Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

Ospedale San Giuseppe
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PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

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Interstiziopatie fumo-correlate

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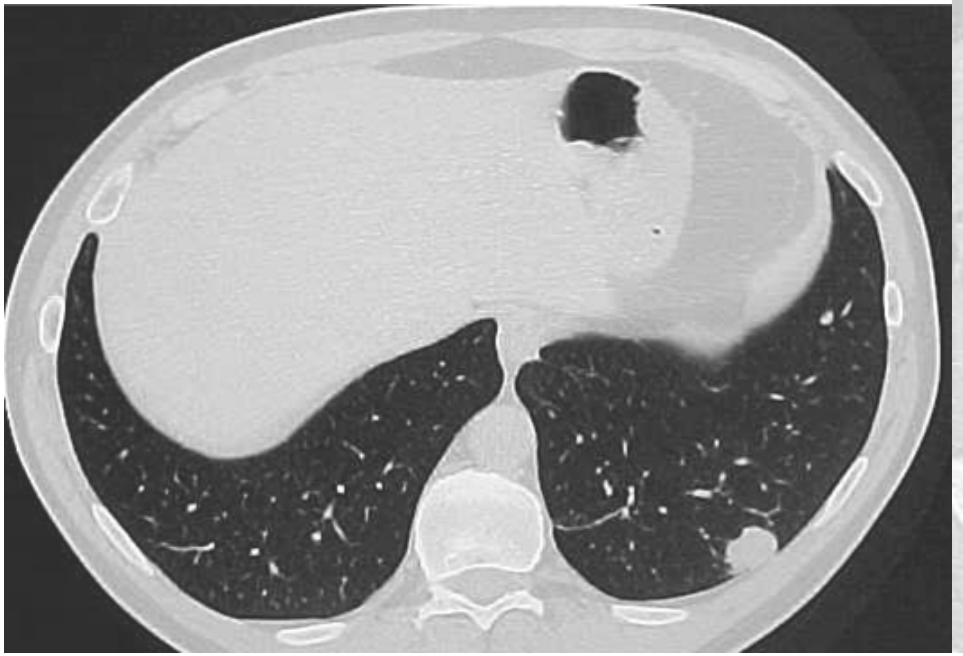
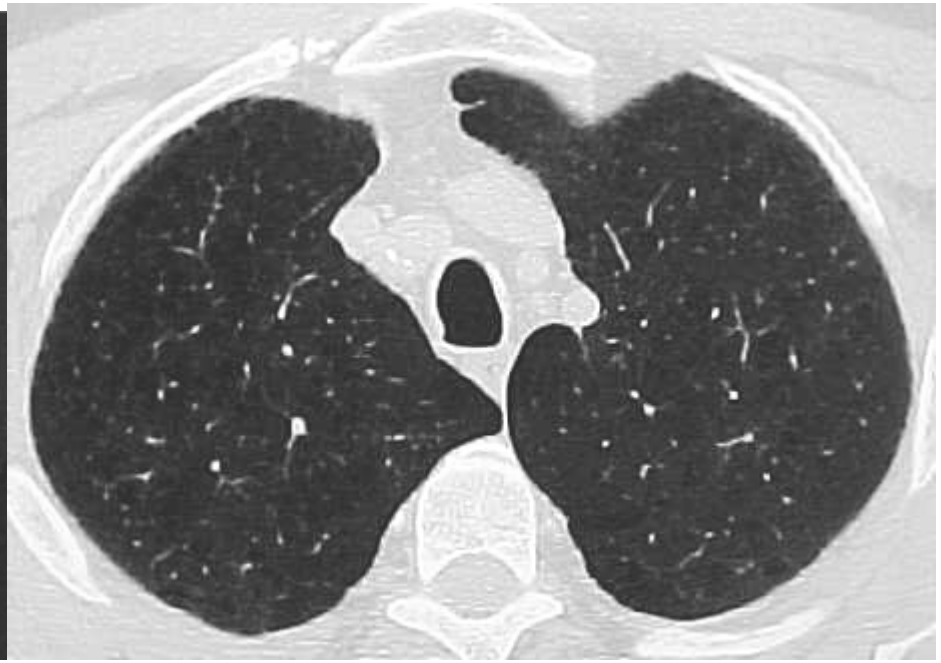
Cigarette smoking affects many organs and remains the most preventable cause of morbidity and premature death

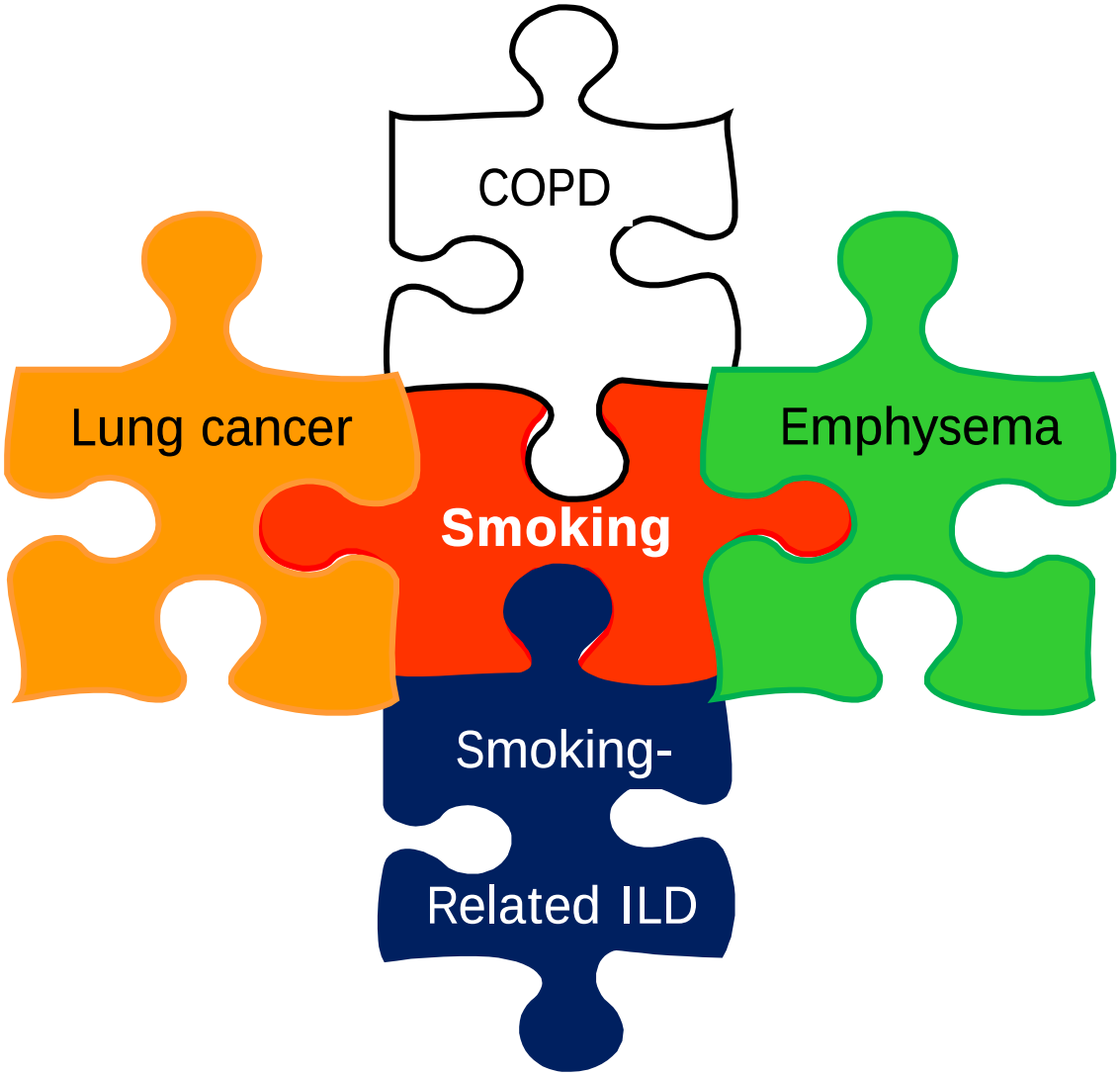
Smoking and lung

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





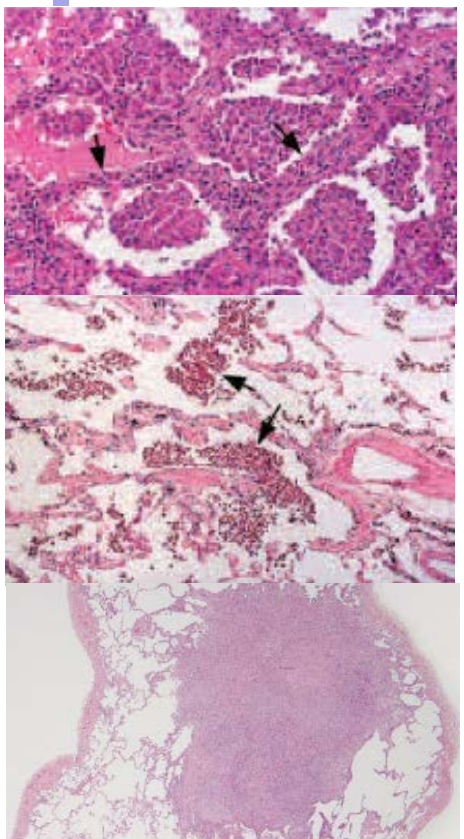
Recent Advances



Smoking-related interstitial lung diseases

1969 1974 1986 2000

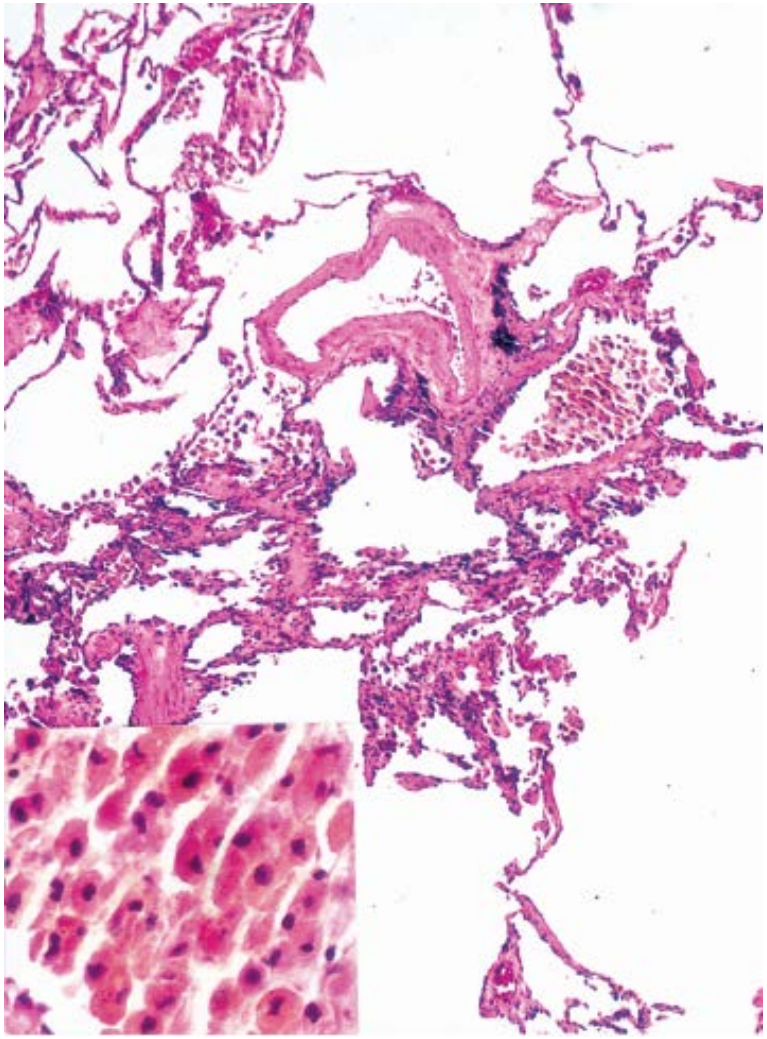
Liebow and Carrington Niewoehner Mayers



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

Respiratory Bronchiolitis

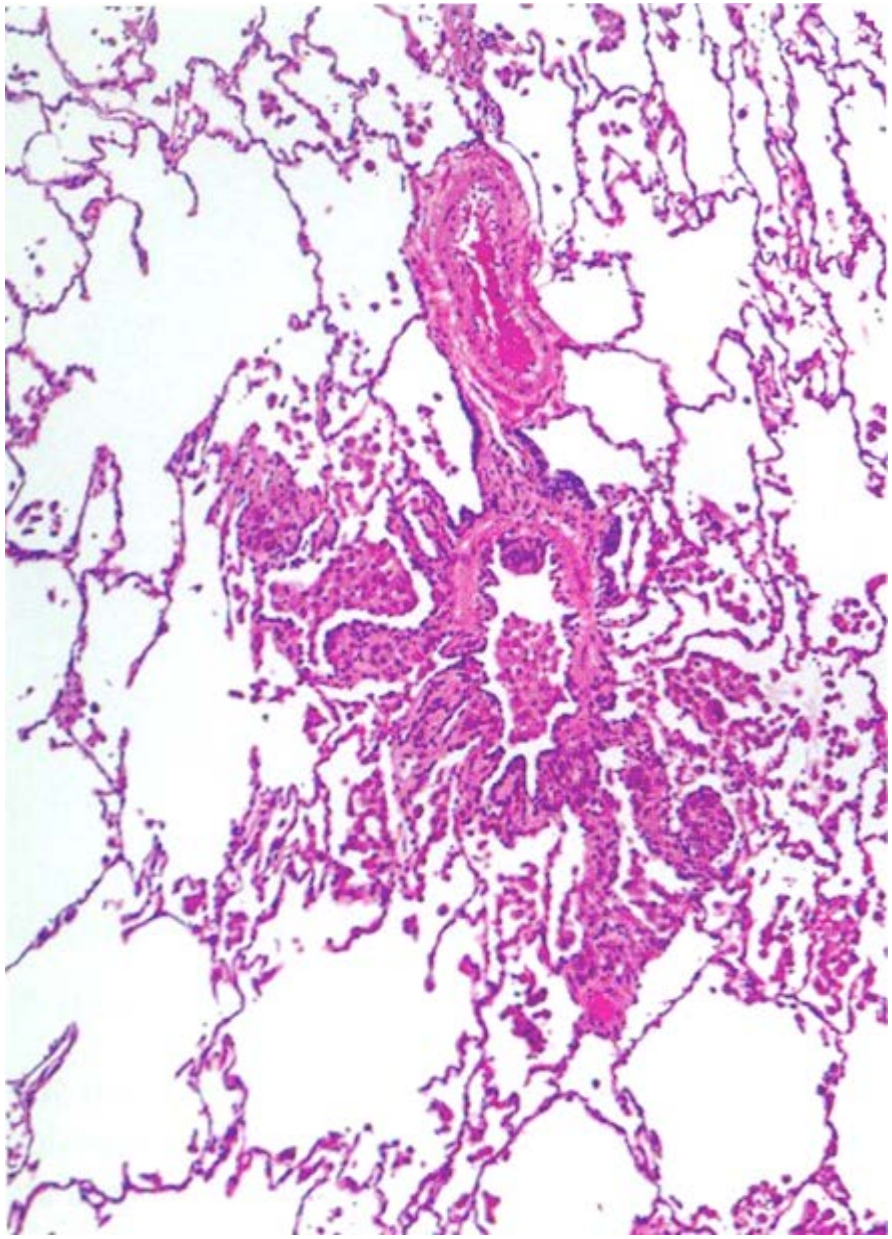
- presence of tan brown pigmented macrophages in respiratory bronchioles spilling into neighbouring alveoli
- Strictly peribronchiolar alveolar septal thickening characteristically radiating in a stellate fashion from the bronchiole

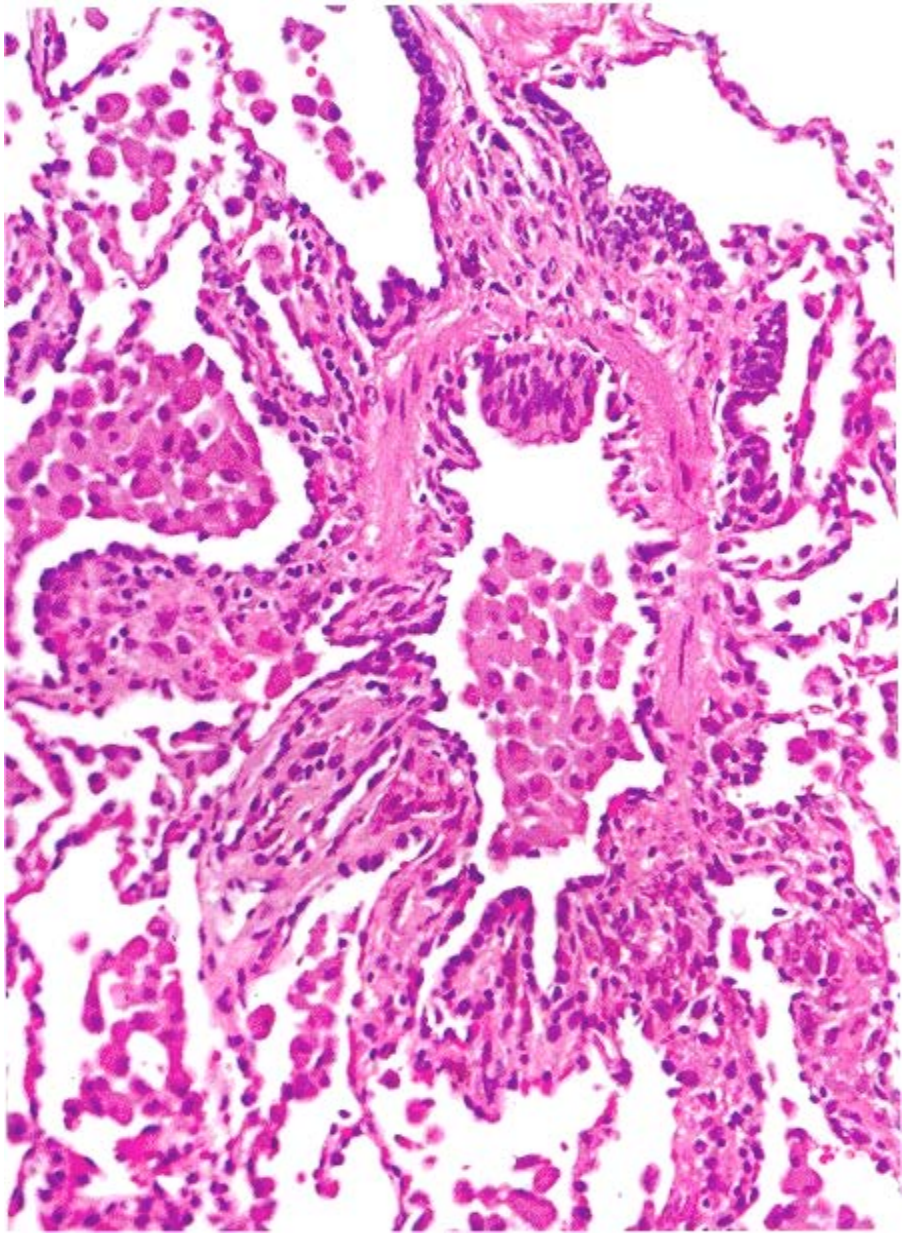


Fraig M et al. ***Am J Surg Pathol 2002; 26: 647–653***

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

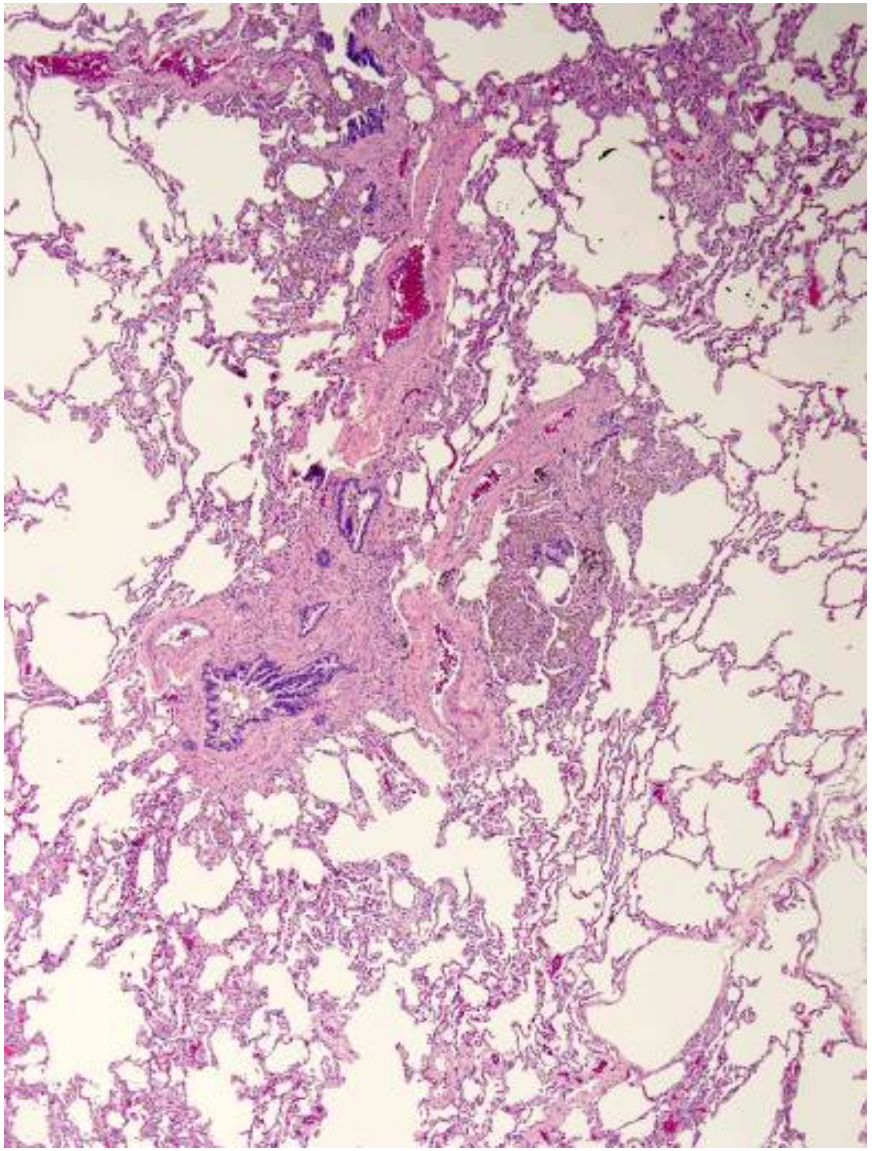




From Travis et al. Non-neoplastic disorders of the lower respiratory tract

RB-ILD

- All smokers
- Symptomatic
- Restrictive PFT’s
- Centrilobular nodules
- Ground glass
- Good diagnosis



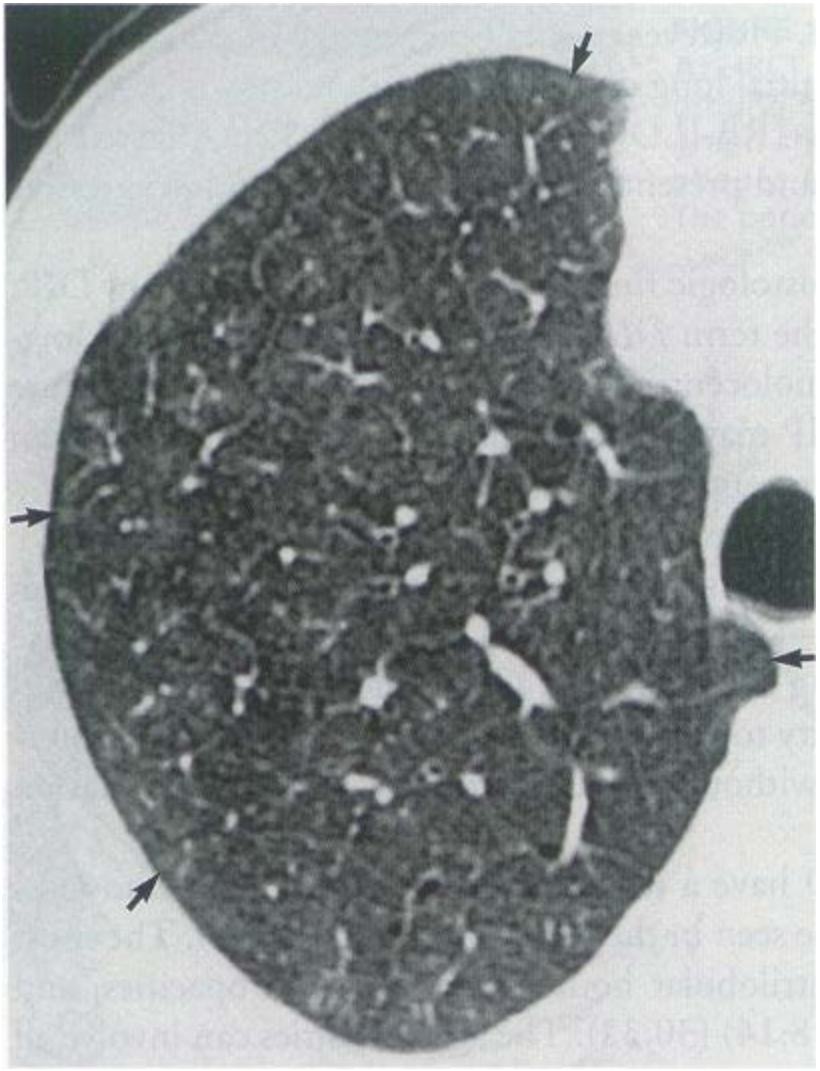
Clinical features

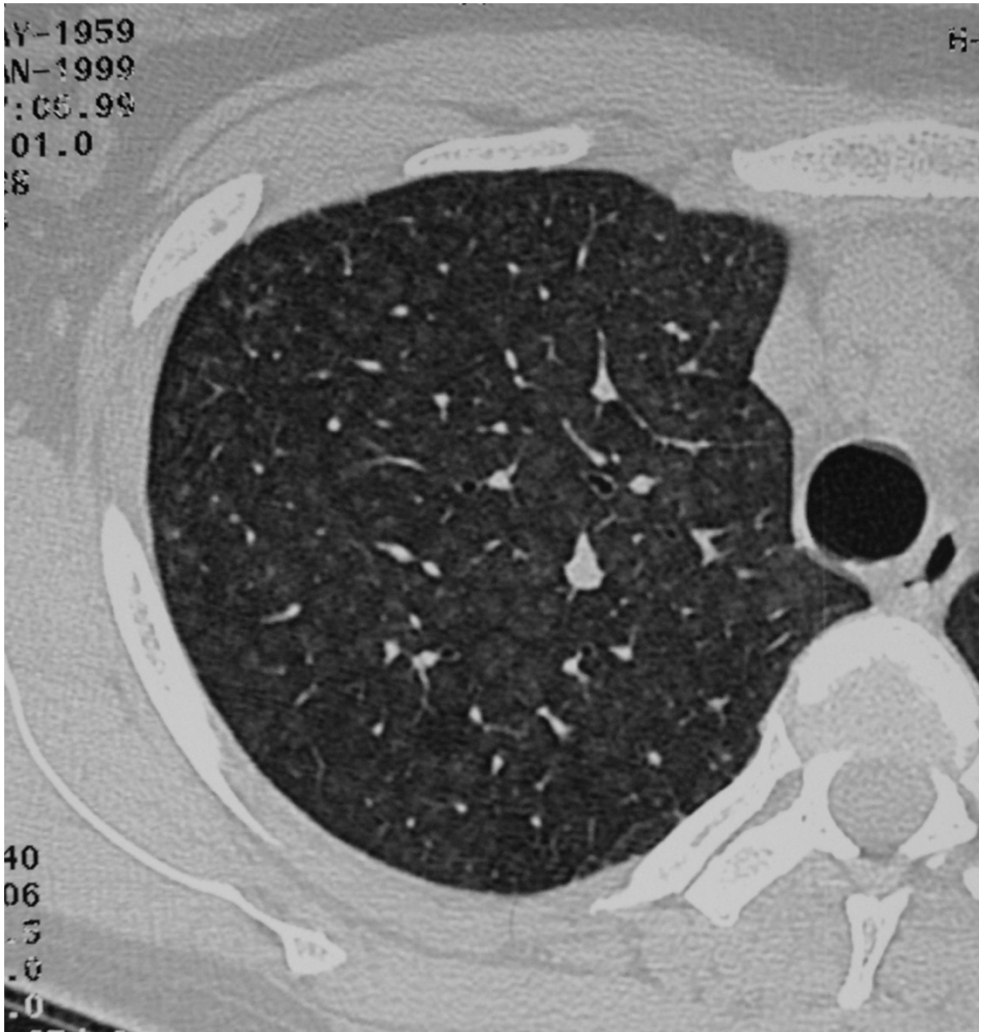
- Current smokers in the fourth and fifth decades of life
- Mild symptoms
- Gradual onset of dyspnea and hypoxemia, cough
- Many patients improve after cessation of smoking
- Progression to dense pulmonary fibrosis has not been reported

Radiology - HRCT

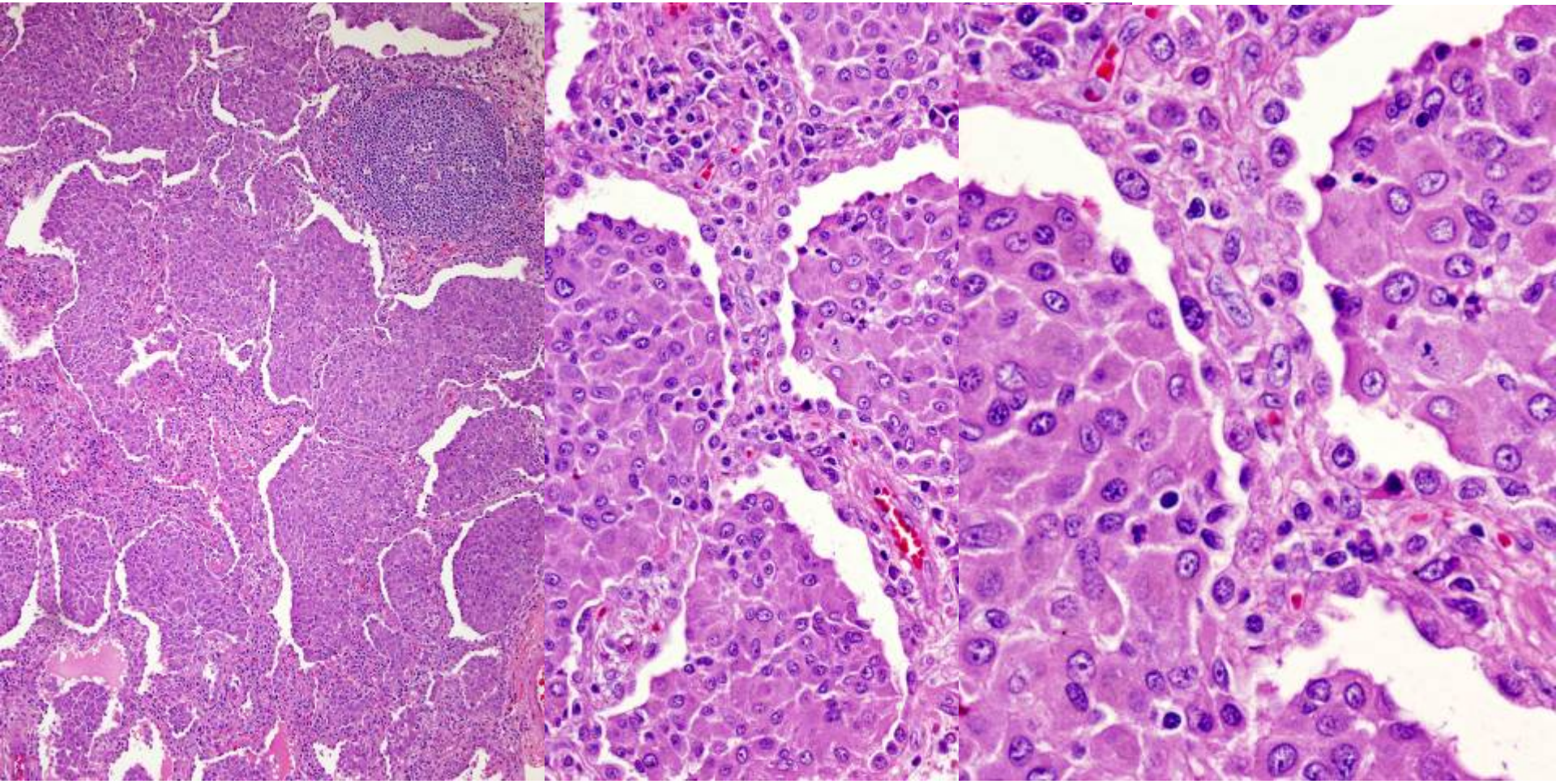
- Centrilobular nodules
- Patchy ground-glass
- Thickening of the walls of central and periferal airways
- Patchy areas of hypoattenuation due to air-trapping

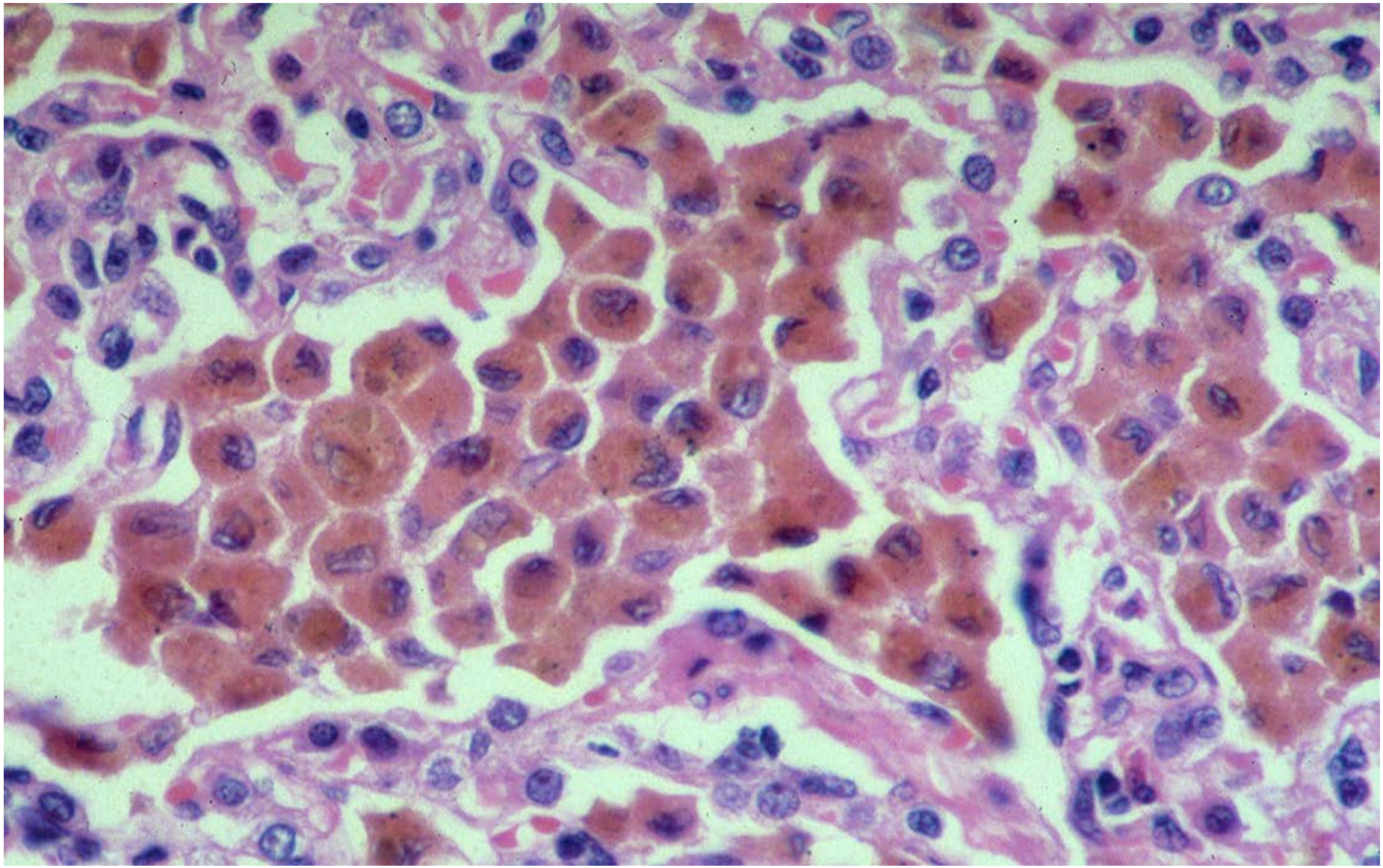
Radiology





DIP





DIP

- 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

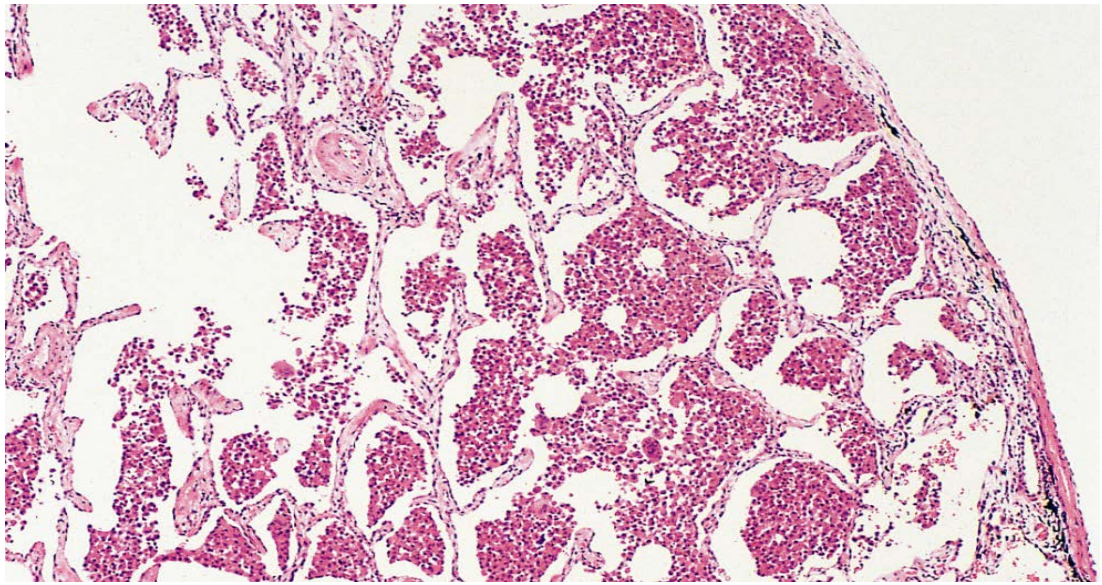
- Affects primarily cigarette smokers in their fourth or fifth decades of life
- Insidious onset of dyspnea and dry cough
- Digital clubbing develops in about half
- May progress to respiratory failure
- Normal lung volumes or a mild restrictive abnormality; DLCO is moderately decreased

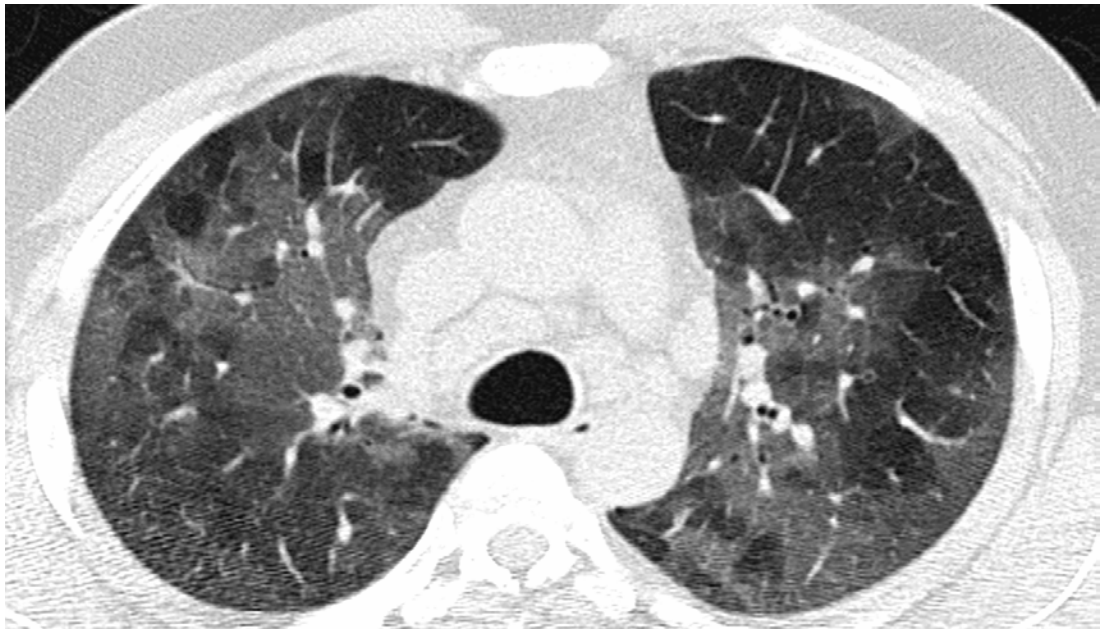
Radiology

- 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

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% after 10 yr

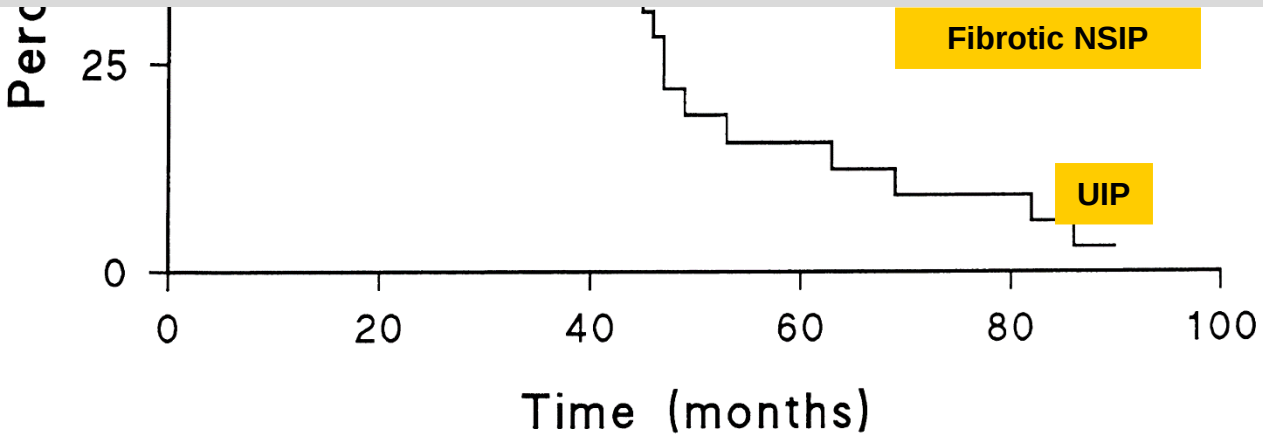
Survival in IIP

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)

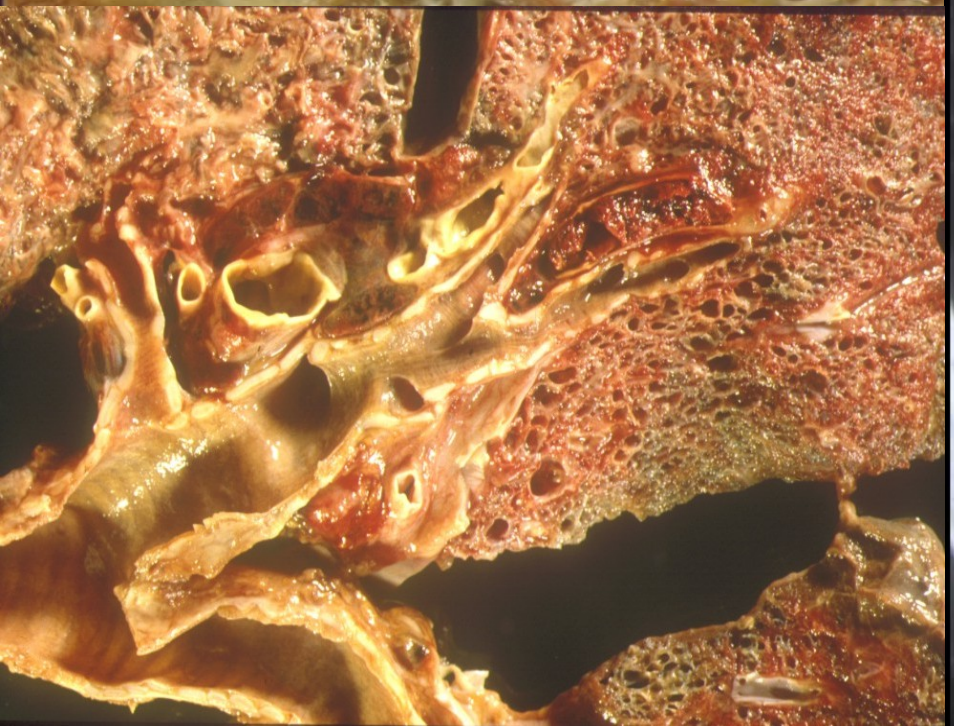
- There is some evidence to suggest that smoking cessation may suffice as the initial therapeutic maneuver for patients with RB-ILD
- It remains unclear whether corticosteroid therapy favorably alters the natural history of DIP and RB-ILD, particularly since the effect of smoking status on the clinical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

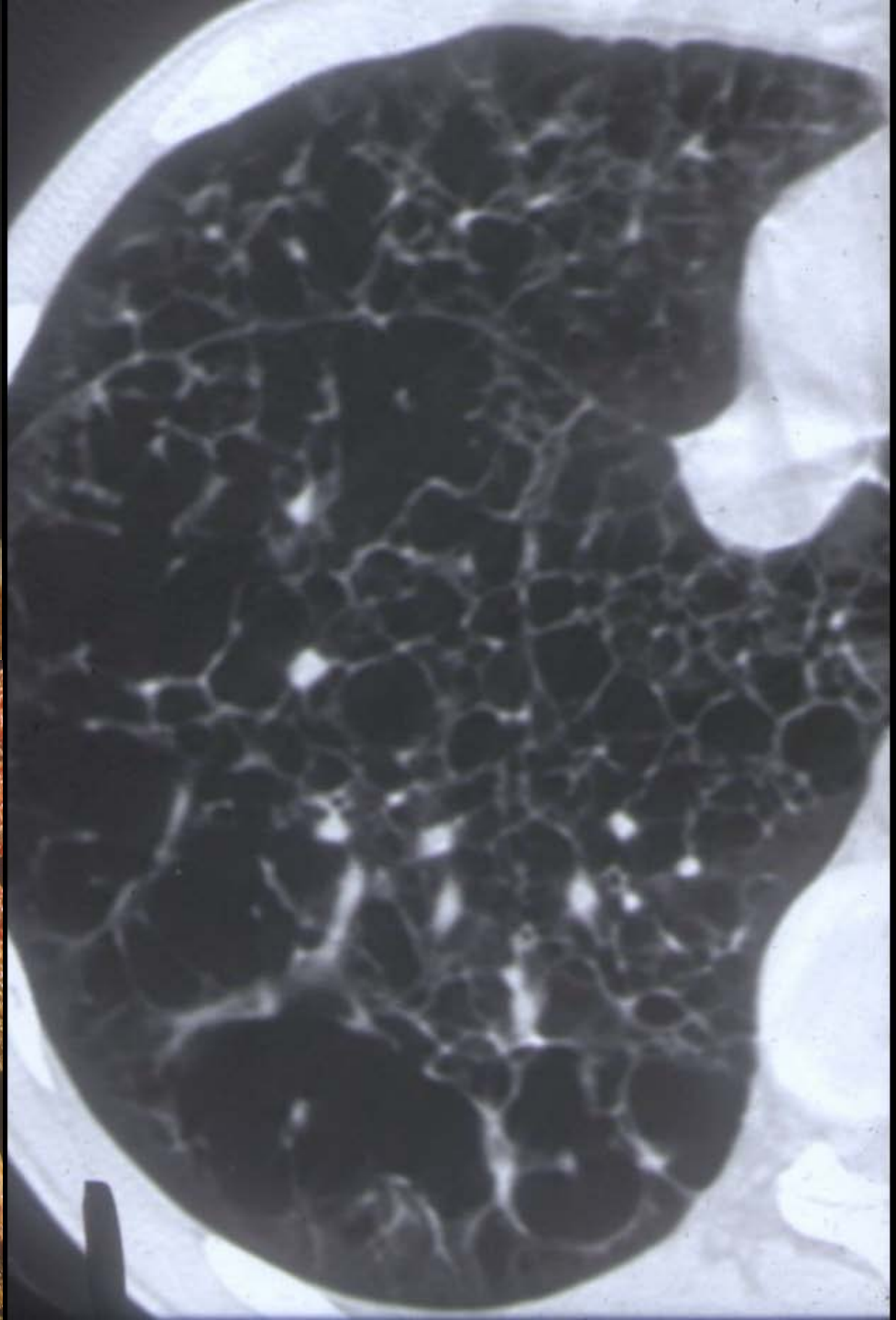
DIP/RB-ILD therapy: Available evidence

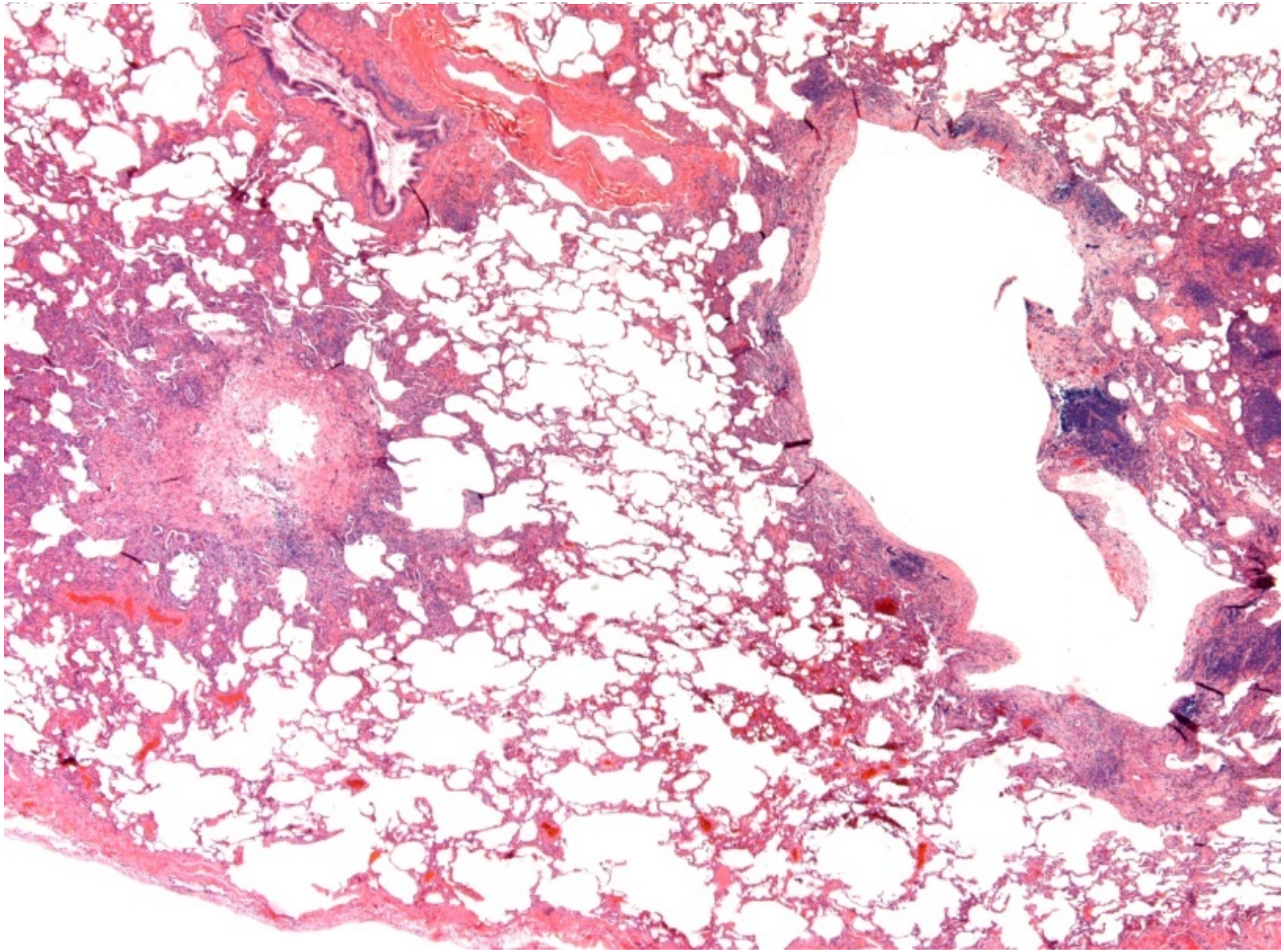
- *No published RCTs or CCTs.*
- Good empiric evidence for an effect of smoking cessation.
- Empiric evidence for a transient positive effect of corticosteroids.

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

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







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

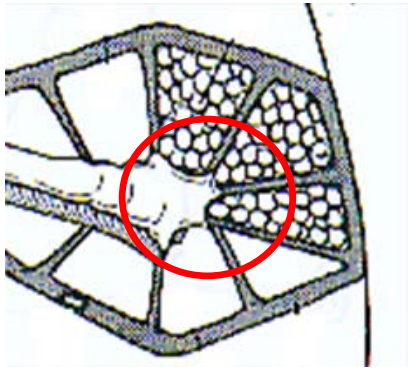
A similar proportion of males and females, or even a slight predominance of females, was observed

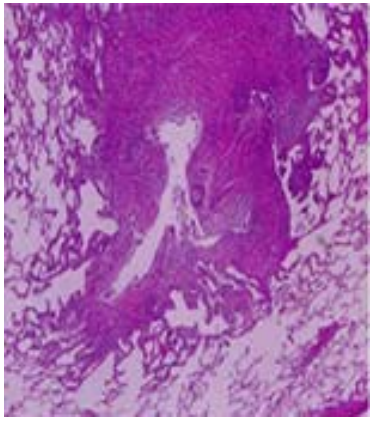
Pulmonary function at diagnosis

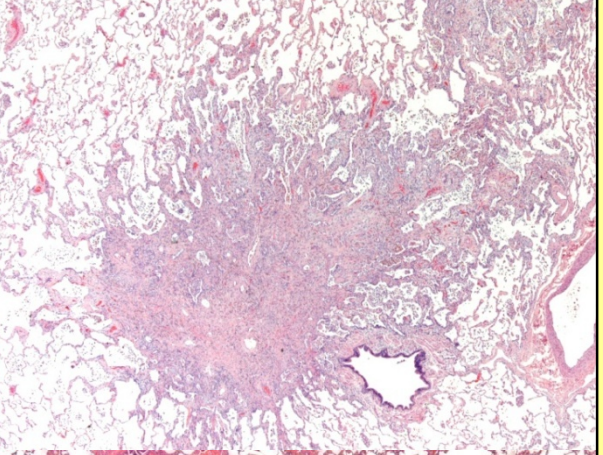
		Normal	Obstructive	Restrictive	Mixed	Reduction in *D*LCO
Schonfeld	1993	-	ES 27% / LS 71%	ES 19% / LS 29%	-	ES 84% / LS 100%
Travis	1993	26%	28%	23%	23%	59%
Watanabe	2001	77%	9%	24%	-	45%
Westerlan	2002	57%	43%	-	-	57%
Vassallo	2002	14%	27 %	46 %	5%	
Harari	2015	43%	43%	10,5%	3,5%	78%

ES= early stage; LS = late stage

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

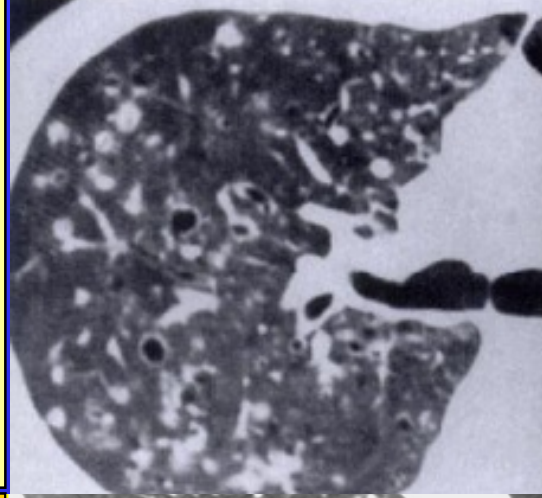


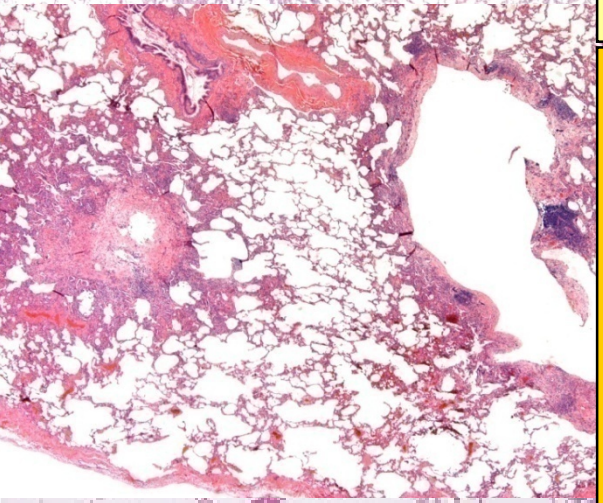




➢ *Early stage:*

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

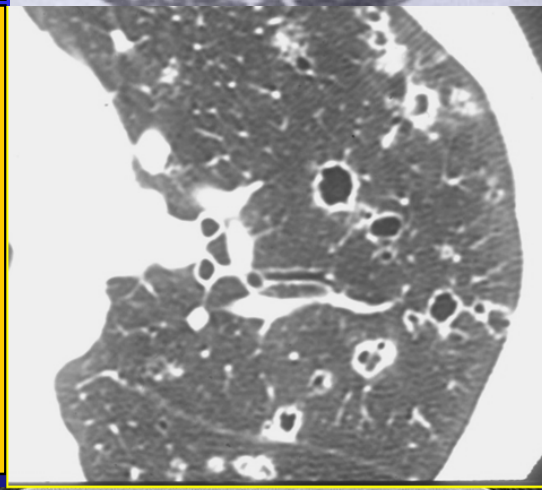


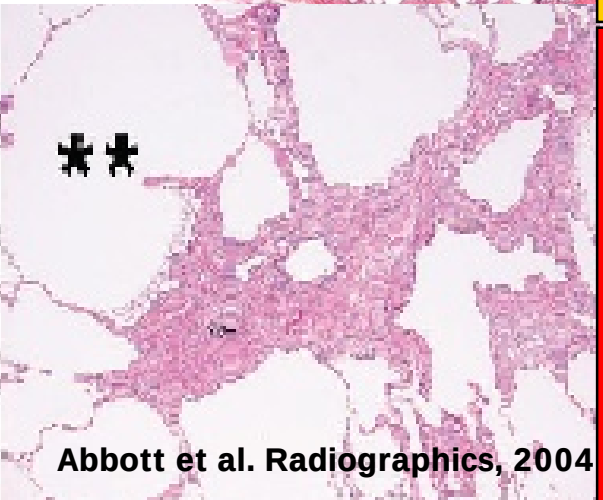


➢ *Disease progression:*

Increasing numbers of nodules and **cavitary nodules**

Appearance of **fibrotic scars**

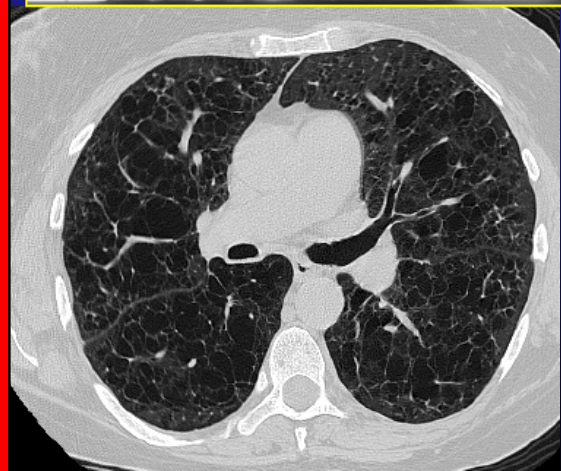




Abbott et al. Radiographics, 2004

➢ *End stage:*

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



First Symptoms

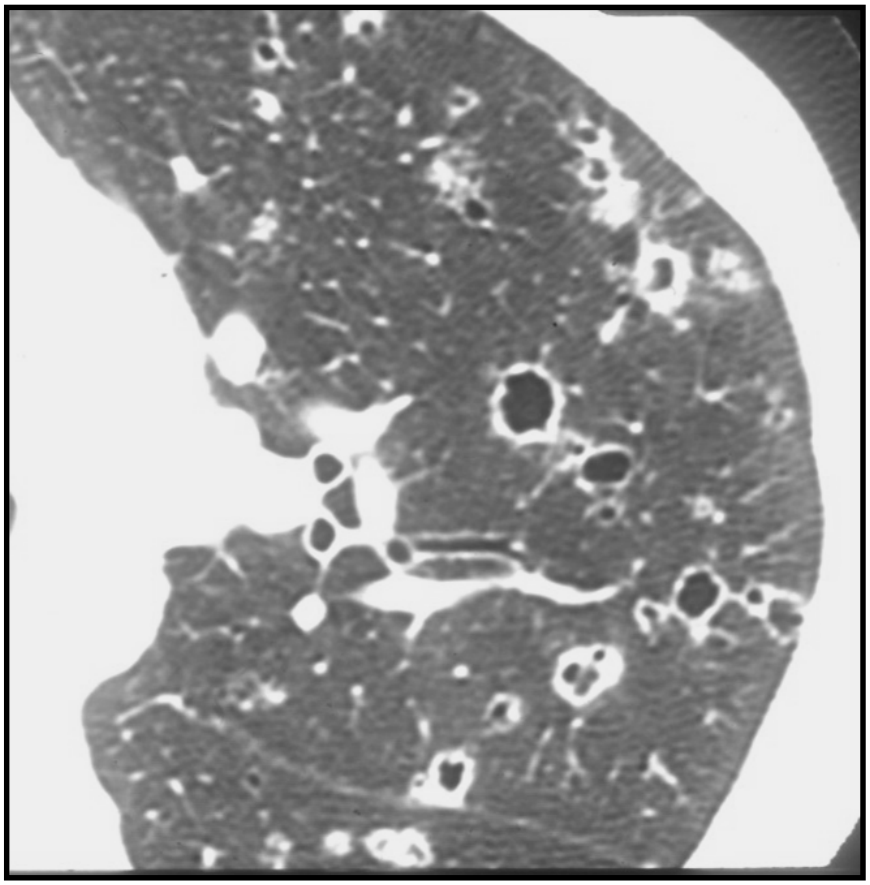
Symptoms	Number of patients (40)
Exertional dyspnea	15
Cough	13
Pneumothorax	7
Diabetes Insipidus	2
Bone lesions	2
Hemoptysis	1
Skin lesions	1

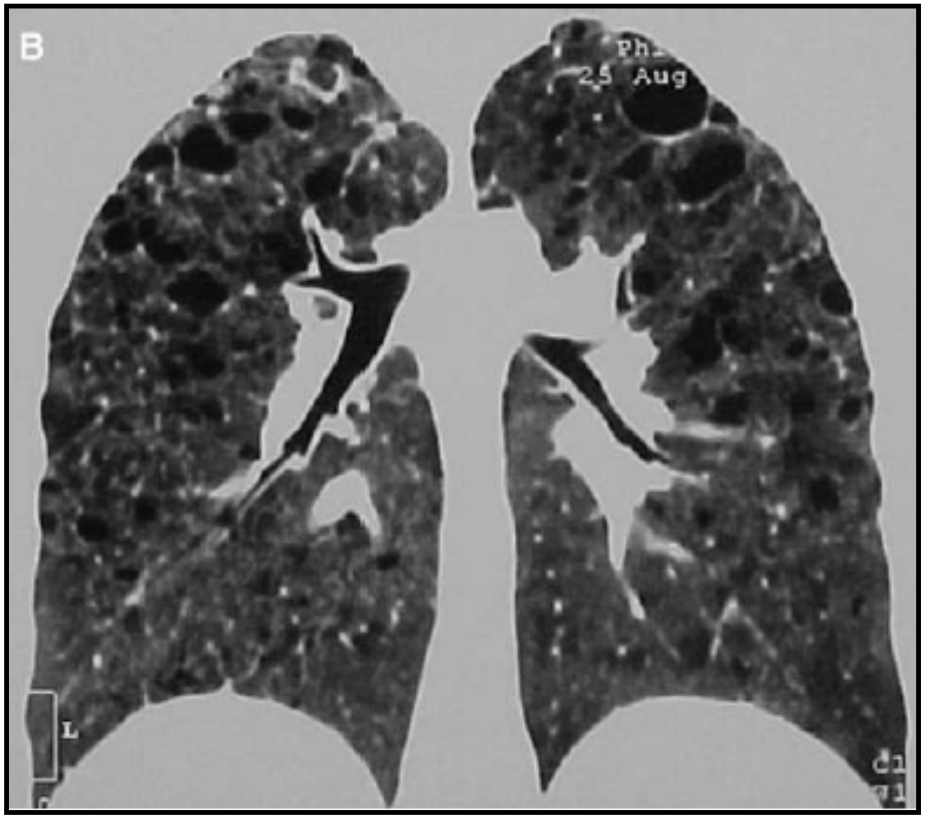
Diagnosis Achievement

	Patients (40)
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 Int Med 2015

PLCH – Radiological 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*

PLCH

Case 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

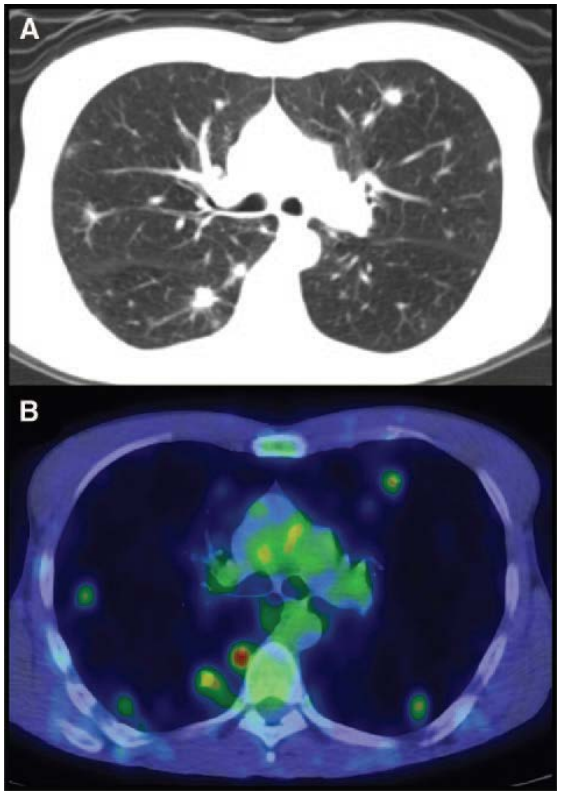
The role of surgical lung biopsy

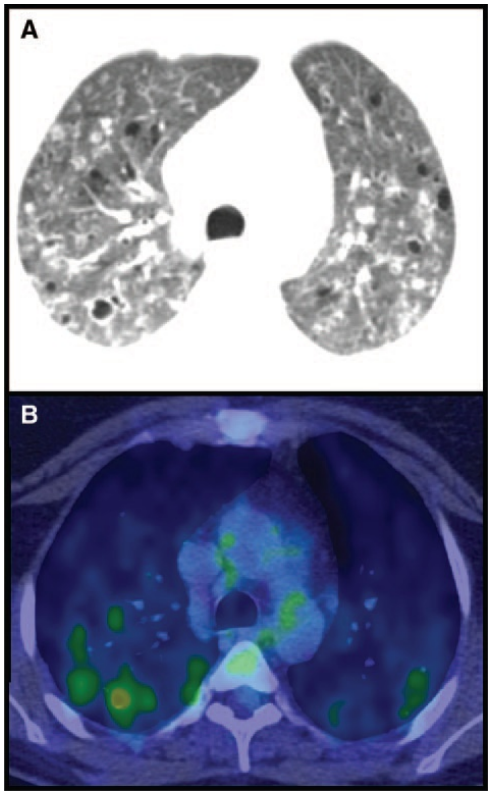
The decision to perform a surgical (VATS or open) lung biopsy depends on

- 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.

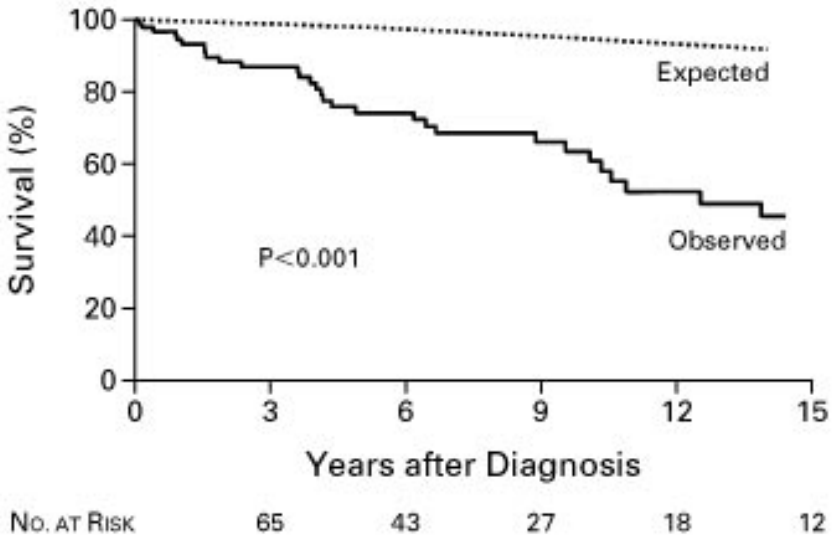
Friedman et al. Medicine 1981
Schonfeld N, et al. Respiration 1993

- 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.

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

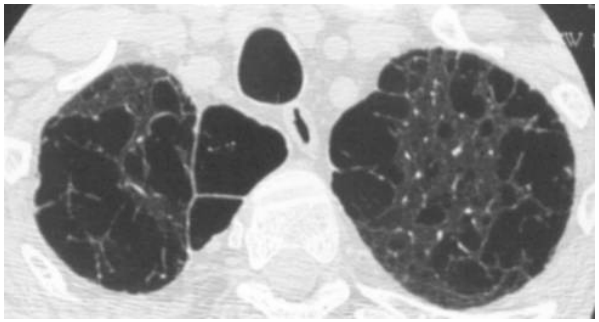
PLCH and neoplasm

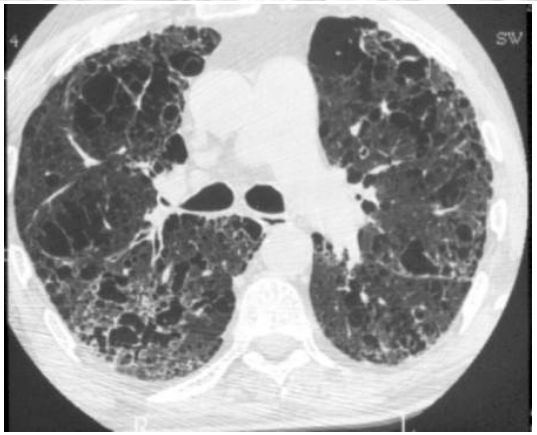
The association between PLCH and a variety of neoplasms (lymphoma, multiple myeloma, adenocarcinoma of the lung, and other solid tumors) has been reported by several authors

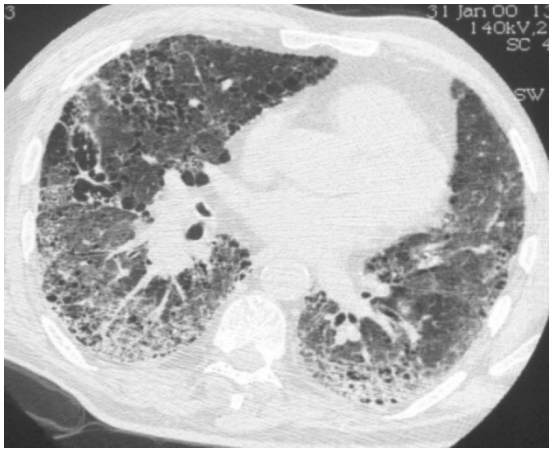
Cigarette smoking, prior treatment with chemotherapeutic agents, and chromosomal or genetic abnormalities are factors that may confer a predisposition to the development of malignant neoplasms in patients with pulmonary Langerhans'-cell histiocytosis.

Relapsing pulmonary Langerhans cell histiocytosis after lung transplantation

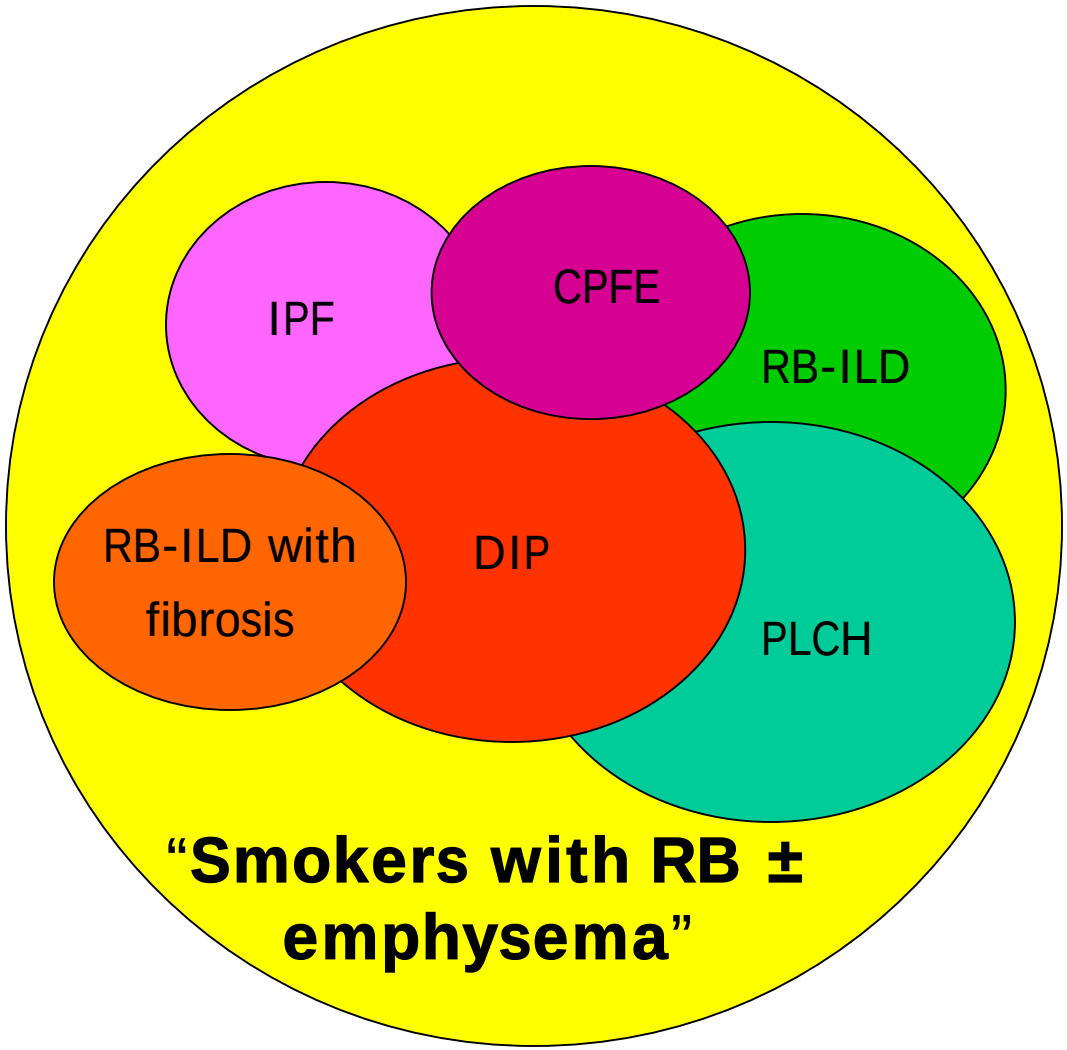
Etienne B.et coll. **Am J Respir Crit Care Med 1998 Jan;157(1):288-291**







- 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