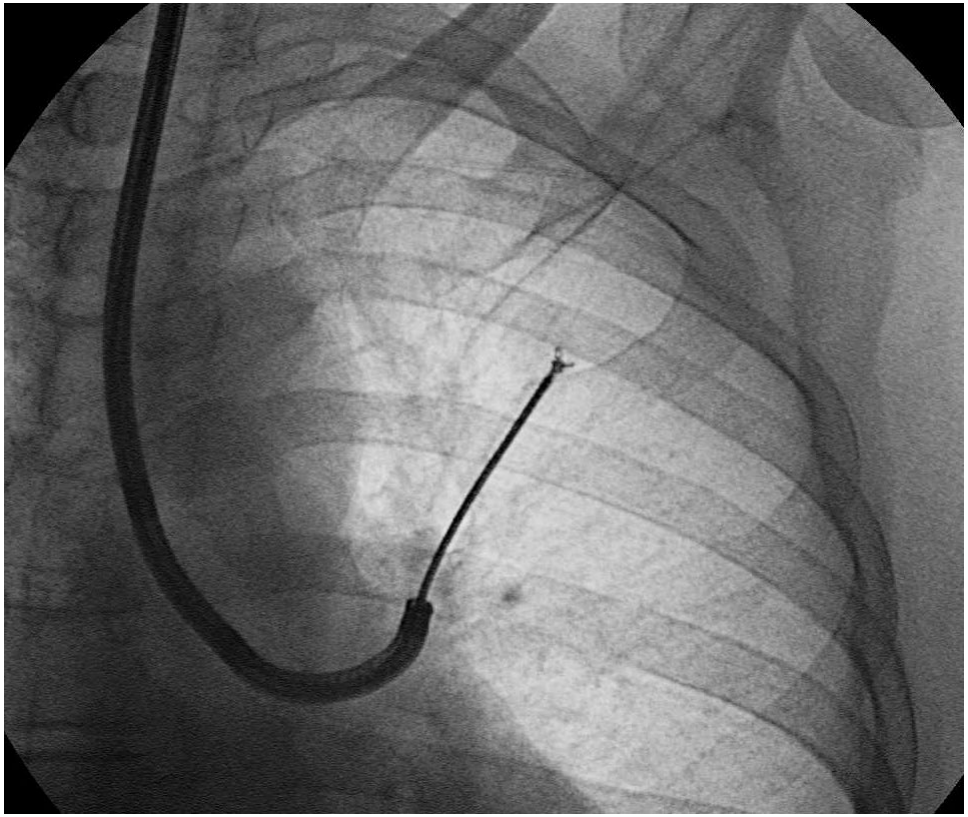




Biopsia transbronchiale (TBB)

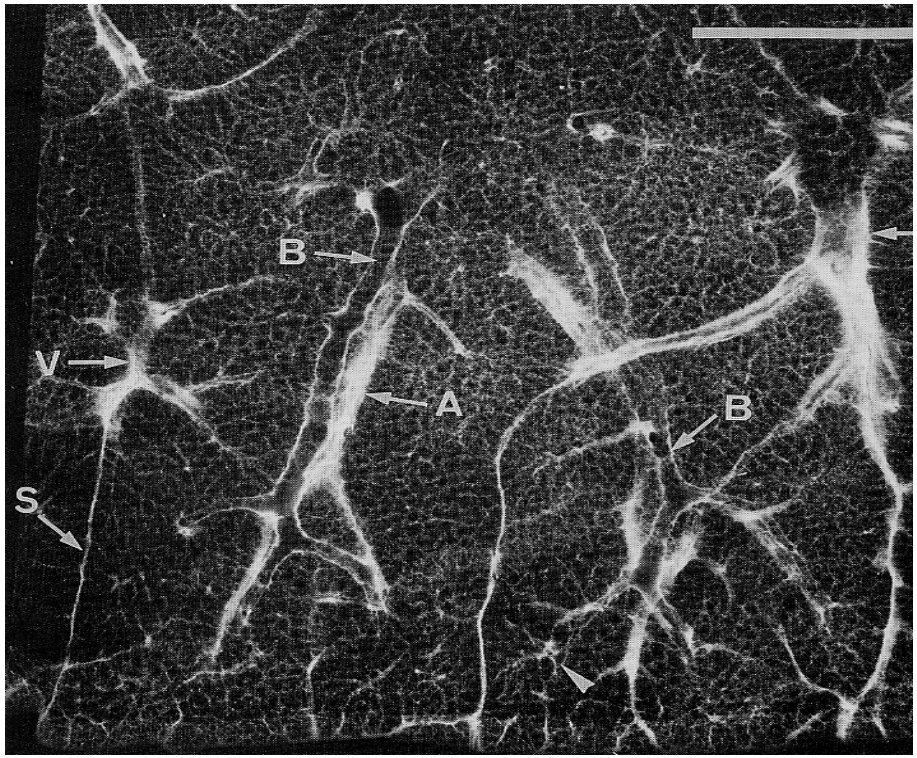
definizione

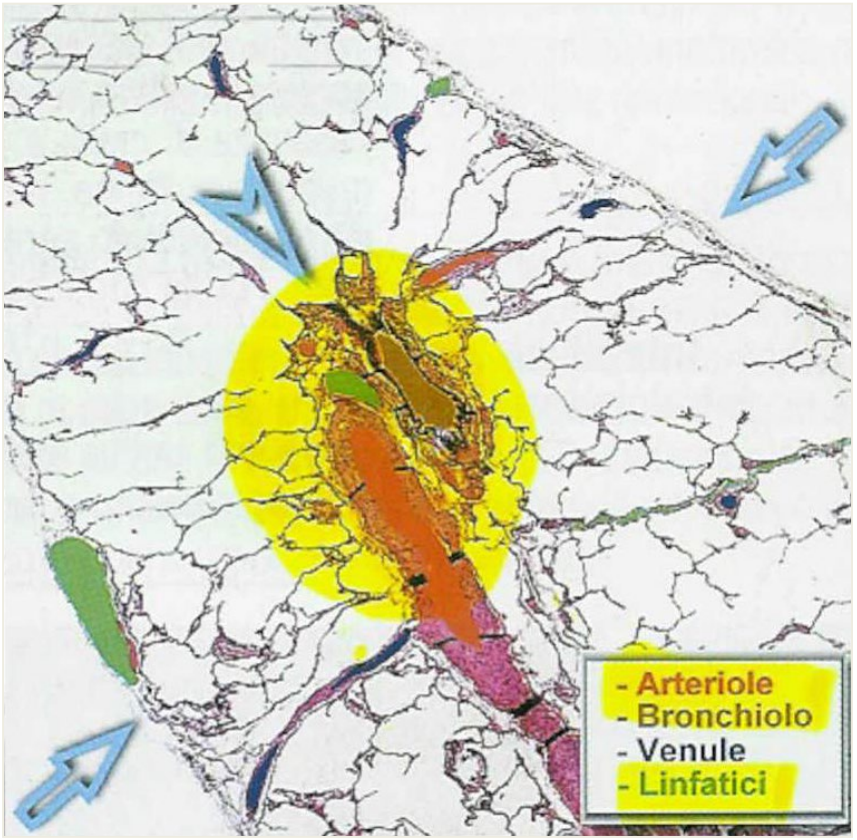
La biopsia transbronchiale (TBB) è una tecnica che permette il campionamento tissutale del parenchima polmonare e che differisce dalla biopsia bronchiale che consiste nel prelievo di tessuto a carico delle vie aeree centrali



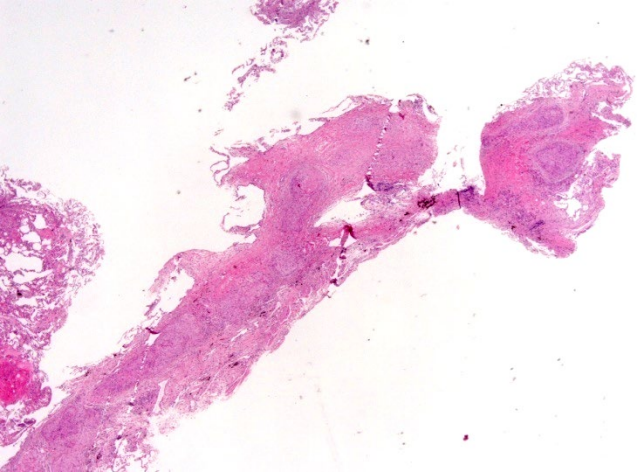
Biopsia Transbronchiale

….distribuzione delle lesioni nel lobulo secondario



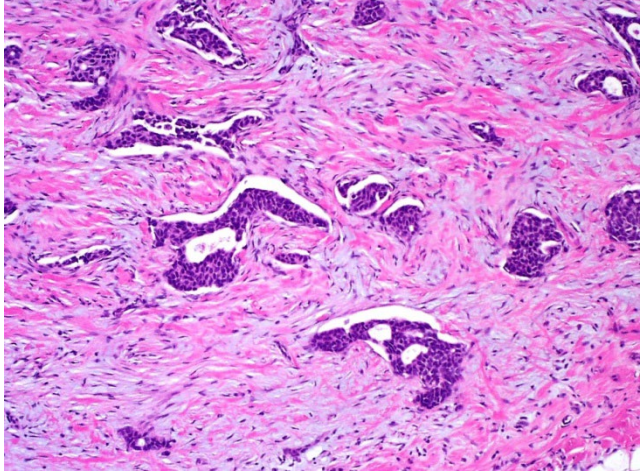


Maffessanti & Dalpiaz

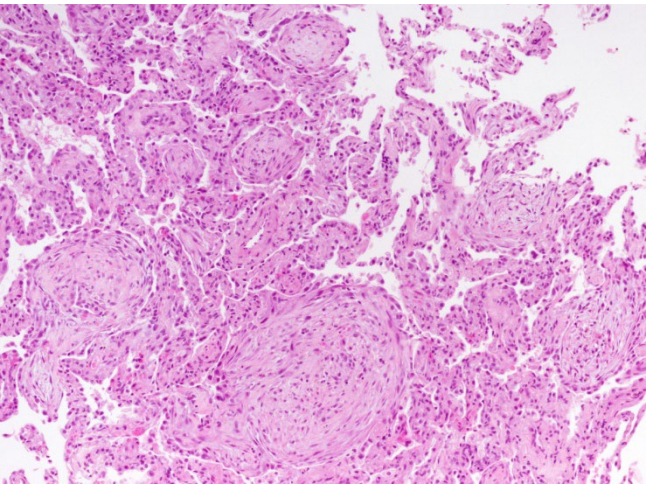


Sarcoidosi

T

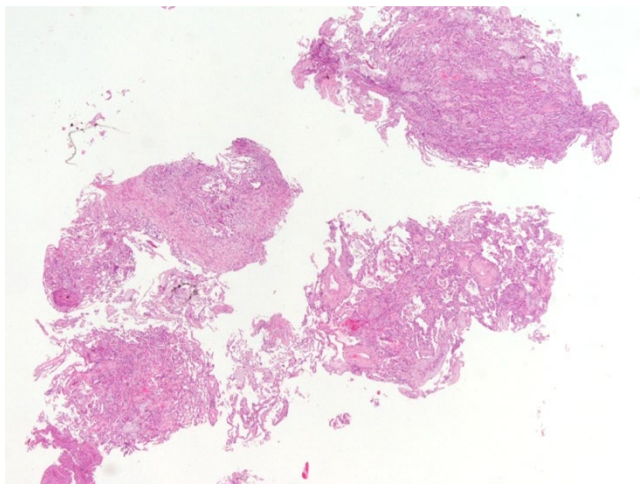


Adenocarcinoma



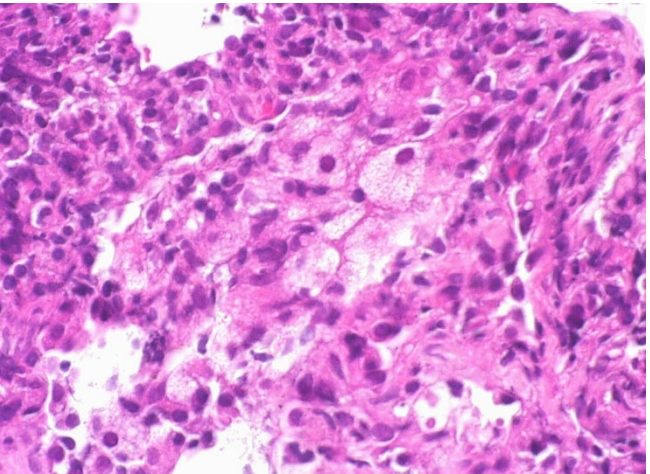
OP

B

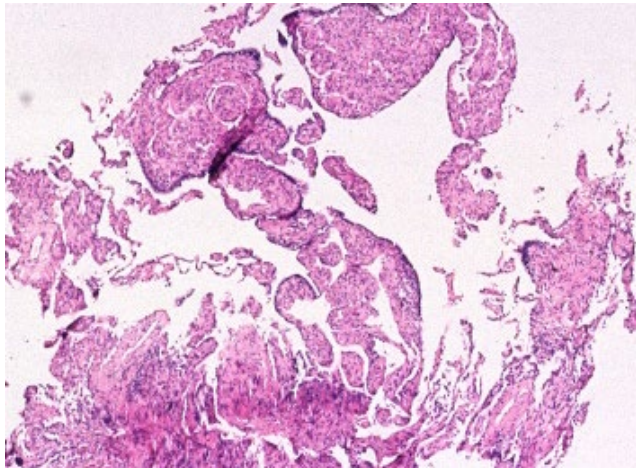


Polmonite eosinofila

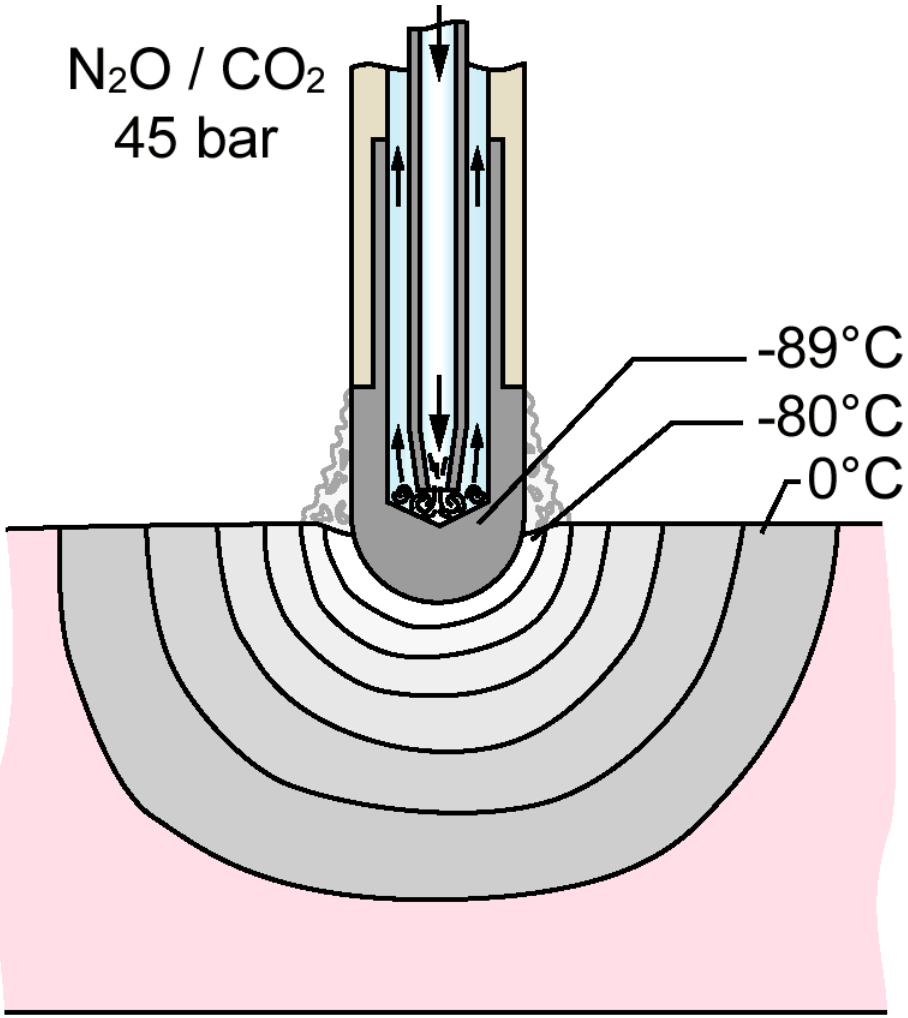
B



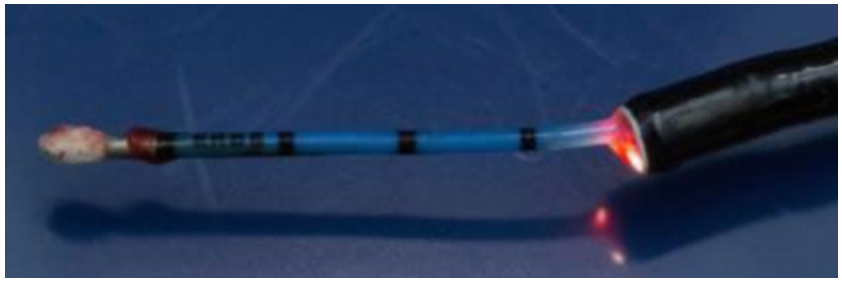
Polmonite da ipersensibilità



Linfangioleiomiomatosi



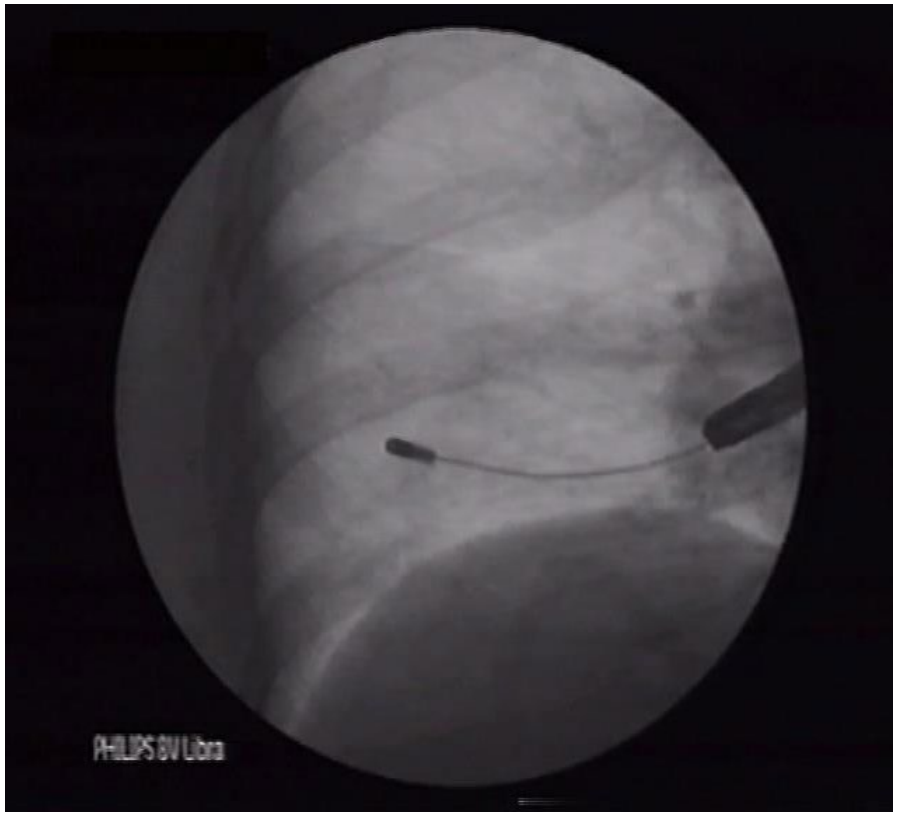
Cryoprobe with water iceball

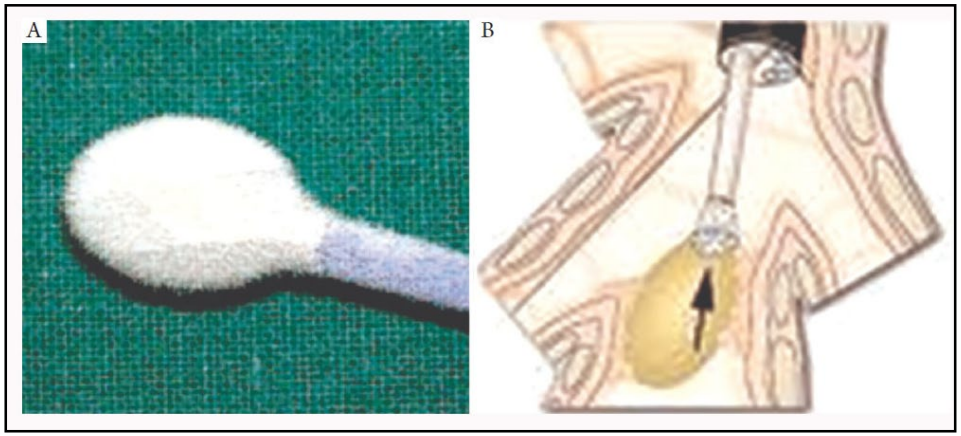


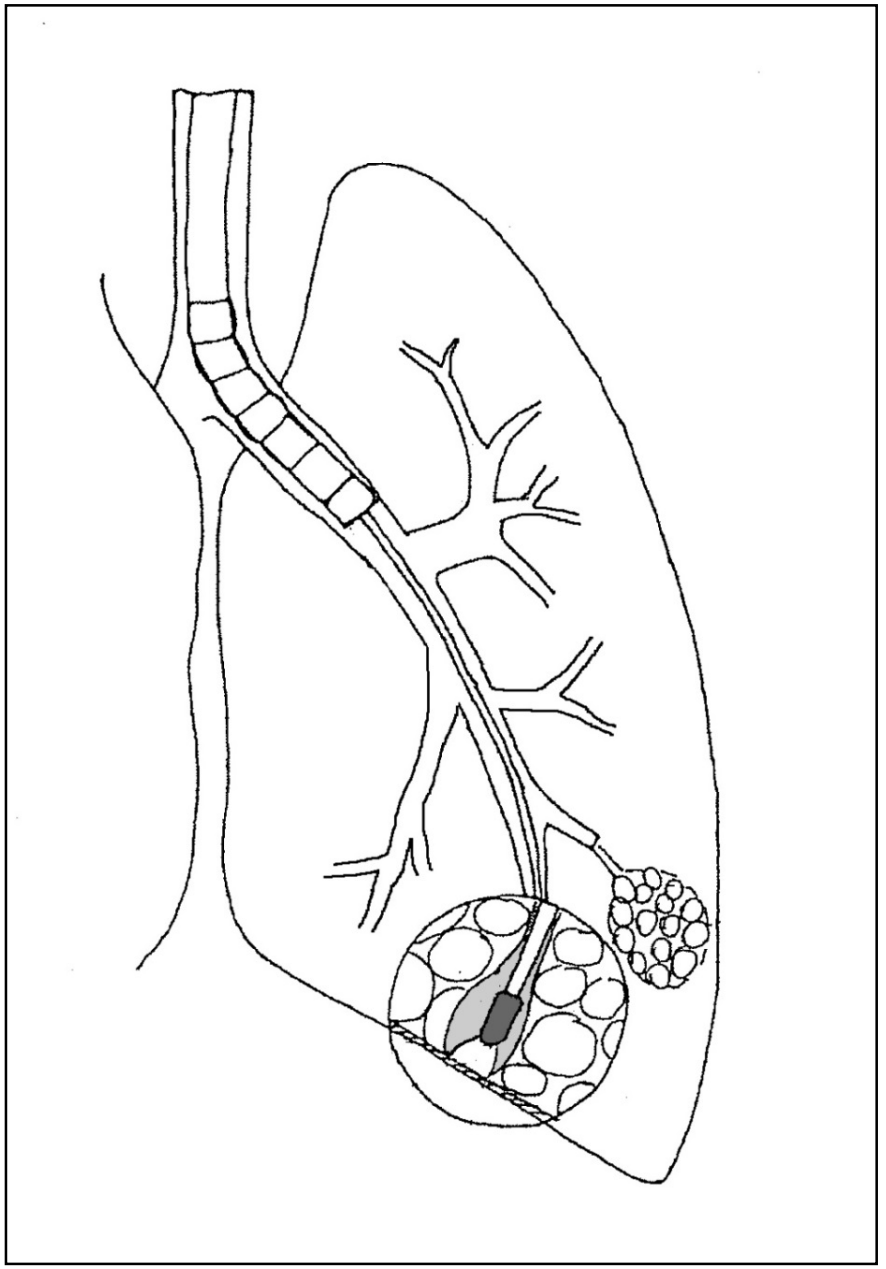
Cryoprobe with tissue-iceball

The gas at the tip expands due to the sudden difference in pressure **(Joule-Thomson effect), resulting in a drop in** temperature at the tip of the probe.

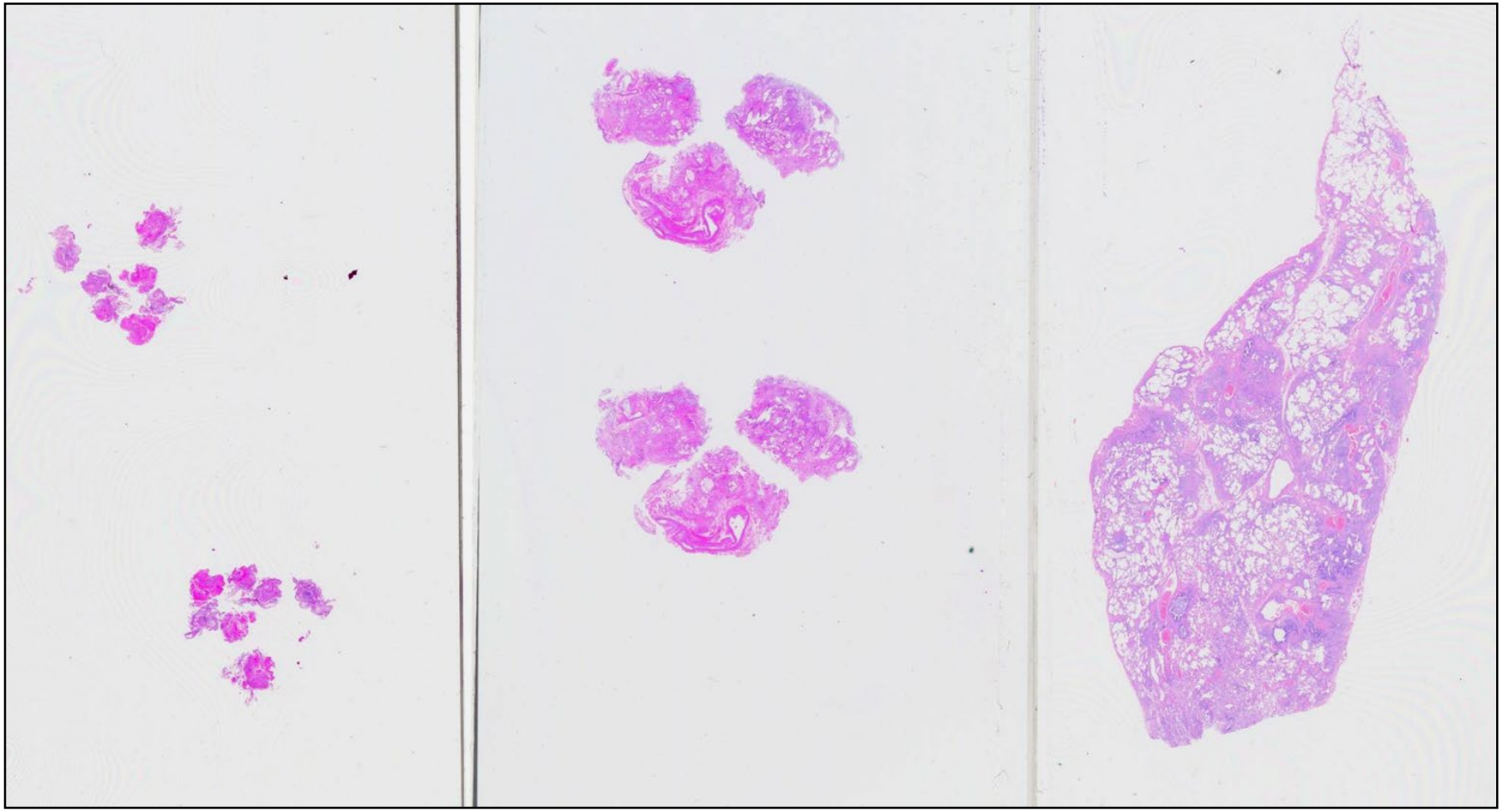
Cryobiopsy: the technique

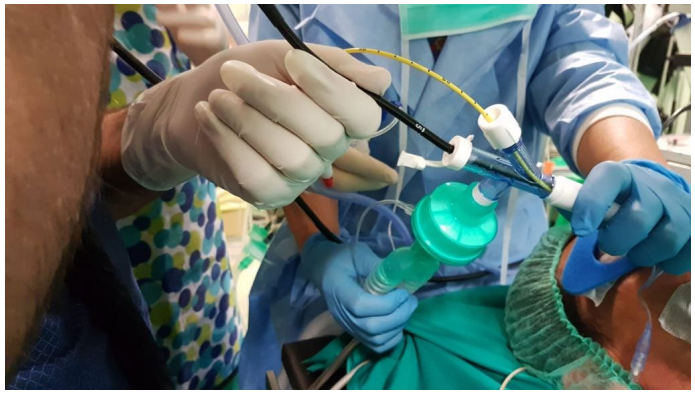


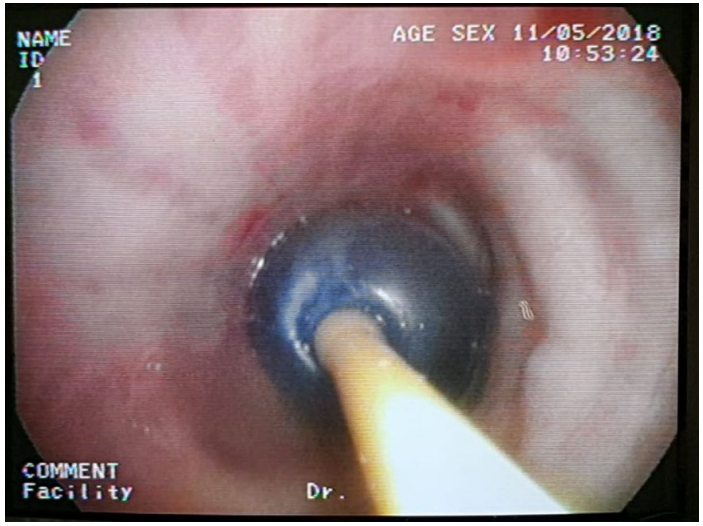


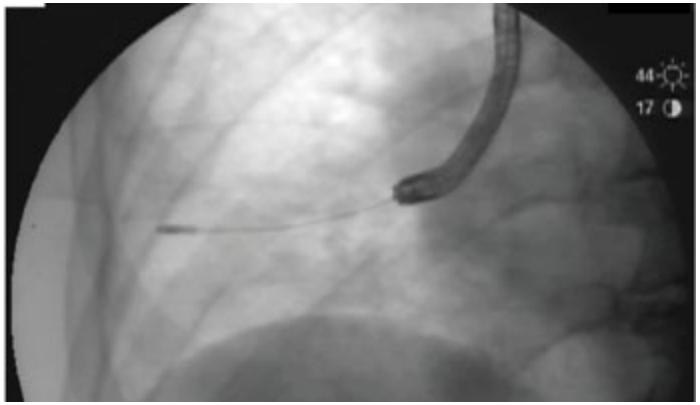


TBB **Cryobiopsy** **Lung biopsy**







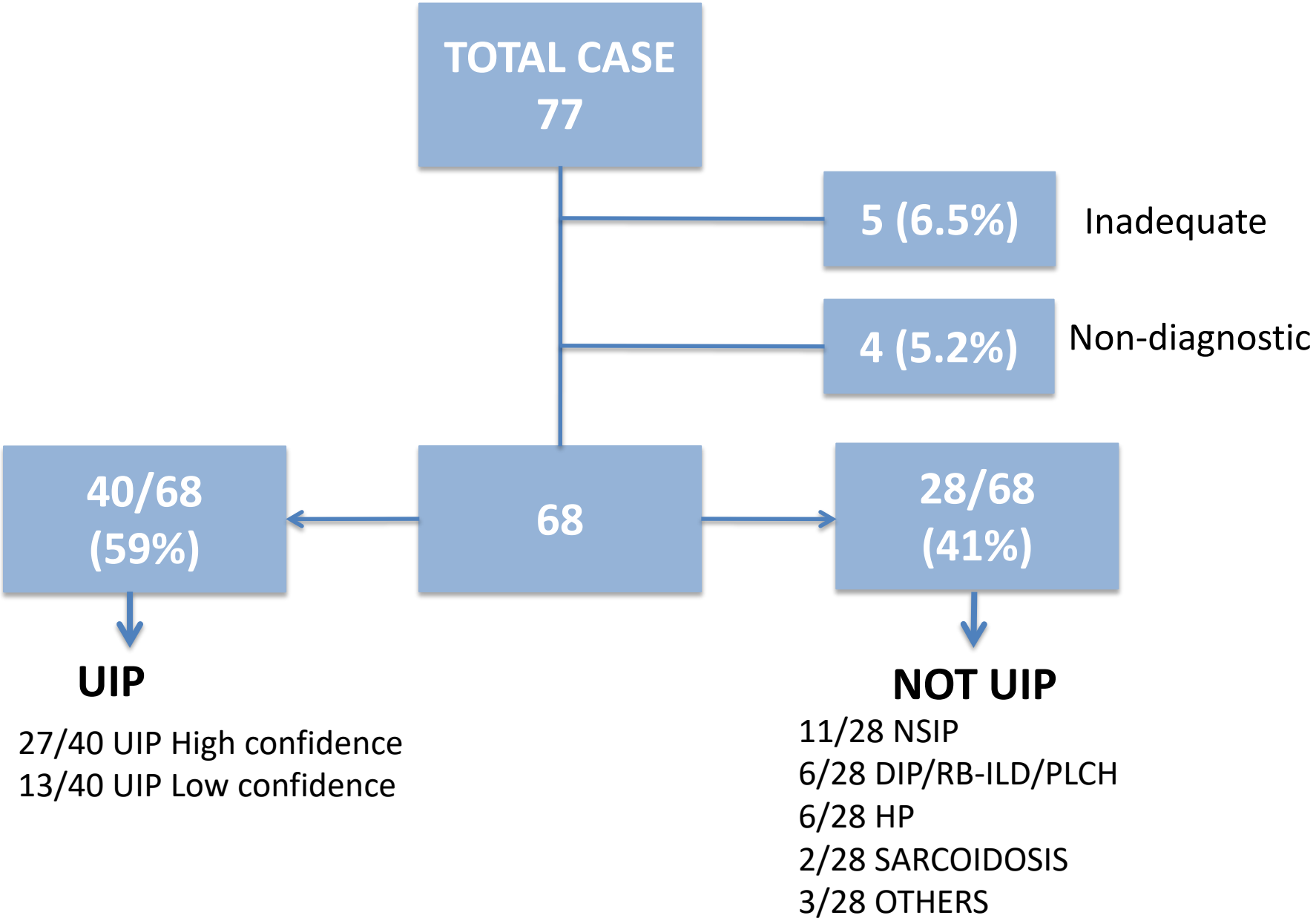


Transbronchial cryobiopsy San Giuseppe H's custom

- General anesthesia
- Intubated patient
- Flexible bronchoscope
- Endobronchial blocker
- Fluoroscopic control
- Cryoprobe 1.9 mm
- A distance of approximately <= 10 mm from the thoracic wall
- The 1.9 probe is cooled for > 3-5 s

3-4 samples: it takes 20 minutes

San Giuseppe experience (May 2015 – up to now)



test
for the
eement occurs
discussion with

Pneumologo

Radiologo

Anatomo-
patologo

Flaherty 2004

Anamnesi

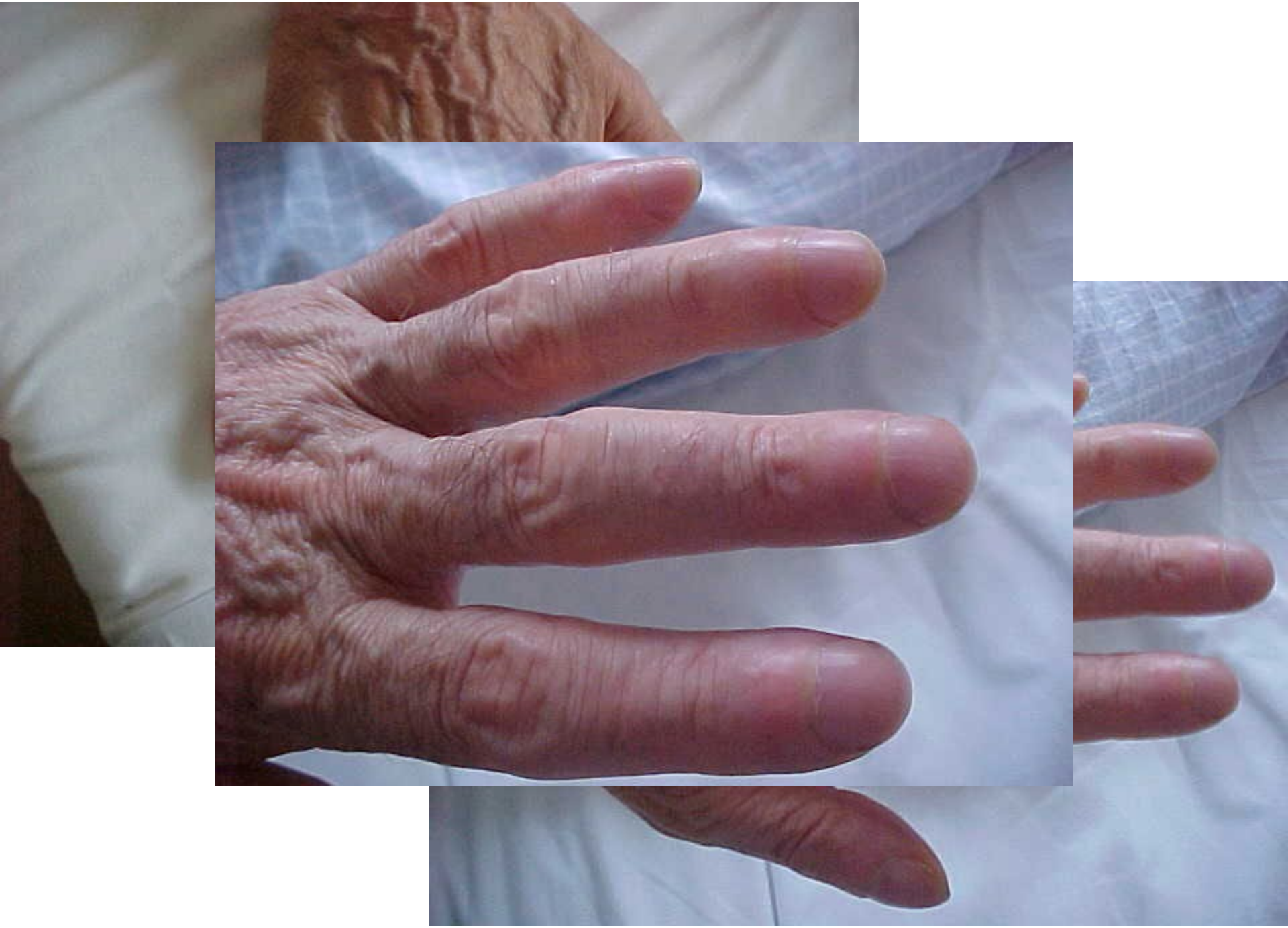
- L.T., uomo di 68 anni, ex-fumatore (30 pacchi/anno), non patologie degne di rilievo in anamnesi
- Non esposizioni professionali
- Non assume farmaci
- Da alcuni anni comparsa di dispnea da sforzo e sporadica tosse secca
- Negli ultimi due/tre mesi progressiva accentuazione della dispnea e tosse secca prevalentemente notturna

Esame obiettivo

- Pz obeso: peso Kg 111, altezza 177 cm, BMI 35.5
- Eupnoico a riposo, decubito indifferente
- Sub-cianosi periferica, non adenomegalie periferiche
- **EOT: presenza di rantoli crepitanti ai campi polmonari inferiori**

Esame obiettivo

- Toni cardiaci validi, ritmici, normofrequenti
- Addome globoso per adipe, trattabile, non dolente
- Non edemi declivi
- **Presenza di ippocratismo digitale**
- Nega ortopnea e nicturia
- PA 140/80, FC 60R, Sat.O2 in AA 94%, FR 20 atti/min



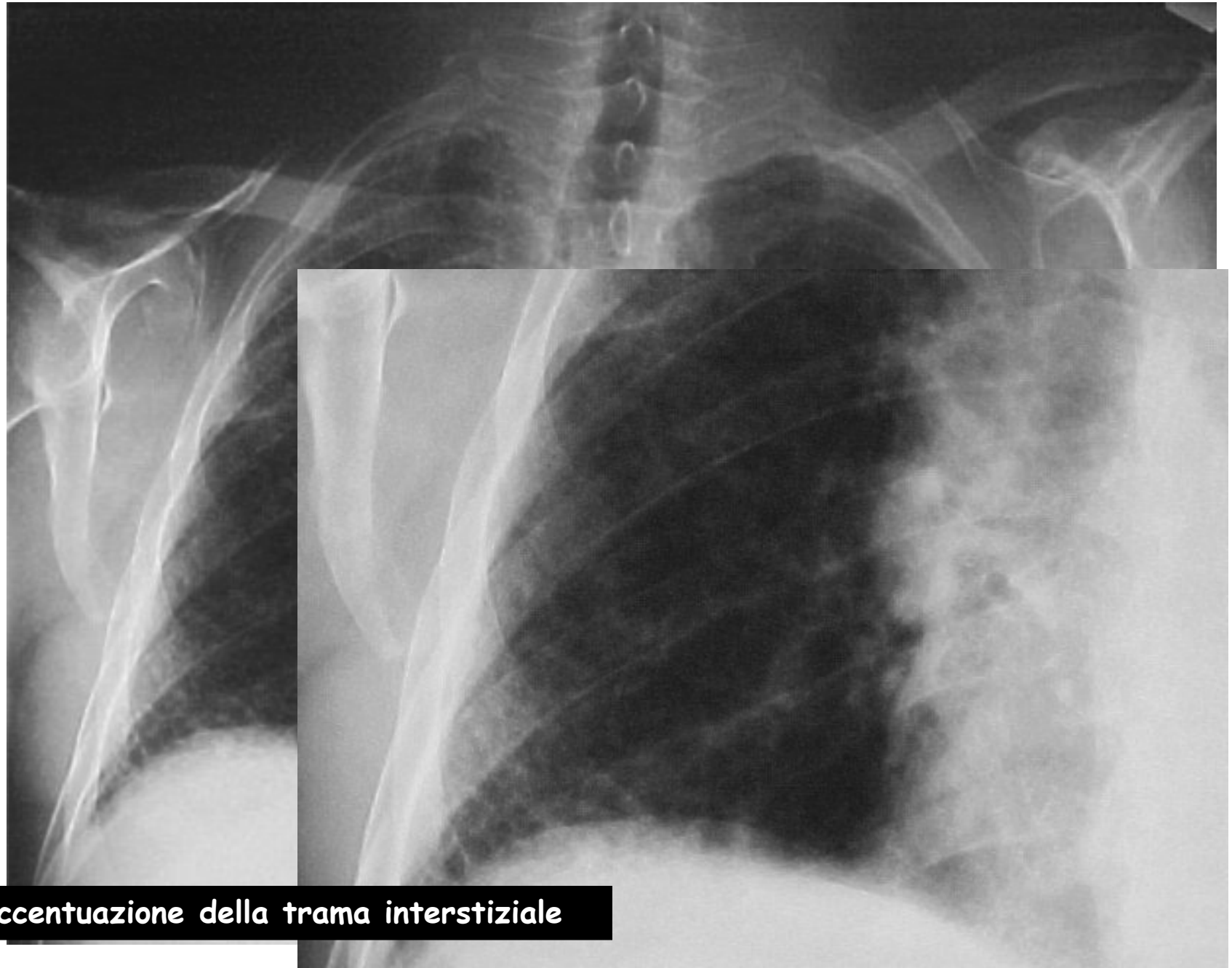
What's the problem?

- Patologia cardiaca?
- BPCO?
- Neoplasia polmonare?
- Insufficienza respiratoria in obeso?
- Interstiziopatia polmonare?

Quali indagini?

- HRCT del torace?
- Rx torace?
- EGA + PFR + DLCO?
- Test da sforzo cardio-polmonare?
- Scintigrafia polmonare?

Riduzione di volume polmonare



Accentuazione della trama interstiziale

Funzionalità respiratoria

- EGA in AA: PaO2 68.2 mmHg, PaCO2 47.3 mmHg, pH 7.43, Sat.O2 94.1%
- PFR: VC 2.44L 61%, FVC 2.44L 63%, FEV1 2.16L 72%, FEV1/SVC 89%, TLC 2.95L 44%, RV 0.52L 21%, DLCO 20 77%

Interpretazione

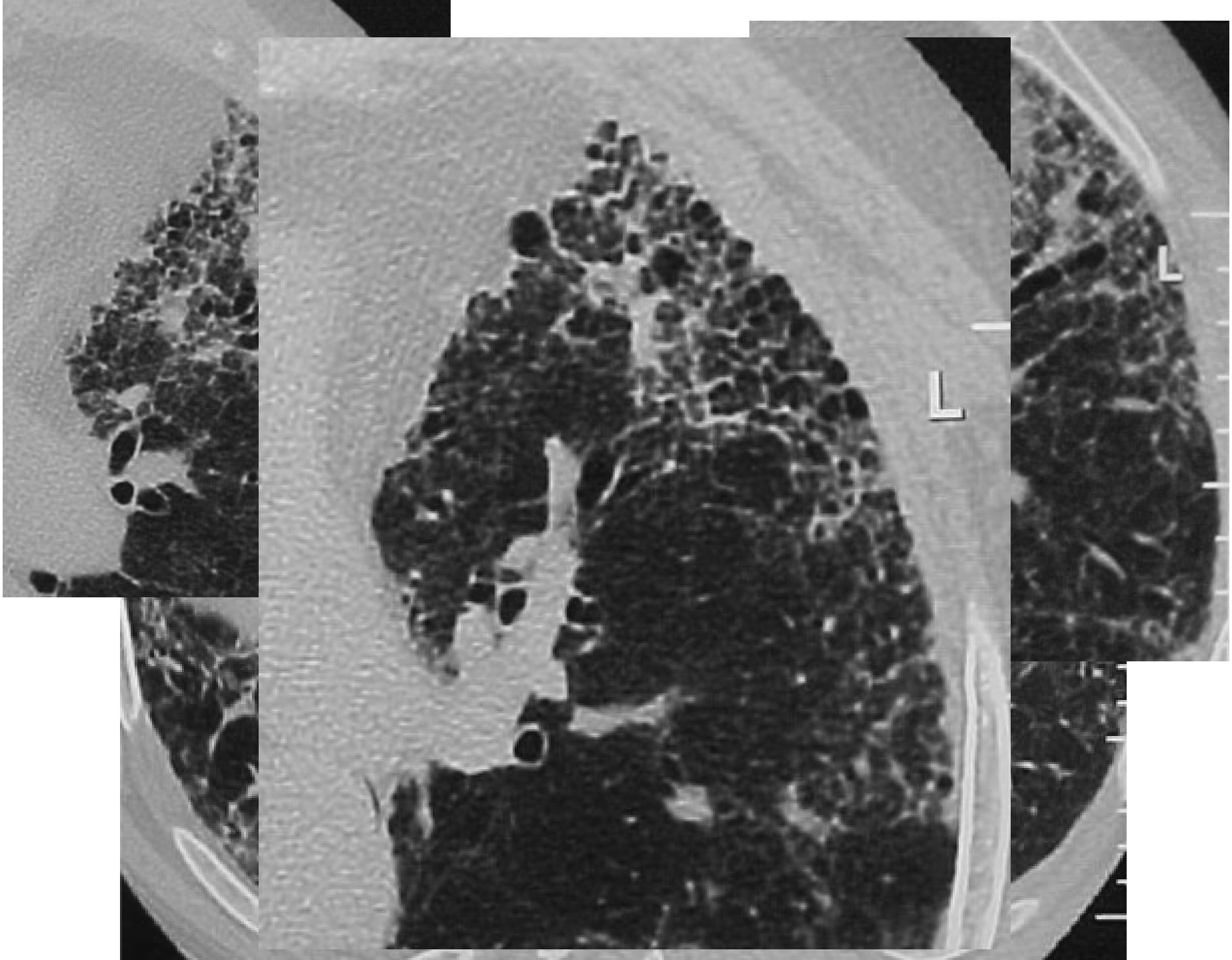
- Quadro funzionale ed emogasanalitico nella norma
- Insufficienza respiratoria globale compensata in deficit restrittivo
- Insufficienza respiratoria globale compensata in deficit ostruttivo

What's the problem?

- Patologia cardiaca?
- BPCO?
- Neoplasia polmonare?
- Insufficienza respiratoria in obeso?
- Interstiziopatia polmonare?

Quali indagini?

- HRCT del torace?
- Esami emato-chimici?
- Ecocardiogramma?
- Test da sforzo cardio-polmonare?
- Scintigrafia polmonare?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Laboratorio

- Emocromo con formula nella norma
- Esami ematici nella norma
- Ricerca autoanticorpale (ANA, ENA, fattore reumatoide, Waaler-Rose) negativa

Diagnosi:

Fibrosi Polmonare idiopatica