Fumo e polmone: non solo BPCO
Le interstiziopatie fumo-correlate

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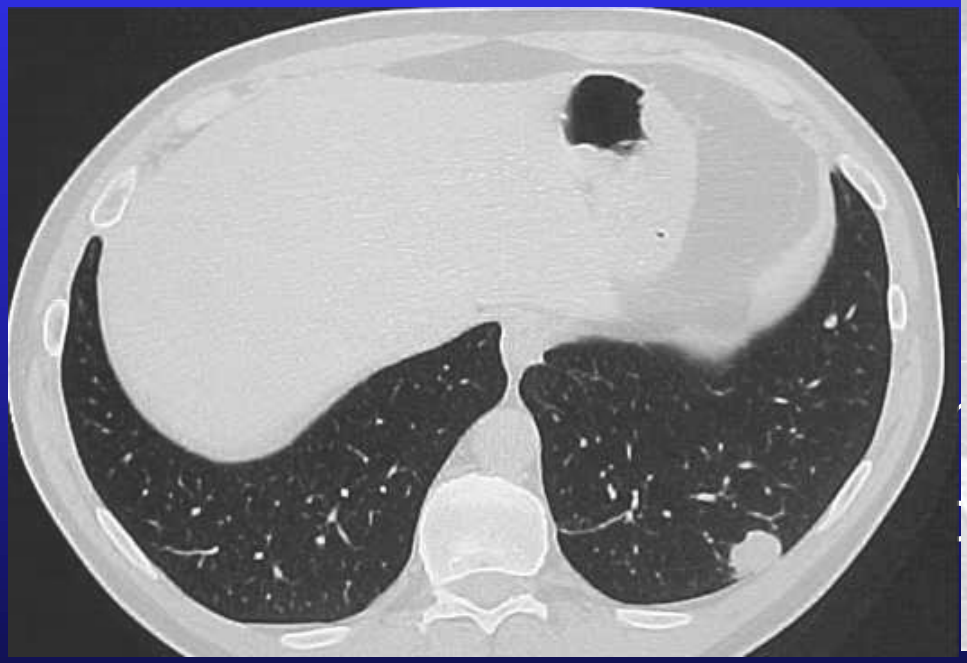
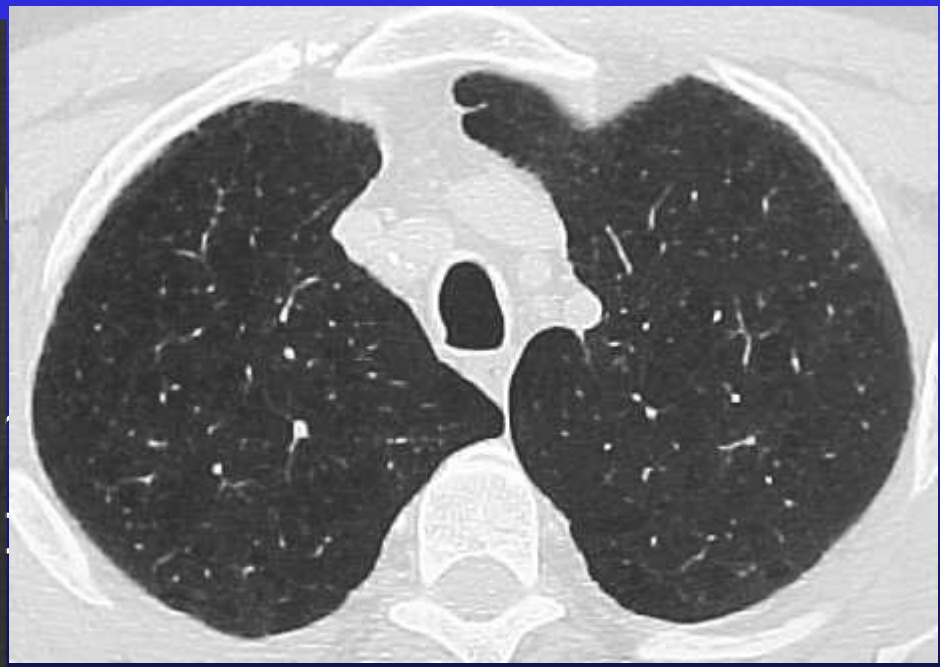
Cigarette smoking affects many organs and remains the most preventable cause of morbidity and premature death

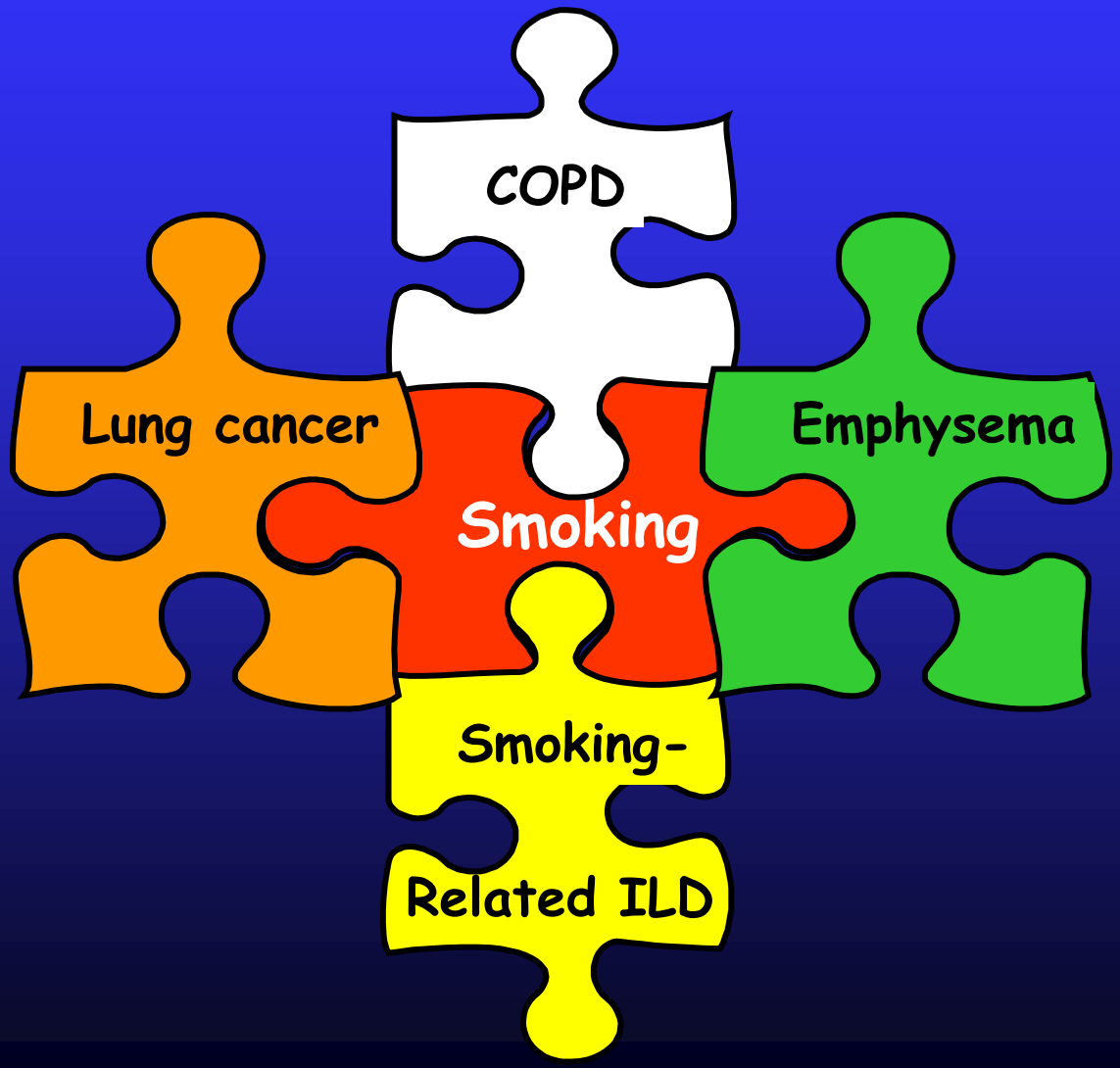
Smoking and lung

- Cigarette smoking as a cause of emphysema, obstructive lung disease and lung cancer is well





Recent Advances



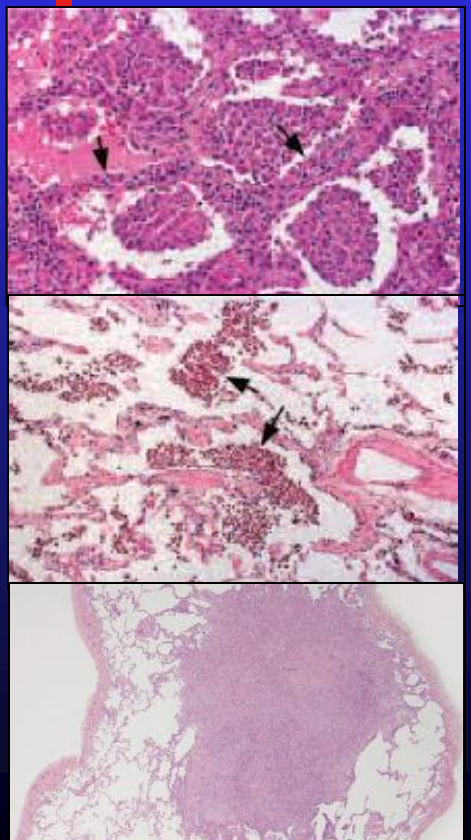
Smoking-related interstitial lung diseases

1969 — Liebow and Carrington

1974 — Niewoehner

1986 — Mayers

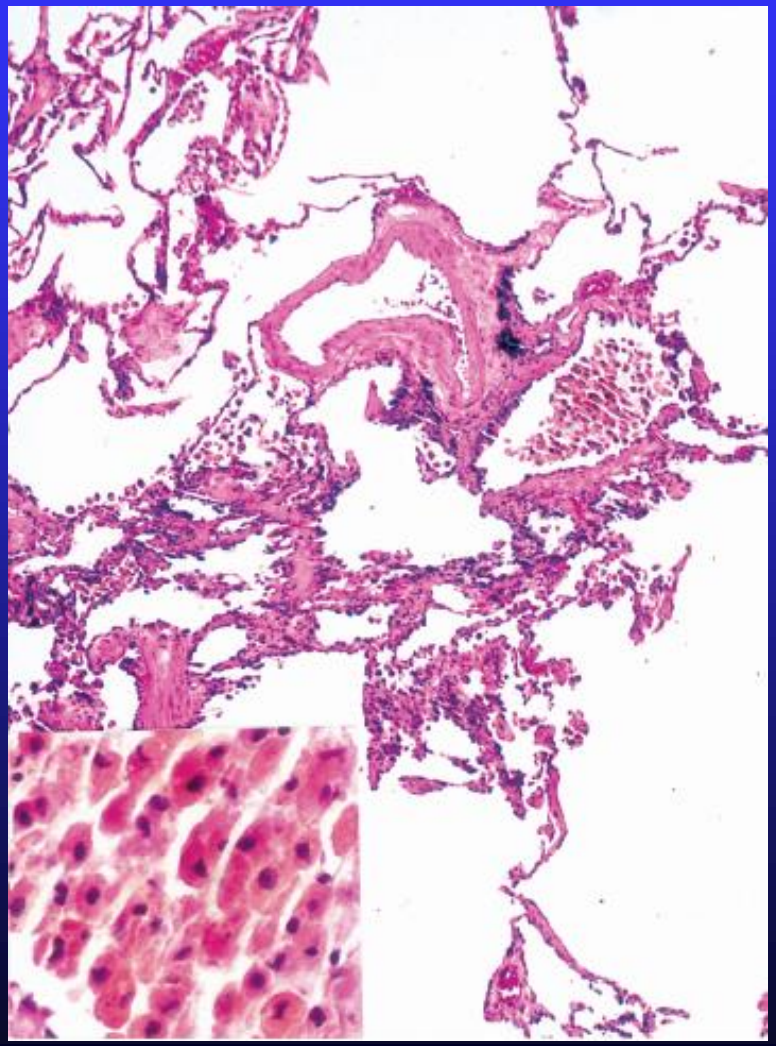
2000



"smoking related interstitial lung disease" which would include pulmonary Langerhans' cell histiocytosis, RB-ILD, and DIP

Respiratory Bronchiolitis

- presence of tan brown pigmented macrophages in respiratory bronchioles spilling into neighbouring alveoli
- Strictly peribronchiolar alveolar septal thickening characteristically radiating in a stellate fashion from the bronchiole



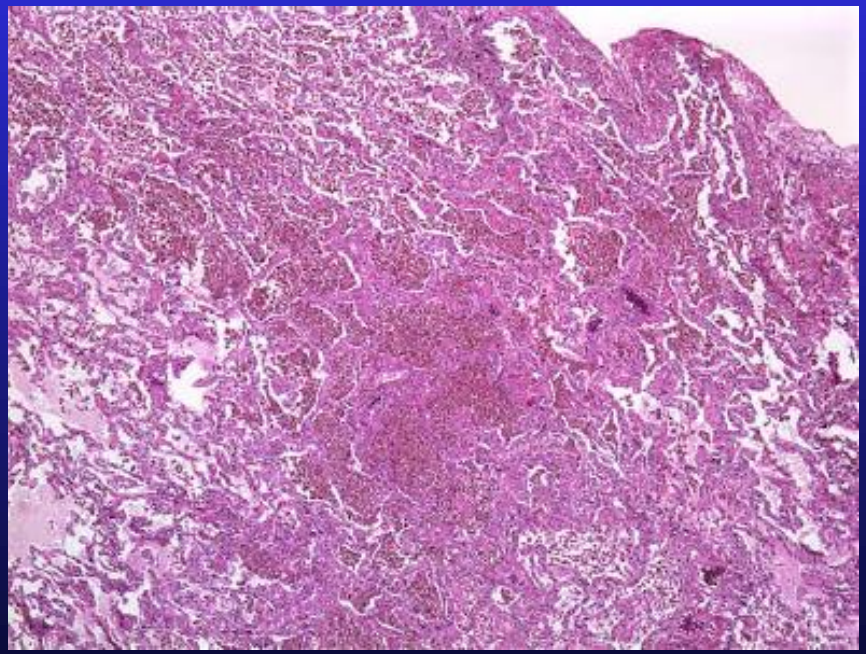
Fraig M et al. *Am J Surg Pathol 2002; 26: 647–653*

RB-ILD: WHAT IS IT AND WHAT IS IT NOT

- Respiratory bronchiolitis (RB) is an extremely common, and often incidental histopathological finding in cigarette smokers
- The finding of changes indicative of RB on biopsy simply indicates a pattern of injury induced by smoking in that individual and does not equate with RB-ILD
- Very rarely, symptomatic interstitial lung disease may occur in some individuals who smoke in whom the biopsy shows RB: these individuals have RB-ILD

RESPIRATORY BRONCHIOLITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE (RB-ILD)

- All smokers
- Symptomatic
- Restrictive PFT's
- Centrilobular nodules
- Ground glass
- Good prognosis



CLINICAL FEATURES

- Current smokers in the fourth and fifth decades of life
- Mild symptoms
- Gradual onset of dyspnea and hypoxemia, cough
- Many patients improve after cessation of smoking
- Progression to dense pulmonary fibrosis has not been reported

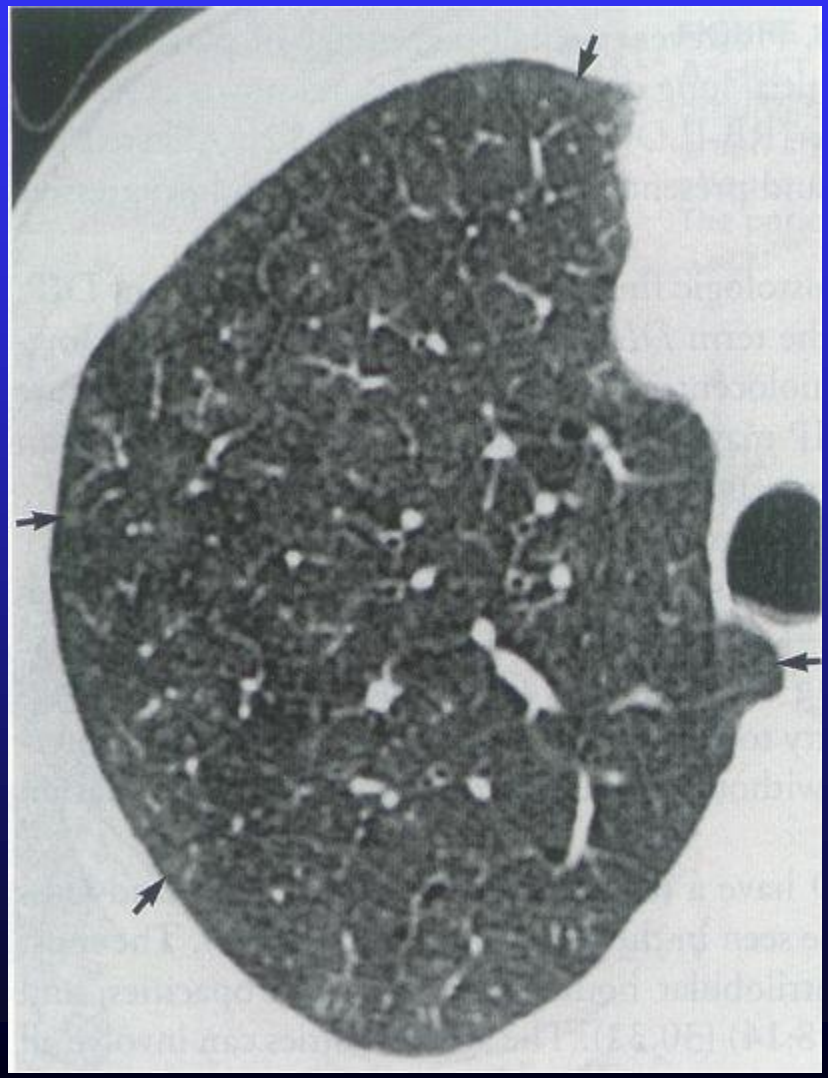
RADIOLOGY

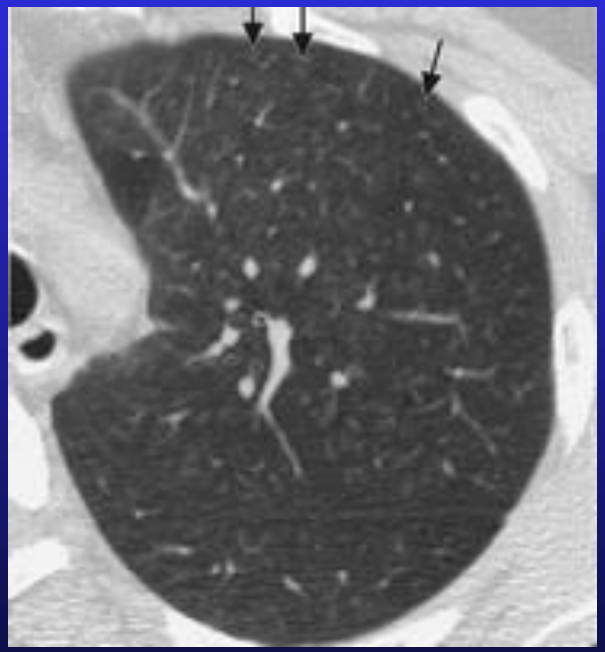
- Thickening of the walls of central or peripheral bronchi (75%)
- Ground glass (60%)
- Chest radiograph normal (14%)

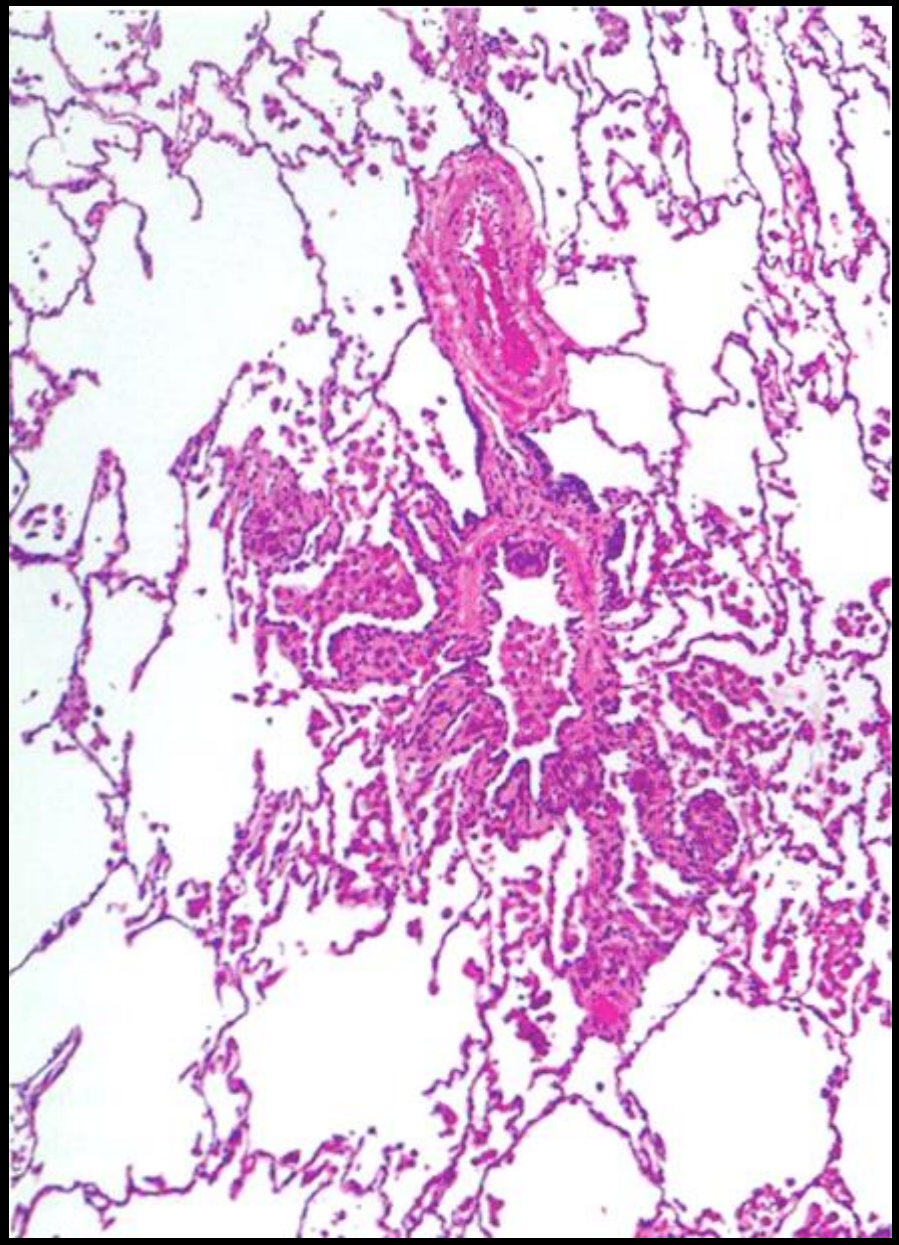
RADIOLOGY - HRCT

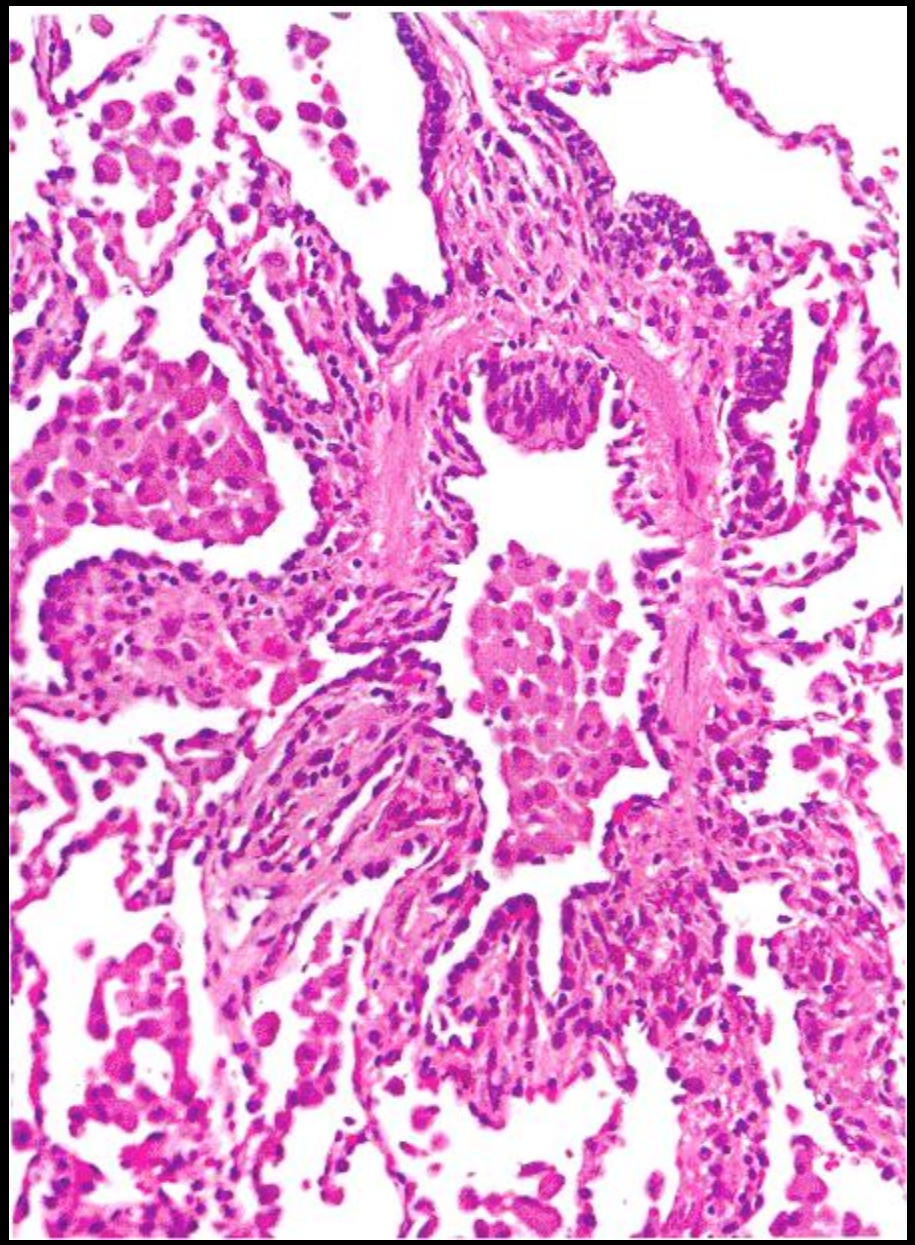
- Centrilobular nodules
- Patchy ground-glass
- Thickening of the walls of central and periferal airways
- Patchy areas of hypoattenuation due to air-trapping

RADIOLOGY





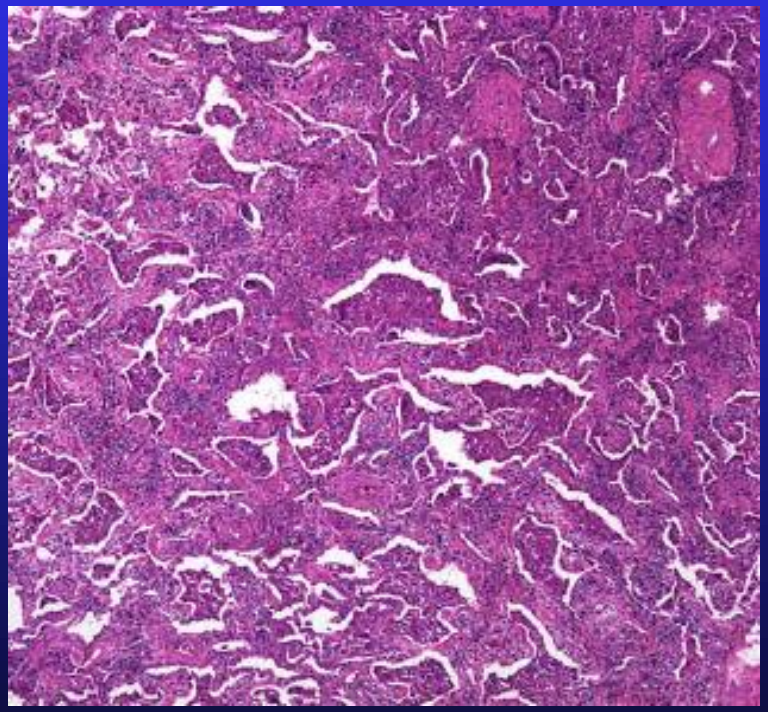




From Travis et al. Non-neoplastic disorders of the lower respiratory tract

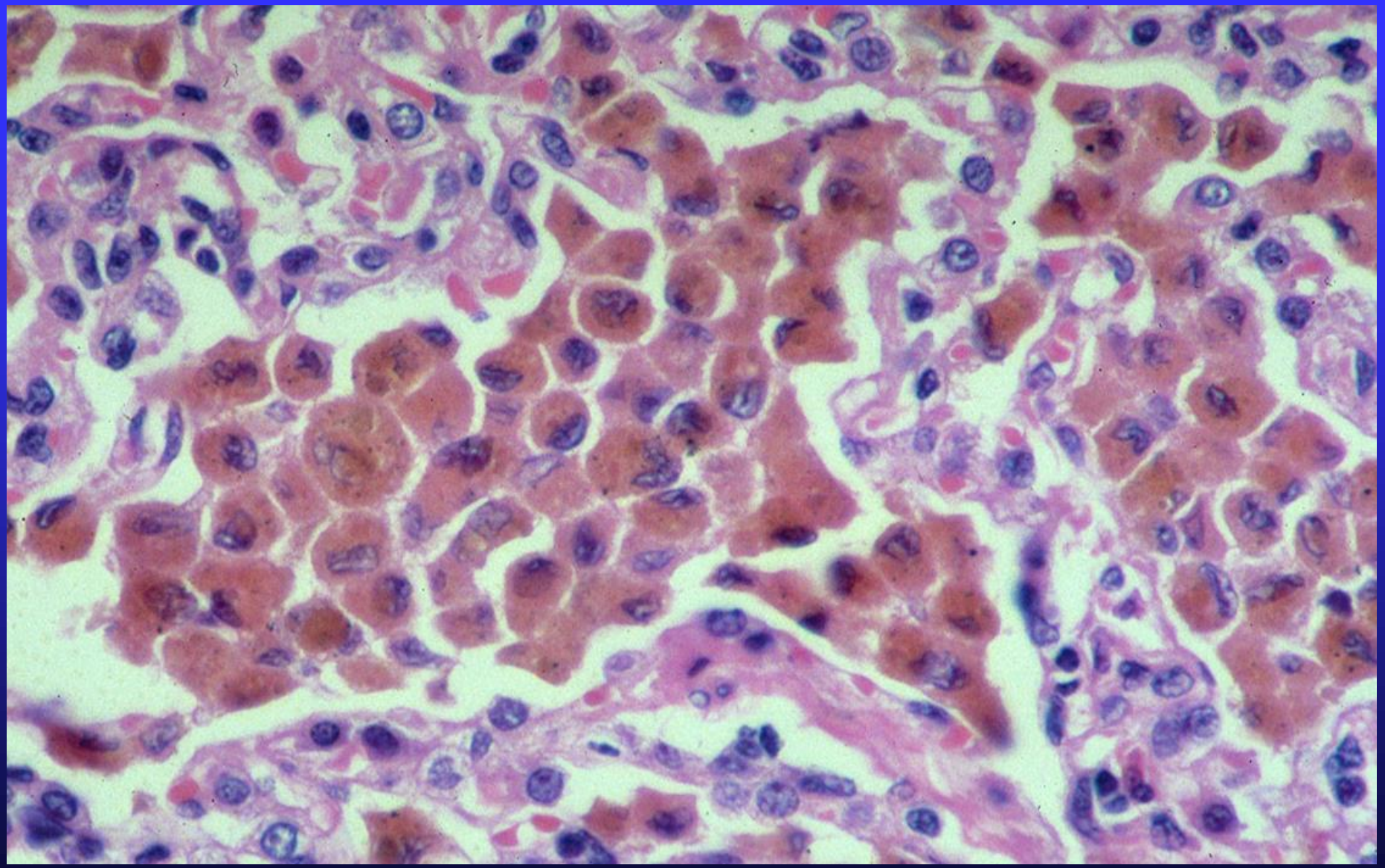
DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP)

- 98% smokers
- Symptomatic
- Restrictive PFT's
- Uniform process
- ground glass in the lower lobe
- Minimal fibrosis
- 70% survival



Desquamative Interstitial Pneumonia

- Liebow 1965
- DIP because desquamation of epithelial cells thought to be the dominant feature (suggested new nomenclature of alveolar macrophage pneumonia)
- It is one of the idiopatic interstitial pneumonias with a significantly better prognosis than UIP



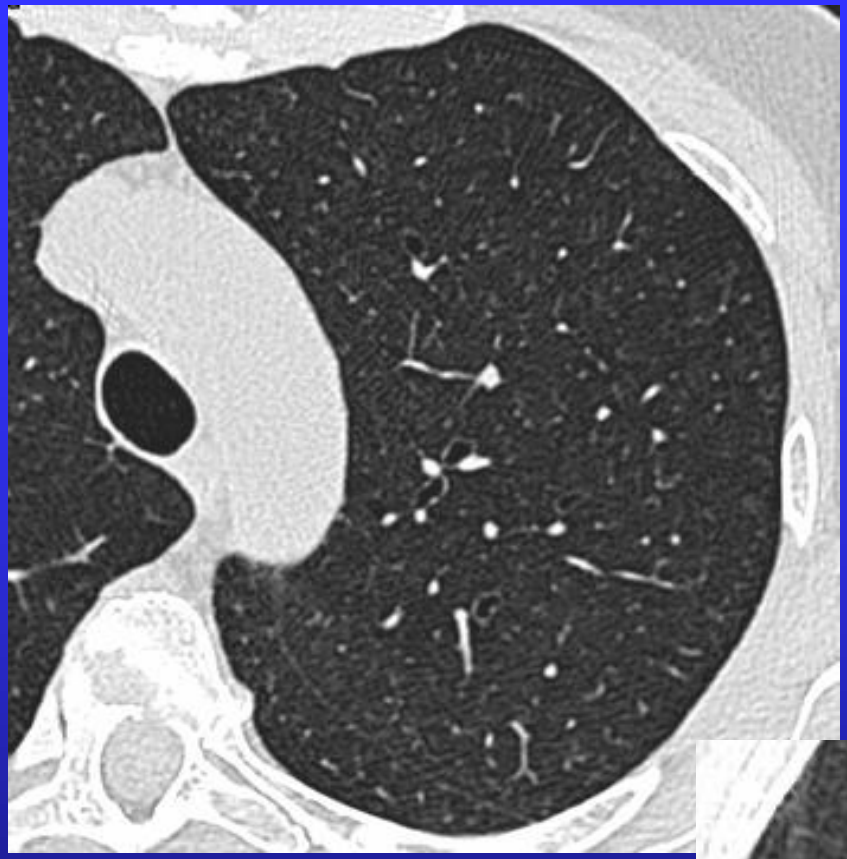
CLINICAL FEATURES

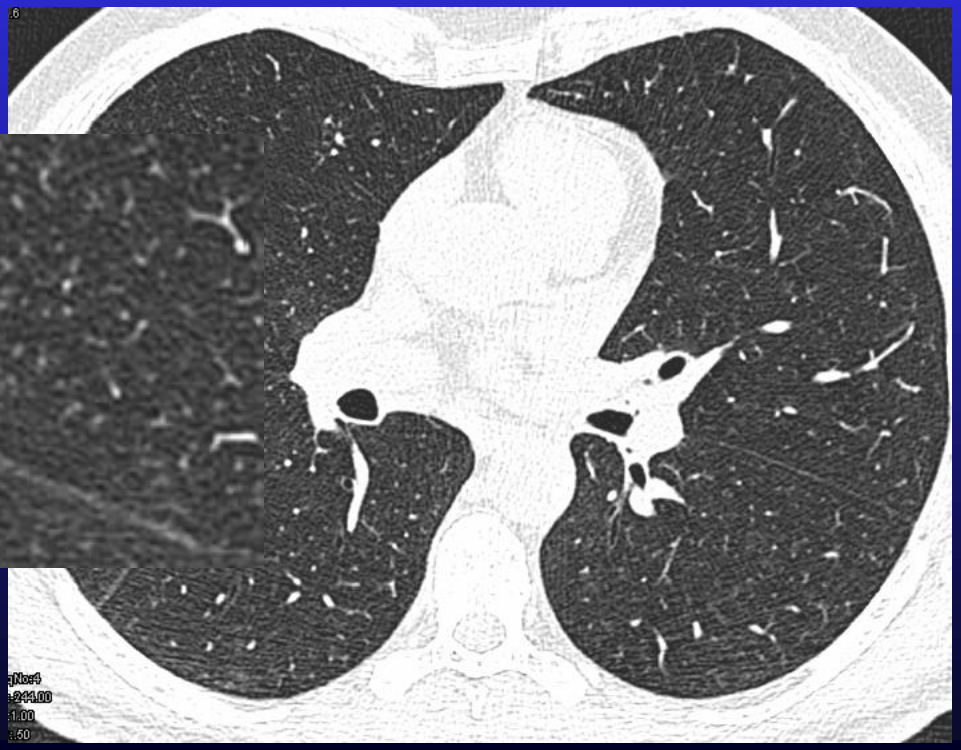
- Affects primarily cigarette smokers in their fourth or fifth decades of life
- Insidious onset of dyspnea and dry cough
- Digital clubbing develops in about half
- May progress to respiratory failure
- Normal lung volumes or a mild restrictive abnormality; DLCO is moderately decreased

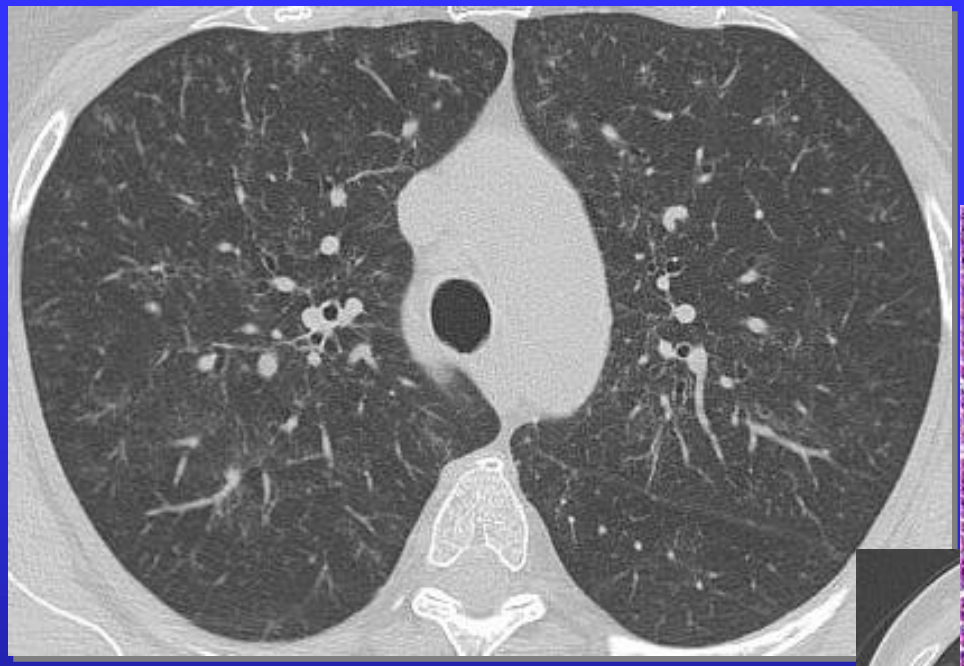
RADIOLOGY

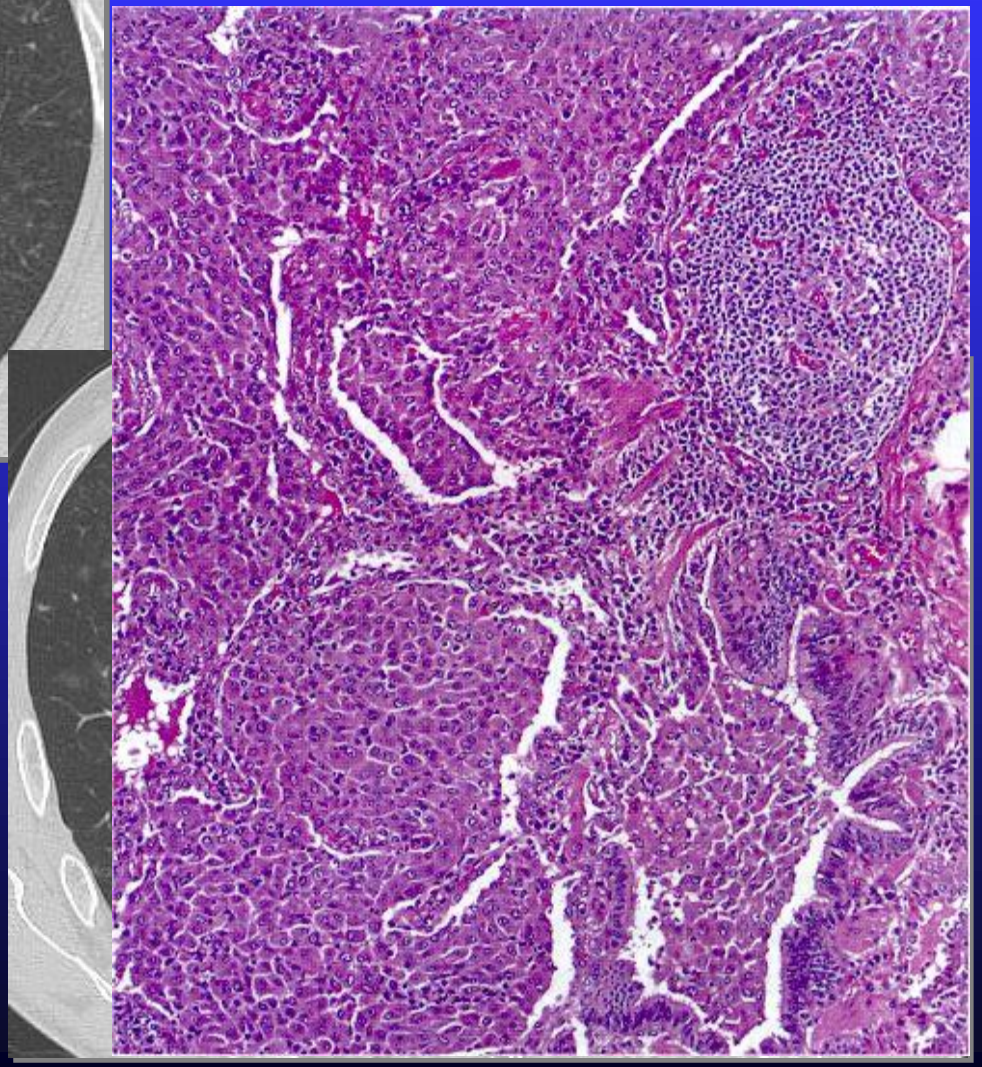
- Chest radiograph is relatively insensitive (normal in 3-22% of biopsy-proven cases)

- HRCT features:
  - Ground glass opacification
  - This has a lower zone distribution in the majority









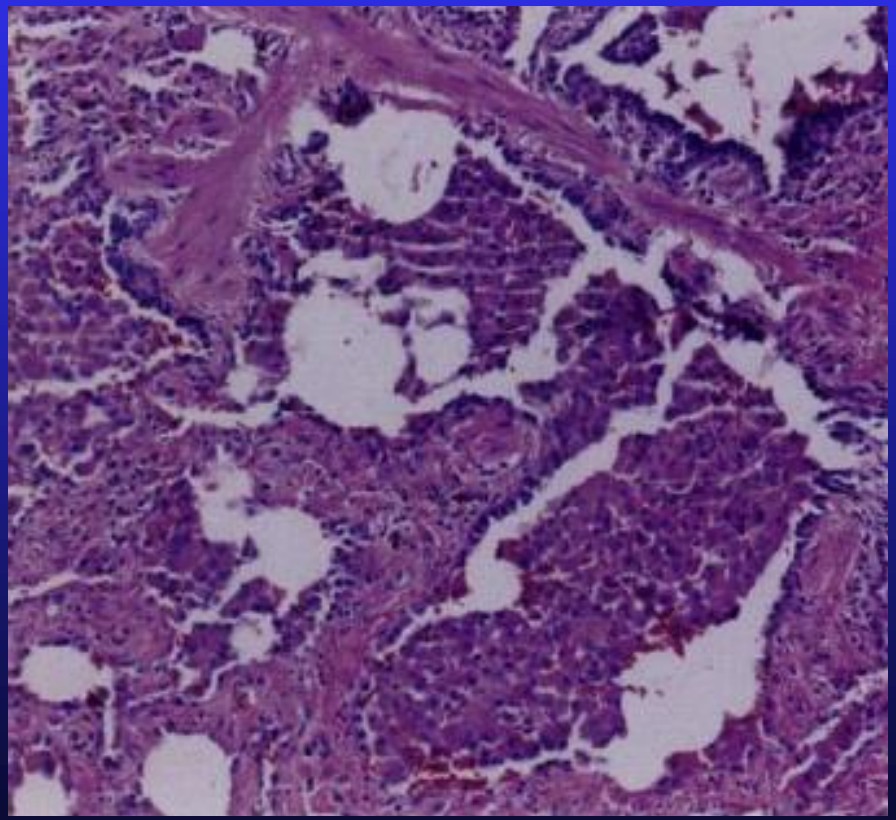
RADIOLOGY

	UIP	DIP	NSIP	Chronic HP
Subpleural predominance	++	++	0	±
Peribronchovascular predominance	0	0	+++	0
Ground glass	±	+++	+++	+++
Reticular	+++	+++	+++	+++
Honeycombing	++	±	±	±
Nodules	0	0	0	++
Mosaic attenuation/air trapping	0	0	0	+++
Cysts	0	++	0	0

Misumi S and Lynch DA. Proc Am Thorac Soc 2006; 3: 307-314

DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP)

- Diffuse and uniform accumulation of macrophages in distal airspaces
- Dusty brown pigment in macrophages
- alveolar septa thickened by a sparse inflammatory infiltrate



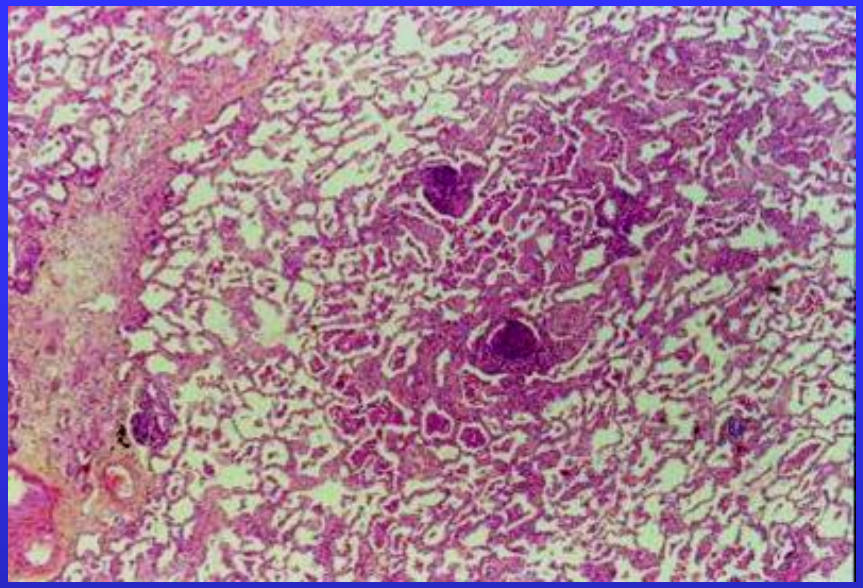
BAL

RB-ILD

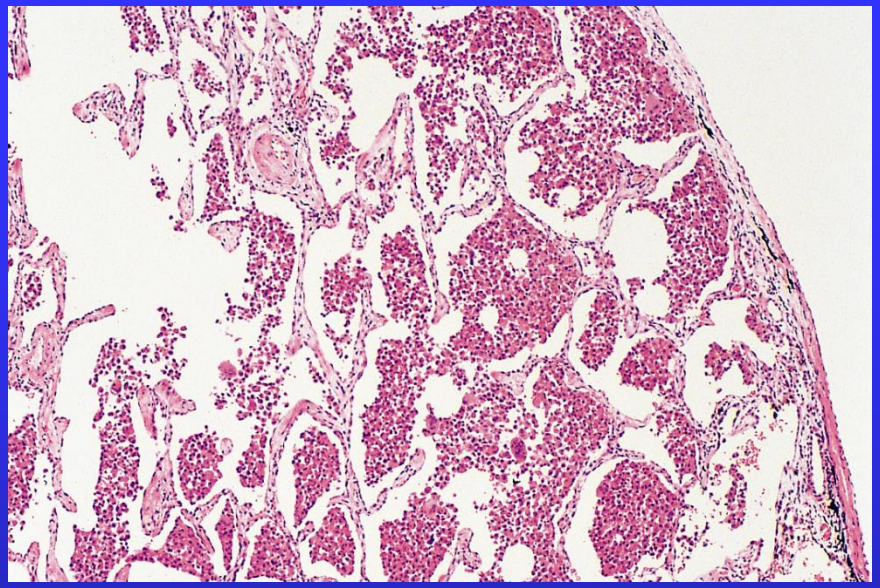
- Alveolar macrophages with varying golden, brown, or black pigmented inclusions
- Modest increase in neutrophils

DIP

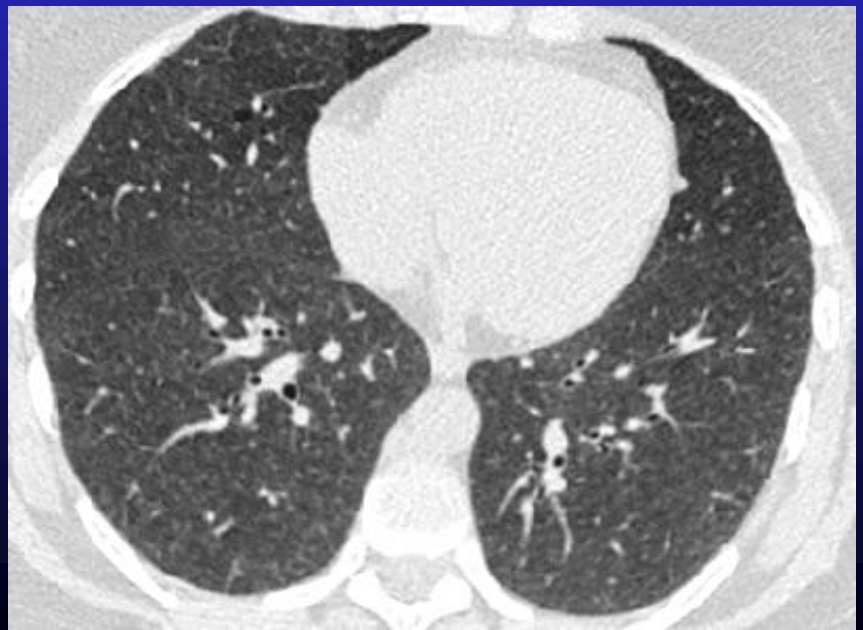
- Increased numbers of alveolar macrophages with granules of “smoker’s pigment”
- Increases of neutrophils, eosinophils and lymphocytes

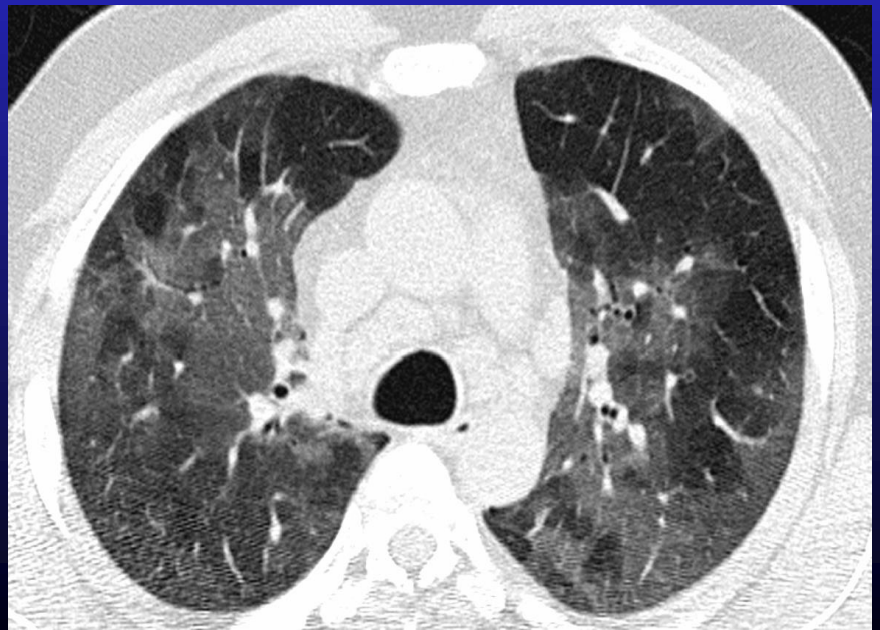


RB-ILD



DIP





TREATMENT

RB-ILD

- Cessation of smoking
- Progression to dense pulmonary fibrosis has not been reported

DIP

- Most patients improve with smoking cessation and corticosteroids
- Prognosis is generally good
- Survival is about 70% after 10 yr

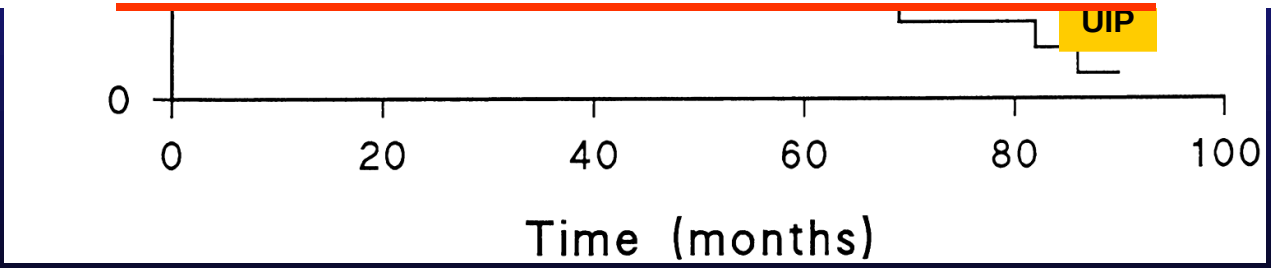
SURVIVAL IN IIP

Carrington et al. 27.5% mortality rate in 40 pts with DIP

Yousem et al. 32% mortality rate in 36 pts with DIP

Ryu et al. 26% mortality rate in 23 pts with DIP

No deaths in pts with RB-ILD



Nicholson AG et al. *Am J Respir Crit Care Med* 2000; 162: 2213

Recurrence of Desquamative Interstitial Pneumonia after Lung Transplantation

- more favorable prognosis than other forms of idiopathic pulmonary fibrosis
- good response to corticosteroid therapy
- patients can progress to end stage disease, and may require lung transplantation as definitive treatment
- relapse of this disease suggests that in certain individuals, DIP represents a pulmonary manifestation of a systemic disease

Barberis M et al. Transplant Proc 1992; 24:2660

King MB et al. Am J Respir Crit Care Med 1997; 156:2003

Werleden et al. Eur Respir J 1998;11: 971

DIP/RB-ILD: Conclusions (1)

- DIP/RB-ILD are relatively uncommon forms of ILD and are strongly associated with cigarette smoking
- clinical and radiologic characteristics are not specific
- ground-glass opacities are the predominant finding on chest imaging by CT scan
- conventional chest radiograph findings are normal in up to 22% of biopsy-proven cases of DIP

DIP/RB-ILD: Conclusions (2)

- The majority of patients demonstrate a stable clinical course, although radiologic abnormalities tende to persist
- Several deaths occur in patients with DIP from respiratory causes, while no deaths are observed in the RB-ILD group
- RB-ILD appears to be associated with a more benign clinical course compared to that of DIP

DIP/RB-ILD: Conclusions (3)

- There is some evidence to suggest that smoking cessation may suffice as the initial therapeutic maneuver for patients with RB-ILD
- It remains unclear whether corticosteroid therapy favorably alters the natural history of DIP and RB-ILD, particularly since the effect of smoking status on the clinical course of patients with these disorders has not been fully delineated

DIP/RB-ILD THERAPY: AVAILABLE EVIDENCE

- *No published RCTs or CCTs.*
- Good empiric evidence for an effect of smoking cessation.
- Empiric evidence for a transient positive effect of corticosteroids.

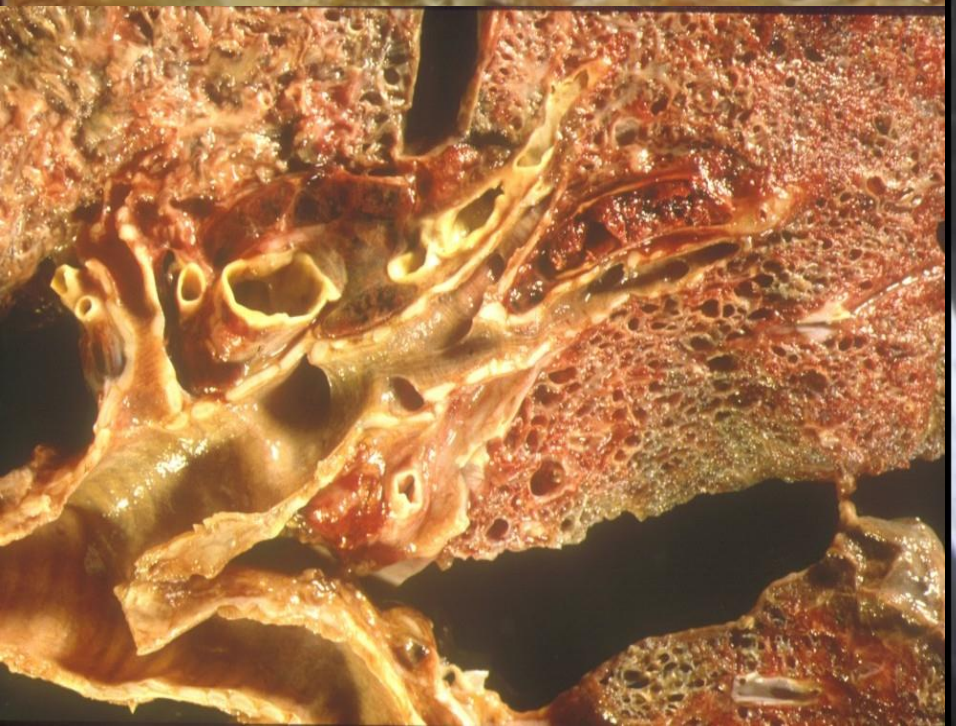
Ryu JH et al. *Am J Respir Crit Care Med* 2003; 168: 1277-92

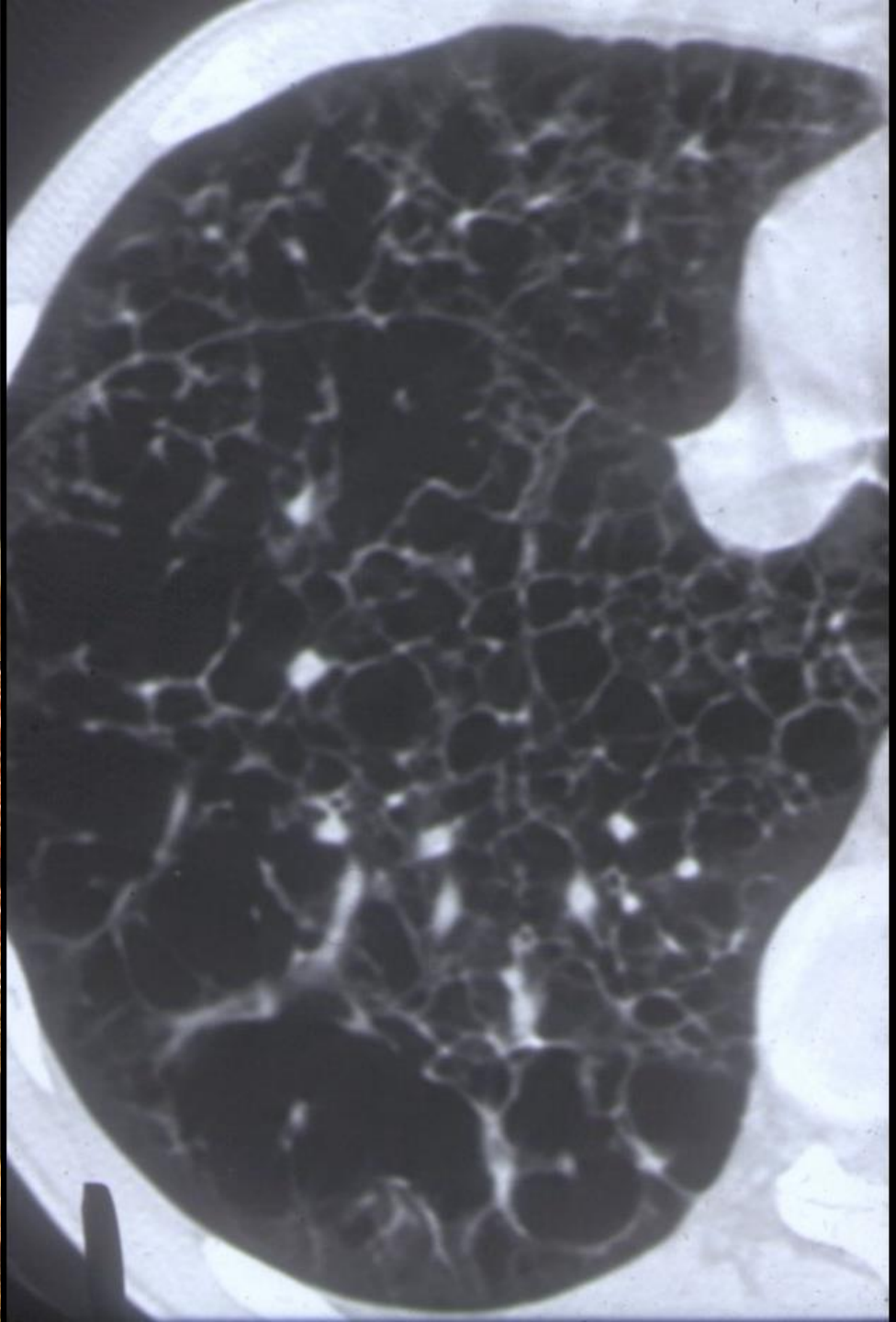
Ryu JH et al. *Chest* 2005; 127: 178-84

SMOKING-RELATED ILDs

- Pulmonary Langerhans cell histiocytosis
- Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)
- Desquamative interstitial pneumonia (DIP)

Are these three ILDs a spectrum of patterns of interstitial lung injury that may occur in certain individuals who smoke?

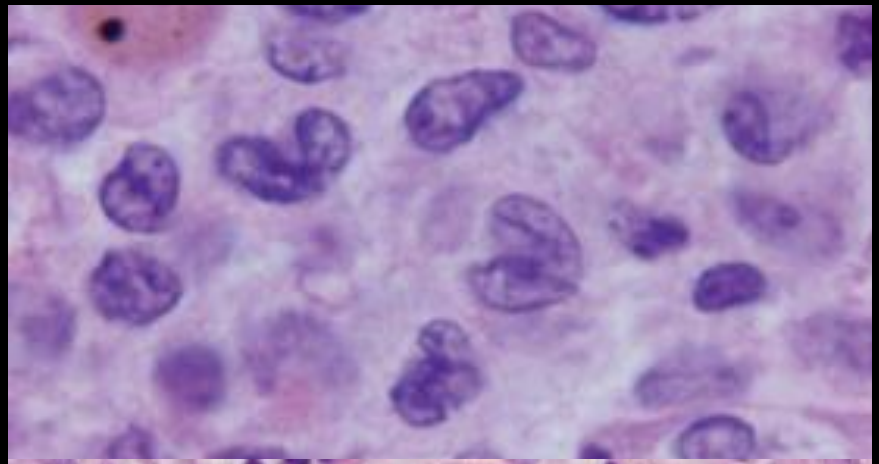


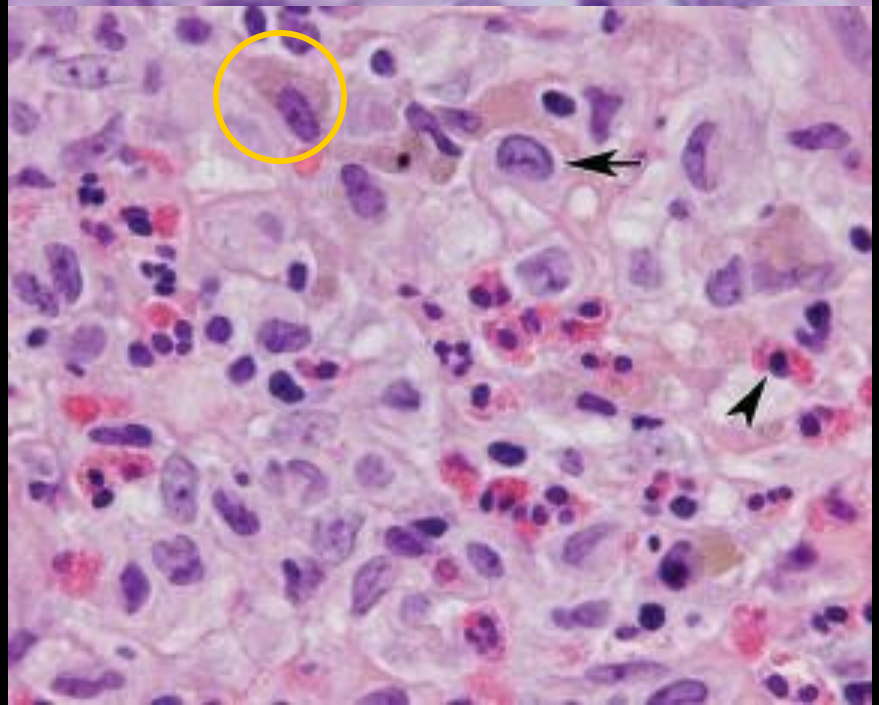


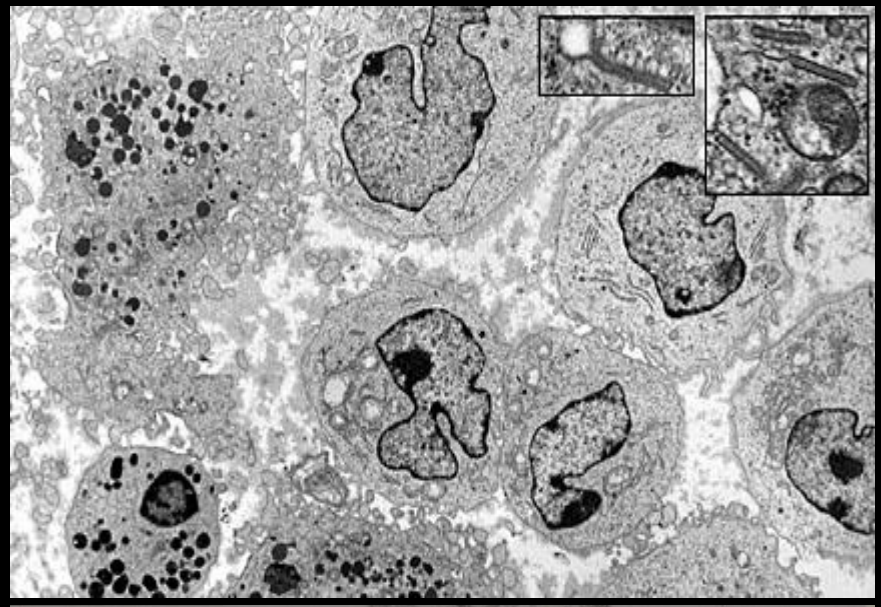
PULMONARY LANGERHANS CELL HISTIOCYTOSIS (LCH)

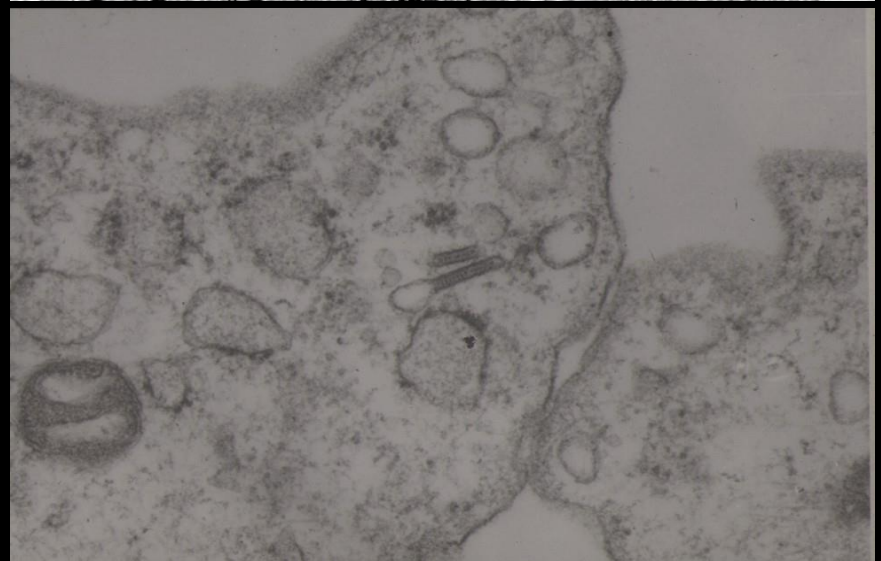
- is an uncommon interstitial lung disease that primarily affects young adults
- incidence and prevalence are unknown
- several familial cases have been described but is essentially sporadic
- diagnosis is made in less than 5% of lung biopsies for interstitial lung diseases
- nearly all affected pts have a history of current or prior cigarette smoking

LANGERHANS CELL



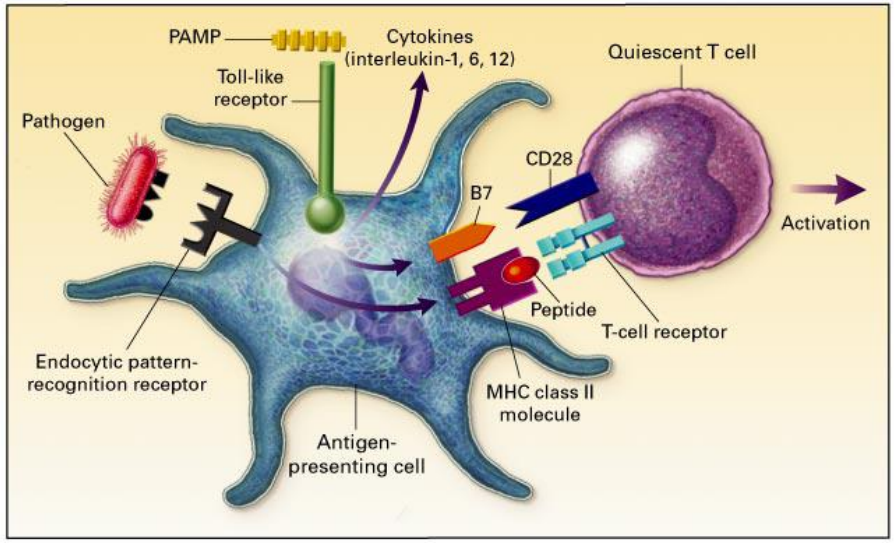






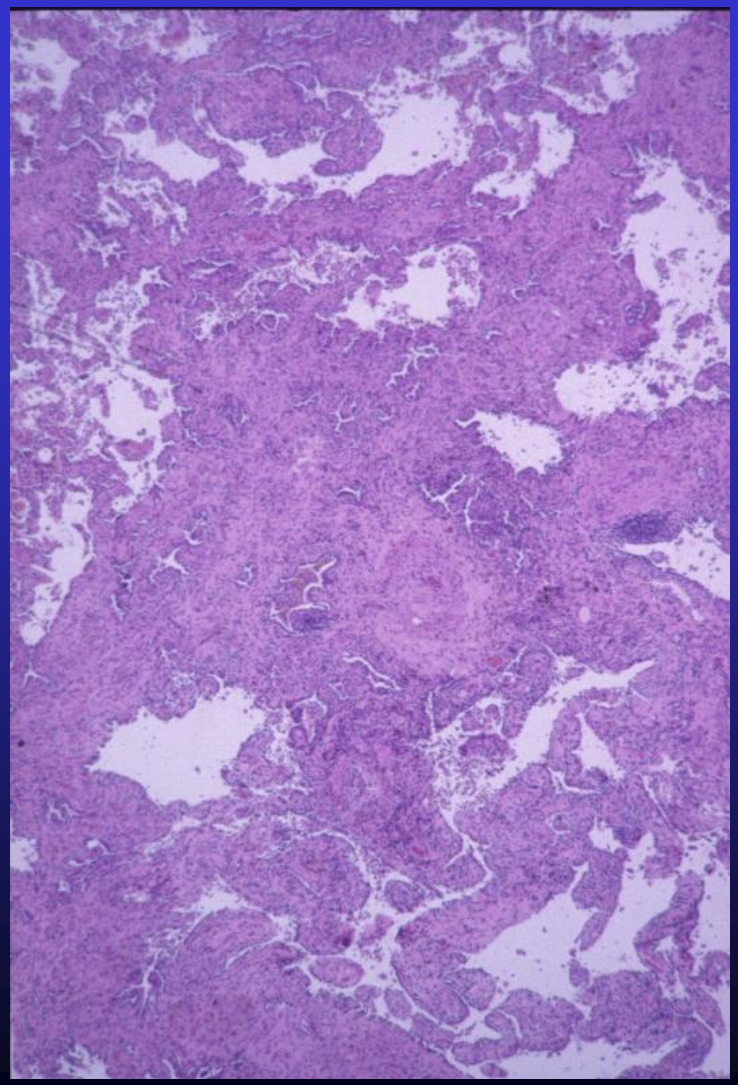
Langerhans' cell Histiocytosis (LCH)

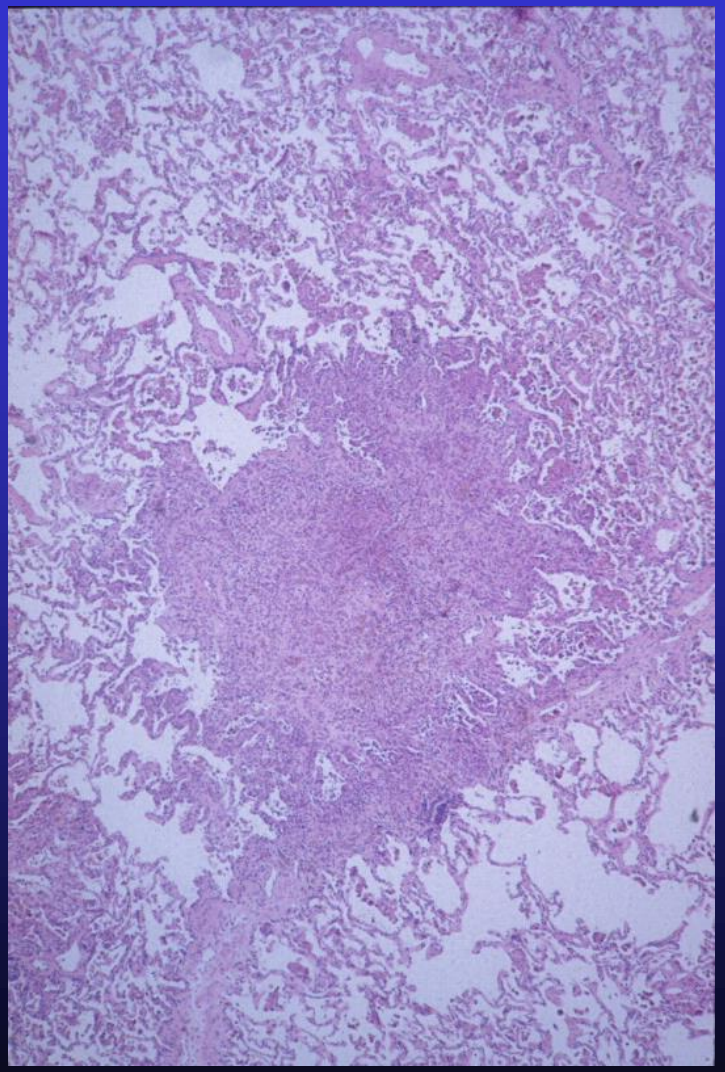
Langerhans' cell histiocytosis (LCH) includes several disorders that are characterized by excessive proliferation of **Langerhans cells (LC)**



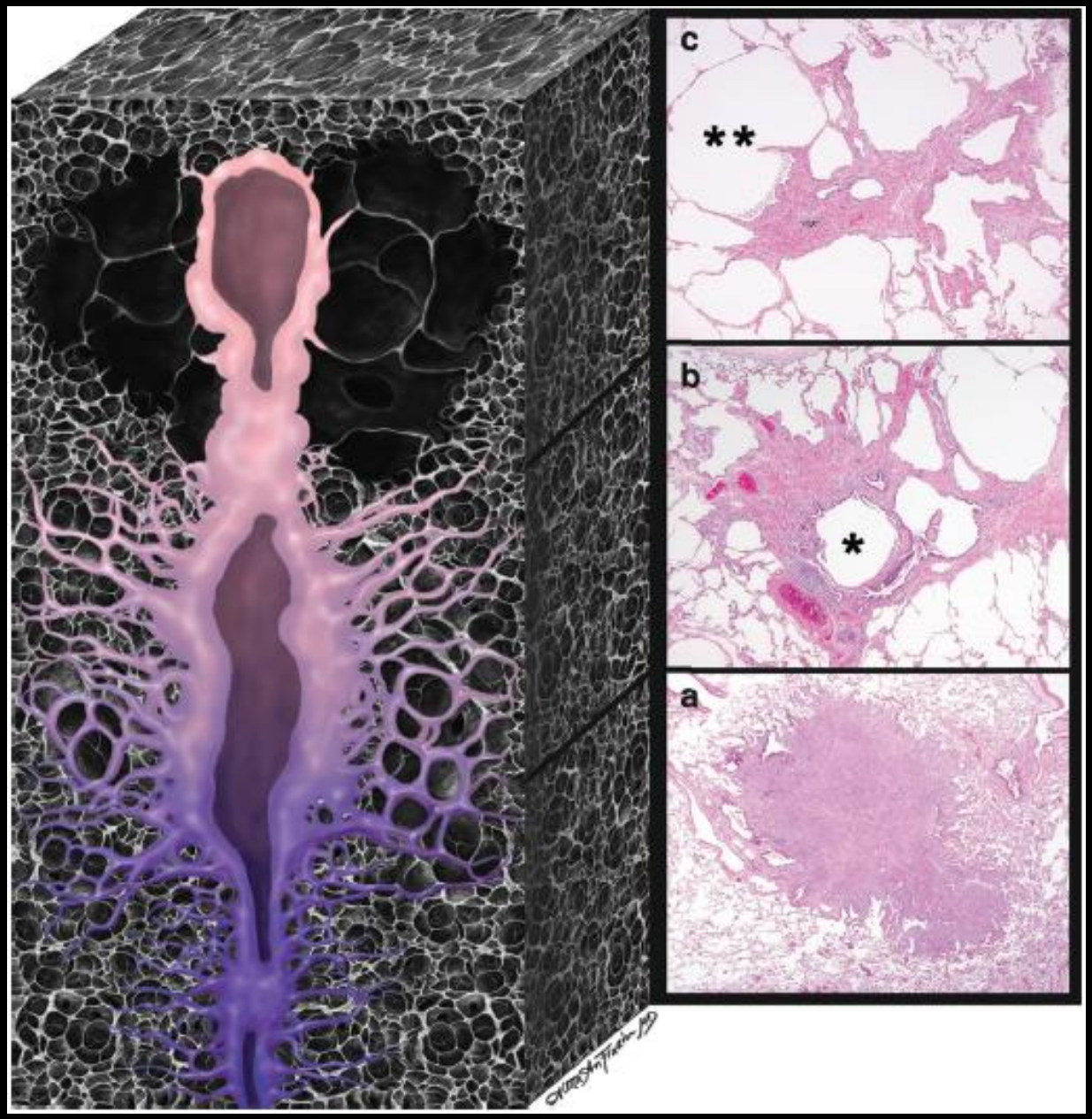
Langerhans cell is a specialized immune cell belonging to the family of dendritic cells that form a network of antigen-presenting and migratory cells in lymphoid and nonlymphoid organs such as the skin, heart, and lung.

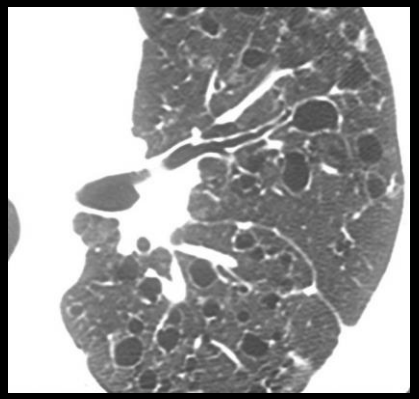
PLCH HISTOPATHOLOGY

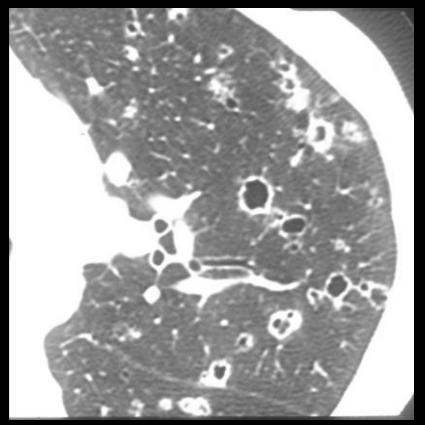


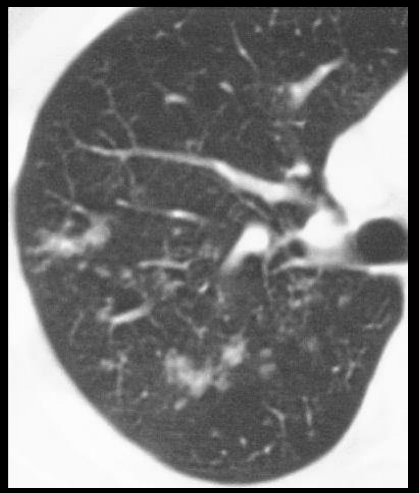


Kindly provided by Prof. A. Pesci

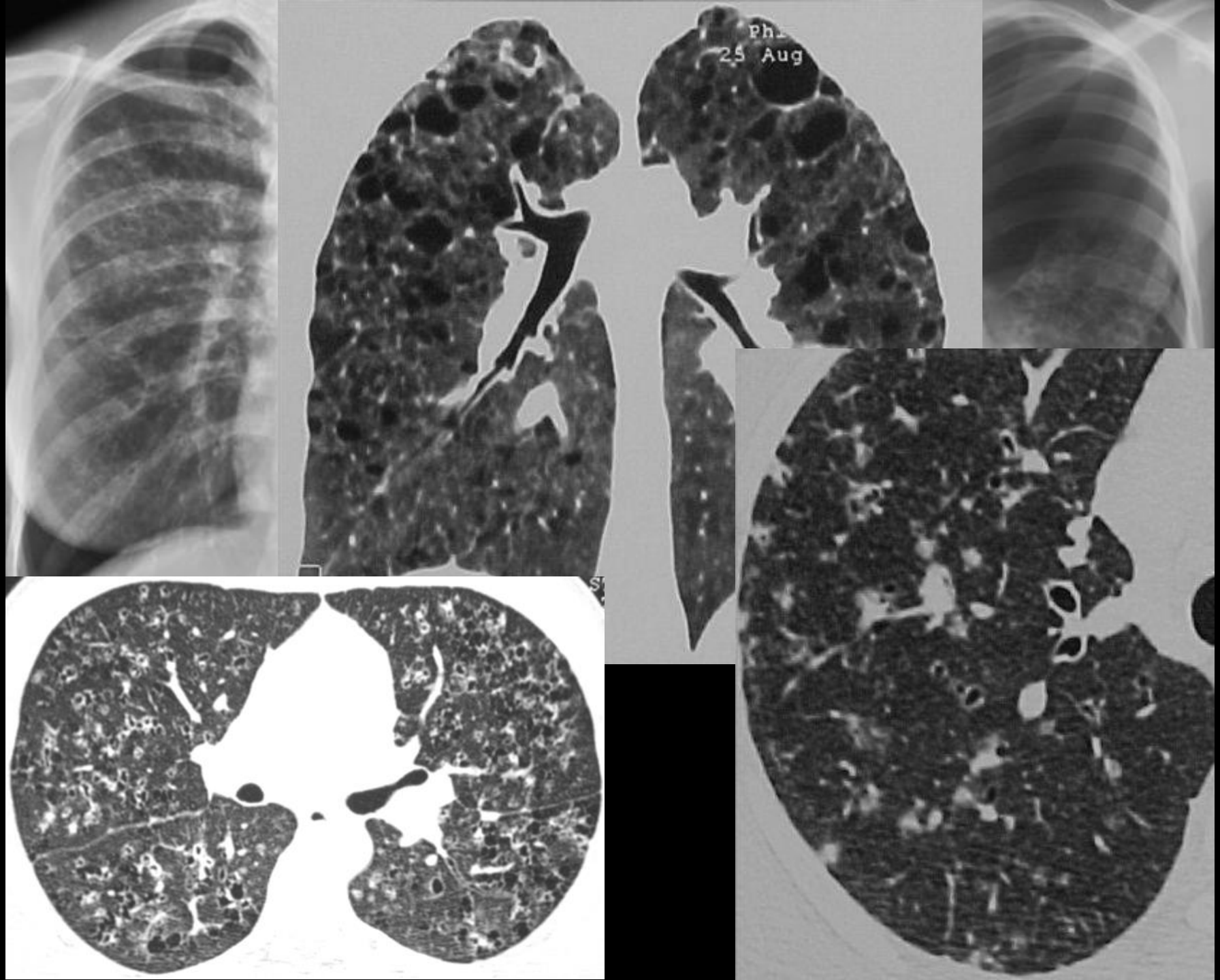








Abbott GF et al. RadioGraphics 2004; 24:821-841


25 Aug

SYMPTOMS

- 25% of patients are asymptomatic
- Nonproductive cough (56-70%)
- Dyspnea (40-87%)
- Chest pain, frequently pleuritic (10-21%)
- Fatigue (approximately 30%)
- Weight loss (20-30%)
- Fever (15%)

Costabel U and Corrin B Respir Med 2003; 1960-67
Harari S. et coll. Sarcoidosis Vasc diff Lung Dis 2001; 18 (3) 253-62

PHYSIOLOGIC TESTING

- TLC and expiratory flow rates are often preserved
- DLCO is disproportionately reduced (due to vascular involvement?)
- a subgroup of patients shows predominantly restrictive disease
- airflow limitation and hyperinflation occur in a minority of patients and can sometimes be associated with reactive airways

DIAGNOSIS

***A* history of recurrent pneumothorax, diabetes insipidus or bone pain suggest the diagnosis**

- **BAL:** >5% Langerhans cells, positive for S-100 protein and CD1a, strongly suggests the diagnosis
- **TBB:** low sensitivity (10-40%) and high rate of Pnx
- **VATS biopsy:** is generally definitive but may be not diagnostic in advanced disease

COMPLICATIONS

- Recurrent spontaneous pneumothorax (25% of patients)
- Hemoptysis (13%)
- Cystic bone lesions (4-20%)
- Diabetes insipidus (15%)
- Malignant and nonmalignant tumors:

  bronchogenic carcinoma (5%), Hodgkin's and non-Hodgkin's lymphoma, pulmonary carcinoid tumor, mediastinal ganglioneuroma

Costabel U and Corrin B Respir Med 2003; 1960-67
Harari S. et coll. Sarcoidosis Vasc diff Lung Dis 2001; 18 (3) 253-62

LCH - CLASSIFICATION

LCH includes an extremely large clinical spectrum of disorders, extending from an acute disseminated form which usually occurs in infants and carries a poor prognosis, to the presence of lesions localized to a single tissue which follows a more benign clinical course

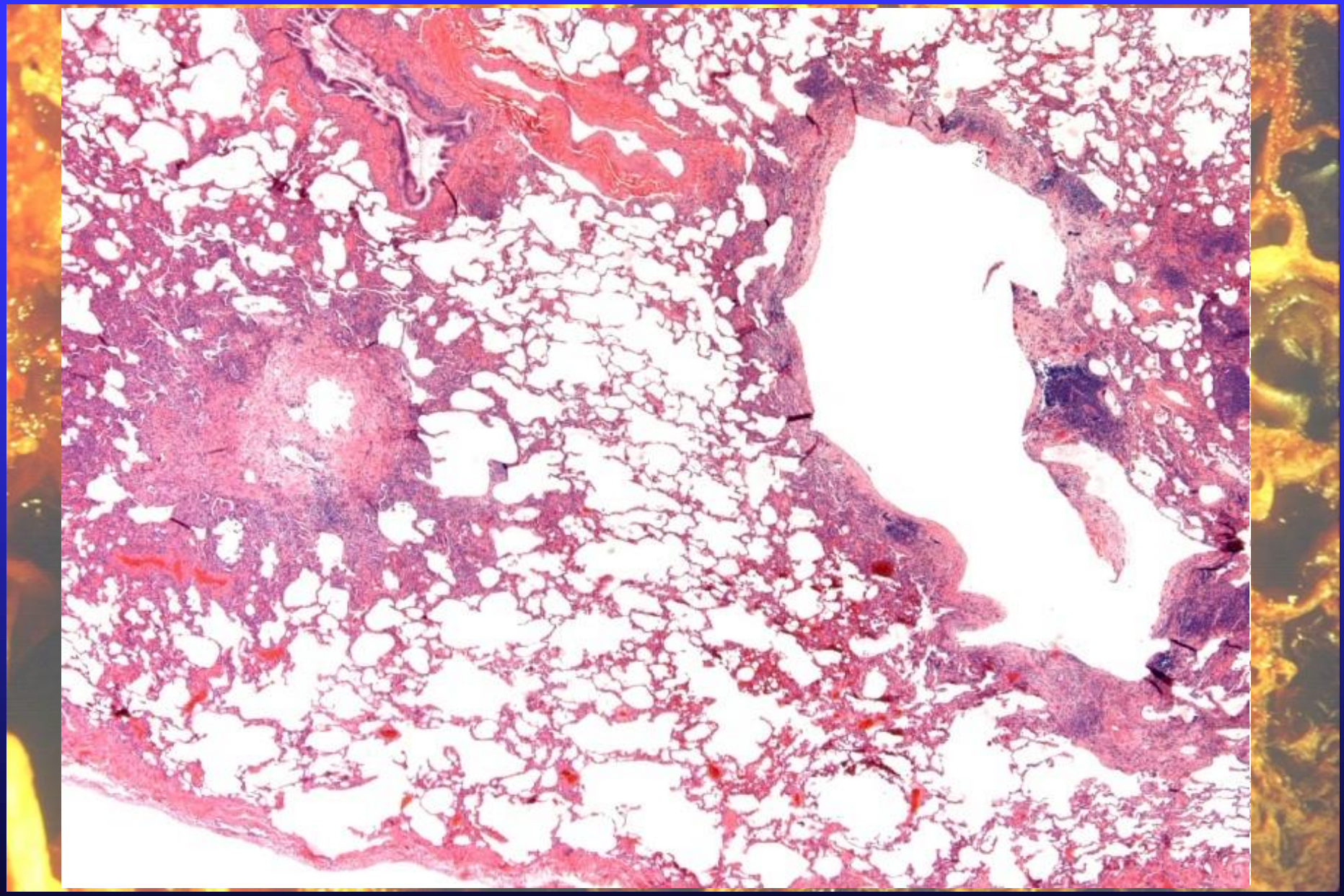
1997

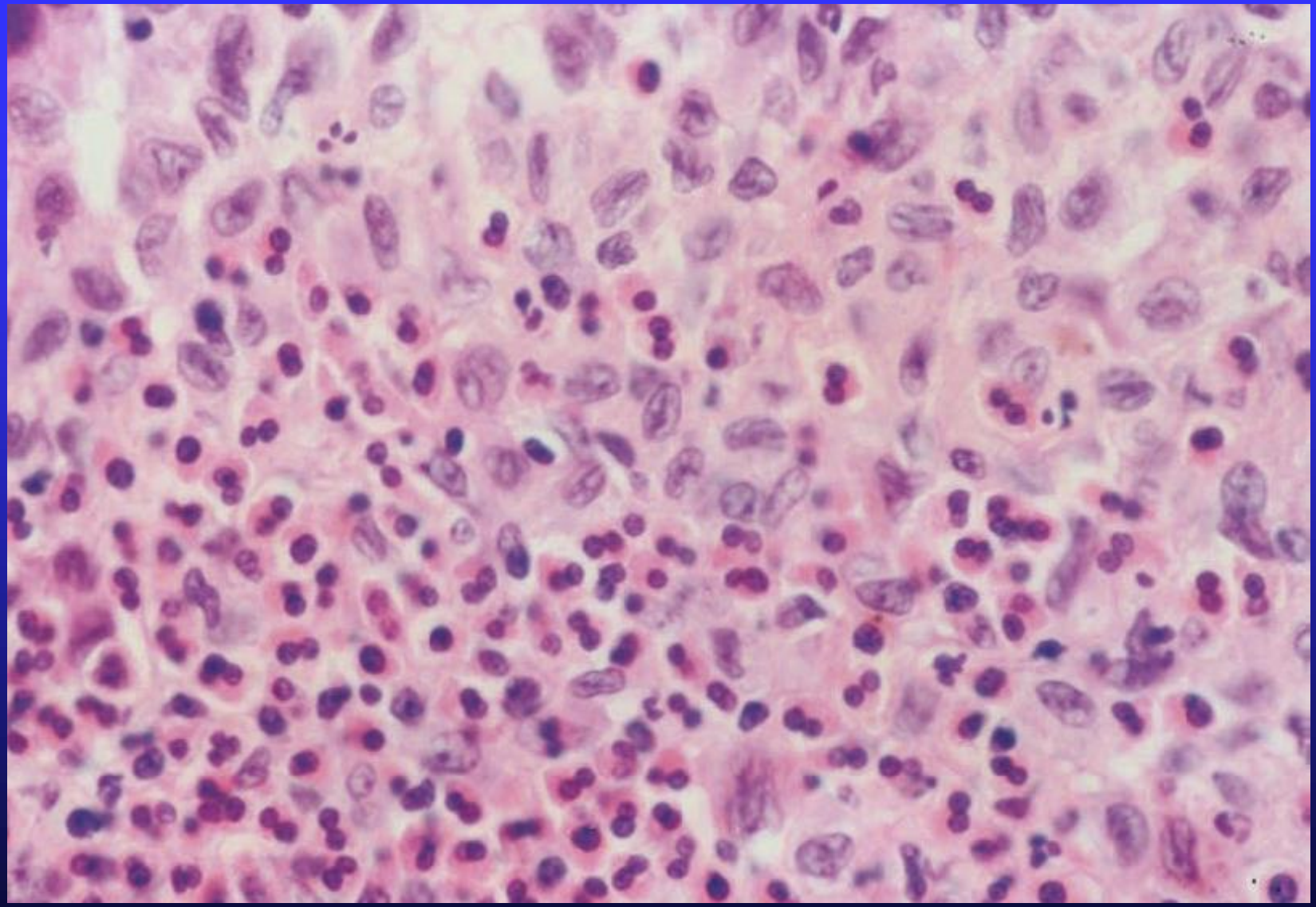
- single-organ involvement
- multiorgan involvement
- multisystem disease

2004

- single-organ disease
  - **- Lung**
  - **- Bone**
  - **- Skin**
  - **- Pituitary**
  - **- Lymph nodes**
  - **- Other sites**
- multisystem disease
  - **multi-organ disease with lung involvement**
  - multi-organ disease without lung involvement
  - multi-organ histiocytic disorders

MATURE CELL	Interstitial DC	Langerhans DC
Cell Markers		
CD11c;CD13;CD33	+	+
CD123	-	-
CD40;CD54;CD80;CD86	+	+
CD11b	+	+
MHC Class II	+	+
CD1a	-	+
Birbeck granules	-	+
Langerin	-	+
E-cadherin	-	+
Functions		
CD4 & CD8 priming	+	+
IL-12 secretion	+	+
Other	Induces B-cell differentiation	





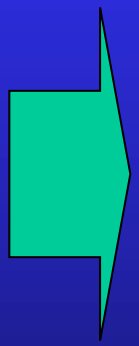
Langerhans'-cells

Birbeck granules (cytoplasmic organelles)

Surface CD1a antigen

Cytoplasmic S100 protein (not specific)

Eosinophils
Lymphocytes
Macrophages
Plasma cells
Fibroblasts



- Early stage:

Infiltrates invade the bronchiole, destroying the bronchiolar wall in an eccentric fashion and forming **nodules**

- Disease progression:

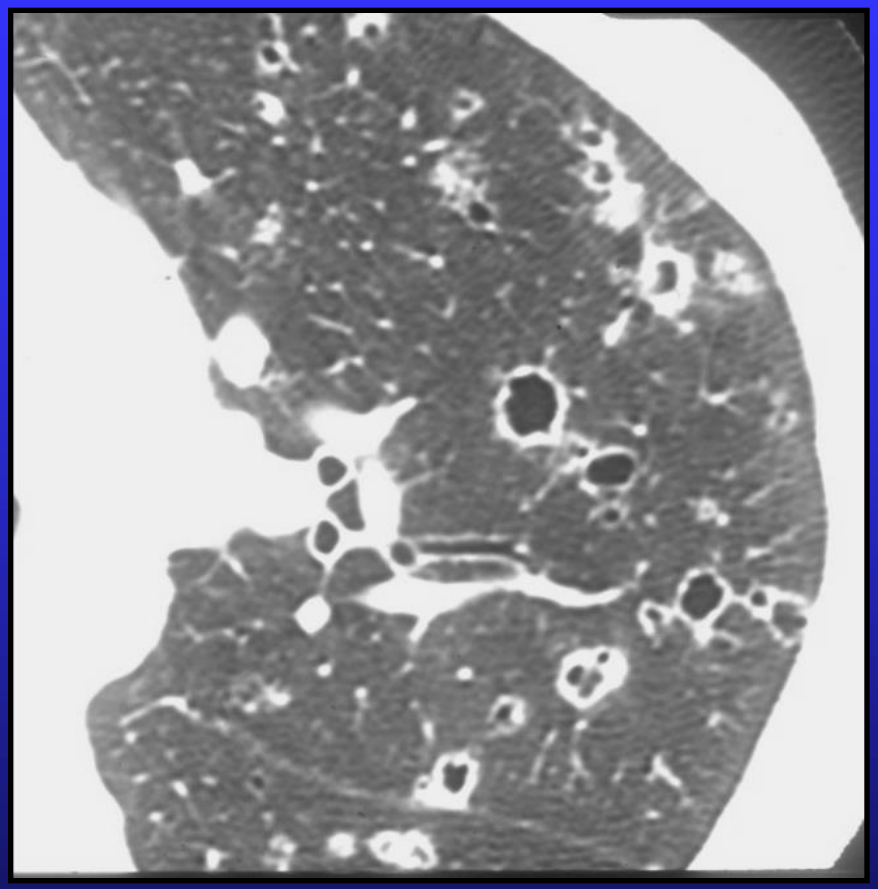
Increasing numbers of nodules and **cavitary nodules**

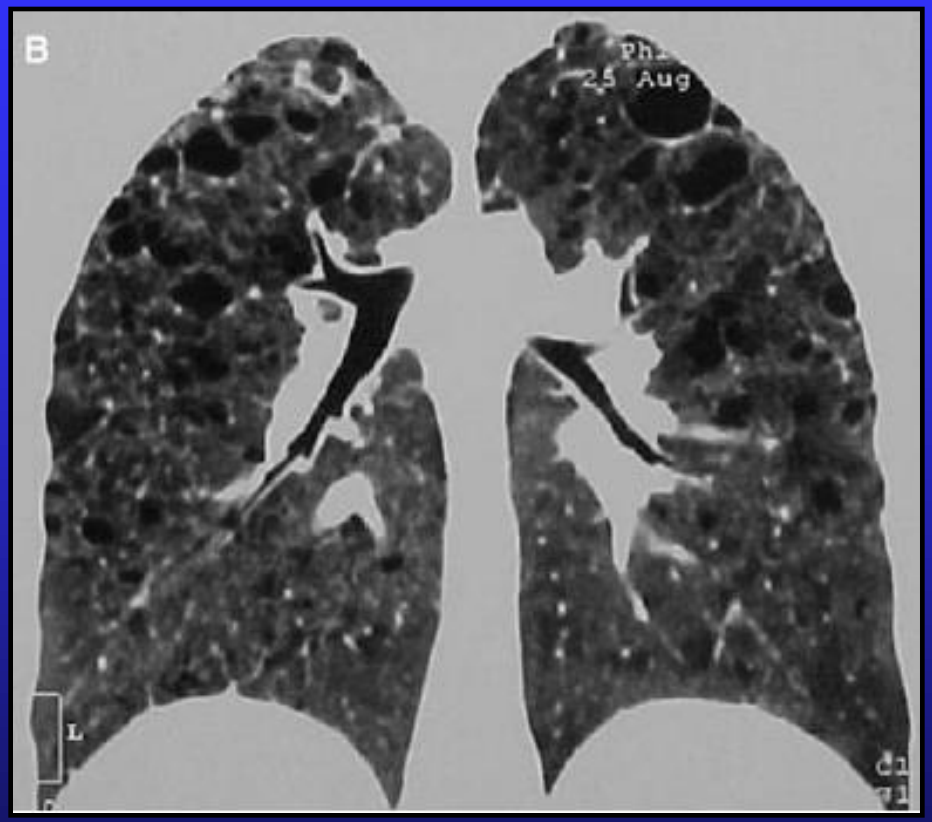
Appearance of **fibrotic scars**

- End stage:

Prominent fibrotic scars surrounding **cystic spaces** of variable diameter and paracicatricial enphysema

PLCH - RADIOLOGYCAL FEATURES





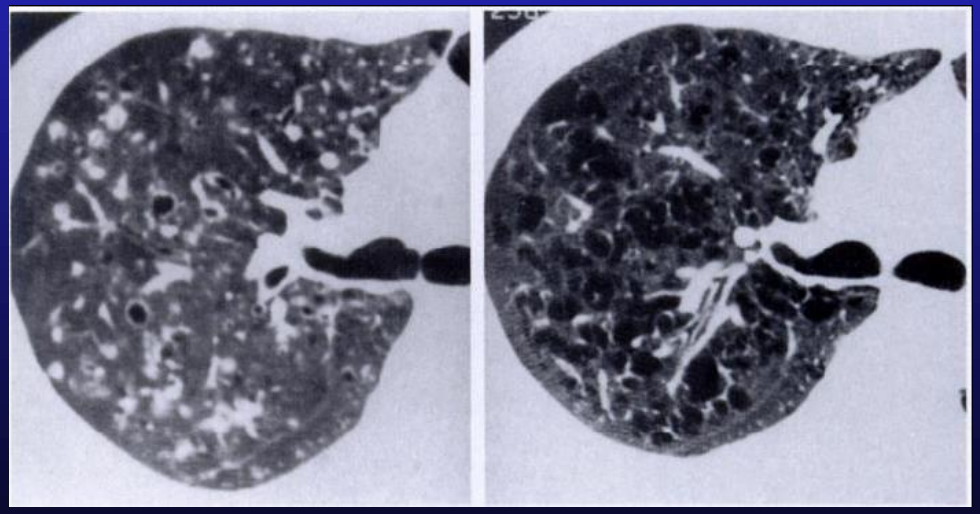
The combination of multiple cysts and nodules with a mid to upper zone predominance and sparing of lung bases in a young smoker is so characteristic that may be diagnostic

Harari et al. Proc Am Thorac Soc, 2006

PLCH: evolution of lesions on CT scans

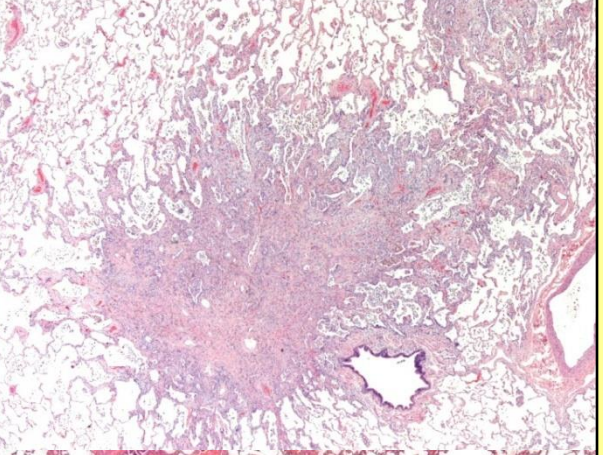
Longitudinal observation of CT features suggest the following evolutionary sequence for pulmonary lesions of PLCH:

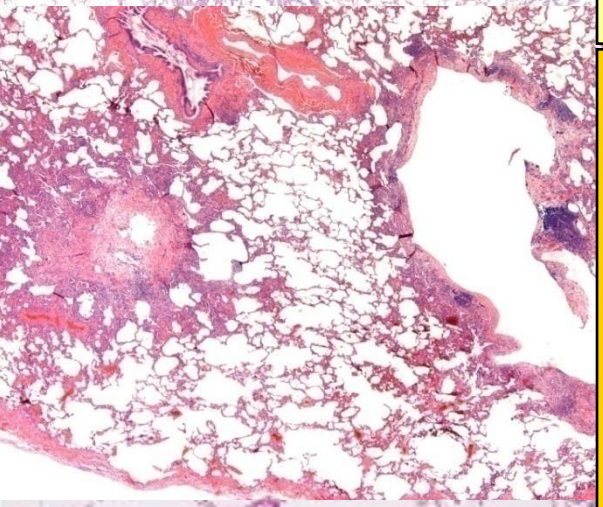
Nodule → **Cavitated nodule** → **Thick walled cysts** → **Thin walled cysts**

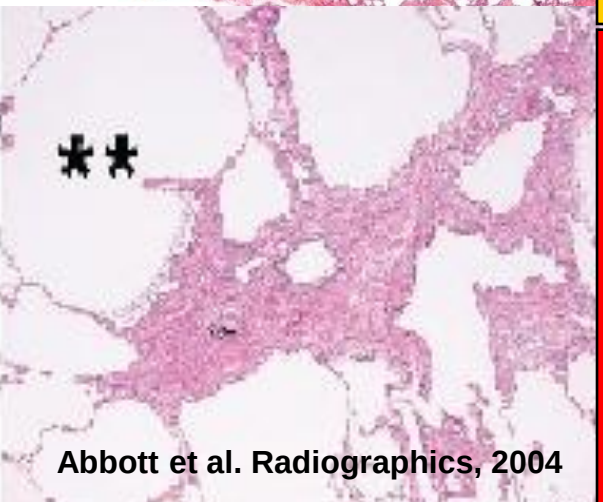


Brauner et al. Radiology 1997

Harari et al. AJRCCM 1997



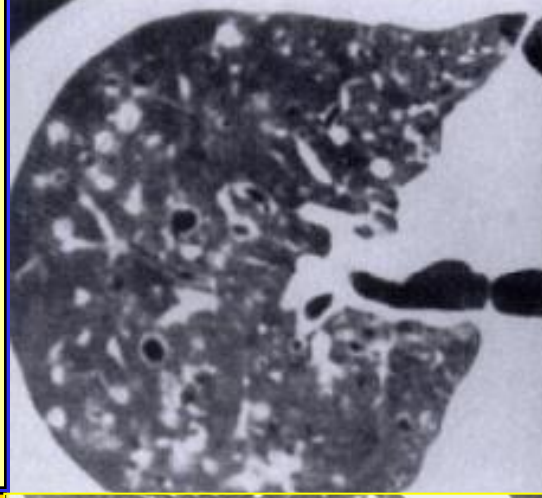




Abbott et al. Radiographics, 2004

➢ *Early stage:*

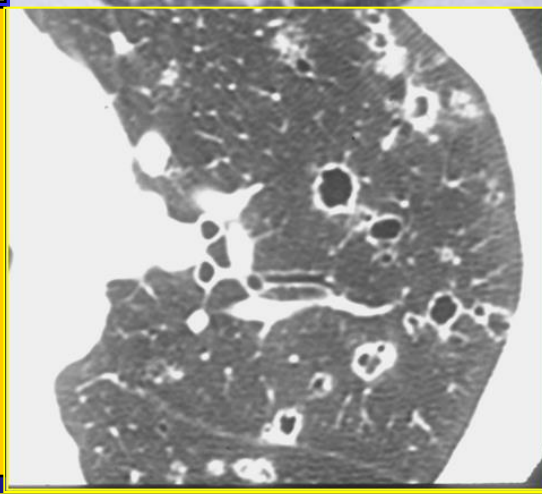
Infiltrates invade the bronchiole, destroying the bronchiolar wall in an eccentric fashion and forming **nodules**



➢ *Disease progression:*

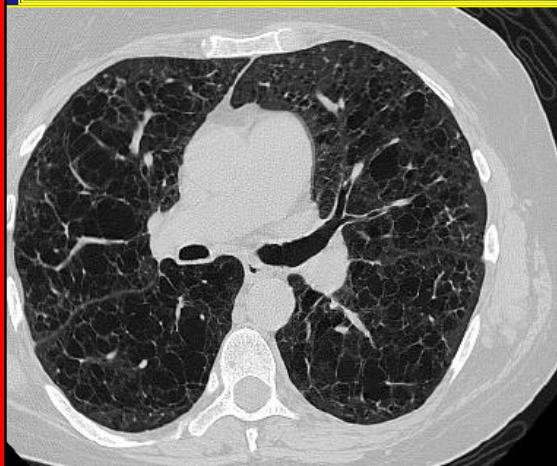
Increasing numbers of nodules and **cavitary nodules**

Appearance of **fibrotic scars**

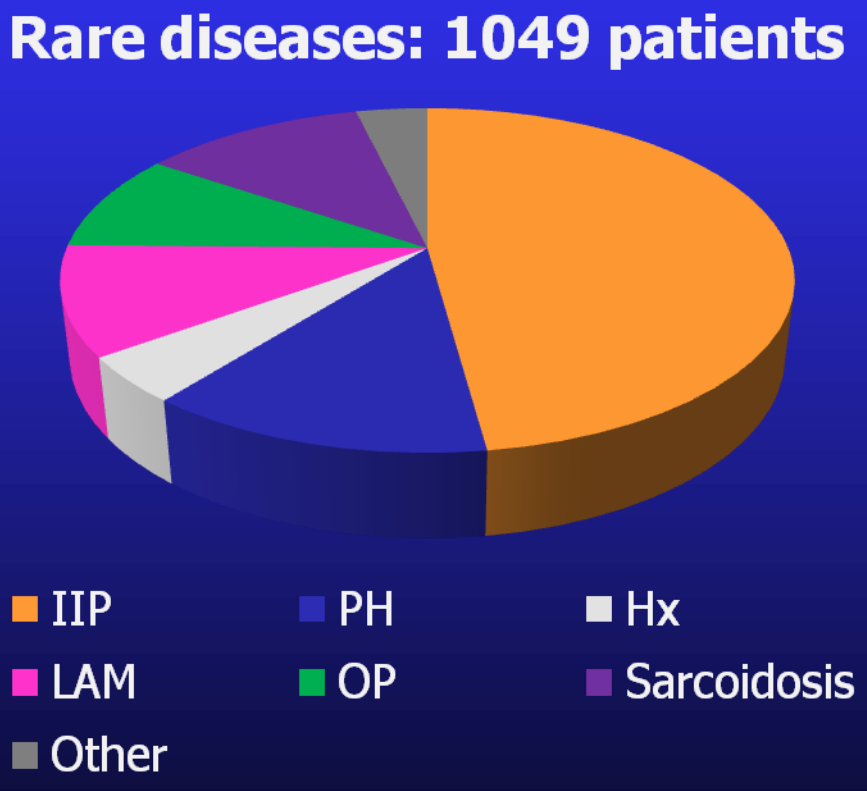


➢ *End stage:*

Prominent fibrotic scars surrounding **cystic spaces** of variable diameter and paracicatricial enphysema



PLCH
Ospedale San Giuseppe 2001- 2014



Characteristics at the time of the diagnosis of **40 pts** with PLCH

	n°
Sex	
▪Male	22
▪Female	18
Age	
▪Mean	40±14
Years from symptoms	2±3.7
Smoking status	
Current /ex smokers	19/21

Harari S et al. Eur J Intern Med 2015; 26: 351

CLINICAL PRESENTATION
Ospedale San Giuseppe - 40 pts

Symptoms at diagnosis	n°
Pneumothorax	7
Exertional dyspnea	15
Cough	13
Diabetes insipidus	2
Hemoptysis	1
Bone lesions	2
Skin lesions	1

Extrapulmonary manifestations	n°
Diabetes insipidus	5
Bone lesions	7
Skin lesions	1

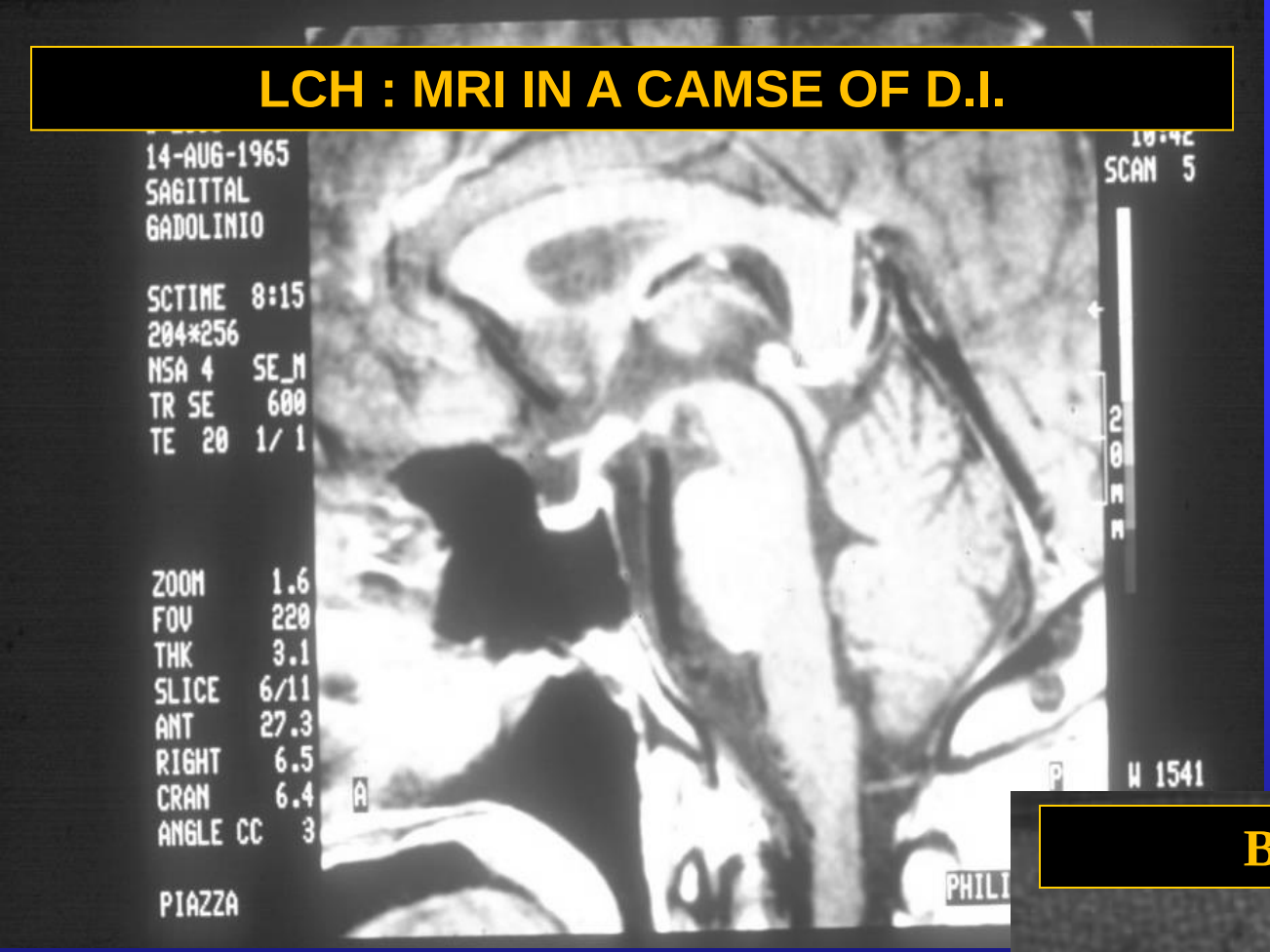
Harari S et al. Eur J Intern Med 2015; 26: 351

DIAGNOSIS 40 pts
Ospedale San Giuseppe

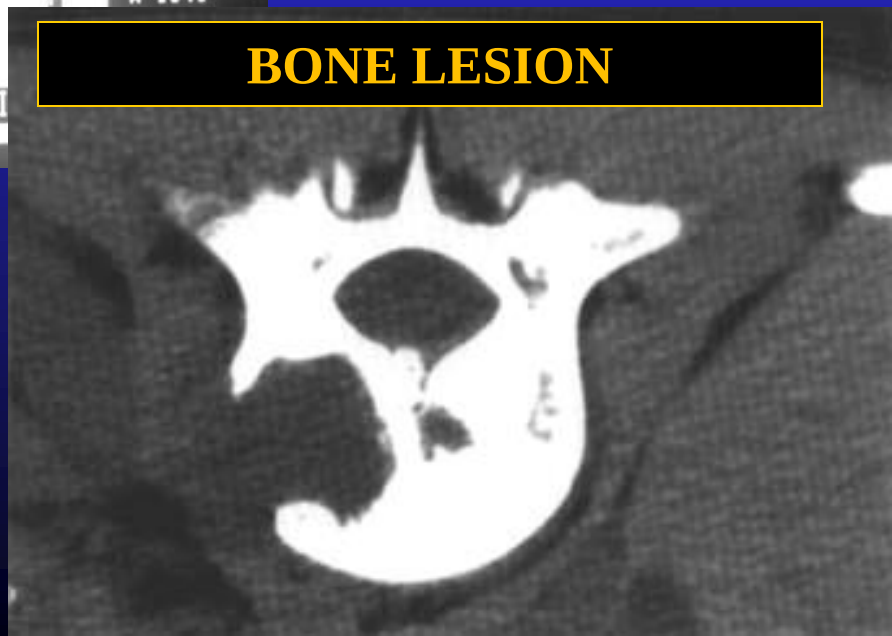
	Patients
Clinical-radiological data	20
Search of CD1a+ cells in the bronchoalveolar lavage	10
Lung biopsy	8
Cystic bone lesions	2

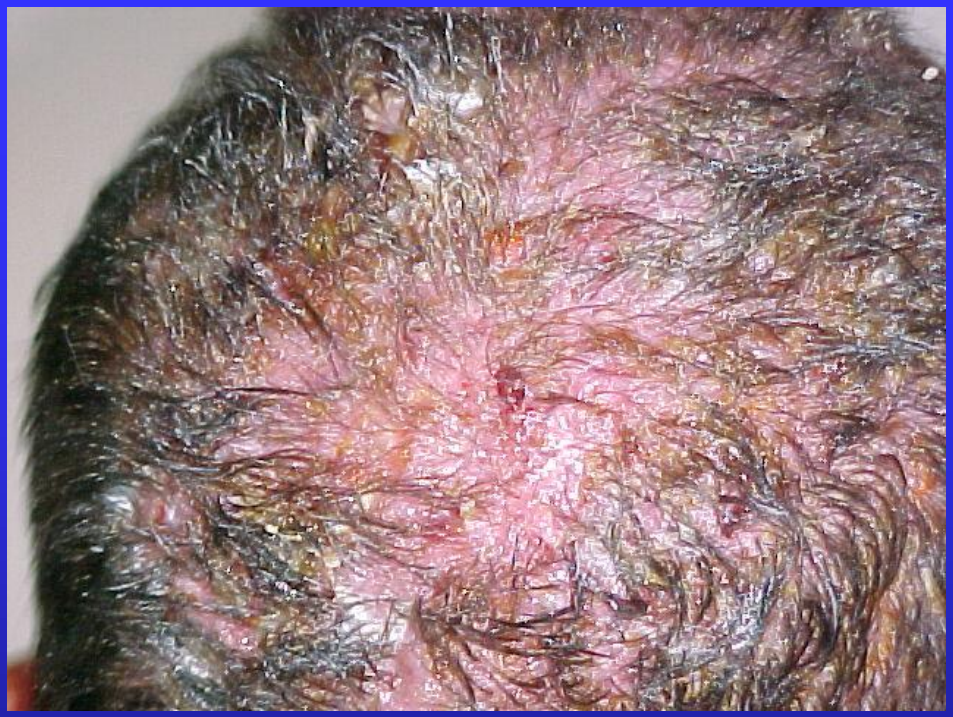
Harari S et al. Eur J Intern Med 2015; 26: 351

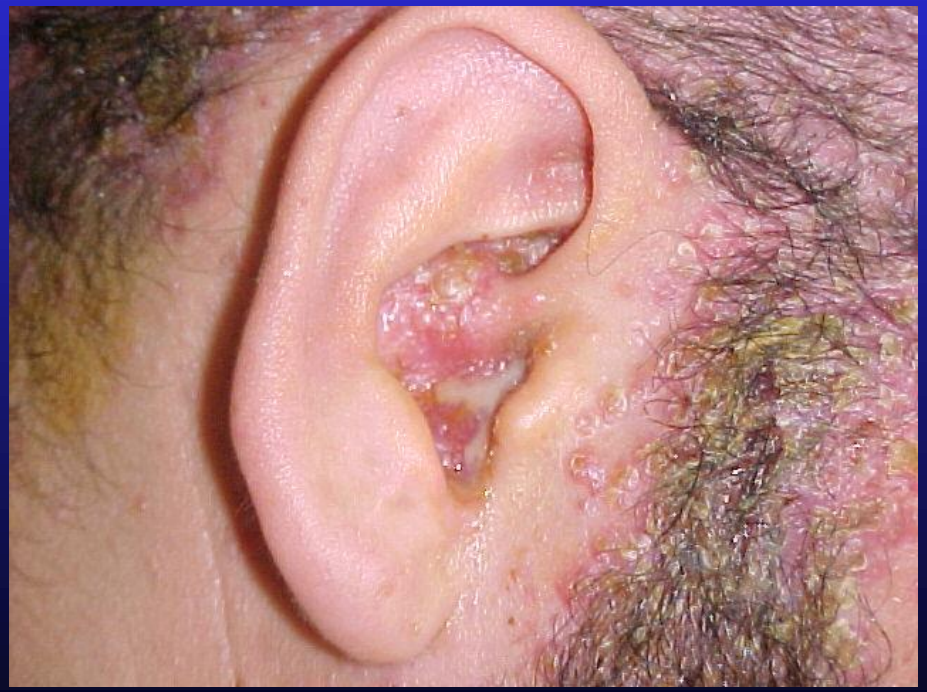
LCH : MRI IN A CAMSE OF D.I.



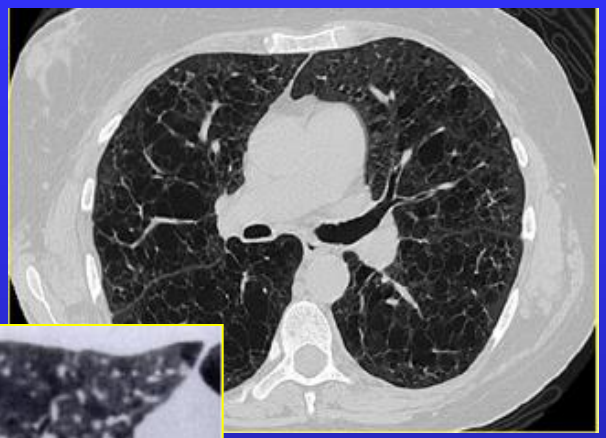
BONE LESION

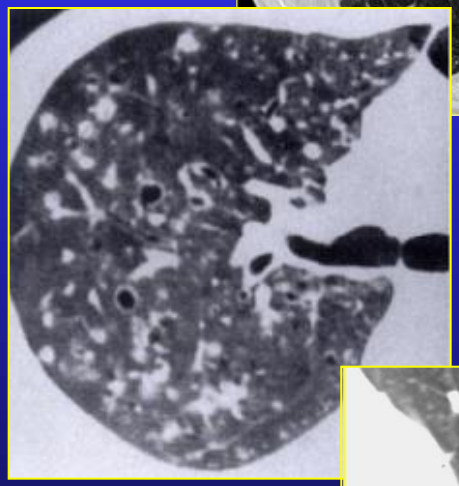


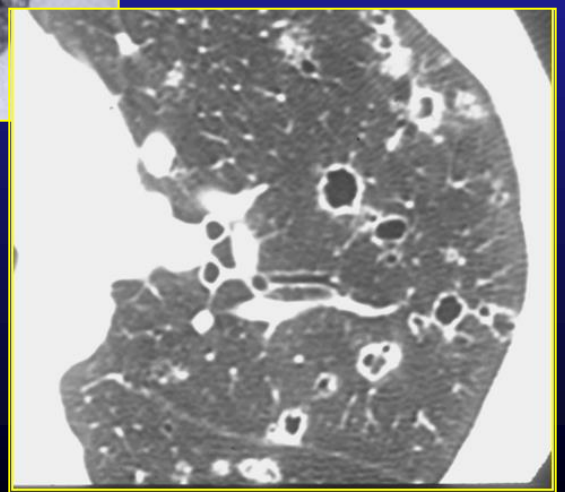




Chest CT scan imaging







In 25 patients chest CT scanning revealed weird-shaped cysts within the lung parenchyma, with upper lobe predominance and costophrenic sparing

A micronodular pattern of the middle-upper zone was found in 9 patients

6 patients presented with a combination of the two radiological patterns of the disease.

Pulmonary Function Tests (PFTs)

- PFTs were normal in 22 patients, obstructive in 16 patients, restrictive in 2 patients.
- On average, a moderate reduction in TLCO was found, only 7 patients presented with a normal TLCO value.
- The average six-minute walking distance (6MWD) was 420.37 meters; however, 4 patients walked less than 200 meters, and 6 patients required oxygen supplementation to perform the test.

Harari S et al. Eur J Intern Med 2015; 26: 351

Echocardiography

- 24 patients underwent echocardiography with evaluation of pulmonary arterial systolic pressure (PAPs) measurement.
- No significant morphological alterations were found.
- In 4 patients, PAPs was higher than 35 mmHg (mean value: 66 ± 24.65 mmHg); all of these patients had an obstructive pattern on PFTs, with a mild/severe degree of severity.

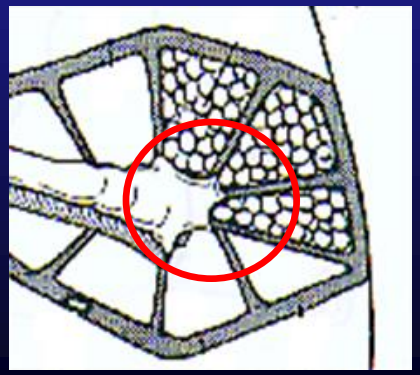
Harari S et al. Eur J Intern Med 2015; 26: 351

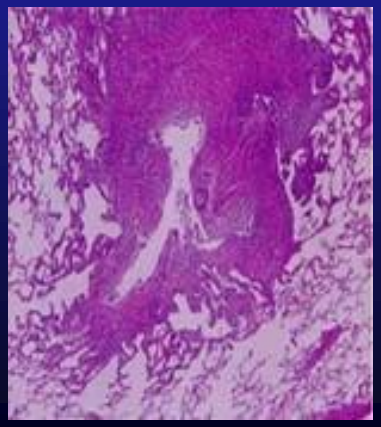
PULMONARY FUNCTION AT DIAGNOSIS

		Normal	Obstructive	Restrictive	Mixed	Reduction in *D*LCO
Schonfeld	1993	-	ES 27%/LS 71%	ES 19%/LS 29%	-	ES 84%/ LS 100%
Travis	1993	26%	28%	23%	23%	59%
Watanabe	2001	77%	9%	24%	-	45%
Westerlan	2002	57%	43%	-	-	57%
Vassallo	2002	14%	27 %	46 %	5%	
Harari	2015	43%	43%	10,5%	3,5%	78%

ES= early stage; LS = late stage

Often the degree of airway obstruction appears out of proportion to total cigarette consumption

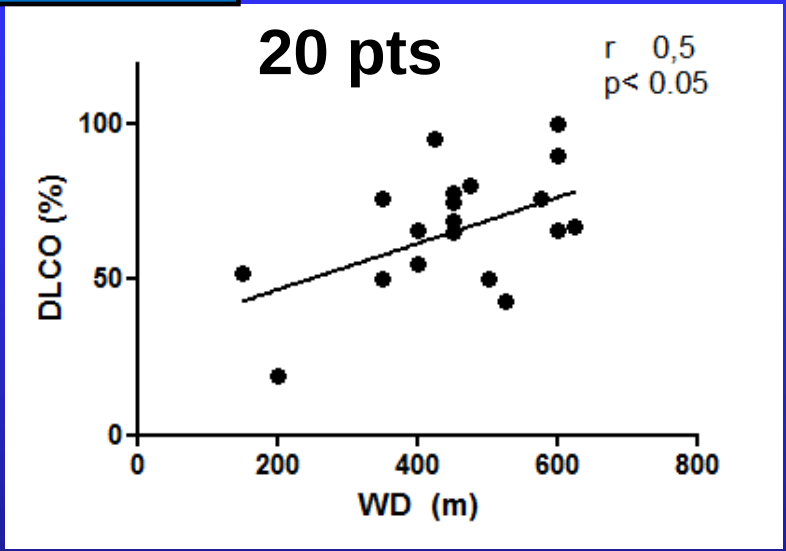




EXERCISE EVALUATION AT DIAGNOSIS

6 minute walking test

Characteristic	meanvalue
Walk distance (m)	432
SaO2 at rest (%)	97
Final SaO2 (%)	93
ΔSaO2 > 4%	4 Pts



No correlation between WD and - FEV1 (%) - FEV1/VC (%) - TLC (%)

Harari, unpublished

Cardio-pulmonary exercise test

Strong correlations between overall exercise performance (% predicted VO2max) and indices reflecting pulmonary vascular involvement (DLCO, baseline VD/VT, exercise VD/VT) have been found

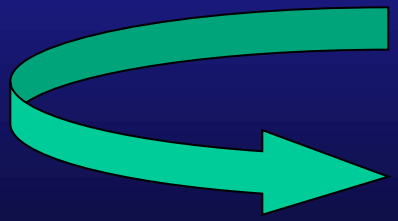
Crausman RS, AJRCCM 1996

Exercise limitation may be ascribed to vascular impairment

DIAGNOSIS

- medical history
  clinical setting
  radiological features (HRCT)

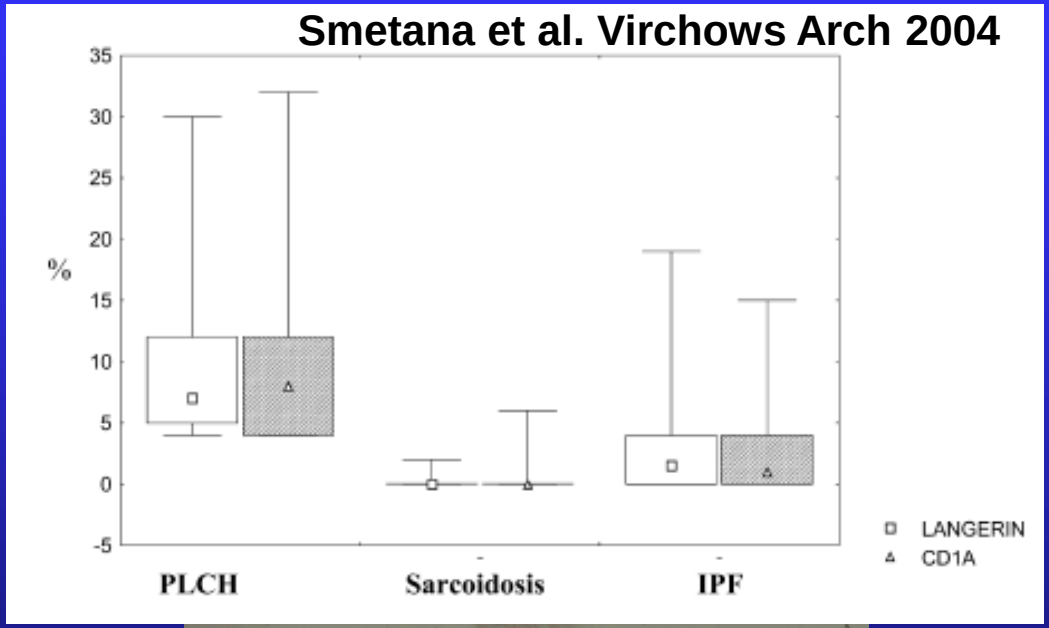
- morphologic confirmation

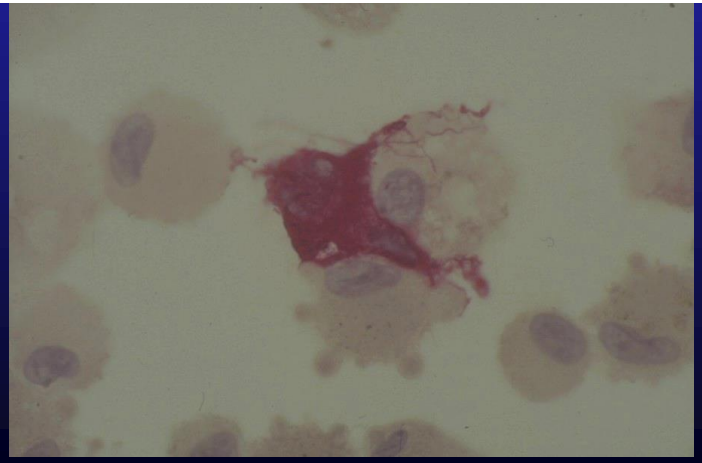


- **Surgical lung biopsy**
- ***TBB***
- ***BAL***

BAL and TBB in PLCH

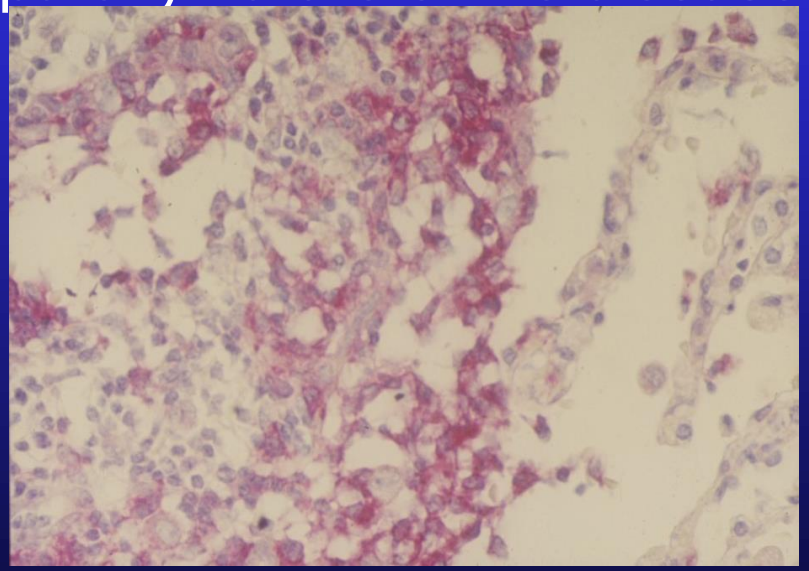
BAL





TBB

Low diagnostic yield (10-40%) because of the small amount of tissue obtained and the patchy nature of the disease



PLCH

CASES FROM 1993 TO 2008

27 PLCH - smokers 22, ex smokers 5; mean age at diagnosis 35±17 years; M/F 12/15

- ***16 BAL*** → **4 pos CD1a > 5% (25%)**
- ***3 TBB*** → **1 diagnostic (with neg. BAL)**
  1 Pnx (no chest tubes) - 1 fever
- ***7 VATS*** → ***all*** **diagnostic**
  (4 pts with negative BAL, 2 pts with negative TBB)
- ***3 Thoracotomy*** → **all diagnostic**
- ***2 Bone biopsy*** → **all diagnostic**
- ***10 Clinical-radiological Diagnosis***

Harari S et al. Respir Med 2012; 106: 1286

PLCH

CASES FROM 1992 TO 2008

27 PLCH - smokers 22, ex smokers 5; mean age at diagnosis 35±17 years; M/F 12/15

- ***16 BAL*** **→ 4 pos CD1a > 5% (25%)**

10 pts: **conventional cytology and cytofluorimetric evaluation with search for CD1a**

6 pts: **only conventional cytology**

No discrepancy was found between conventional cytology and cytofluorimetry.

Harari S et al. Respir Med 2012; 106: 1286

Relationship between HRCT pattern and results obtained by BAL and TBB in patients with PLCH

	Positive BAL/tot BAL (n)	Positive TBB/tot TBB (n)
Cystic lesions	1/6 (17%)	1/1
Nodules	0/2 (0)	-
Nodules and cysts	3/8 (37.5%)	0/2

Harari S et al. Respir Med 2012; 106: 1286

The diagnosis of PLCH: a role for BAL and TBB?

BAL

- High specificity (CD1a>5%) but low sensitivity

- In an appropriate clinical context BAL can be used to establish the diagnosis of PLCH

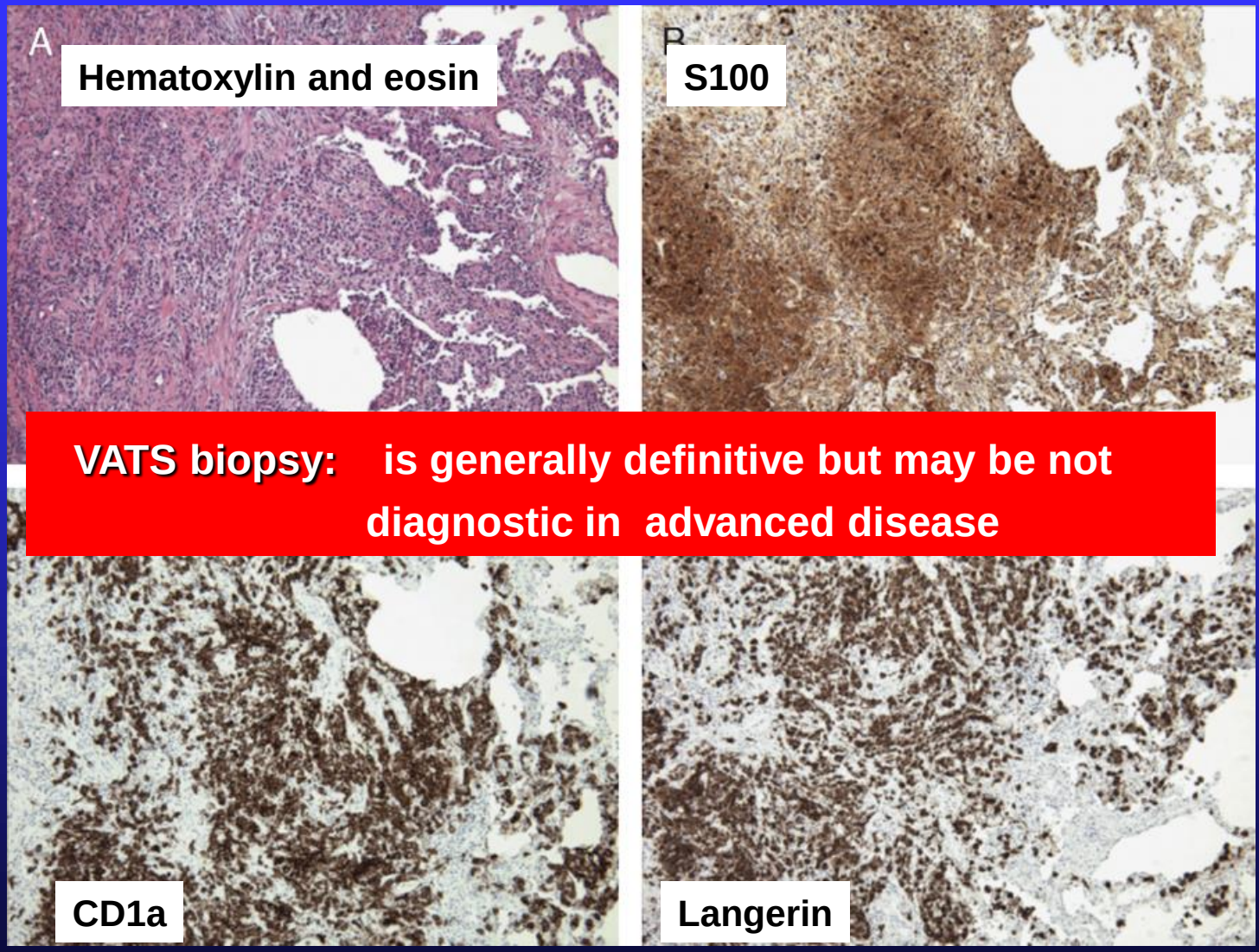
- In patients with atypical clinical and/or radiological presentation it can be used to role out interstitial lung diseases with more typical lavage findings (e.g. sarcoidosis) and pulmonary infections (excavated forms of *Pneumocystis Jiroveci* pneumonia or mycobacterial infections)

Tazi A, Eur respir J 2006

TBB

- Low diagnostic yield (10-40%) because of the small amount of tissue obtained and the patchy nature of the disease

SURGICAL LUNG BIOPSY



VATS biopsy: is generally definitive but may be not diagnostic in advanced disease

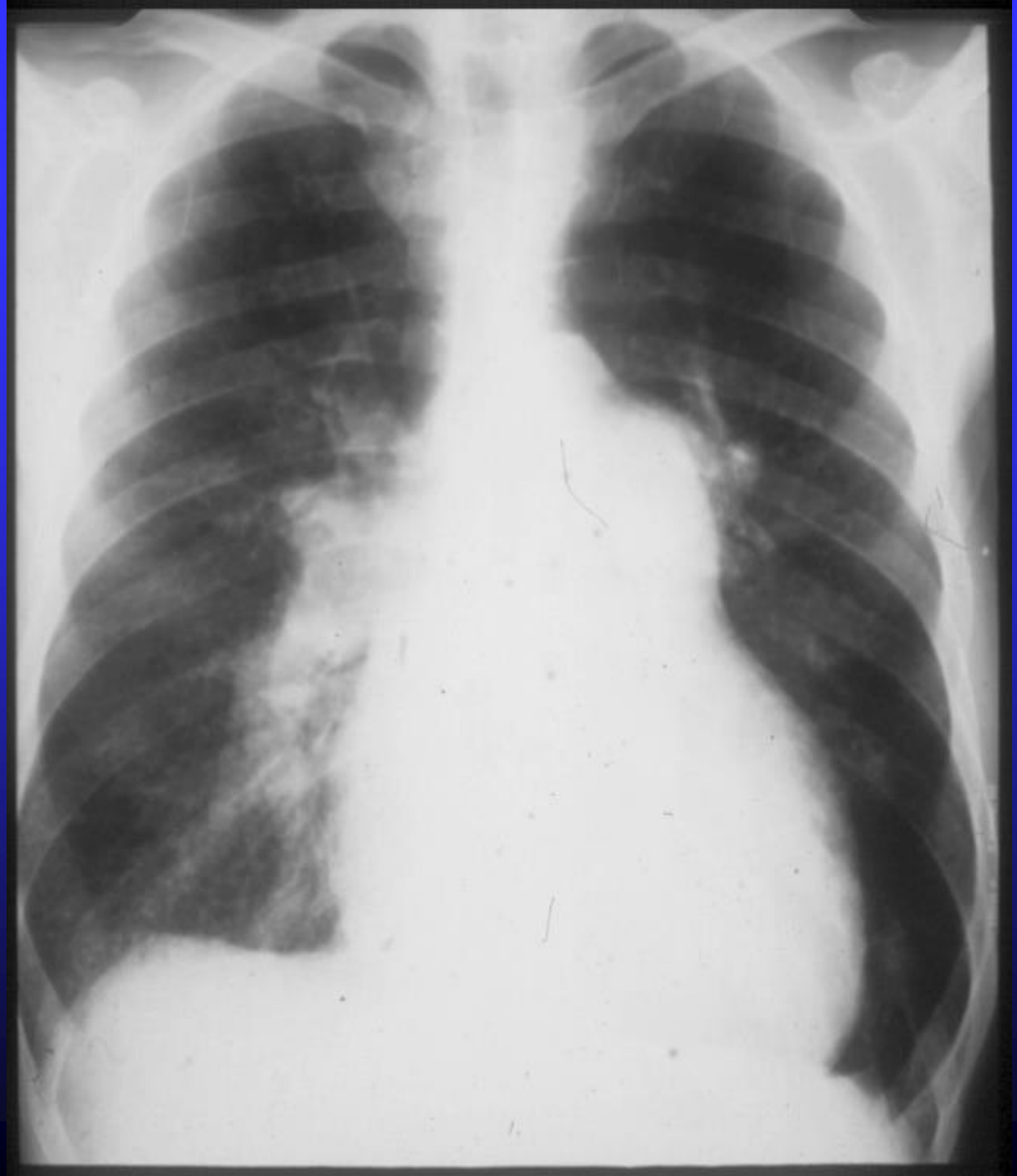
Shool et al. Am J Surg Pathol 2007

THE ROLE OF SURGICAL LUNG BIOPSY

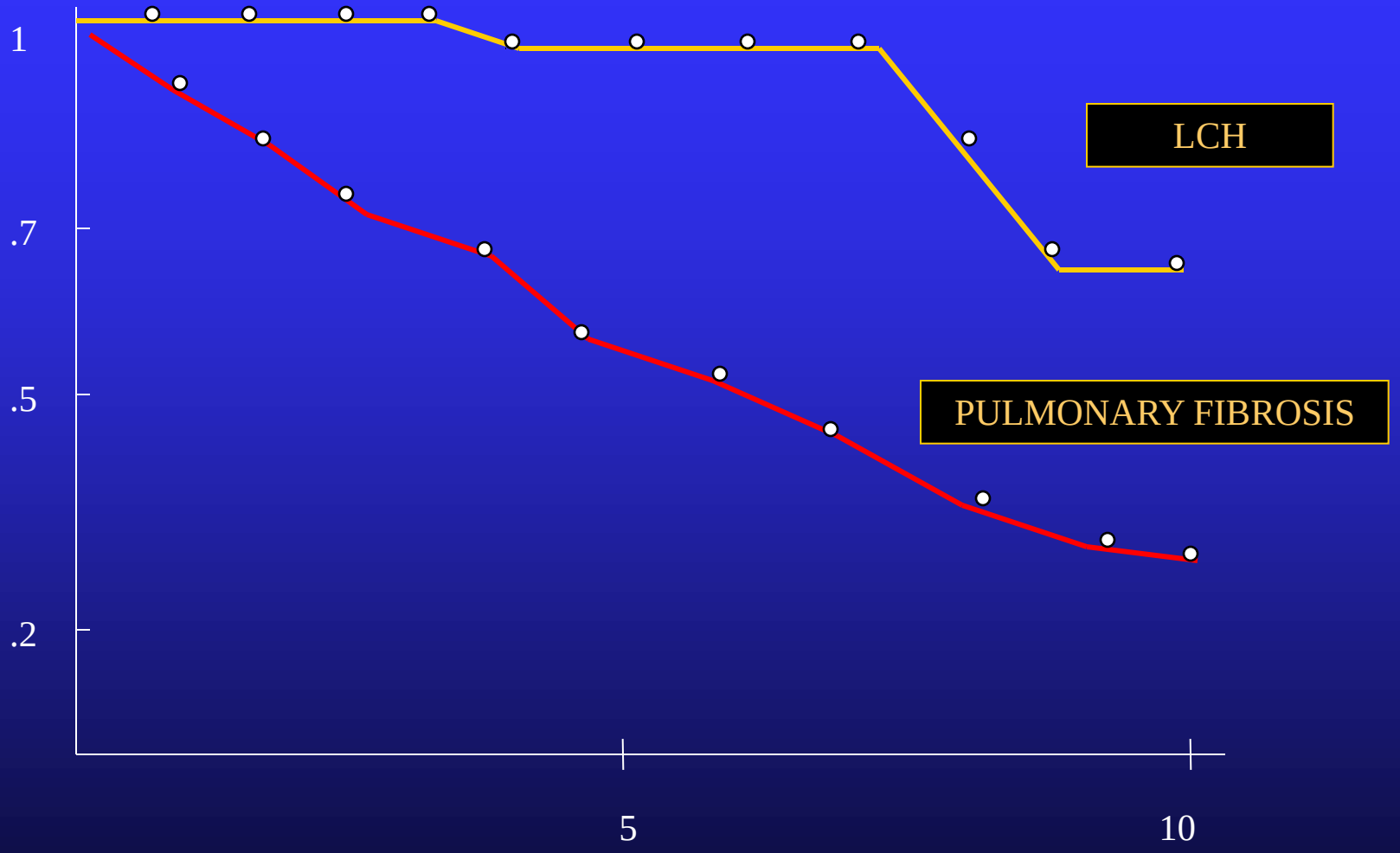
The decision to perform a surgical (VATS or open) lung biopsy depends on

- how confident you are of making a preliminary diagnosis based on clinical/ BAL / HRCT findings
- how confident you are that other diseases that may mimic PLCH have been excluded (eg LAM, HSP, sarcoidosis, infection etc)
- what therapeutic options you are considering for your patient

Biopsy of an extrathoracic lesion, for instance in a bone, may provide the diagnosis when the pulmonary manifestations are consistent with LCH.



LCH: SURVIVAL VERSUS PULMONARY FIBROSIS

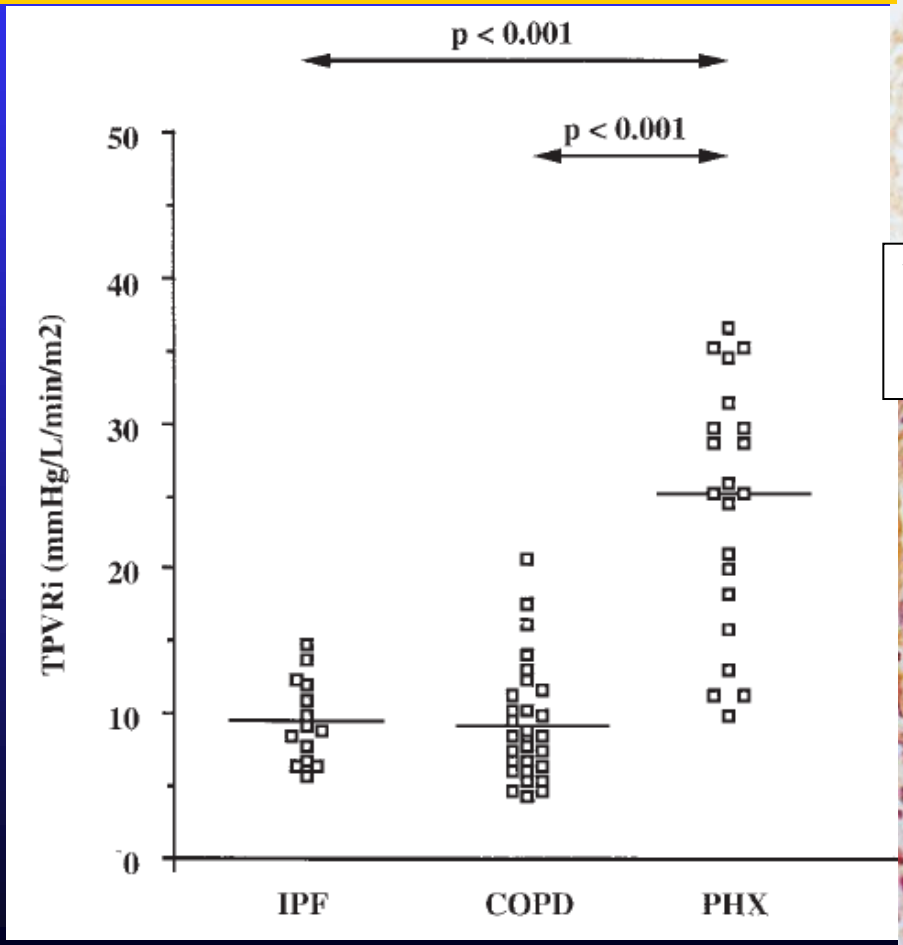


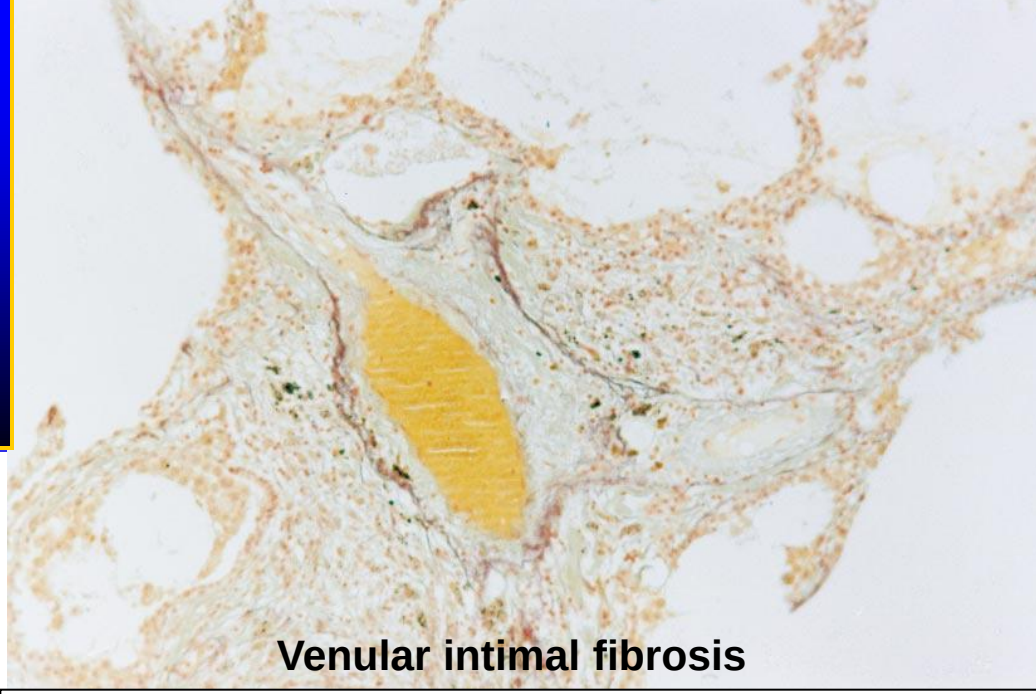
Harari S., Simonneau G. Brenot F. et Coll.

J Heart Lung Transplant 1997 Apr;16(4):460-463

Severe PH in Histiocytosis X

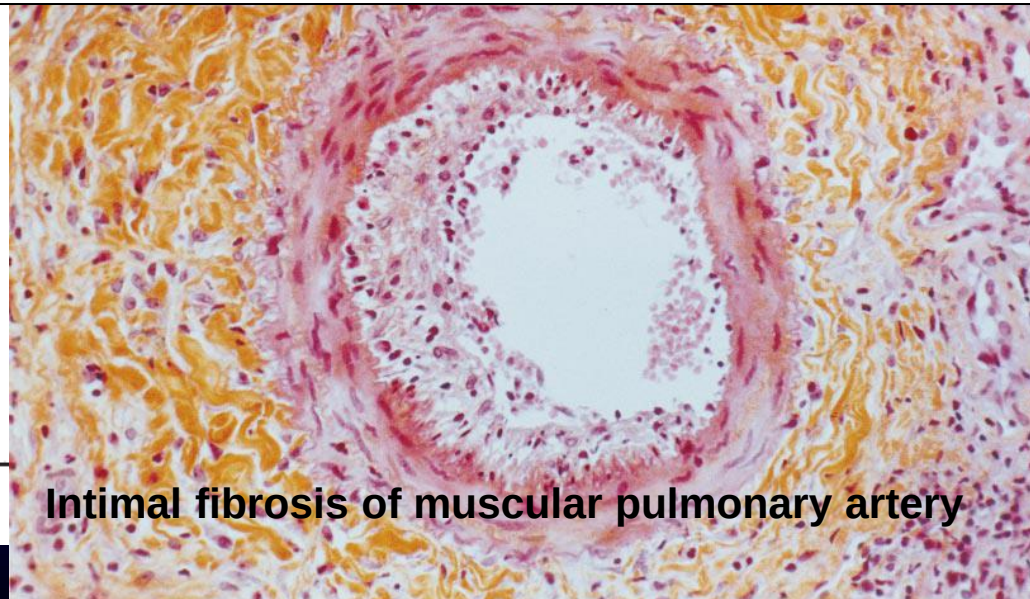
Fartoukh, AJRCCM 2000





Venular intimal fibrosis

Veno-occlusive like disease with venular obliteration, hemosiderosis, and capillary dilatation was seen in one-third of the patients



Intimal fibrosis of muscular pulmonary artery

Severe PH in Histiocytosis X
Fartoukh, AJRCCM 2000

Pulmonary hypertension in pulmonary histiocytosis X might be related to an intrinsic pulmonary vascular disease, in which the pulmonary circulation is involved independent of small airway and parenchymal injury

Severe pulmonary hypertension in histiocytosis X: long-term improvement with bosentan

Kiakouama L, Cottin V, Etienne-Mastroïanni B et al ERJ. 2010 Jul;36(1):202-4.

TABLE 1 Overview of clinical, functional and haemodynamic features

	Year of assessment				
	1988	1998	2003	2007	2009–2010
NYHA	I	II	III	II	II
FVC % pred	65	61	65	70	71
FEV_1 % pred	65	44	40	45	40
FEV_1/VC %	81	52	49	50	44
RV % pred	51	150	139	133	171
$D_{L,CO}$ % pred	69	16	<5	7	7
K_{CO} % pred	92	19	5	15	10
P_{a,O_2} at rest[#] kPa	8.7[¶]	7.8[¶]	9.4[+]	9.1[+]	9.5[+]
6-min walk distance m	ND	ND	335	378	444
RVSP mmHg	ND	40	55	45	41
P_{pa} mmHg	ND	ND	41	ND	30
P_{pcw} mmHg	ND	ND	13	ND	10
PVR $dyn \cdot s \cdot cm^{-5}$	ND	ND	649	ND	300
CI $L \cdot min^{-1} \cdot m^{-2}$	ND	ND	1.9	ND	2.6
RAP mmHg	ND	ND	9	ND	5
S_{v,O_2} %	ND	ND	63	ND	69
REF %	ND	ND	15	33	32
Therapy	None	Nasal oxygen commenced	Nasal oxygen, bosentan commenced	Nasal oxygen plus bosentan	Nasal oxygen plus bosentan

DIAGNOSED CANCERS IN THE STUDY GROUP
Vassallo, NEJM 2002

Type of Cancer	No. of Patients	Sex	At Diagnosis of Cancer		At Diagnosis of PLCH*		At Follow-up		
			Age	Tobacco Use	Age	Tobacco Use	Age†	Vital Status	Smoking History
			yr		yr		yr		pack-yr
Hematologic	6								
Multiple myeloma		F	60	Current	62	Current	64	Dead	60
Polycythemia vera		M	61	Former	61	Former	62	Dead	50
Essential thrombocythemia		F	39	Current	41	Current	46	Alive	15
Chronic myelomonocytic leukemia		F	61	Current	52	Current	62	Alive	60
T-cell lymphoma		F	63	Former	53	Current	63	Dead	30
Acute myelogenous leukemia‡		F	51	Current	51	Current	51	Dead	25
Pulmonary	5								
Adenocarcinoma									
Patient 1		F	61	Current	61	Current	62	Dead	40
Patient 2		F	45	Former	66	Current	66	Dead	80
Patient 3§		M	60	Former	64	Current	66	Alive	40
Bronchoalveolar-cell carcinoma		F	54	Current	54	Current	58	Alive	35
Small-cell carcinoma		F	56	Former	56	Former	56	Dead	90
Other	5								
Prostate cancer§		M	60	Former	64	Current	66	Alive	40
Oligodendroglioma		M	45	Current	46	Current	47	Alive	14
Metastatic squamous-cell cancer (unknown primary source)		M	47	Current	47	Current	53	Alive	85
Breast cancer‡		F	46	Current	51	Current	51	Dead	25
Pancreatic cancer		F	71	Former	58	Former	71	Dead	100

PLCH and NEOPLASMS

The association between PLCH and a variety of neoplasms (lymphoma, multiple myeloma, adenocarcinoma of the lung, and other solid tumors) has been reported by several authors

Cigarette smoking, prior treatment with chemotherapeutic agents, and chromosomal or genetic abnormalities are factors that may confer a predisposition to the development of malignant neoplasms in patients with pulmonary Langerhans'-cell histiocytosis.

TREATMENT AND PROGNOSIS

- Natural history is quite variable
- the disease may regress with the **cessation of smoking**
- **corticosteroids and cytotoxic** agents are of limited value
- **lung transplantation** should be considered in patients with advanced, progressive disease
- **radiotherapy** is palliative for symptomatic bone lesions

PROGNOSTIC FACTORS

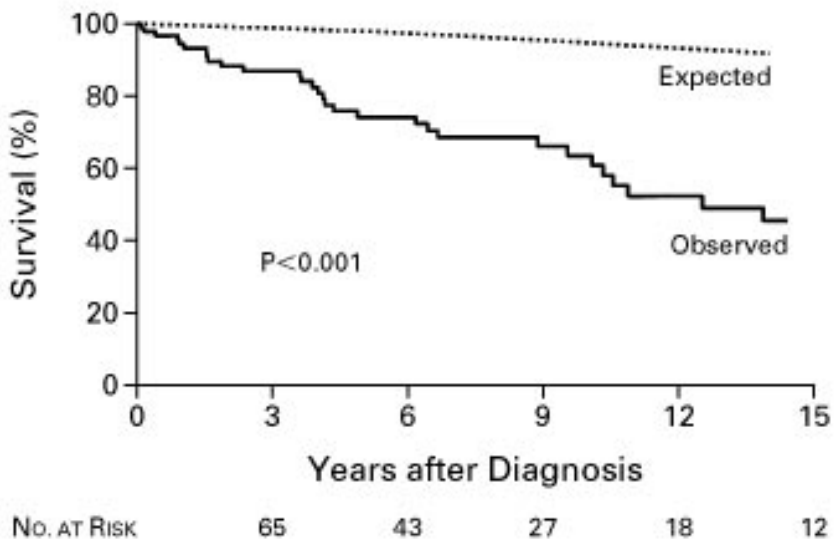
- Onset of disease at very young or advanced age
- Multiorgan involvement
- Increasingly severe airway obstruction (lower FEV1/FVC ratio and higher residual volume/total lung ratio)
- Reduced DLCO
- Extensive cysts and honeycombing
- Steroid therapy

A. Delobbe et al. Eur Respir J 1996; 9:2002-6

Caminati A and Harari S. Proc Am Thorac Soc 2006; 3:299

PLCH - PROGNOSIS

Survival of adults with PLCH



Vassallo, NEJM 2002

In a univariate analysis, variables predictive of shorter survival included

- **an older age (p=0.003)**

- **a lower forced expiratory volume in one second (FEV1) (p=0.004)**

- **a higher residual volume RV (p=0.007)**

- **a lower ratio of FEV1 to forced vital capacity (FVC) (p=0.03)**

- **a reduced D_{LCO}(p=0.001)**

THERAPY

Chemotherapeutic agents (**vinblastine, methotrexate, cyclophosphamide, etoposide, cladribina**) have been used in patients with progressive disease that are unresponsive to corticosteroids or with multiorgan involvement

Because of the limited data on their efficacy, these drugs should be reserved as **salvage therapy** for patients with progressive disease

THERAPY

- Smoking cessation
- Corticosteroids → limited data support their efficacy

It is reasonable to use corticosteroids for patients who have progressive disease or systemic symptoms

FOLLOW-UP

Long-term follow-up is required

Even after years of apparent quiescence,

lung function can deteriorate and new nodular lesion can develop

Recrudescence of disease activity

FOLLOW-UP

The course of pulmonary Langerhans'-cell histiocytosis in adults is variable and unpredictable, ranging from an asymptomatic course to progressive disease that leads to respiratory failure and death over a period of months

Vassallo R et al. NEJM 2002, 346:484-490

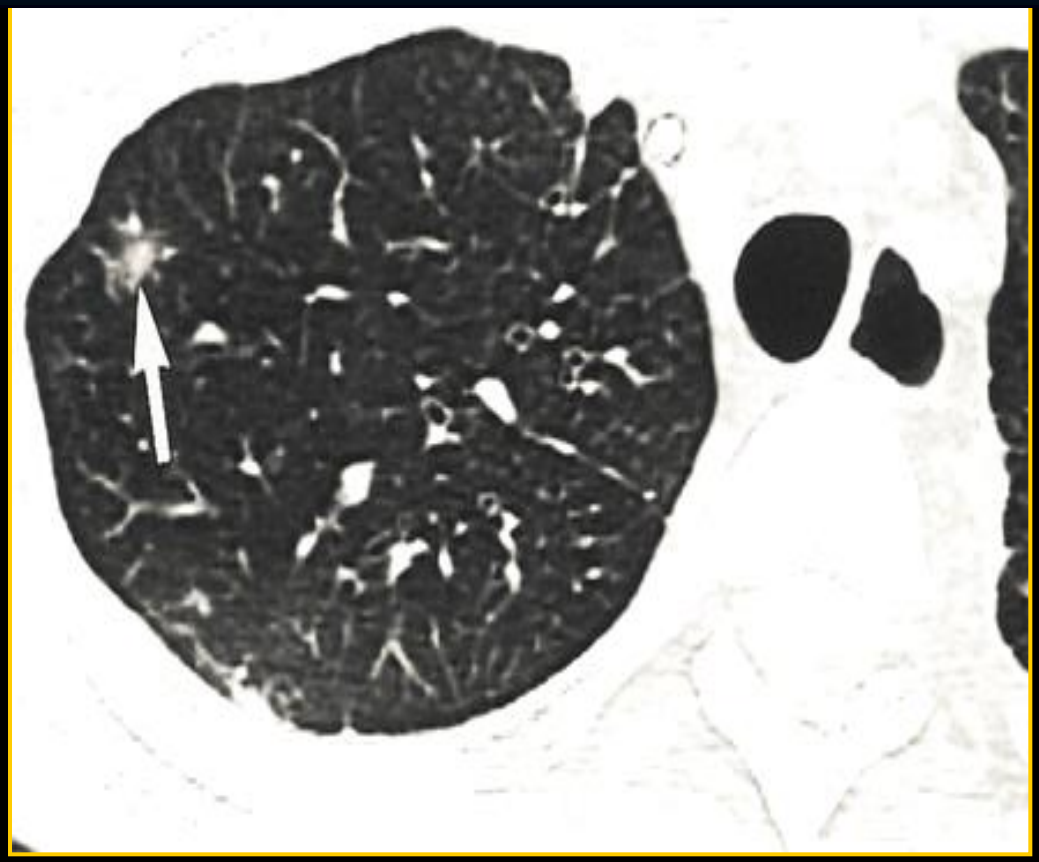
PLCH – LUNG TRANSPLANTATION

- A number of patients with very severe respiratory failure or major pulmonary hypertension have been treated with lung transplantation, with results similar to those found in patients with other patterns of diffuse infiltrating lung disease

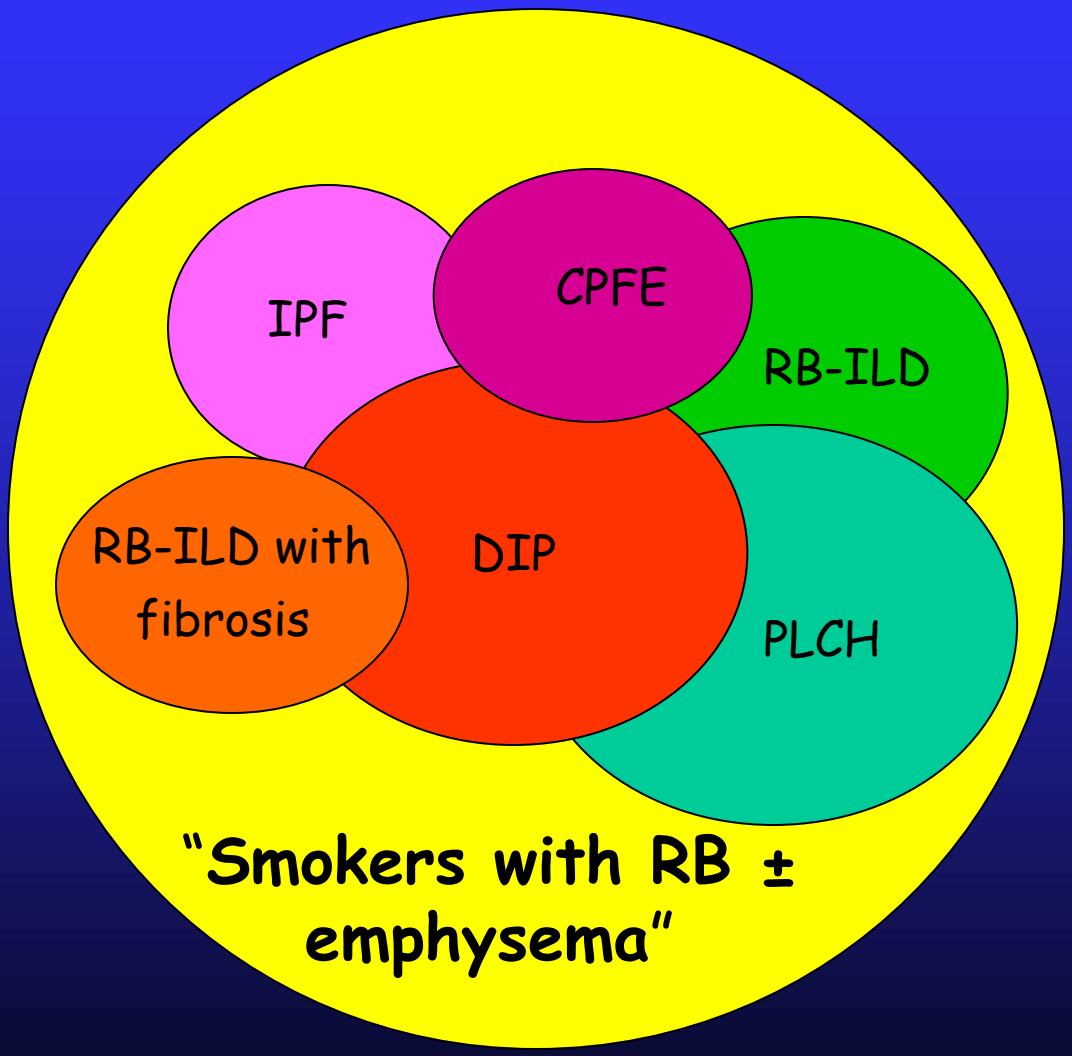
Consider referral for evaluation in patients with progressive disease and respiratory failure and/or severe PH

- Recurrence of the disease in the transplant within the first year has been reported, with possible risk factors being resumption of smoking and extrapulmonary involvement

Relapsing pulmonary Langerhans cell histiocytosis after lung transplantation



Etienne B.et coll. Am J Respir Crit Care Med 1998 Jan;157(1):288-291



Smoking-related interstitial lung diseases