Smoking-related interstitial lung disease

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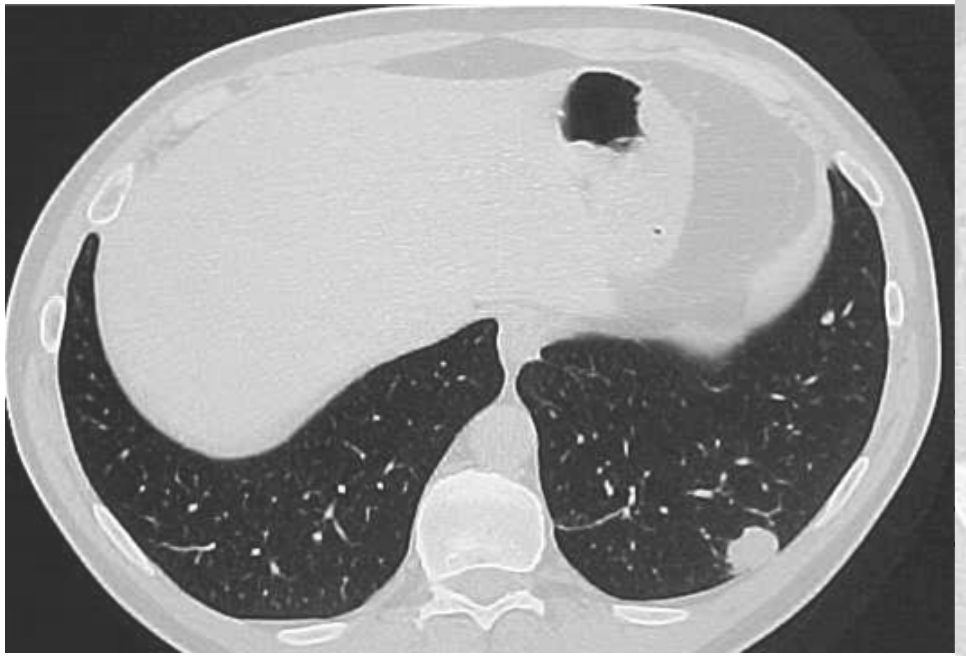
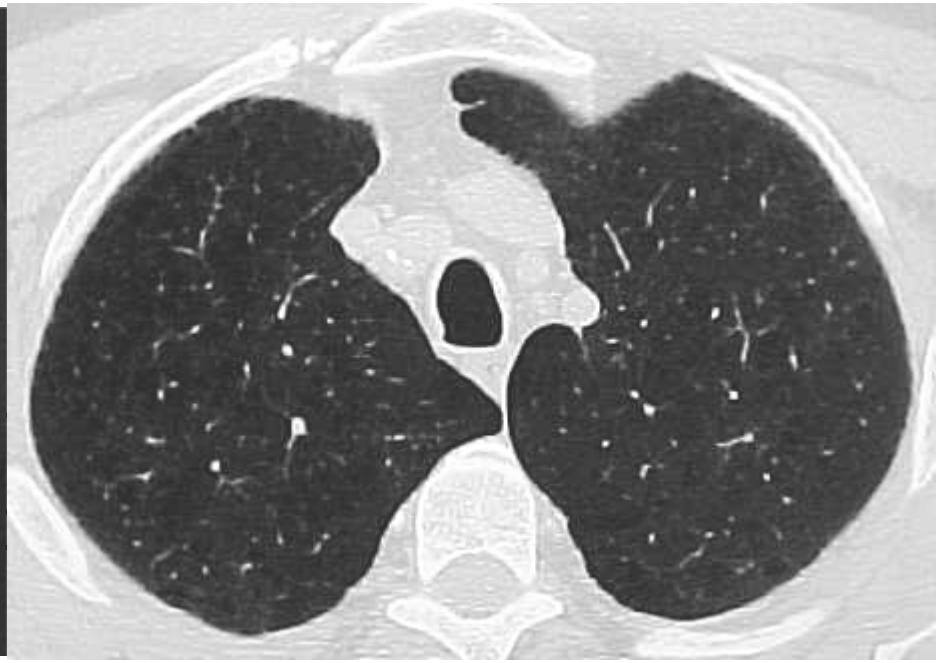
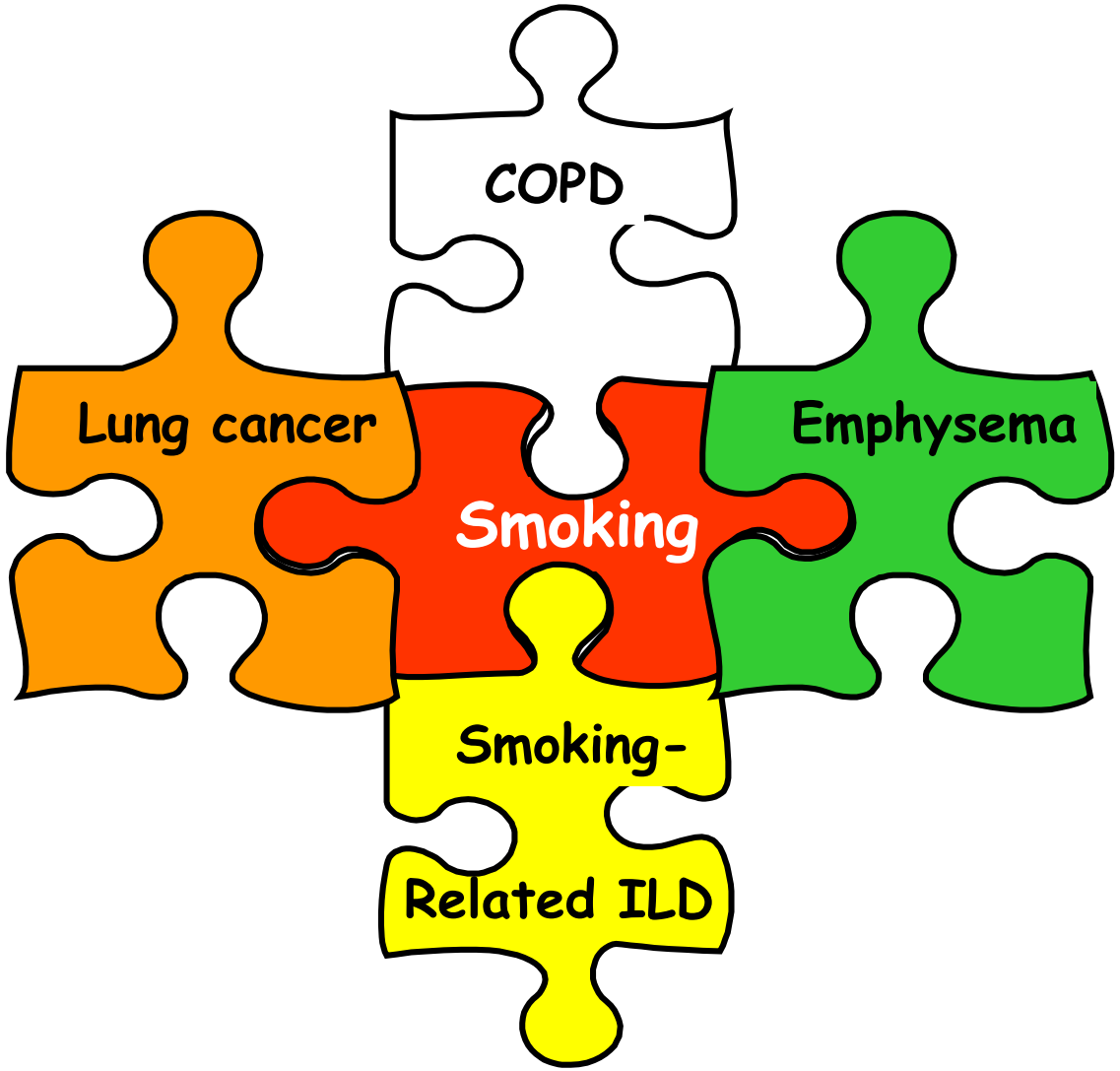
Smoking and lung

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





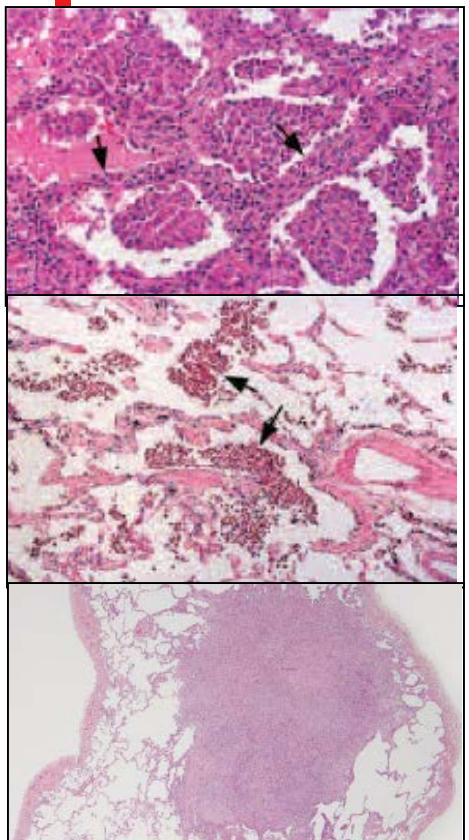
Recent Advances



Smoking-related interstitial lung diseases

1969 1974 1986 2000

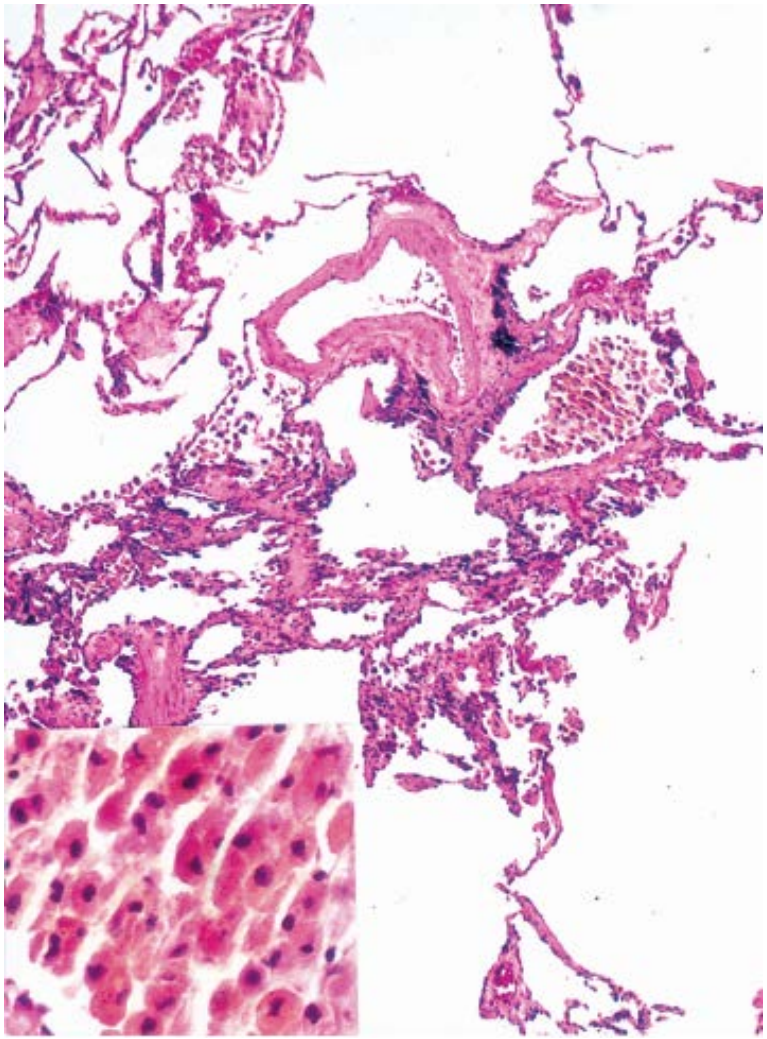
Liebow and Carrington Niewoehner Mayers



"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

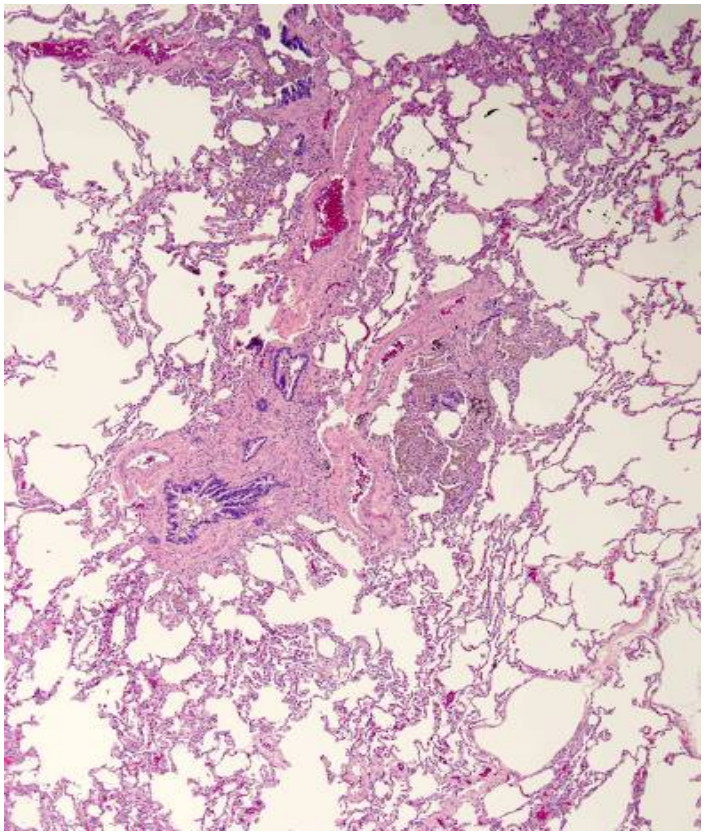
Symptomatic

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

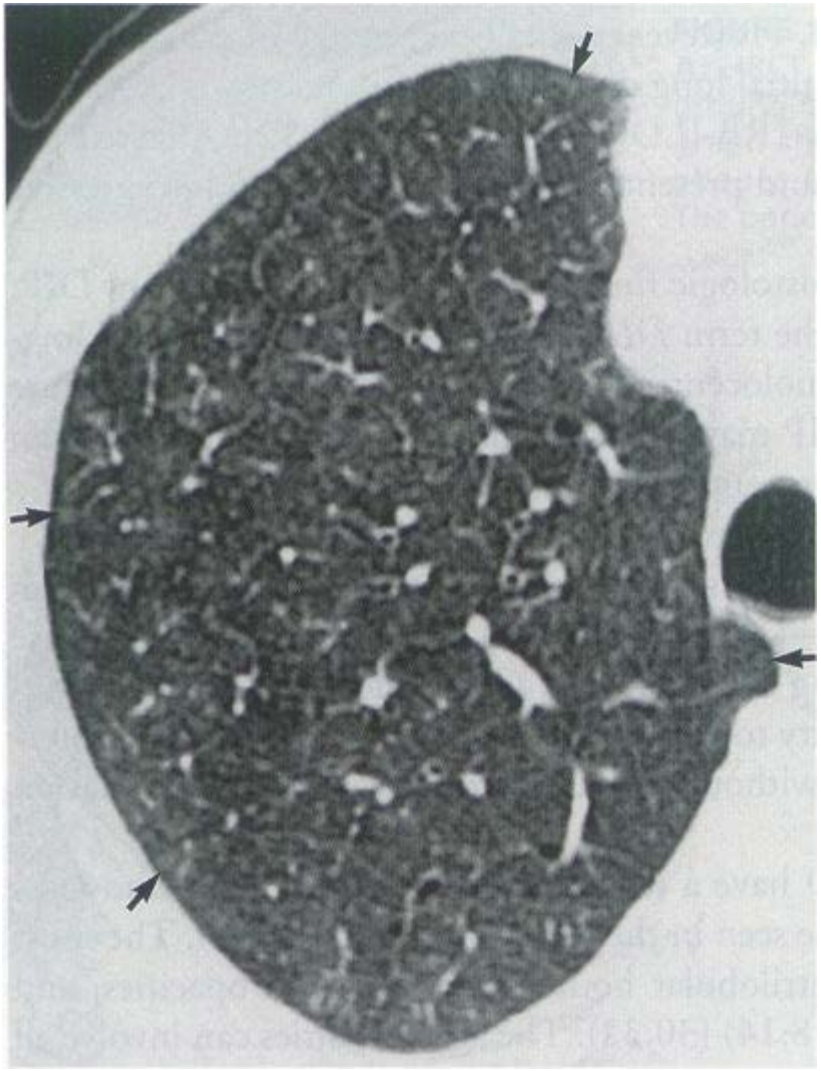
RADIOLOGY

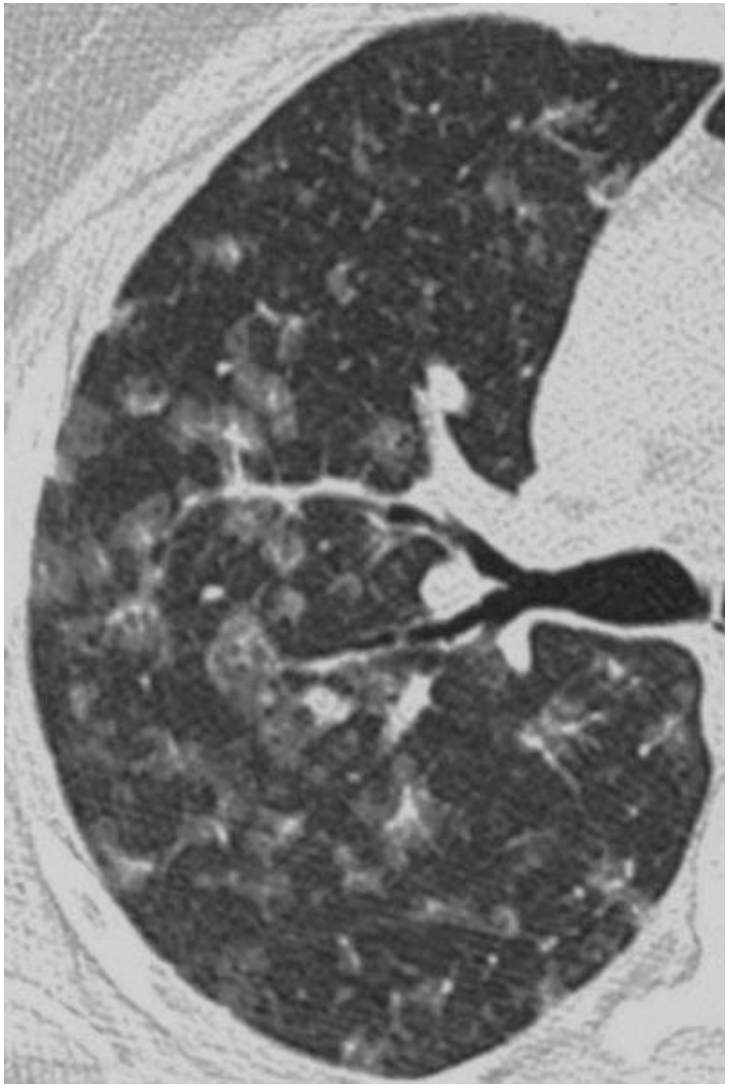
- Thickening of the walls of central or peripheral bronchi (75%)
- Ground glass (60%)
- Chest radiograph normal (14%)

RADIOLOGY - HRCT

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

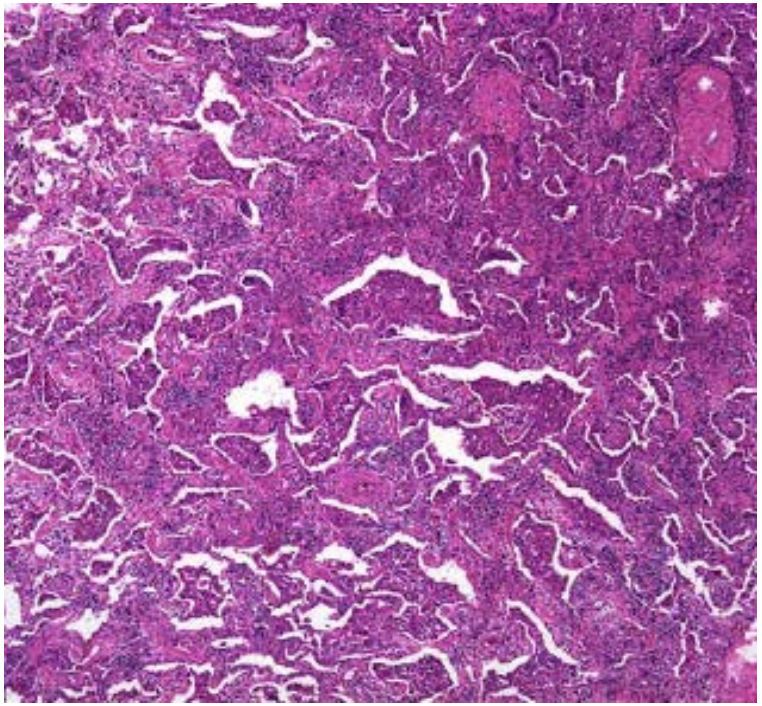
RADIOLOGY



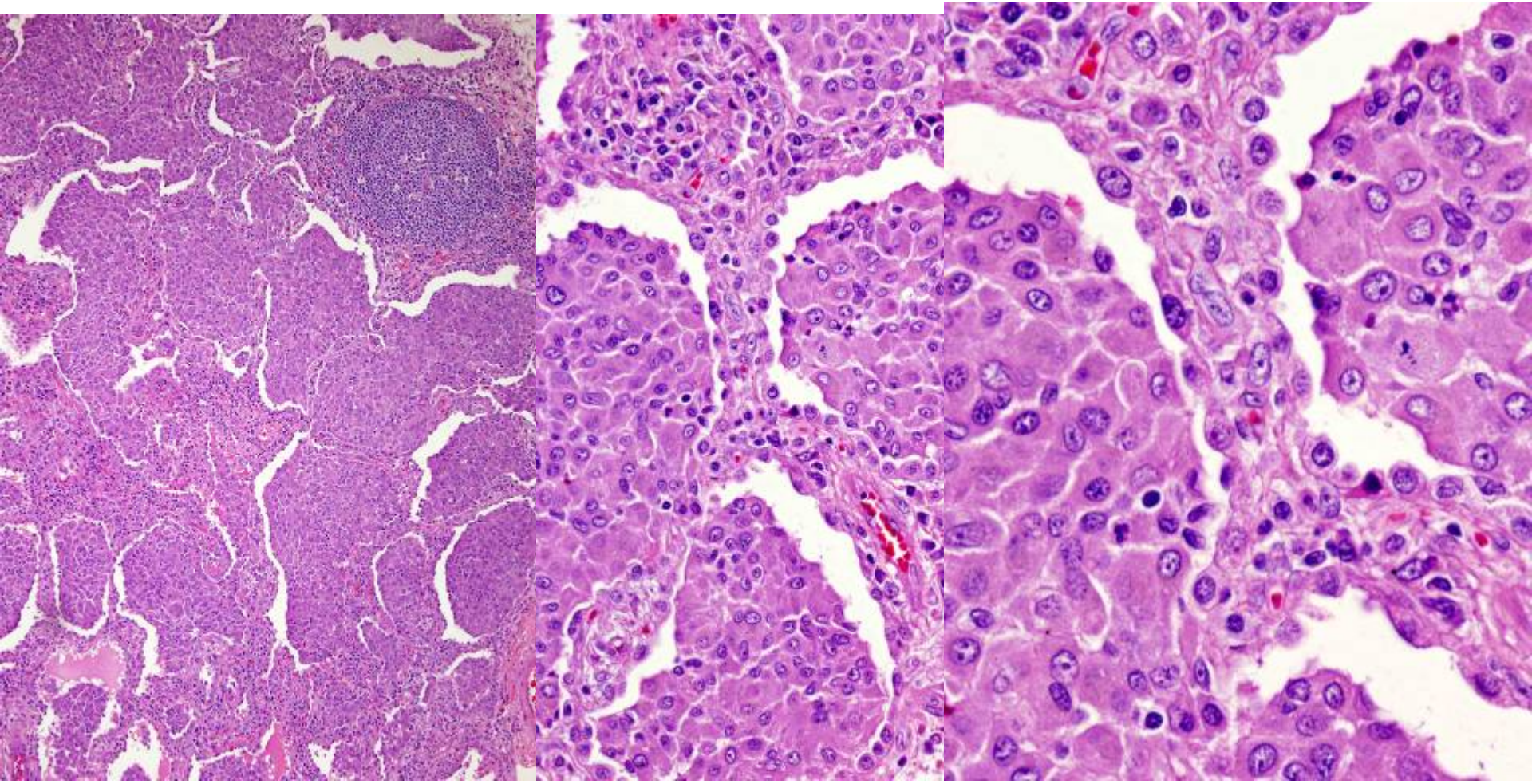


DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP)

- 98% smokers
- Symptomatic
- Restrictive PFT's
- Uniform process
- ground glass in the lower lobe
- Minimal fibrosis
- 70% survival at 10 years



DESQUAMATIVE INTERSTITIAL PNEUMONIA



DIP

- Liebow 1965
- DIP because desquamation of epithelial cells thought to be the dominant feature
- It is one of the idiopatic interstitial pneumonias with a significantly better prognosis than UIP

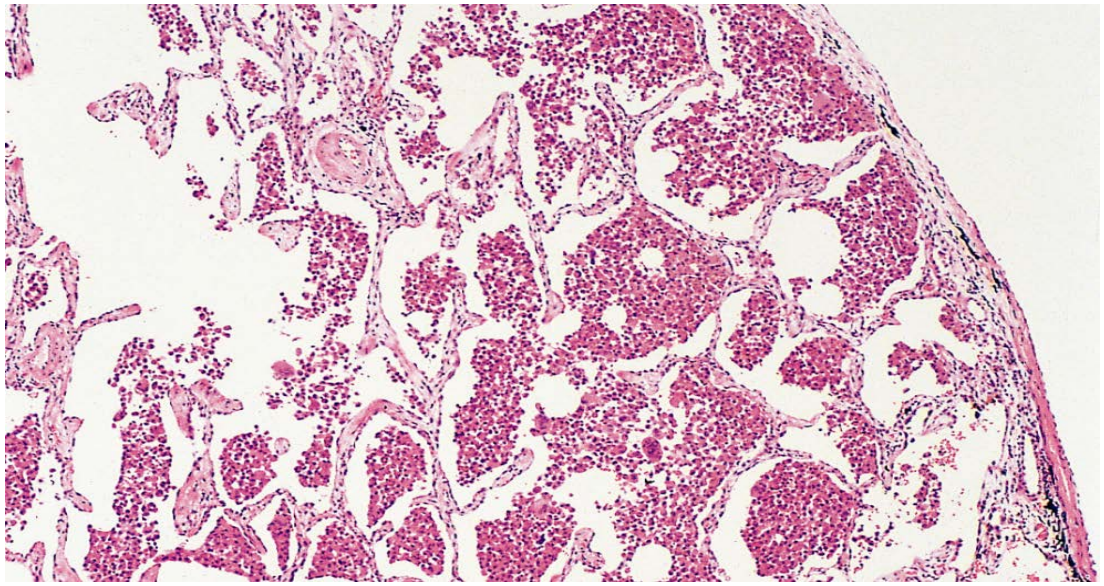
CLINICAL FEATURES

- 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

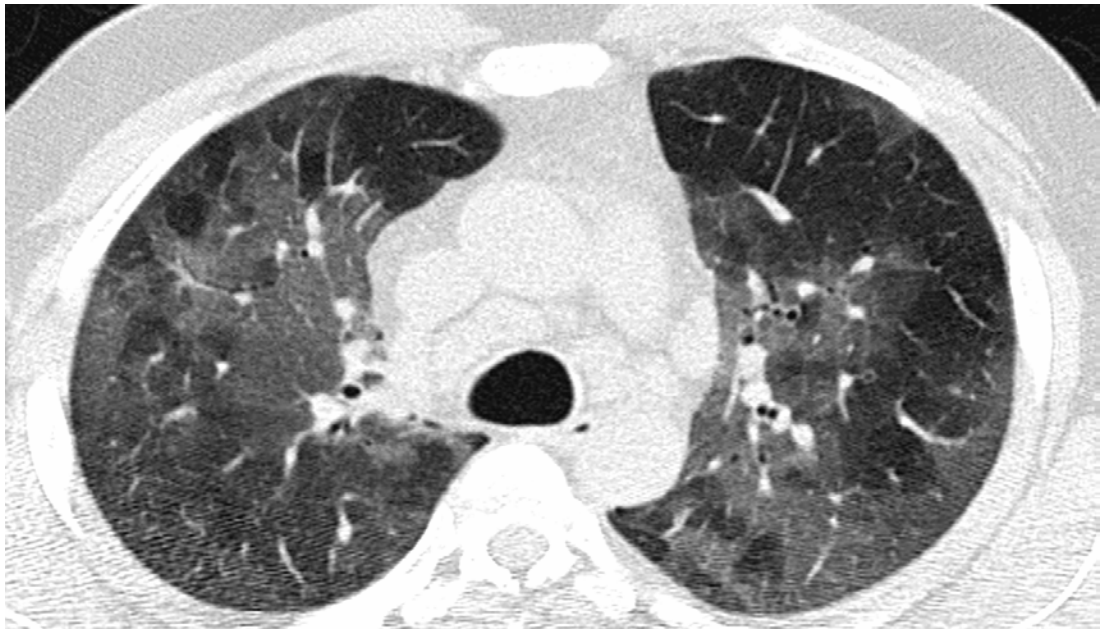
RADIOLOGY

- 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



DIP



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

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

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% at 10 yr

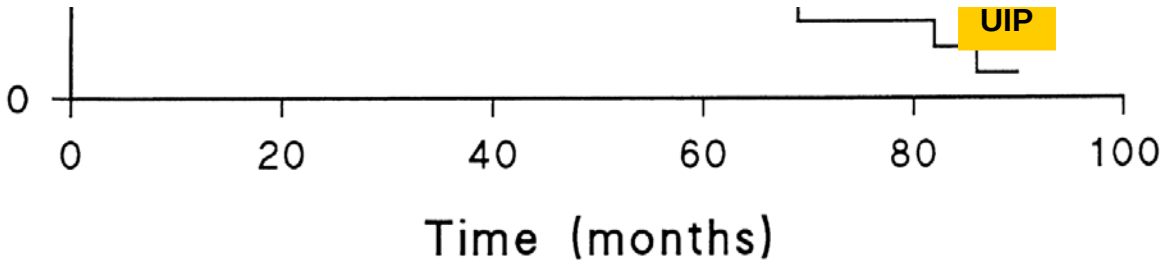
SURVIVAL IN IIP

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

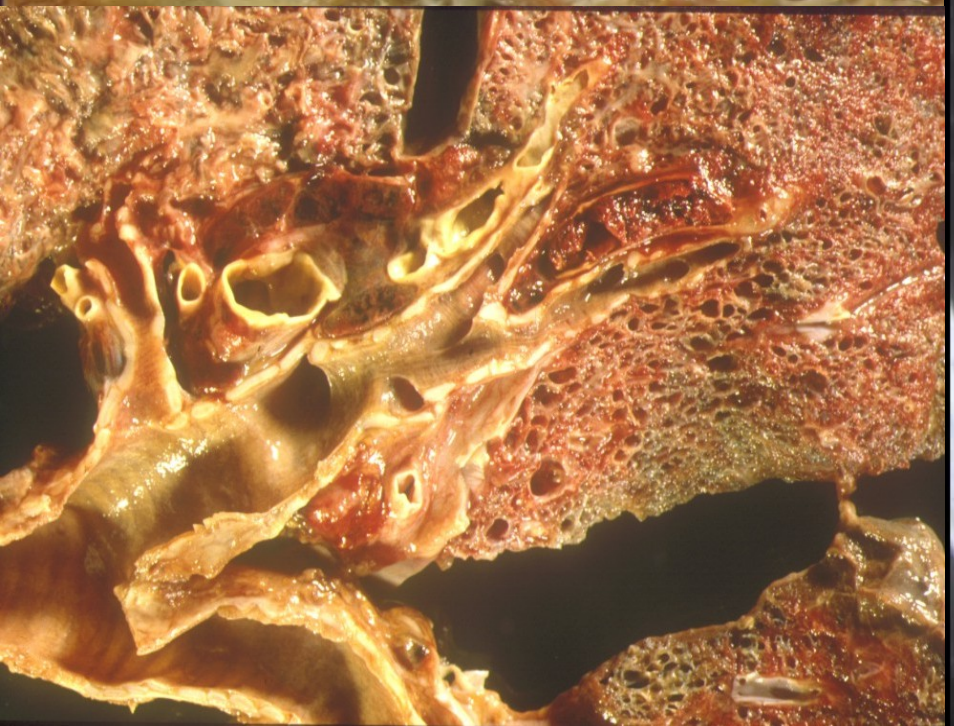
DIP/RB-ILD: Conclusions (3)

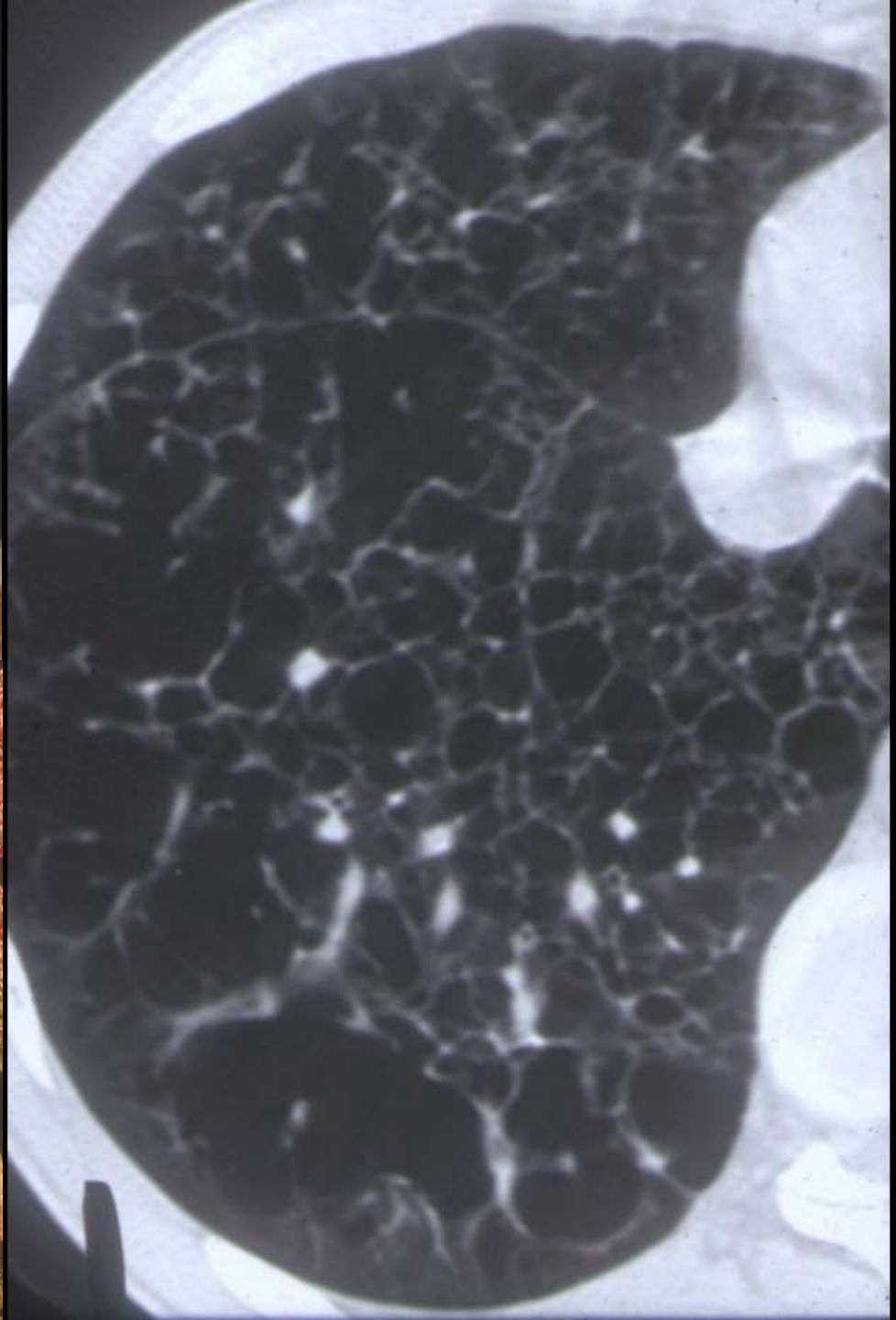
- There is some evidence to suggest that smoking cessation may suffice as the initial therapeutic maneuver for patients with RB-ILD
- It remains unclear whether corticosteroid therapy favorably alters the natural history of DIP and RB-ILD, particularly since the effect of smoking status on the clinical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

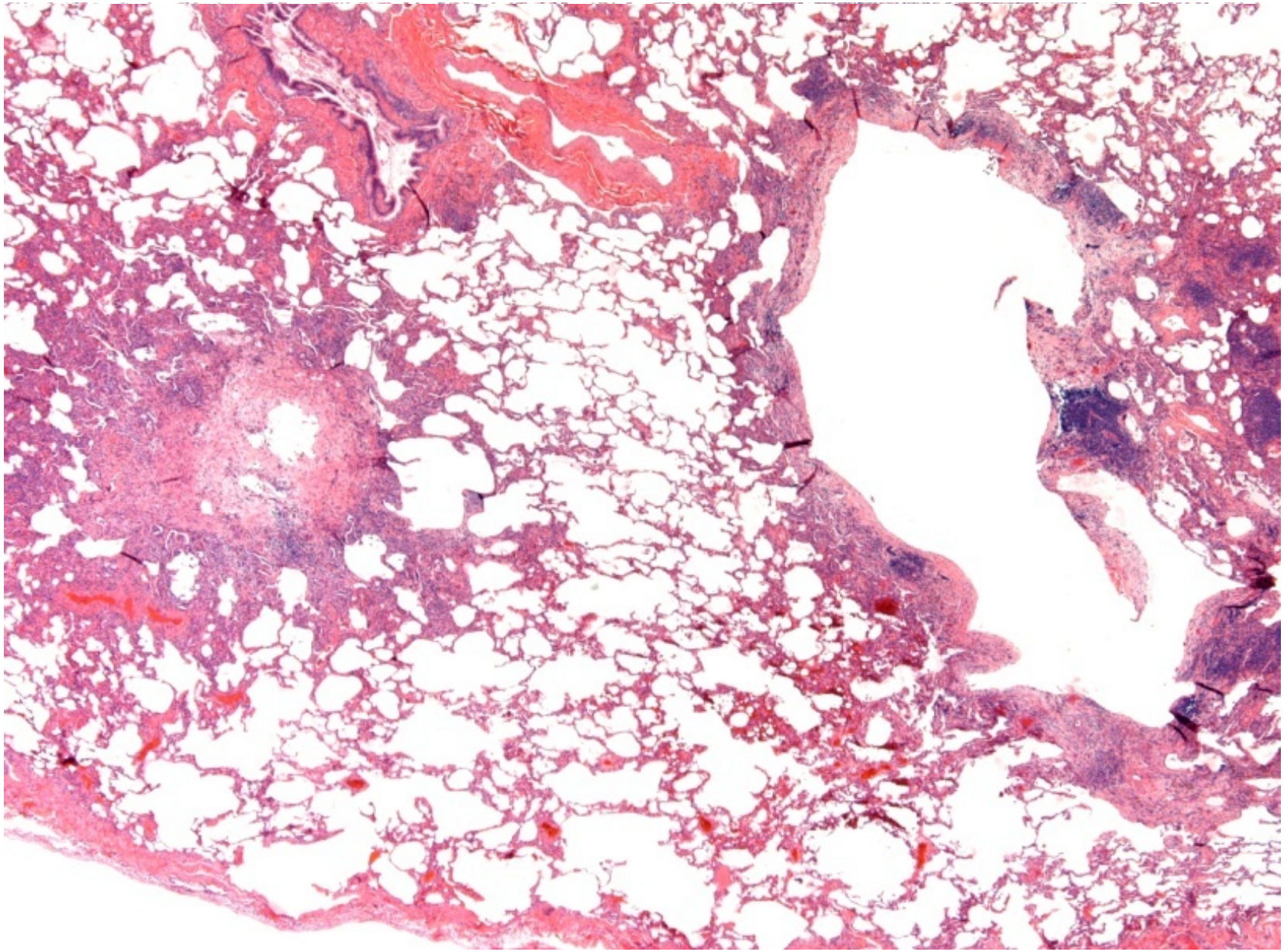
SMOKING-RELATED ILDs

- 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 (PLCH)

- Uncommon interstitial lung disease characterized by proliferation of Langerhans' cell infiltrates
- Primarily affects young adults
- Nearly all affected pts have a history of current or prior cigarette smoking
- Single-organ involvement or multisystem disease

Harari et al. Sarcoidosis Vasc Diffuse Lung Dis. 2005

PLCH - EPIDEMIOLOGY

		Series	Prevalence	
Gaensler	1980	502 Open lung biopsies	3,2% PLCH	12,5% SARCOIDOSIS
Colby	1983	> 6-yr period	15 PLCH	274 SARCOIDOSIS
Delobbe	1996	360pts 5-yr period	3% PLCH	
Watanabe	2001	1-yr period	Males Females	0,27/100000 0,07/100000

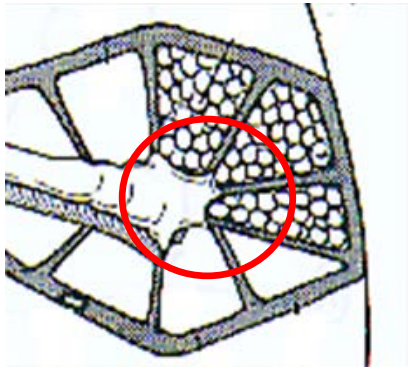
A similar proportion of males and females, or even a slight predominance of females, was observed

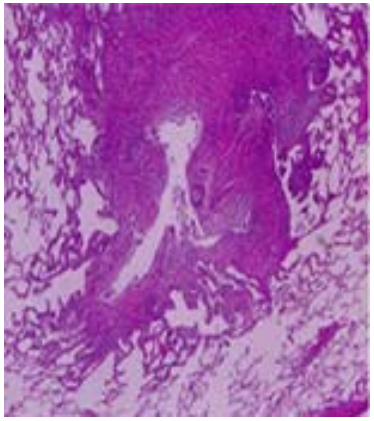
PULMONARY FUNCTION AT DIAGNOSIS

		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

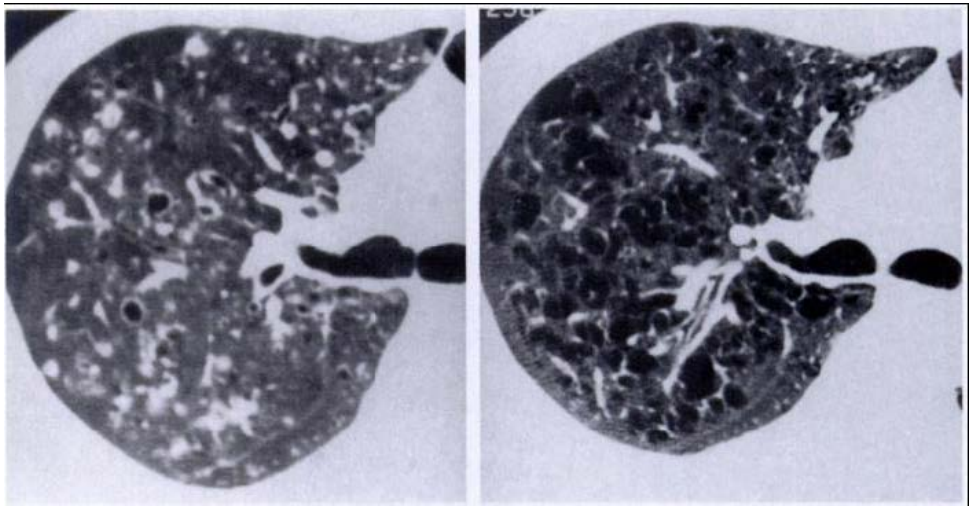




PLCH: evolution of lesions on CT scans

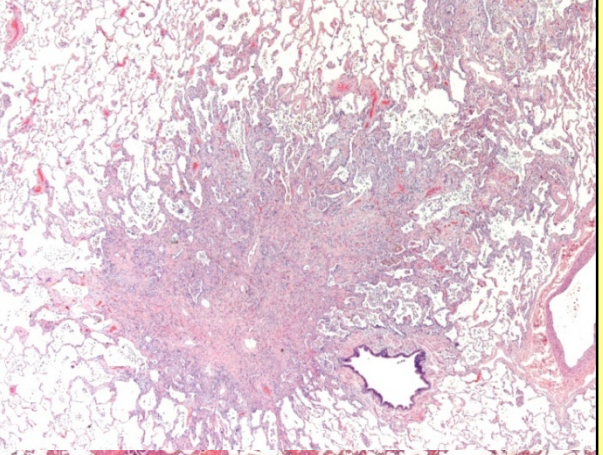
Longitudinal observation of CT features suggest the following evolutionary sequence for pulmonary lesions of PLCH:

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



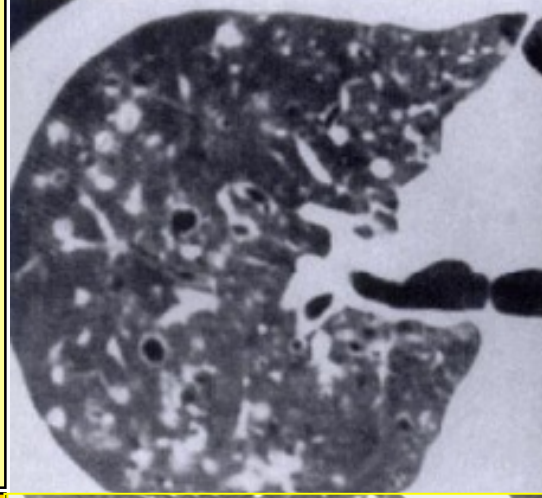
Brauner et al. Radiology 1997

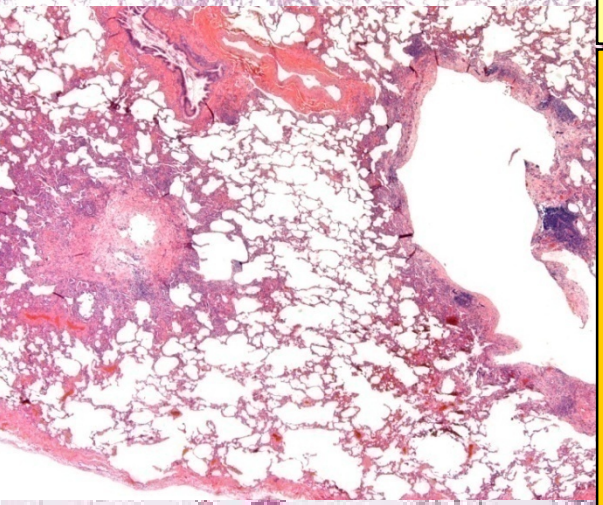
Harari et al. AJRCCM 1997;155 (4) A 329



➢ *Early stage:*

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

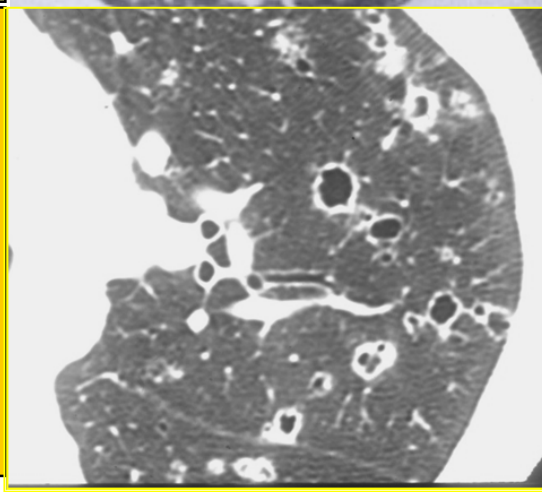


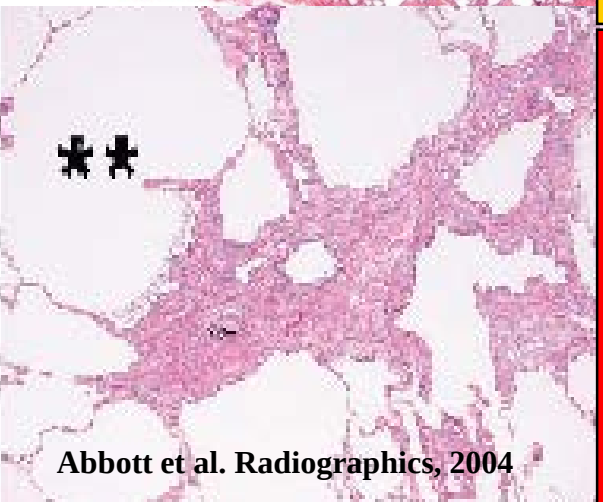


➢ *Disease progression:*

Increasing numbers of nodules and **cavitary nodules**

Appearance of **fibrotic scars**

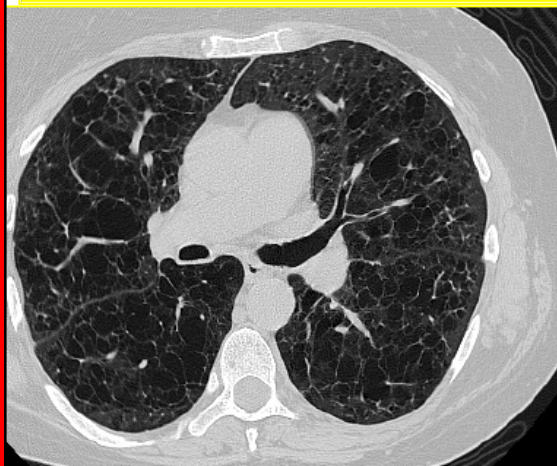




Abbott et al. Radiographics, 2004

➢ *End stage:*

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

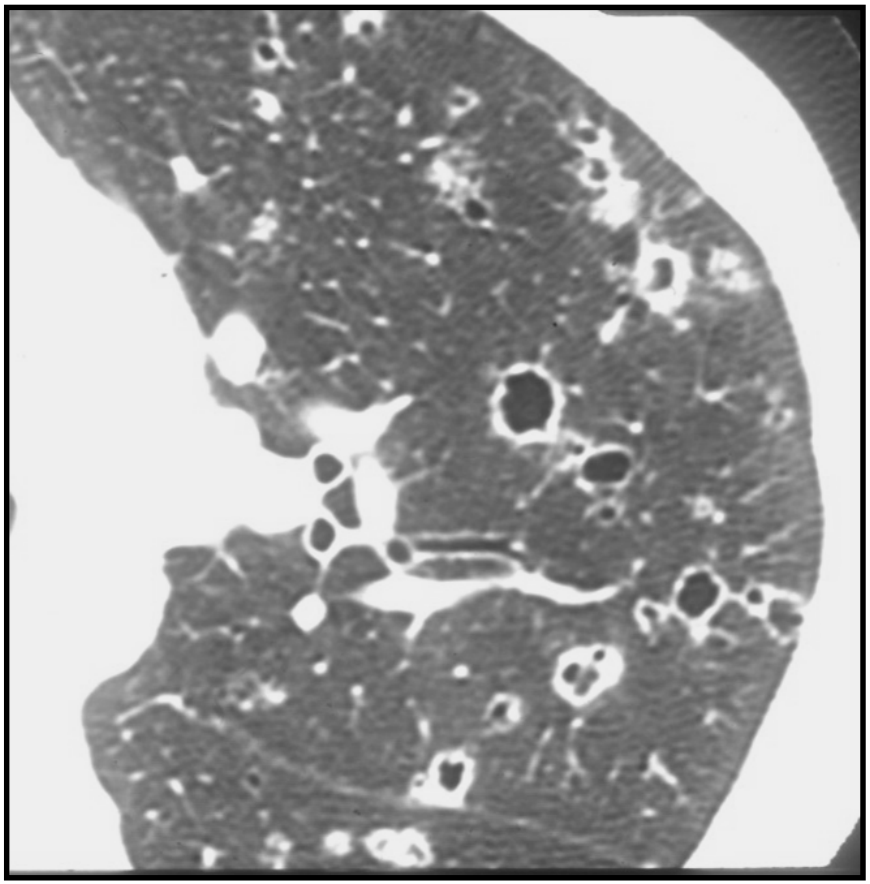


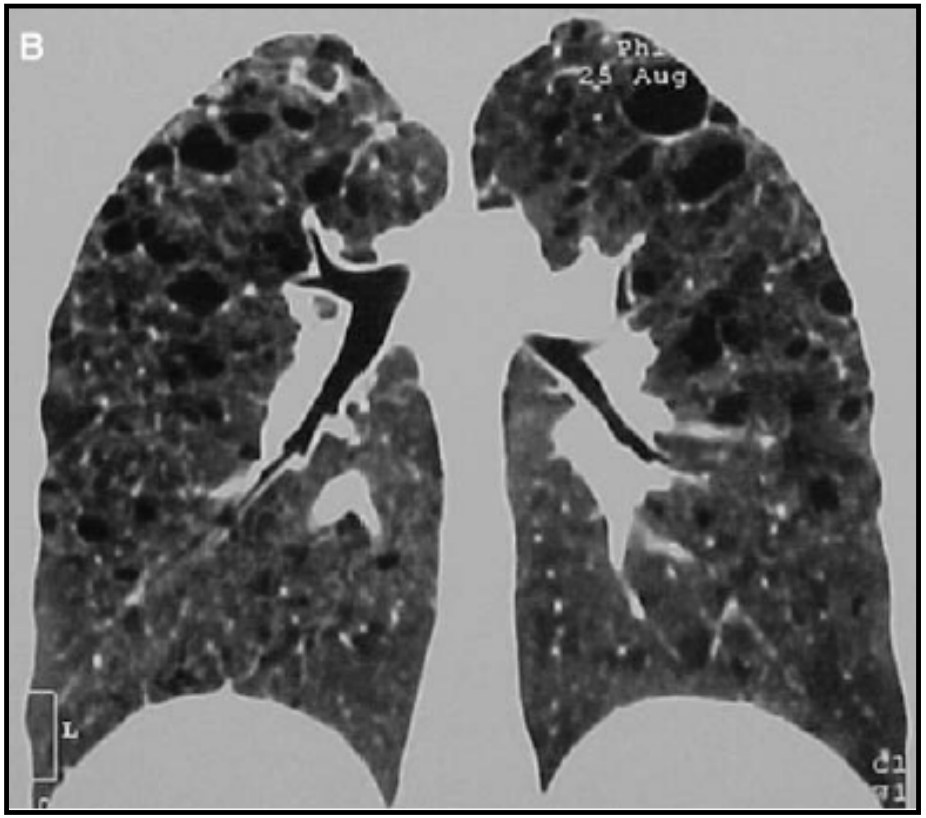
First Symptoms

Symptoms	Number of patients (40)
Exertional dyspnea	15
Cough	13
Pneumothorax	7
Diabetes Insipidus	2
Bone lesions	2
Hemoptysis	1
Skin lesions	1

Harari S. et al. Eur J Int Med 2015

PLCH - RADIOLOGYCAL FEATURES





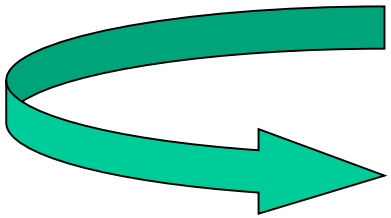
The combination of multiple cysts and nodules with a mid to upper zone predominance and sparing of lung bases in a young smoker is so characteristic that may be diagnostic

Harari et al. Proc Am Thorac Soc. 2006

DIAGNOSIS

- medical history
  clinical setting
  radiological features (HRCT)

- morphologic confirmation



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

Diagnosis Achievement

	Patients (40)
Clinical-radiological data	20
Search of CD1a+ cells in the bronchoalveolar lavage	10
Lung biopsy	8
Cystic bone lesions	2

Elia D. Eur J Int Med 2015

PLCH

CASES FROM 1997 TO 2008

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

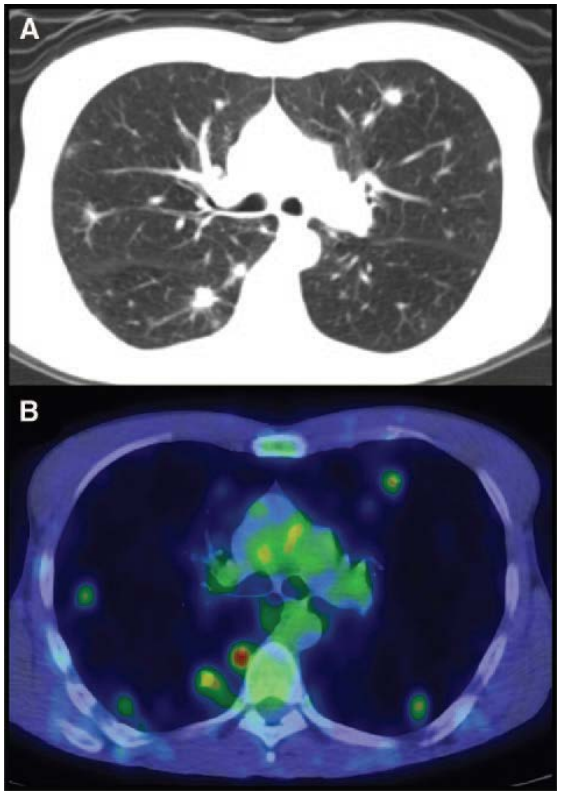
THE ROLE OF SURGICAL LUNG BIOPSY

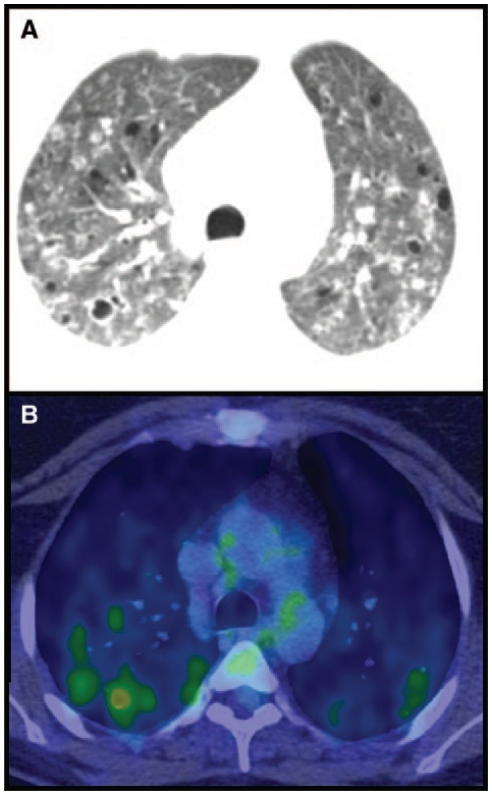
The decision to perform a surgical (VATS or open) lung biopsy depends on

- 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.

PLCH - Fluorodeoxyglucose PET





Krajicek, Chest 2009

PET scanning
- may be usefull in assess of disease activity
- may provide valuable information regarding extrapulmonary involvement
- may not contribute to the workup of suspected malignancy

PLCH needs to be considered in the differential diagnosis of PET scan-positive lung lesions.

PLCH - MANAGEMENT

Smoking cessation is mandatory !

- Resolution of the disease after smoking cessation has been reported

- Recurrence of disease has been reported in transplanted lungs of patients with PLCH upon resumption of smoking

- However, a few cases of recurrence despite smoking cessation have been observed

PLCH – MANAGEMENT
Steroids

- **No prospective or randomized trials.**

- **In retrospective case series and case reports, steroids have been reported to lead to improvement in symptoms and lung function . However none of these studies controlled for the effect of smoking cessation.**

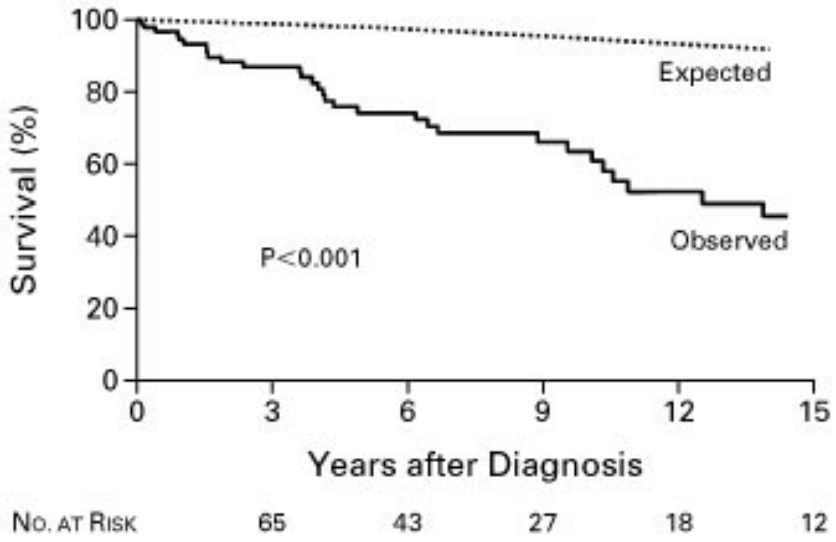
Friedman et al. Medicine 1981
Schonfeld N, et al. Respiration 1993

- **Patients with isolated pulmonary LCH who are symptomatic despite smoking cessation.**

- **If smoking cessation is not achieved, the chance of response to corticosteroid therapy is very small.**

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)

- Chemotherapeutic agents such as vinblastine, cyclophosphamide, chlorambucil, methotrexate, etoposide, and cladribine have been used in patients with progressive disease that is unresponsive to corticosteroids or in those with multiorgan involvement but none has clearly improved the course of the disease .

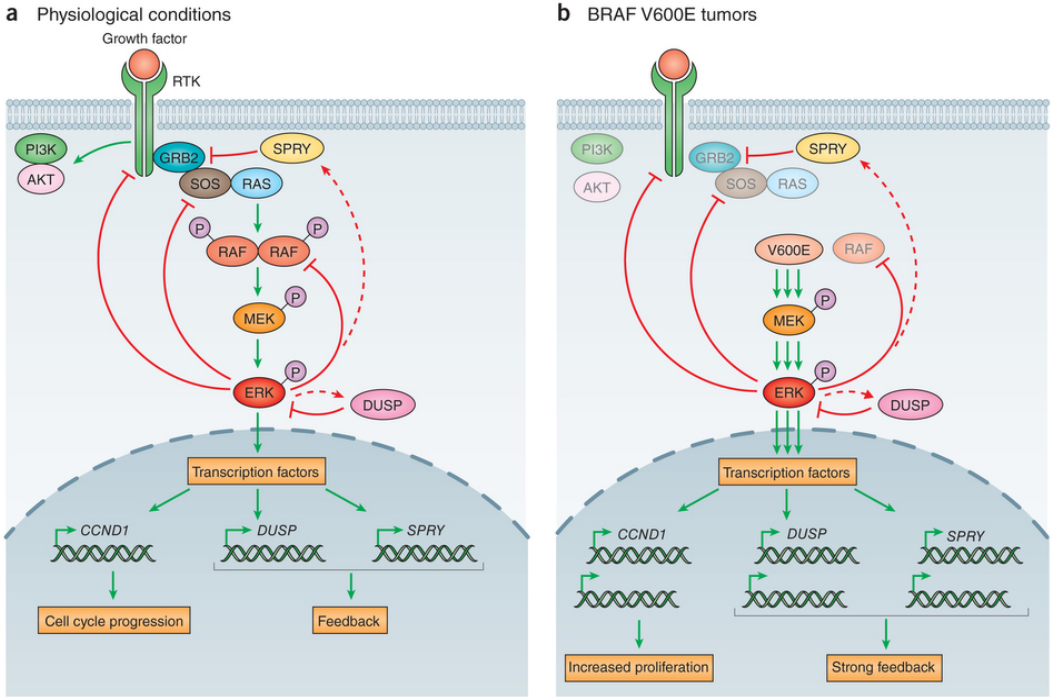
These drugs should be reserved as salvage therapy for patients with progressive disease that is unresponsive to both smoking cessation and a trial of corticosteroid therapy

- Pleurodesis may be needed in patients with recurrent pneumothoraces.

BRAF-V600E

BRAF-V600E mutation induces the activation of the proto-oncogene BRAF causing activation of the RAS-ERK pathway, independently of RAS activation.

The RAS-RAF-MEK-ERK pathway is a cellular signalling pathway, and is involved in various neoplastic diseases, such as melanoma and lymphoblastic leukemia.



Lito, Nature Medicine 2008

BRAF- V600E and PLCH

BRAF-V600E mutation has been described:

- in a 38 to 69% of LCH patients (Badalian-Very G Blood 2010, Satoh Pediatric Disease 2012, Sahm Blood 2012, Hervier Blood 2014)

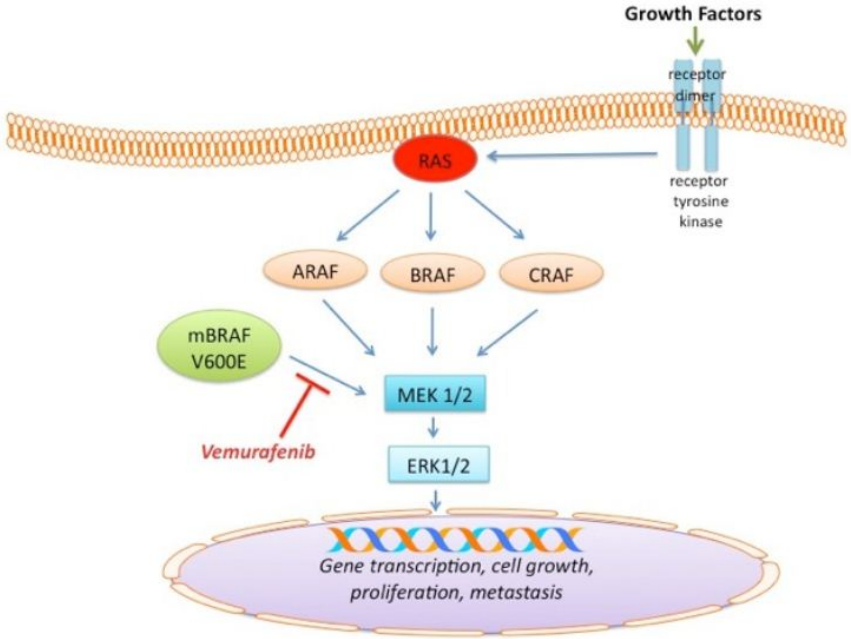
- in 7 of 25 (28%) of patient with PLCH (Rodean Am J Sur Pat 2014)

- in a 54% to 82% of patients with Erdheim Chester Disease (Haroche Blood 2012, Hervier Blood 2014).

  Erdheim-Chester disease (ECD) is a rare non-LC histiocytosis, characterized by the infiltration of tissues by foamy CD68 CD1a histiocytes. Rare cases of ECD associated with LC histiocytosis have been reported.

Vemurafenib

Vemurafenib is an inhibitor of mutant BRAF, and has some efficacy against both $BRAF^{V600E}$ associated melanoma and hairy-cell leukemia



Vemurafenib and histiocitosis

- In 3 patients with multisystemic and refractory ECD with the $BRAF^{V600E}$ mutation, 2 of whom had skin or lymph node LCH involvement the treatment with vemurafenib led to rapid clinical and biologic improvement just 1 month after treatment. (Haroche Blood 2013).

- Vemurafenib was given to 8 patients with multisystemic ECD, refractory to first-line treatment and harbored a $BRAF^{V600E}$ mutation. Four patients also had LCH lesions. All patients had an improvement of general symptoms and a persistent response to vemurafenib, with a median follow-up time of 10.5 months (range, 6 to 16 months). (Haroche JCO 2015).

- in patients with a central nervous system involvement an objective reduction of the lesions at the MRI was observed. Skin adverse effects were frequent and severe. (Haroche JCO 2014).

Future perspectives LCH

- The identification of activating mutations in BRAF-V600E in ~50%-60% of examined cases, has changed the definition from a disorder of immune regulation to a dendritic cell neoplasm with a strong inflammatory components

- Current international LCH trials are focused on further improving the outcome of high-risk multisystem LCH patients, by decreasing the reactivation rate, optimizing early salvage regimens, and preventing late sequelae.

- Although responses to vemurafenib, a BRAF-V600E inhibitor, have been reported in a few cases of LCH and ECD, the development of resistance, as well as the potential risks of cutaneous and pancreatic cancers in patients with BRAF-V600E-mutated melanoma treated with single inhibitors, suggest the need for prospective trials with BRAF inhibitors, alone or in combination with other inhibitors of this pathway, for patients with refractory or multiply-relapsed LCH

- Recent discovery of somatic mutations in ARAF and in MAP2K1, which lead to activation of the RAS-RAF-MEK -ERK pathway in the setting of wild-type BRAF, as well as the finding that activating mutation in MAP2K1 are relatively insensitive to MEK inhibitors, suggest that a more detailed understanding of this pathway in LCH may be necessary for the development of more effective targeted therapies

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

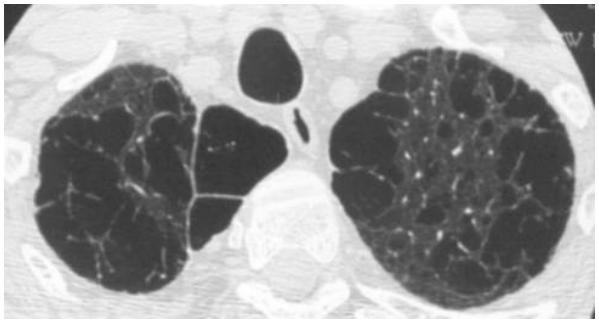
Relapsing pulmonary Langerhans cell histiocytosis after lung transplantation

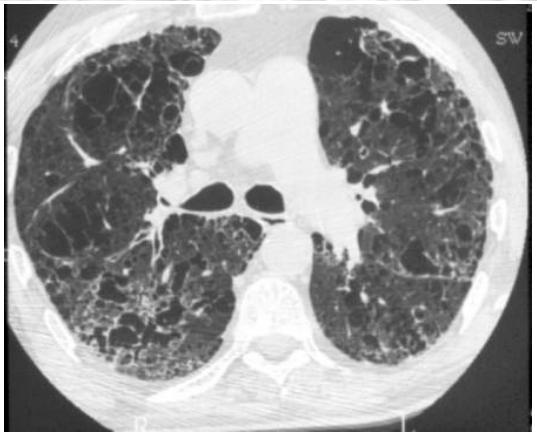
Etienne B.et coll. **Am J Respir Crit Care Med 1998 Jan;157(1):288-291**

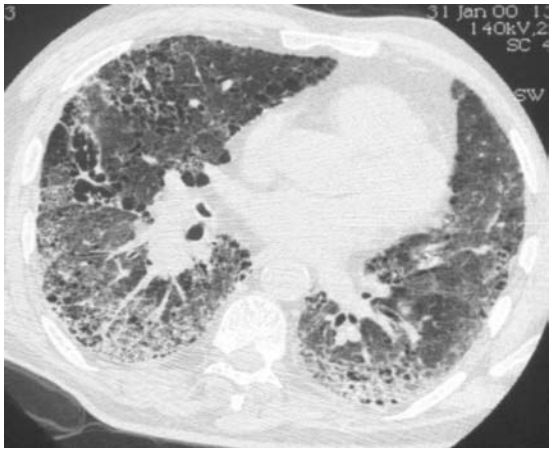
PLCH and NEOPLASMS

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

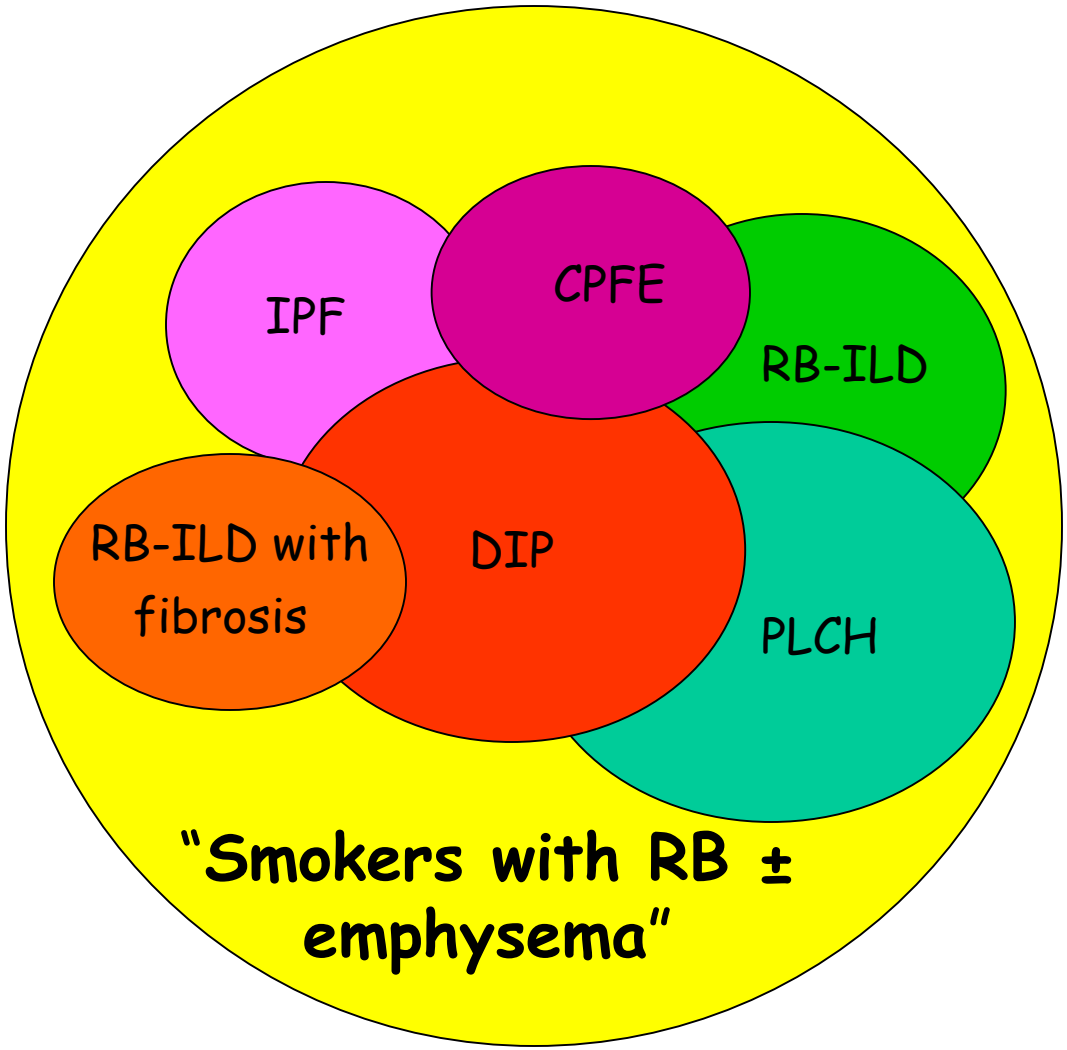
Cigarette smoking, prior treatment with chemotherapeutic agents, and chromosomal or genetic abnormalities are factors that may confer a predisposition to the development of malignant neoplasms in patients with pulmonary Langerhans'-cell histiocytosis.







- CPFE is a distinct *syndrome* with characteristic presentation (including very low diffusion capacity)
- It may be overlooked because of subnormal spirometry ; gas exchanges are severely altered
- Prognosis is related to frequent pulmonary hypertension, with poor prognosis ; lung cancer may be frequent
- Specificities of functional outcome (relevance of decline in FEV1 ?)
- Pathophysiology is challenging : common pathways involved in both emphysema and fibrosis ?



Smoking-related interstitial lung diseases

7TH INTERNATIONAL MEETING ON PULMONARY RARE DISEASES AND ORPHAN DRUGS

PROGRAM

MILANO – ITALY
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PALAZZO DELLE STELLINE

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