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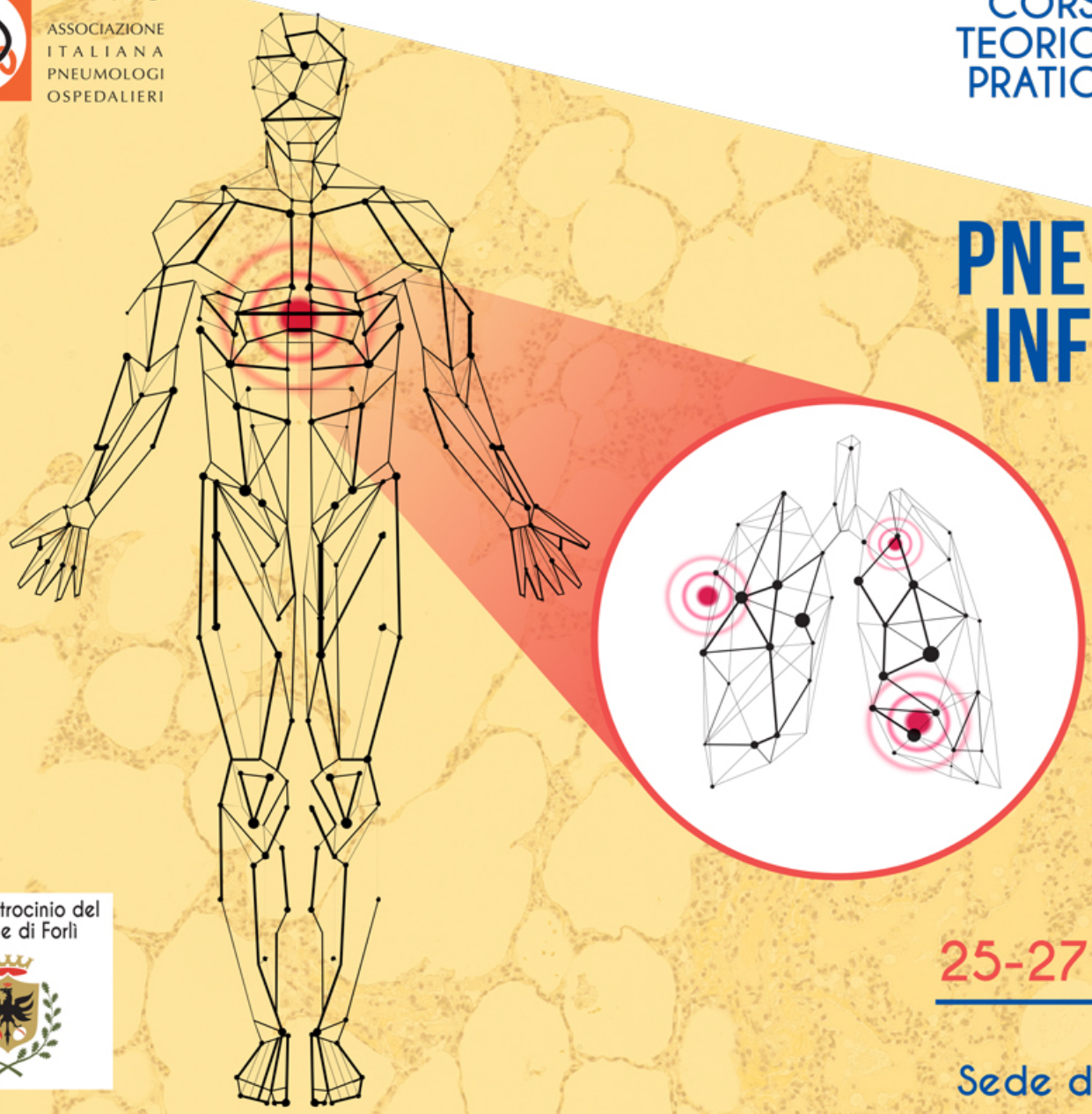
ASSOCIAZIONE ITALIANA PNEUMOLOGI OSPEDALIERI

CORSO TEORICO PRATICO

PID

PNEUMOPATIE INFILTRATIVE DIFFUSE



Con il Patrocinio del Comune di Forlì

FORLÌ

25-27 Giugno 2019

Sala Randi
Sede del Comune di Forlì

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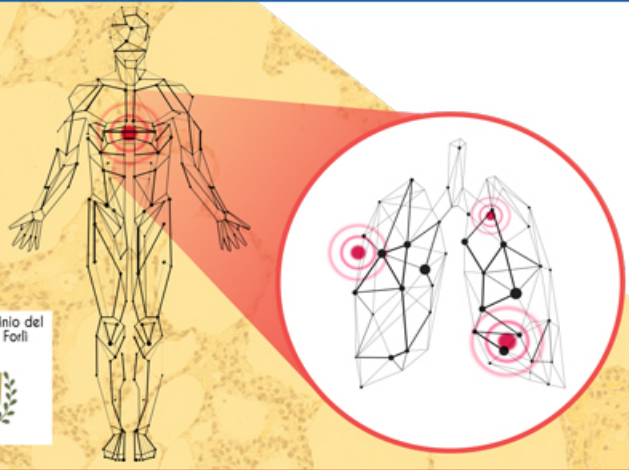


CORSO TEORICO PRATICO
PID
PNEUMOPATIE INFILTRATIVE DIFFUSE

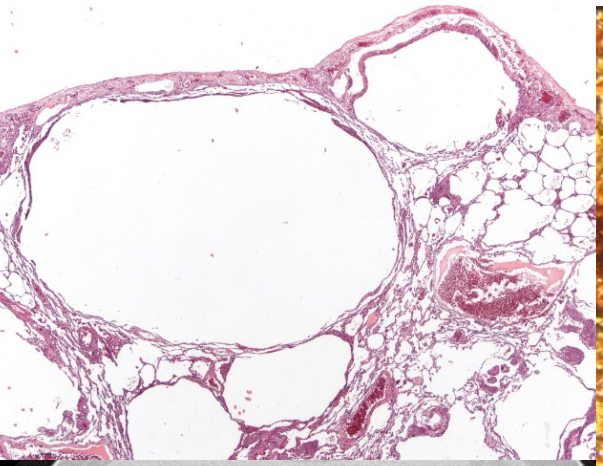
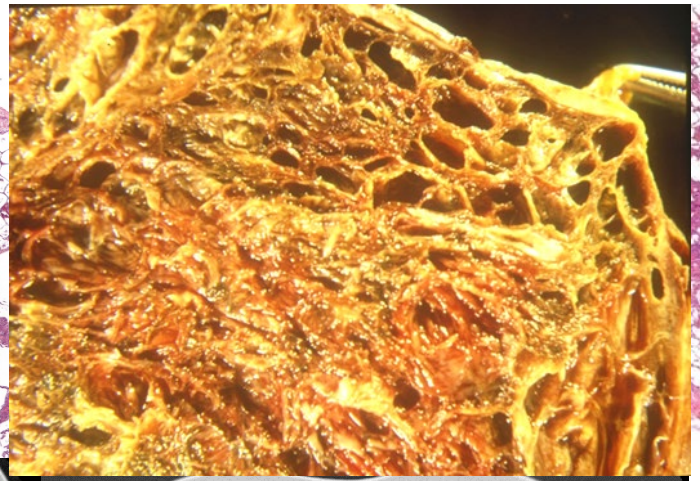
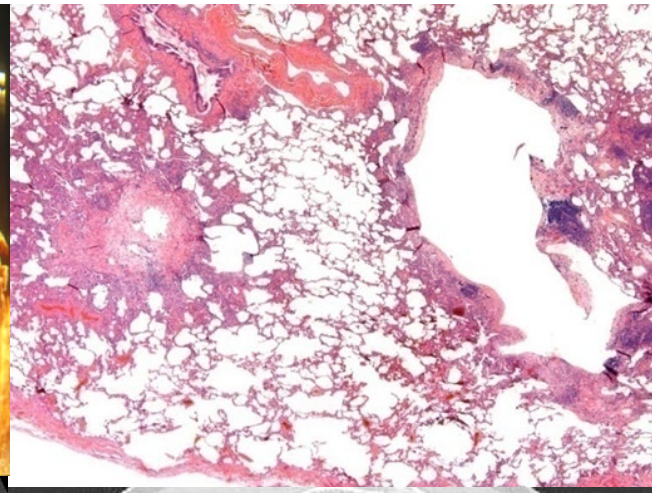
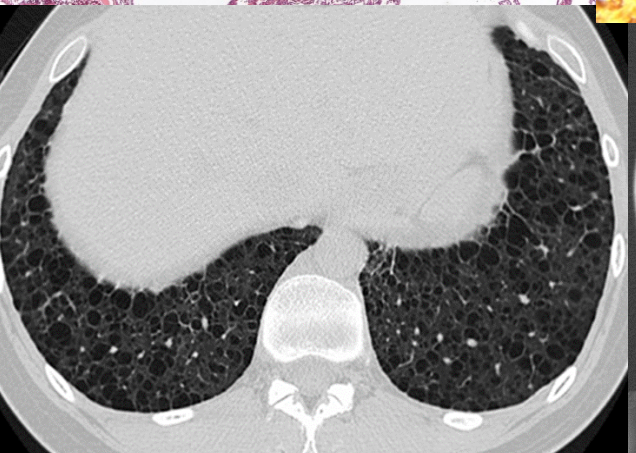
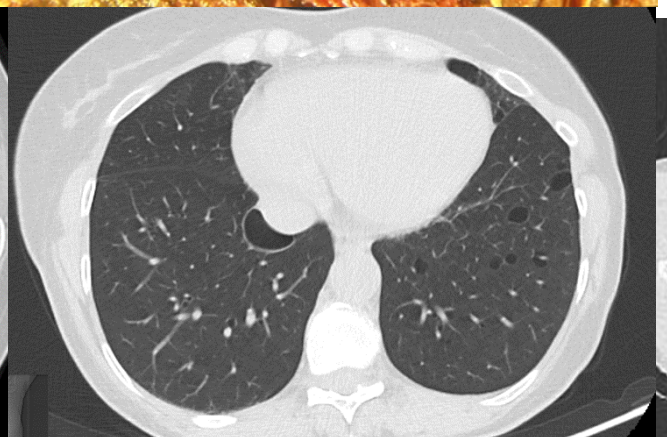
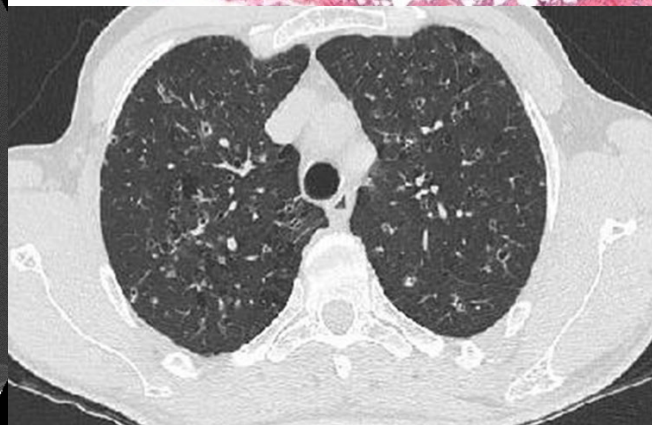
Altre malattie cistiche polmonari

Sergio Harari

U.O. di Pneumologia e UTIR, Servizio di Emodinamica e Fisiopatologia Respiratoria, Ospedale San Giuseppe - Milano

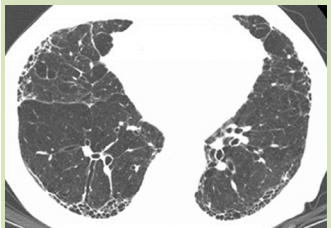
Diffuse Cystic Lung Diseases

Diffuse cystic lung diseases are characterized by cysts in more than one lung lobe, the cysts usually being bilateral.

Classification of DCLDs

Gupta N et al, AJRCCM 2015

1. *Neoplastic*	Lymphangioleiomyomatosis Pulmonary Langerhans cell histiocytosis, and non-Langerhans cell histiocytoses Other primary and metastatic neoplasms such as sarcomas, adenocarcinomas, pleuropulmonary blastoma, etc.
2. Genetic Developmental Congenital	Birt-Hogg-Dubé syndrome Proteus syndrome, neurofibromatosis, Ehlers-Danlos syndrome Congenital pulmonary airway malformation, bronchopulmonary dysplasia,etc.
3. *Associated with lympho – proliferative disorders*	Lymphocytic interstitial pneumonia Follicular bronchiolitis Sjögren syndrome Amyloidosis Light chain deposition disease
4. *Infectious*	Pneumocystis jiroveci Staphylococcal pneumonia Recurrent respiratory papillomatosis Endemic fungal diseases Paragonimiasis
5. *Associated with interstitial lung diseases*	Hypersensitivity pneumonitis Desquamative interstitial pneumonia
6. *Smoking related*	Pulmonary Langerhans cell histiocytosis Desquamative interstitial pneumonia
7. *Other/ Miscellaneous*	Post-traumatic pseudocysts Fire-eater's lung Hyper IgE syndrome
8. *DCLD mimics* 	Emphysema Alpha-one antitrypsin deficiency Bronchiectasis Honeycombing seen in late stage scarring interstitial lung diseases

LANGERHANS CELL HISTIOCYTOSIS

It is a rare histiocytic disorder of unknown origin, characterized by organ infiltration with specialised myeloid cells that share morphological and surface receptors markers with epidermal LCs.

It may affect patients of different ages, but it is most common in children from 1 to 3 years old.

Lung may be involved as a single organ, typically in young smoker adults with equal gender distribution (Pulmonary Langerhans cell histiocytosis, PLCH) or, less frequently, in the systemic form of LCH .

CLINICAL FORMS OF LCH

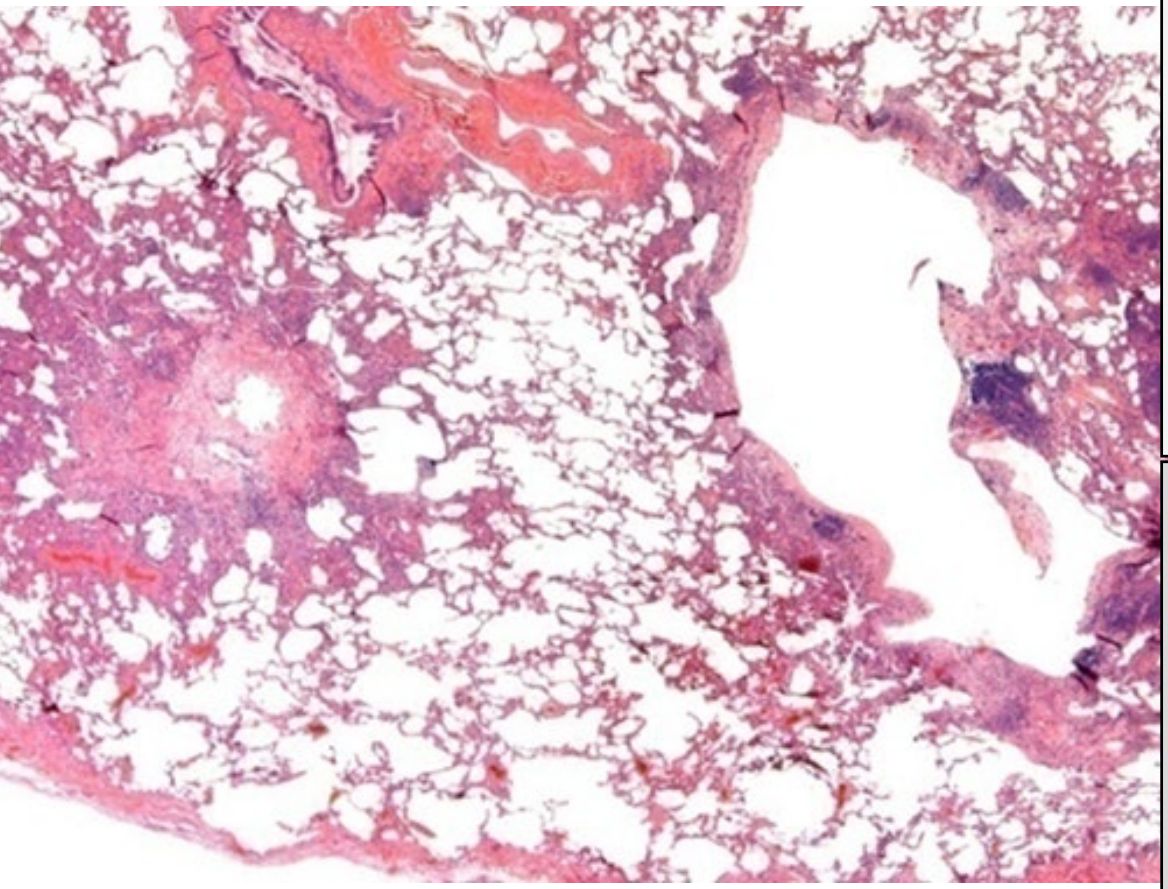
- Localized: affecting one organ (often bone, skin and lung) characterized by a good prognosis with an occasional spontaneous resolution.

- Systemic: involvement of more than one organ or tissue (bone, skin, hypothalamic-pituitary system, lymph nodes, lungs, and more rarely central nervous system).

- An involvement of the so-called risk organs, such as liver, spleen and haematopoietic system, is associate to a worse prognosis.

Emilie JF *et al*. *Blood* 2016, 127: 2673-2681.

PLCH - pathologic findings



- ***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

KEY ELEMENTS ABOUT THE PATHOGENESIS of PLCH

1) the reactive vs neoplastic nature of the disease;

2) the mechanisms of accumulation of large numbers of CD1a+ cell in bronchiolocentric loosely-formed granulomas;

3) the capacity of these granulomatous lesions to destroy and remodel surrounding tissues;

4) the role of smoking in adult PLCH.

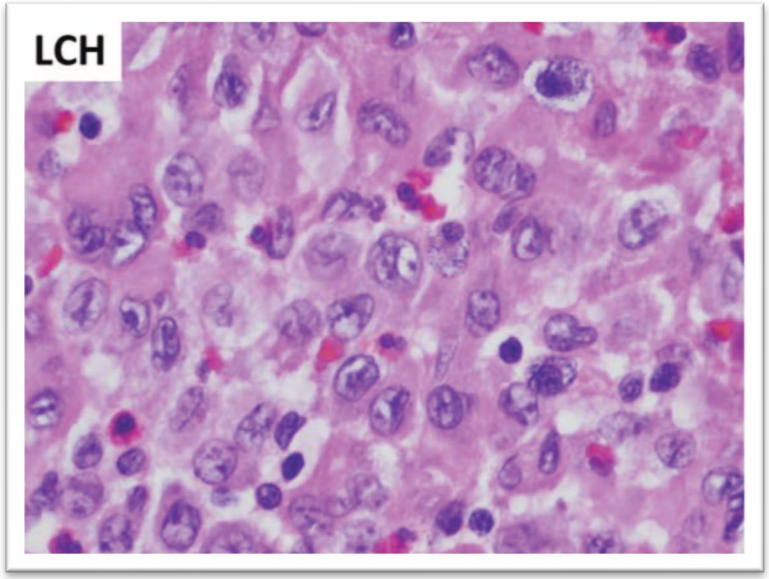
Is it a reactive disease?

This hypothesis is supported by:

- the finding of the presence of CD1a+/CD207+ histiocytes among an inflammatory background including variable numbers of lymphocytes, eosinophils, and macrophage.

- the absence of pathological features like mitotic figures and of recurrent cytogenetic abnormality in the CD1a+ cells of these lesions.

- the frequent spontaneous resolution after the smoking cessation as well as the detection of substantial infiltrating immune cells in PLCH granulomas



Brabencova E *et al*. *Am J Pathol* 1998;152:1143-1149

Is it a neoplastic disease?

The occasionally aggressive nature of the disease and the efficacy of the chemotherapy in severe systemic forms of PLCH favoured a neoplastic mechanism.

Discordant results concerning the clonal nature of CD1a+ cells in different forms of LCH. In any case clonality in immune cells does not necessarily imply malignancy

Willman CL N Eng J Med 1994; Youseman SA Am J Surg Pathol 2001

Identification of recurrent genetic abnormalities involving cellular proliferative pathways in lesional CD1a+ cells obtained from systemic LCH and PLCH provided a strong argument to support the neoplastic hypothesis

Badelian-Very G. Blood 2010
Roden AC Am J Surg Pathol 2014

A major breakthrough supporting this hypothesis came with discovery of recurrent somatic proto-oncogen ***BRAF-V600E*** mutations in histiocytes of LCH lesions

Evidence of clonality in PLCH: *BRAF* mutations

Pulmonary Langerhans Cell Histiocytosis

Profiling of Multifocal Tumors Using Next-Generation Sequencing Identifies Concordant Occurrence of *BRAF* V600E Mutations

Samuel A. Yousem, MD, FCCP; Sanja Dacic, MD, PhD; Yuri E. Nikiforov, MD, PhD; and Marina Nikiforova, MD

Identical BRAF V600E mutation was identified in seven nodules from two cases In other cases distinct nodules lacked any mutation, including *BRAF*

Yousem SA et al, Chest 2013

ORIGINAL ARTICLE

BRAF V600E Expression in Langerhans Cell Histiocytosis

Clinical and Immunohistochemical Study on 25 Pulmonary and 54 Extrapulmonary Cases

28% of PLCH cases were positive for BRAF V600E expression

Roden AC et al, Am J Surg Pathol 2014

B-Raf is part of the intracellular Ras-Raf/MAPK signaling pathway that is responsible for several cell functions

(cell proliferation, differentiation, migration, and senescence/apoptosis)

Mutations in PLCH

- BRAF mutations have been identified in up to 67% of cases of PLCH

- Identical but mutually exclusive MAPK/ ERK pathway mutations (BRAF, MAP2K1) were found supporting a neoplastic/clonal origin

Chilosi M et al, Leuk Lymphoma 2014
Kamionek M et al, Histopathology 2016

- NRAS mutations have been found

BRAF and NRAS mutations can be present in different areas within the same lung lesion supporting a polyclonal nature of LCs

Mourah S et al, ERJ 2016

PLCH: a neoplastic or reactive condition ?

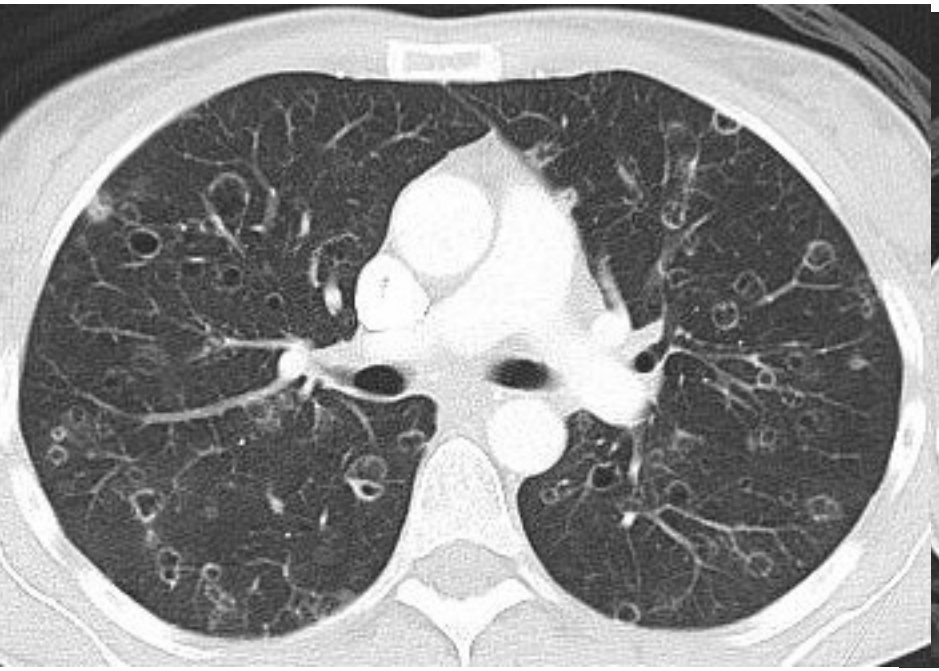
At least a proportion of PLCH is a cigarette smoke induced or promoted dendritic cell neoplasm that is associated with a prominent immune-inflammatory component

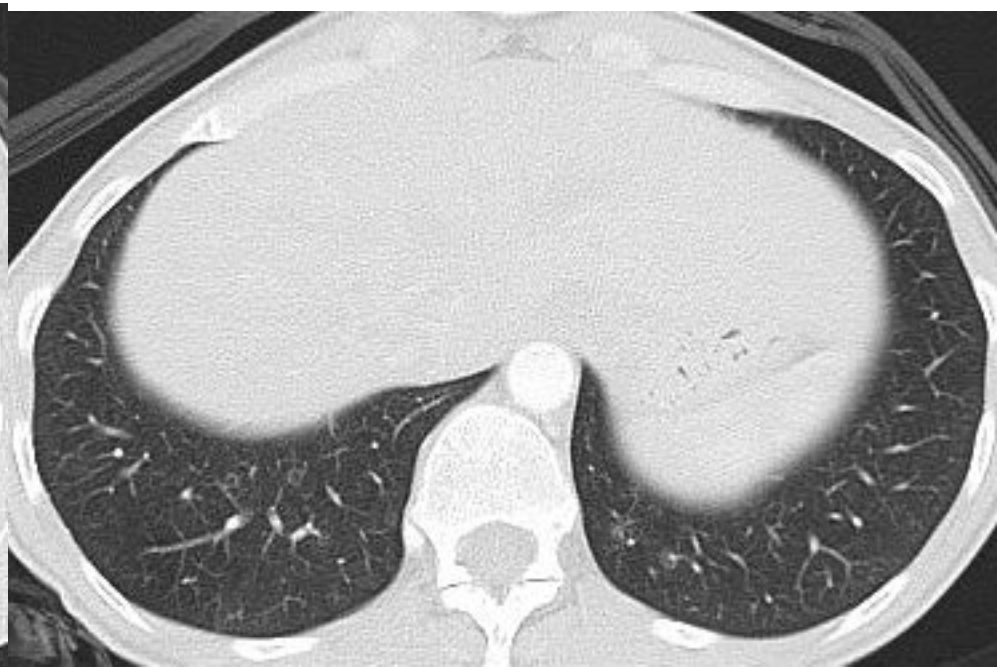
Gupta N et al, AJRCCM 2015

Role of smoking

- Smoking induces accumulation of CD1a+ cells in the lungs
- Smoking stimulates local production of cytokines and osteopontin, which play a role in the recruitment, differentiation and activation of dendritic cells

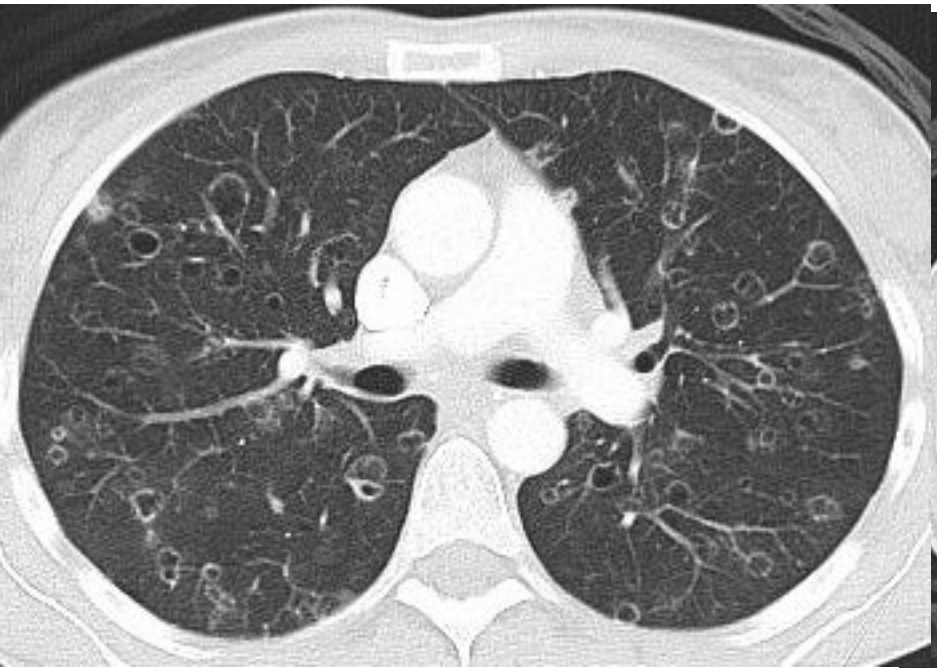
TC torace - PLCH

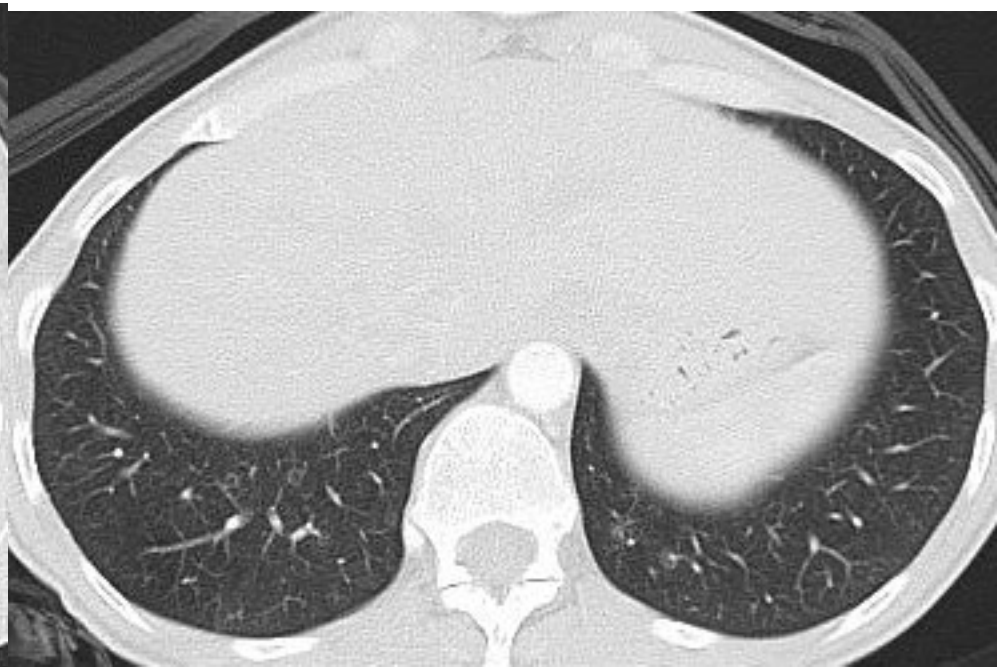




Distribution	Upper/middle lung zones Sparing of costophrenic angles	Associated findings	Nodules, micronodules Cavities Ground glass opacities
Size	Variable		
Shape	Irregular, bizarre		

CT - PLCH



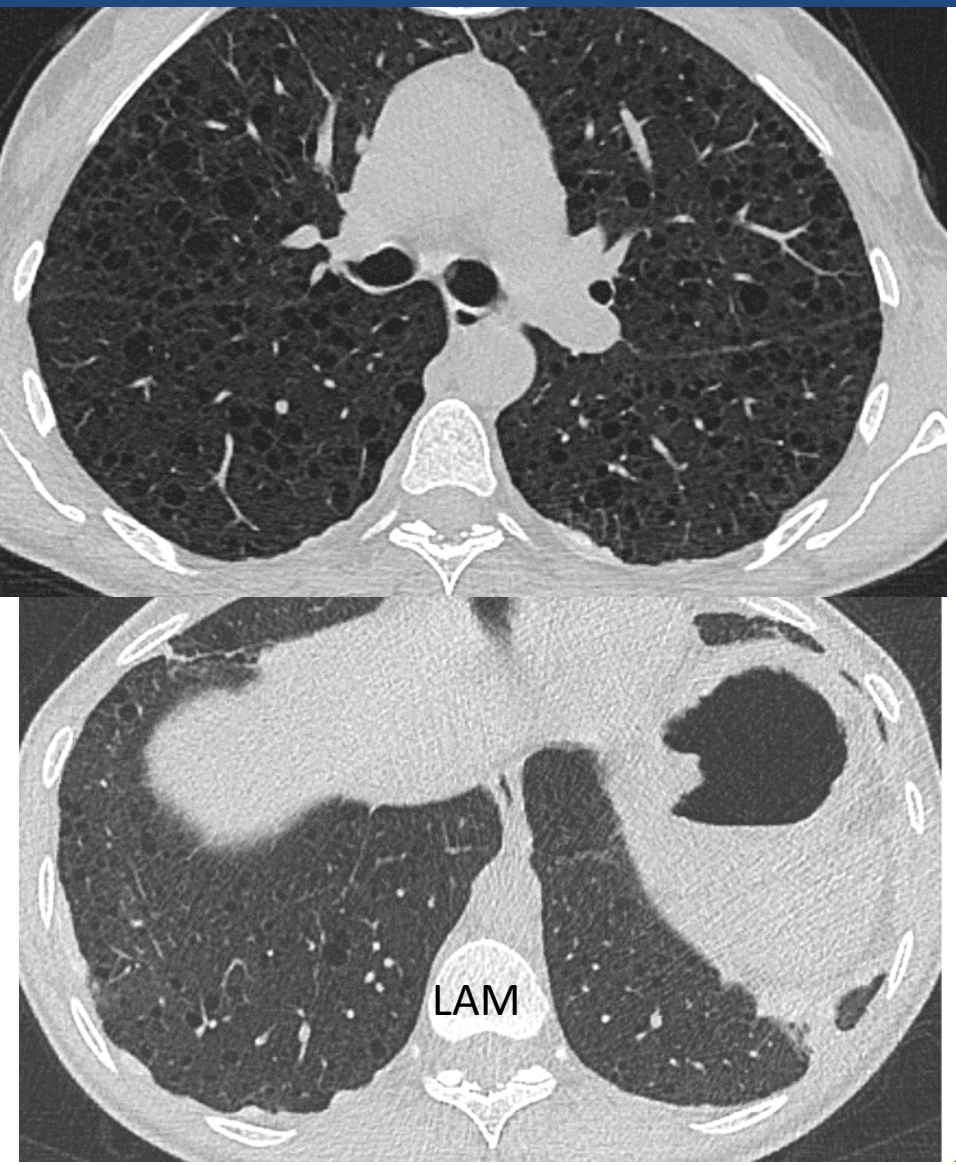


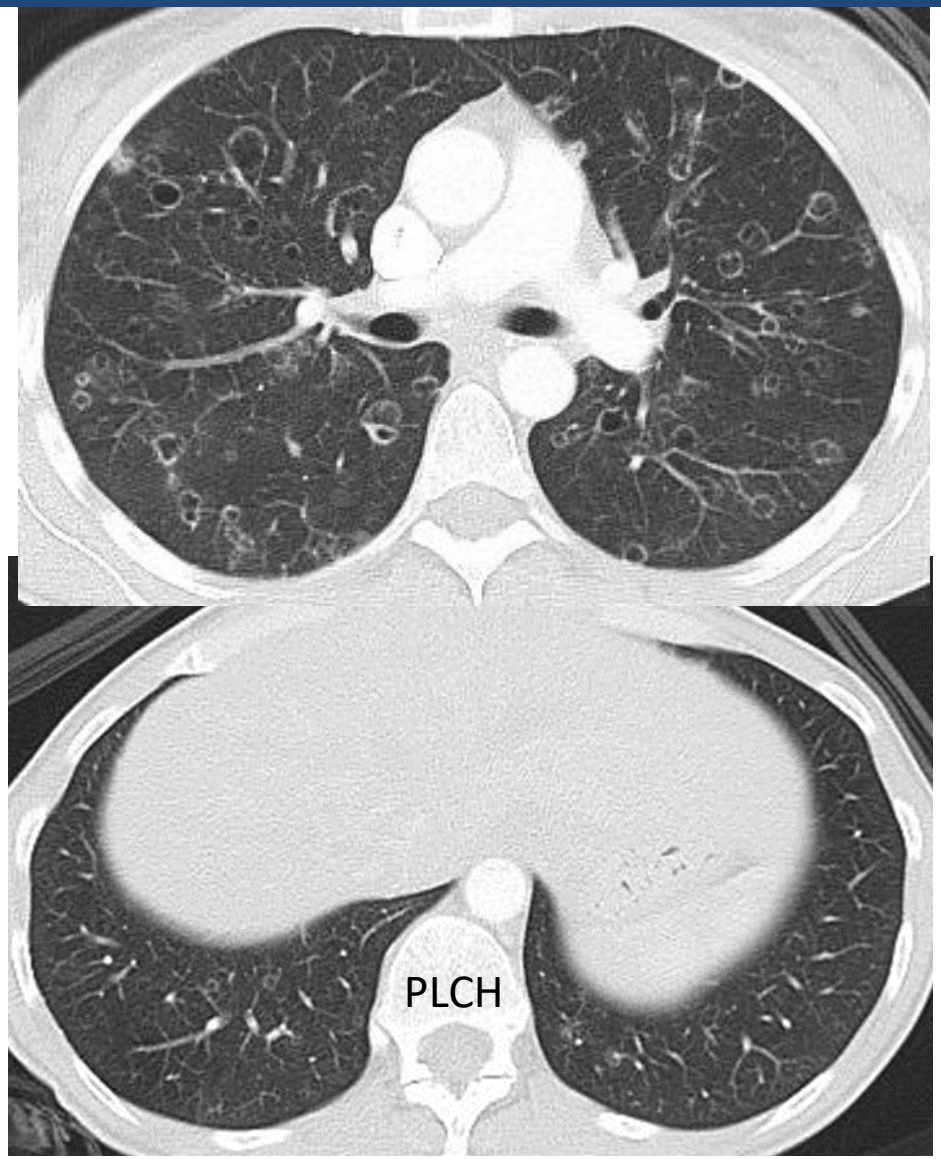
Longitudinal observation of CT features suggests the following evolutionary sequence for pulmonary lesions:

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

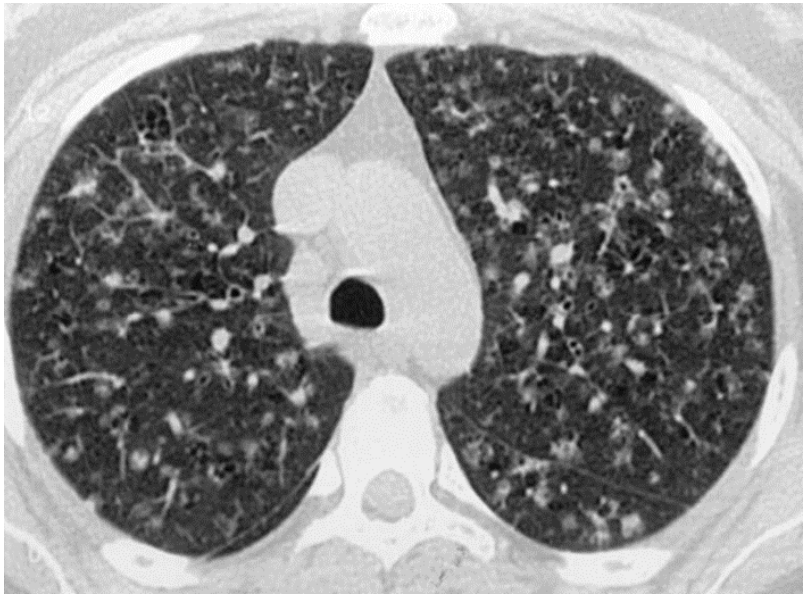
Brauner et al. Radiology 1997

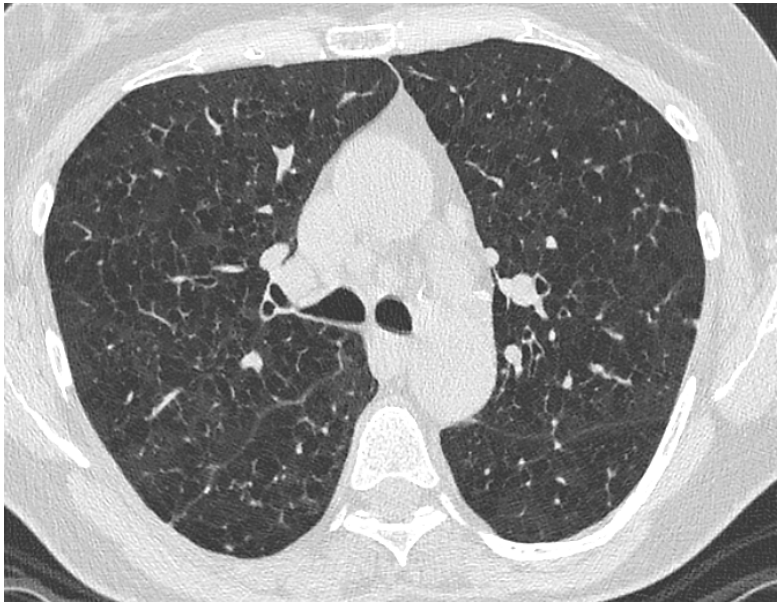
LAM - PLCH

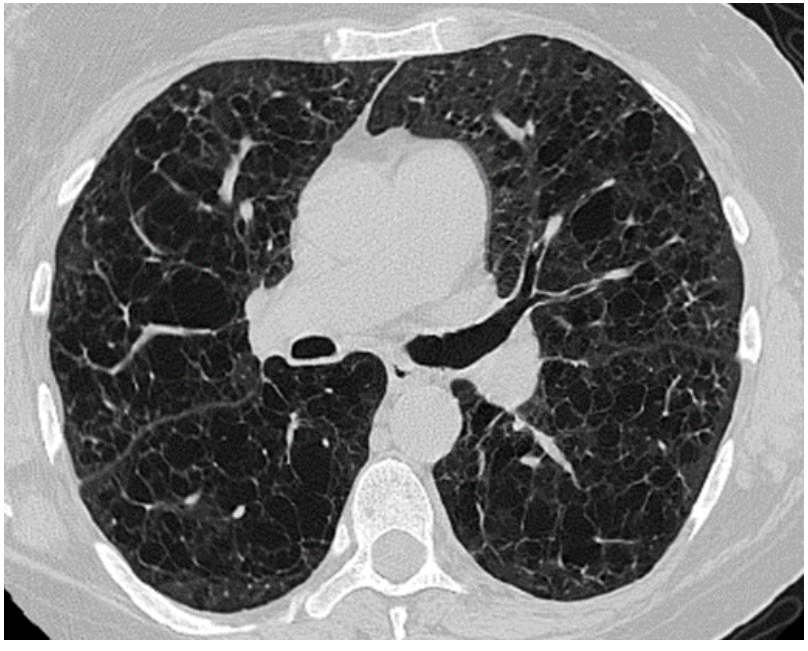


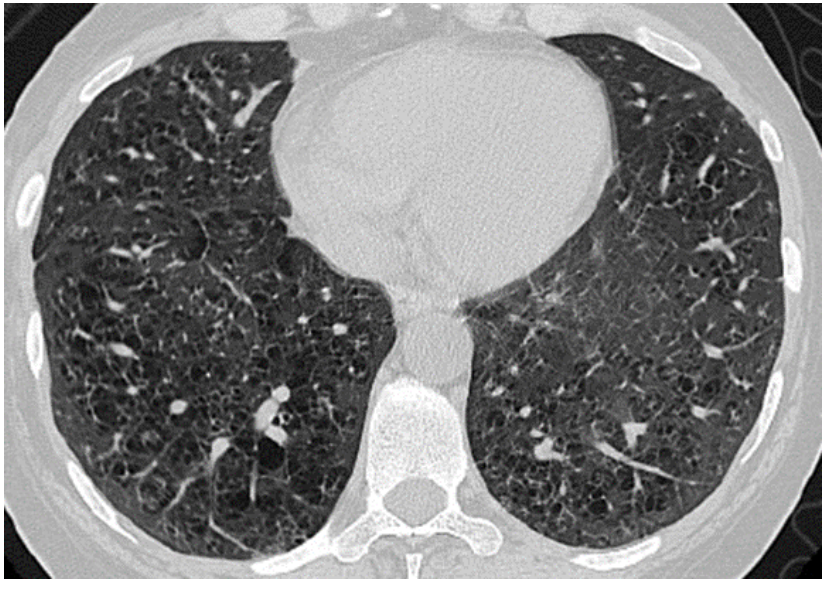


TC torace - PLCH









PLCH – symptoms

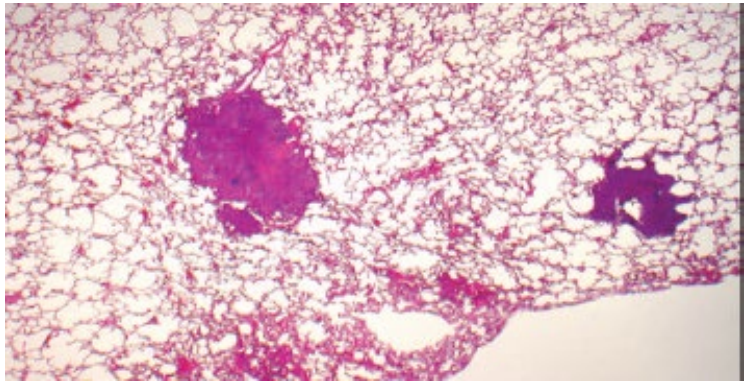
Pulmonary Langerhans Cell Histiocytosis

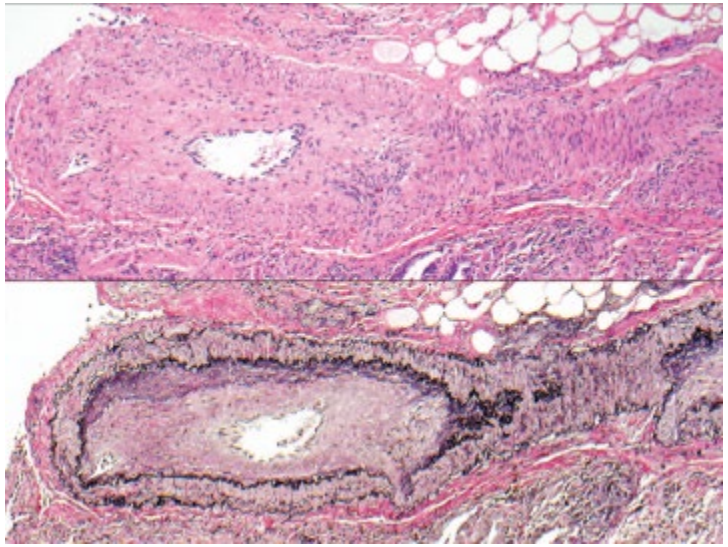
An Update From the Pathologists' Perspective

Anja C. Roden, MD; Eunhee S. Yi, MD

Table 2. Symptoms of Patients With Pulmonary Langerhans Cell Histiocytosis at Time of Presentation

Symptom	Frequency, %
Dyspnea	38–87
Nonproductive cough	32–70
Chest pain (often pleuritic)	9–21
Fatigue	16
Pneumothorax	12–18
Weight loss	9
Fever	8–15
Symptoms related to extrapulmonary disease (polyuria, polydipsia, pain, and/or skin rash)	10–15
Hemoptysis	1–13
Asymptomatic	12–66





Arch Pathol Lab Med. 2016;140:230–240

Our experience

Original Article

Pulmonary Langerhans cell histiocytosis: A comprehensive analysis of 40 patients and literature review

Davide Elia, Olga Torre, Roberto Cassandro, Antonella Caminati, Sergio Harari *

U.O. di Pneumologia e Terapia Semi-Intensiva, Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare Ospedale San Giuseppe Multimedica, via San Vittore 12, 20123 Milano, Italy

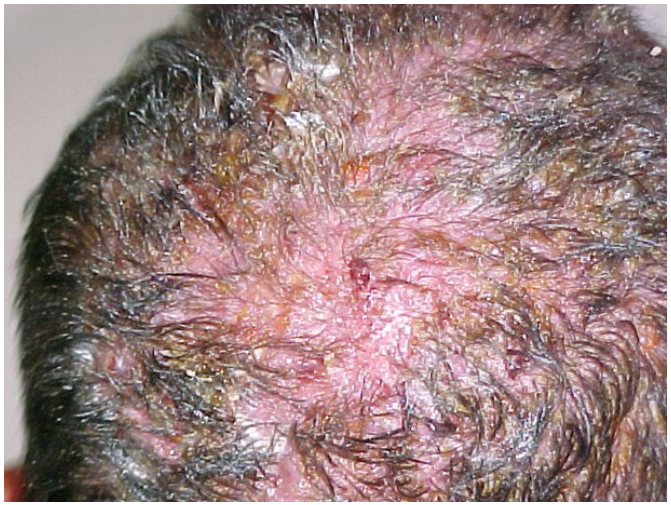
Symptoms	Number of patients (40)
Exertional dyspnea	15
Cough	13
Pneumothorax	7
Diabetes Insipidus	2
Bone lesions	2
Hemoptysis	1
Skin lesions	1

Eur J Intern Med 2015

Extrapulmonary manifestations

- Hypothalamic-pituitary alterations
- Skin lesions
- Osteolytic bone lesions

LCH



Scalp rush

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Endocrine and metabolic assessment in adults with Langerhans cell histiocytosis

L. Montefusco[a,b], S. Harari[b,c,*], D. Elia[b,c], A. Rossi[a,b], C. Specchia[b,d], O. Torre[b,c], G. Adda[a,b], M. Arosio[e]

Observational cross-sectional study on 18adults (7M/11F, 42 ± 12 years)

Hypothalamic-pituitary endocrine alterations were found in 9 patients

- 5 Growth Hormone Deficiency (GHD)
- 5 central hypogonadism
- 3 central hypothyroidism
- 1 central hypoadrenalism
- Hyperprolactinemia
- Hypothalamic syndrome
- All 9 pts had diabete insipidus

PLCH - treatment

Smoking cessation is mandatory!

A prospective study showed that persistence in smoking was associated with longitudinal decline in lung function, while smoking cessation for at least 6 months was associated with reduced lung function decline

Tazi A et al, Orphanet J Rare Dis 2015

PLCH - treatment

- No prospective or randomized trials about steroids
- Chemotherapeutic have been used in patients with progressive disease or in those with multiorgan involvement.

- Case reports and retrospective studies showed improvement of hemodynamic parameters in patients with PH treated with PH-therapies. It should only be considered in selected patients with pulmonary hypertension following right heart catheterization

Kiakouama L et al, ERJ 2010
Le Pavec J et al, Chest 2012

Cladribine in PLCH

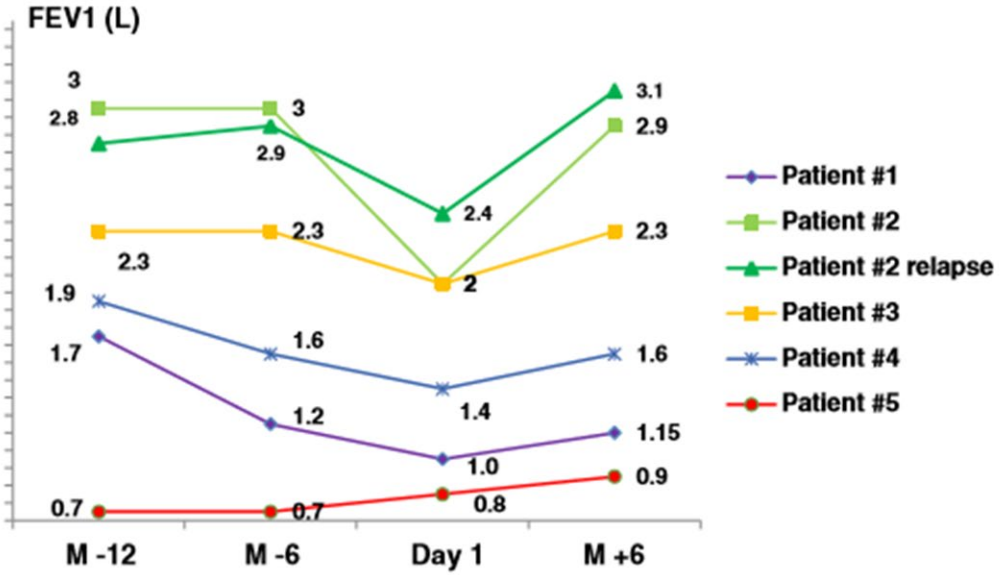
- Cladribine (2-chlorodeoxyadenosine) is a chemotherapeutic agent cytotoxic for lymphocyte and monocyte cells

- Case reports showed efficacy cladribine in PLCH

Effectiveness of cladribine therapy in patients with PLCH

A retrospective study of 5 patients with progressive, symptomatic PLCH with lung function impairment

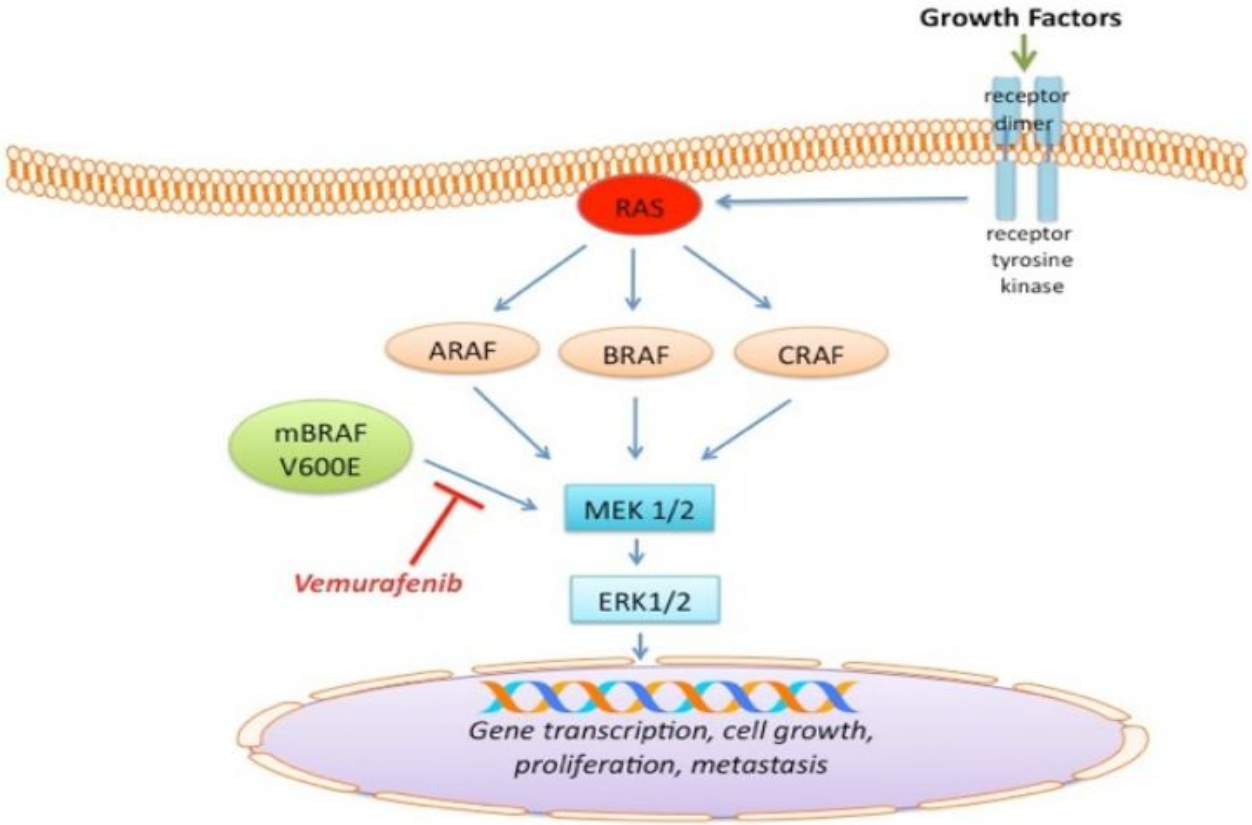
FEV1 increased in all cases after therapy



Grobost et al, Orphanet Journal of Rare Diseases 2014

Therapeutic options in BRAF^{V600E+} patients: Vemurafenib

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



Medscape Source: Access Medicine © 2012 McGraw Hill Companies

Inhibitors of Braf in PLCH

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

122 pts with $BRAF^{V600E}$ mutation–positive non-melanoma cancer

18 pts with ECD/LCH, 14 pts could be evaluated for a response:
Treatment with a BRAF inhibitor resulted in

- Complete response in 1 pt, partial response in 5 pts (RESPONSE RATE 43%)
- Stabilization of disease in 8 pts

None experienced disease progression during treatment

Hyman DM et al, N Engl J Med 2015

Birt-Hogg-Dubè

- Birt-Hogg-Dubè syndrome (BHD) is a rare autosomal dominant condition characterized by
  - benign skin hamartomas
  - increased risk of renal cancer
  - pulmonary cysts

- Pulmonary cysts are usually found in IV-V decade

- High risk of spontaneous pneumothorax (recurrent in 75% of cases)
  (incidence up to 30-fold higher than general population)

Birt-Hogg-Dubè

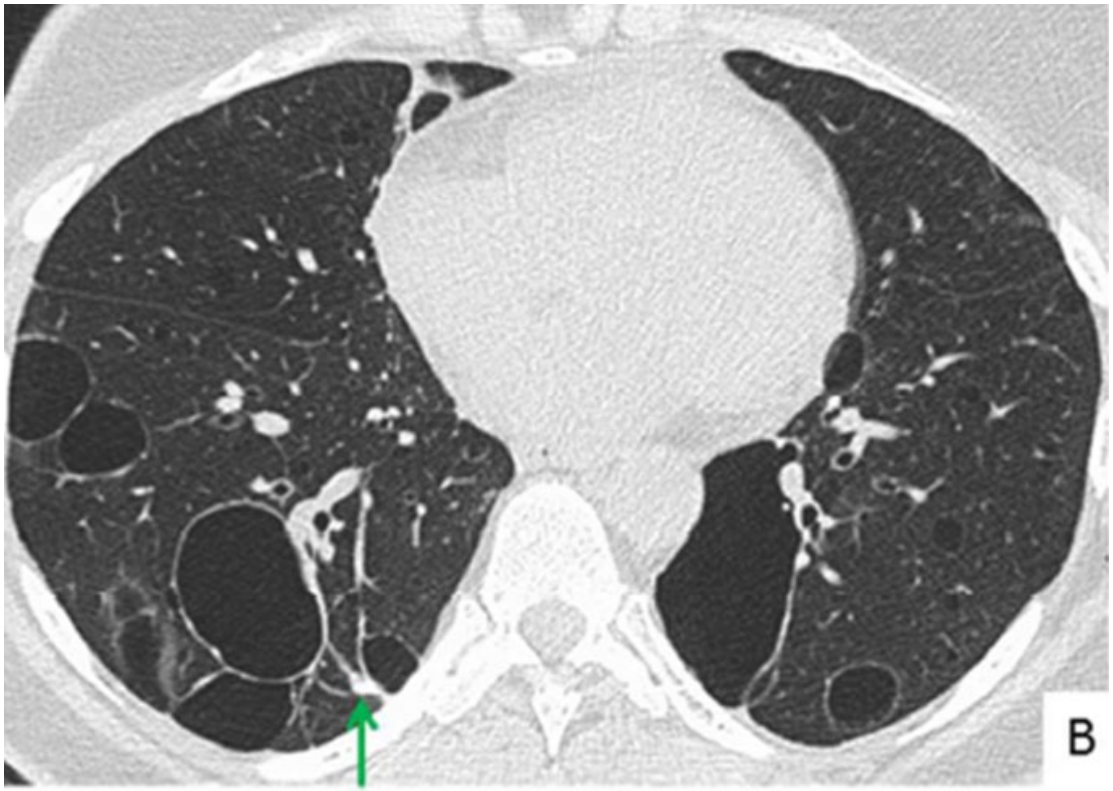
- BHD is caused by germline mutations in the folliculin (*FLNC*) gene

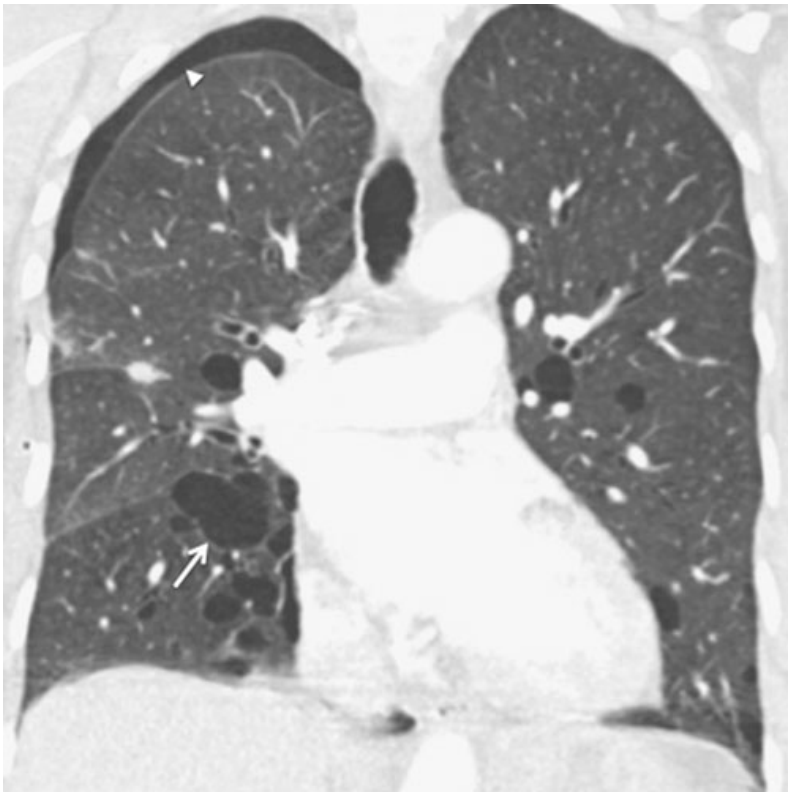
- Its exact mechanism of action remains unclear.

These mutations are thought to cause dysregulation of mTOR pathway; although it is not clear whether in sense of up or down regulation

- Possible mechanism of cysts formation: dysregulation or deficiency of adhesion proteins -> increased alveolar vulnerability to mechanic stretch?

CT - BHD

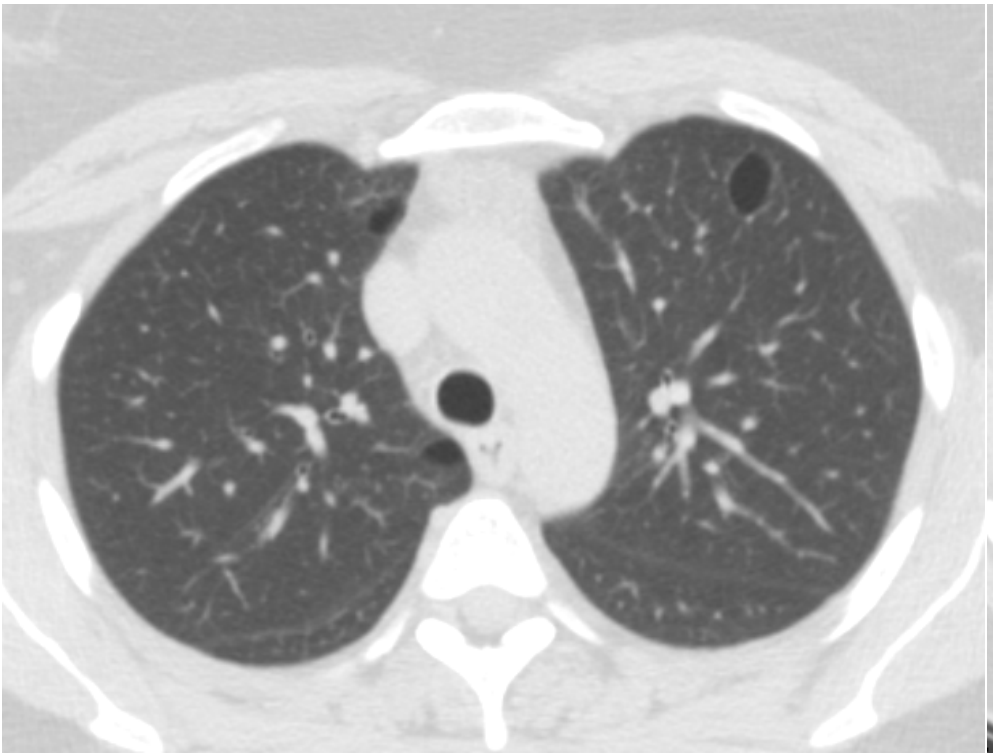


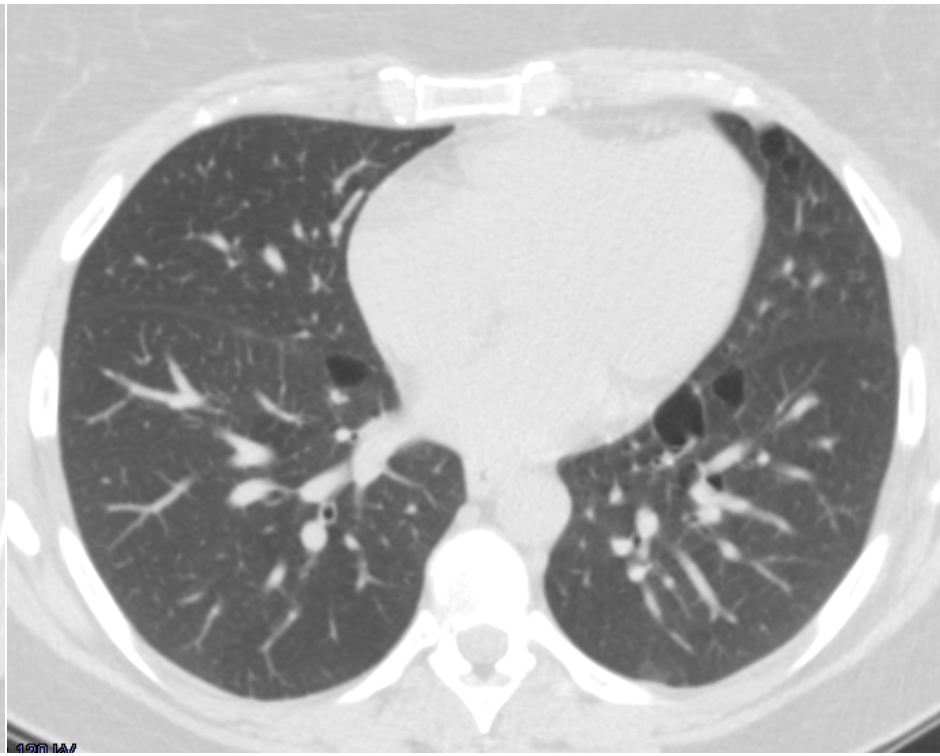


Distribution	Basilar/subpleural and near vessels
Size	Variable, average < 1cm
Shape	Elliptical, lentiform

Associated findings	Cysts abut pleura and vessels

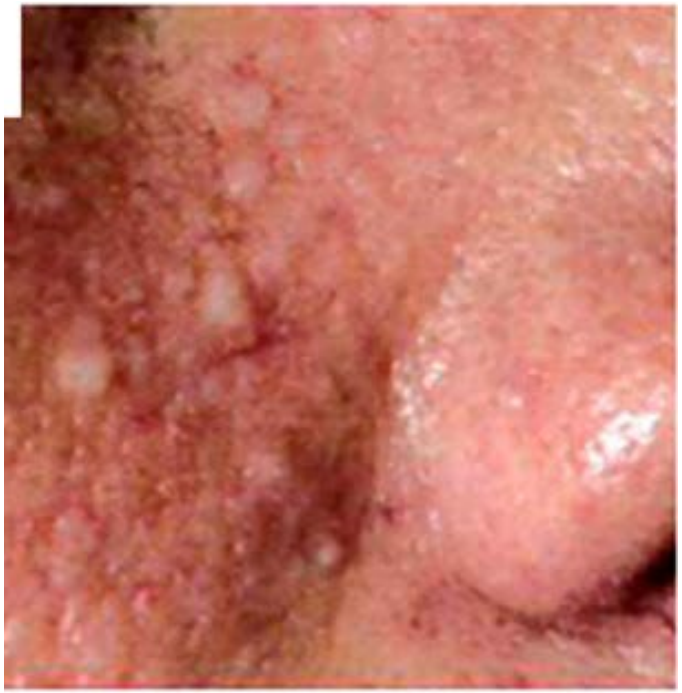
CT - BHD



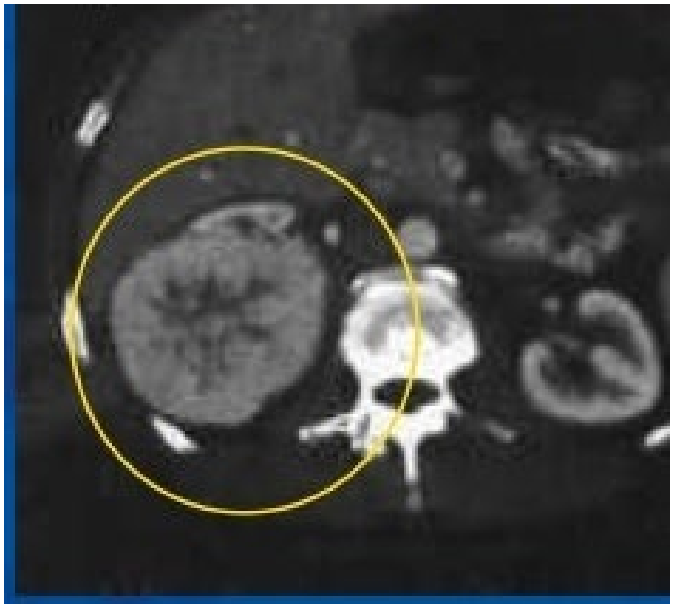


Extrapulmonary manifestations

- Benign skin hamartomas (fibrofolliculomas, trichodiscomas)
- Kidney tumors (wide range of tumor histologies)



Fibrofolliculoma



Oncocytoma

BHD – diagnostic criteria

- Major criteria:

  1) Histologically confirmed fibrofolliculoma o trichodiscoma

  2) identification of *FLCN* mutation

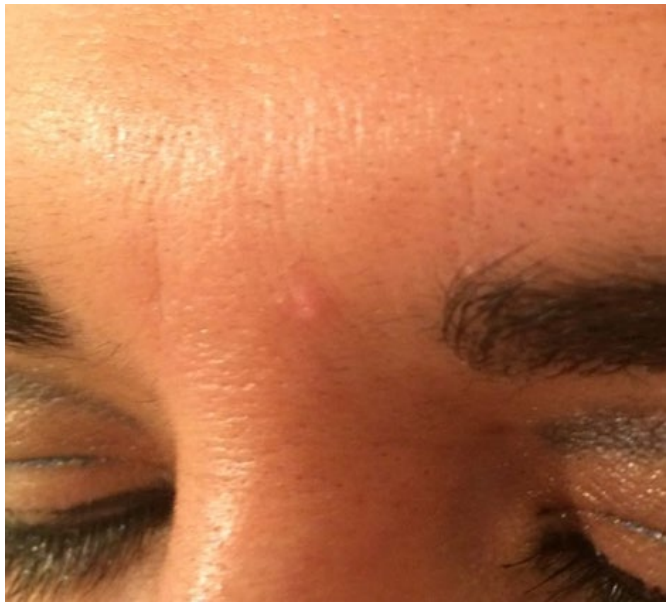
- Minor criteria:

  1) multiple bilateral cysts

  2) bilateral or multifocal renal tumor in a young patient (< 50 years)

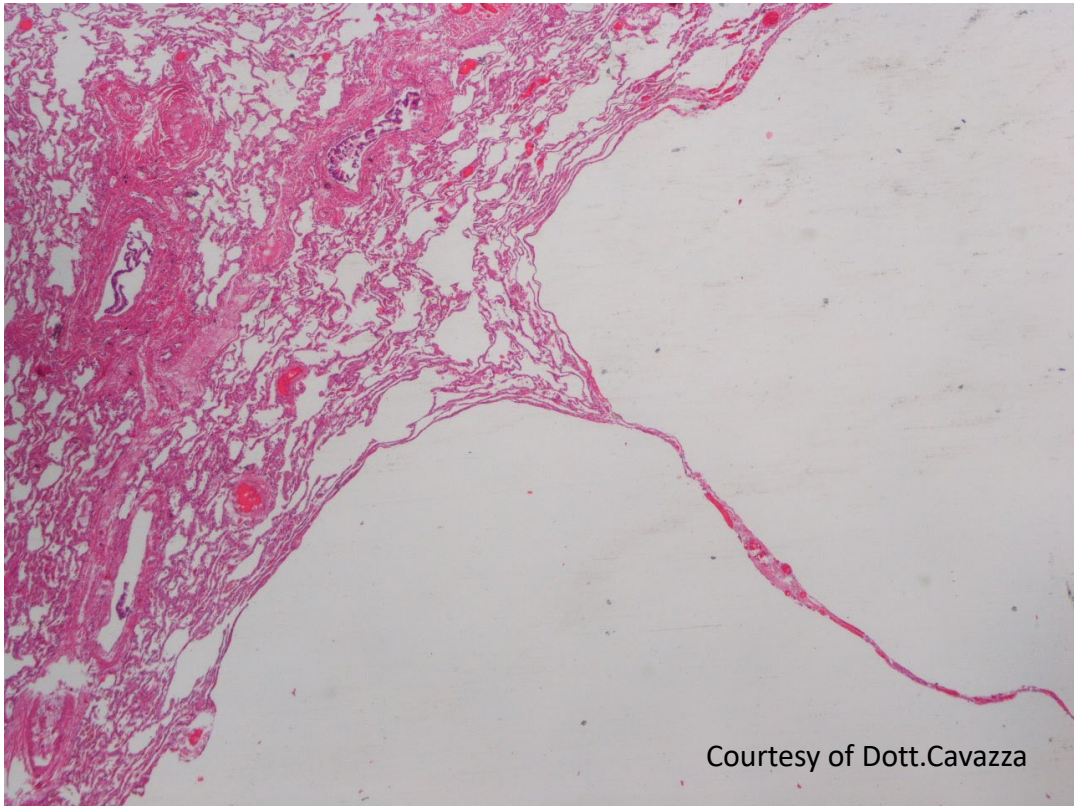
  3) BHD in a first-degree relative

Diagnosis: a major criteria or two minor criteria



Menko FH et al, Lancet Oncol. 2009

BHD – histology



- Histologically lung cysts are lined by normal parenchyma, often cysts abut pleura and vessels, and may contain septa
- No evidence of neoplastic proliferation or inflammation

BHD - trattamento

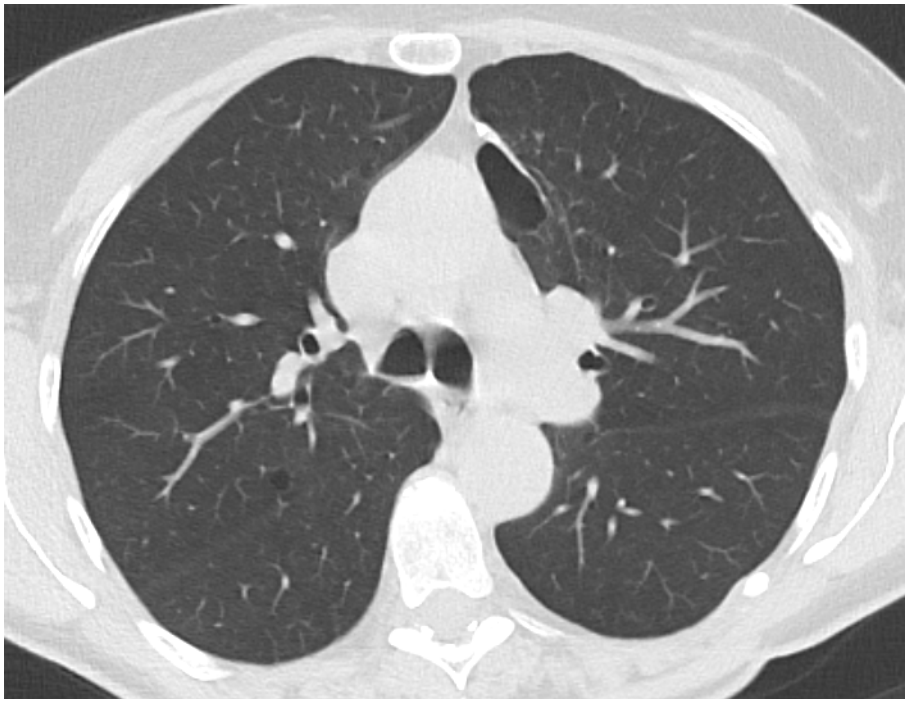
- No pharmacological therapy
- Prevention of pnx (avoid tobacco use, flight, diving…)
- Pts with numerous facial lesions may seek treatment because of cosmetic reasons
- Surgery for renal tumors
- Lifelong surveillance for renal cancer is needed!

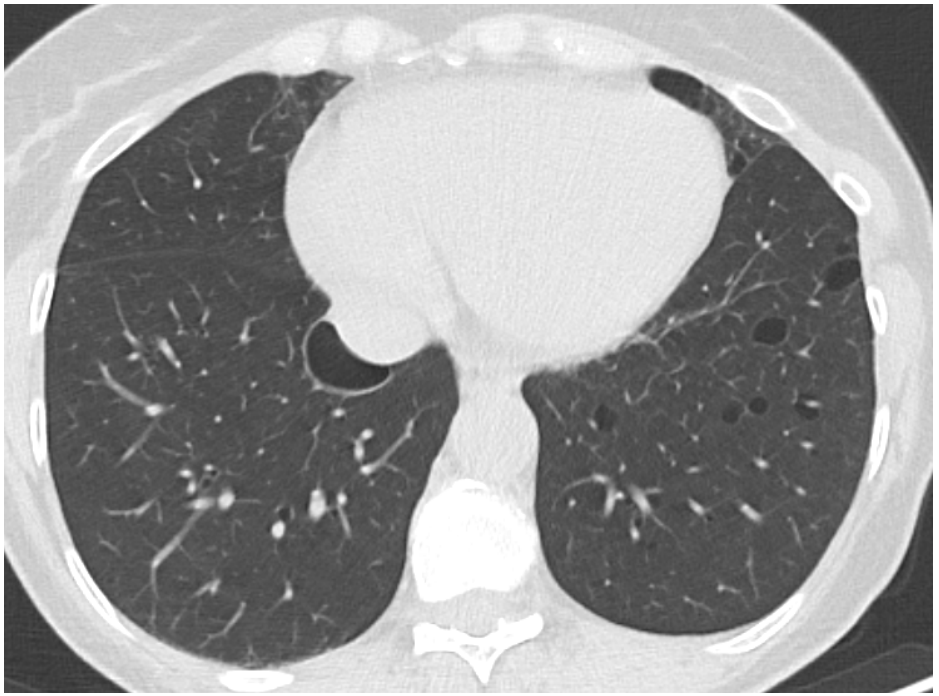
  (MRI or CT)

Other DCLDs

LIP/follicular bronchiolitis	- LIP: a diffuse involvement of lung parenchyma by reactive pulmonary lymphoid tissue - FB: a pattern of lymphoid follicular hyperplasia centered on airways, vessels, and interlobular septa They can be idiopathic or associated with a variety of underlying conditions, most commonly autoimmune disorders like (Sjögren syndrome, etc…) or immunodeficiency states
Amyloidosis	- A heterogenous group of disorders characterized by extracellular deposition of proteins in an abnormal fibrillary fashion. - Systemic or localized - Primary or secondary - Usually pulmonary nodules, rarely as DCLD
Light-chain deposition disease (LCDD)	- A monotypic kappa light chain deposition in the alveolar walls, small airways, and vessels - Usually associated to linfoproliferative disorders

Cystic lung diseases – LIP/FB

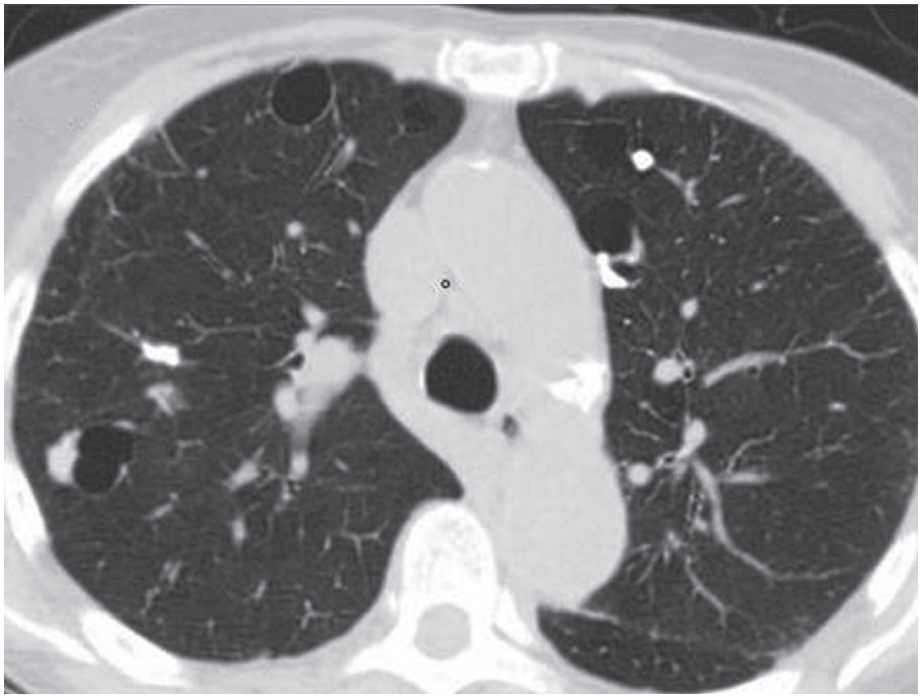




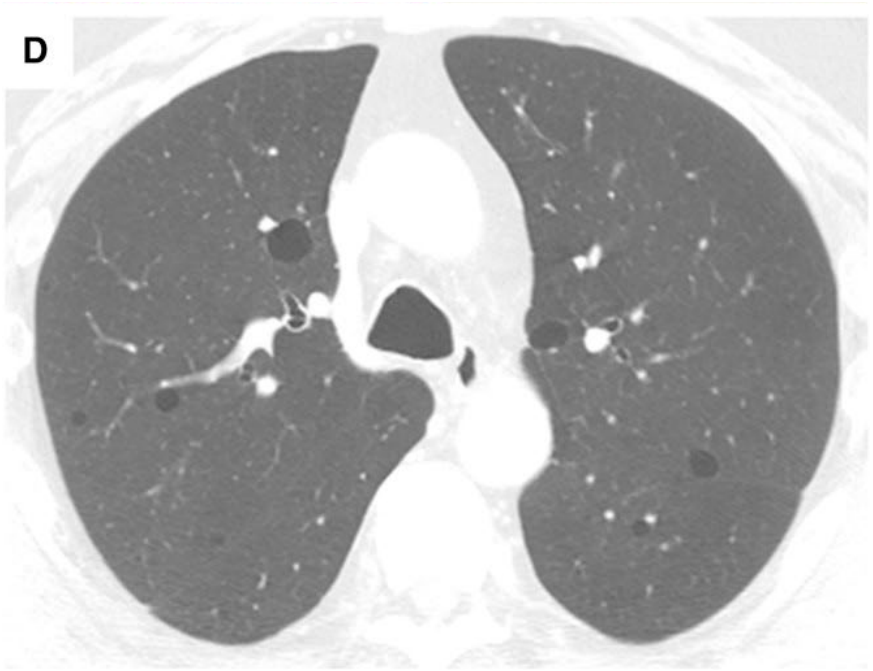
Distribution	Diffuse, random, prevalent in lower lobes often near vessels
Size	Average size 3 mm to 1 cm
Shape	Round, variable

Associated findings	Ground-glass opacities Centrilobular nodules Interlobular septal thickening Internal structures Mediastinal and hilar lymph node enlargement (LIP)

Cystic lung diseases – amyloidosis, LCDD



Amyloidosis



LCDD

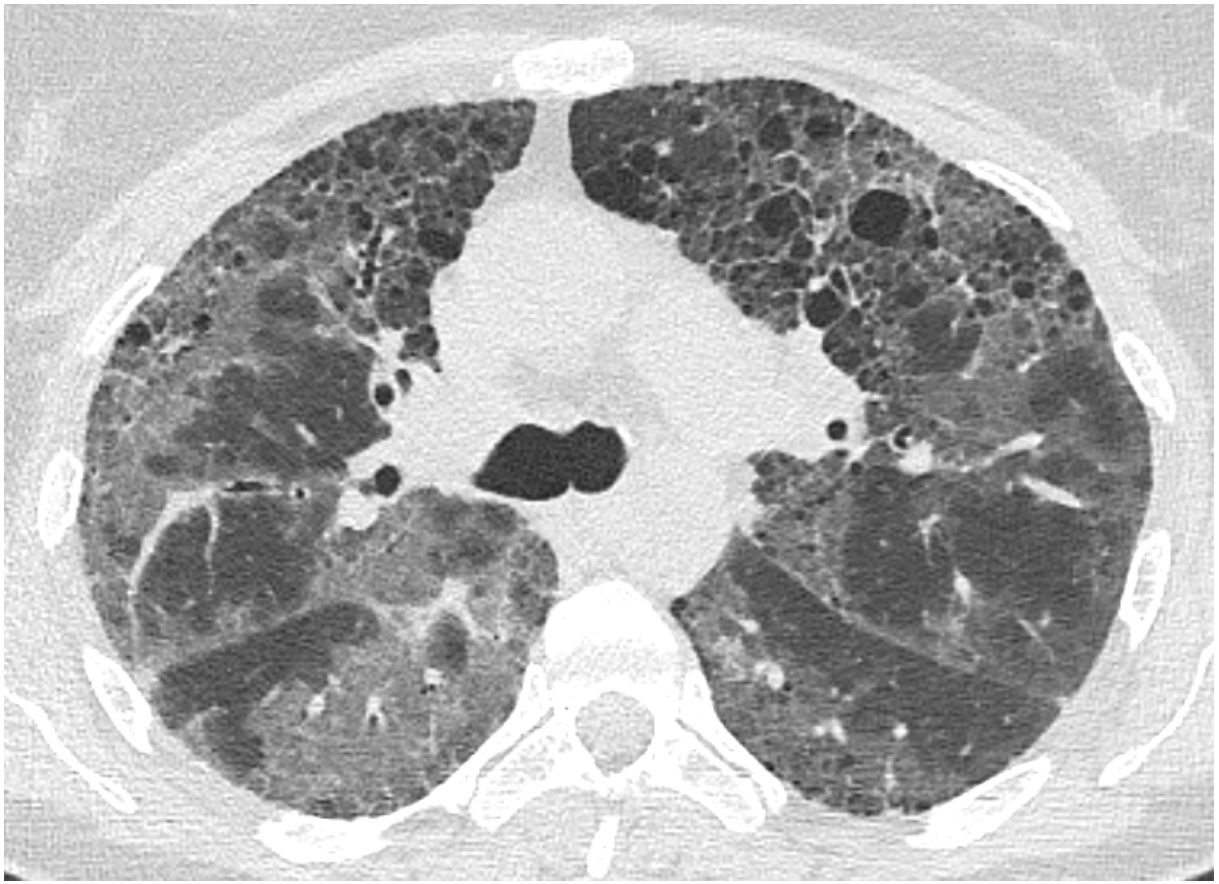
Distribution	Diffuse, random
Size	> 1 cm
Shape	Round, variable

Associated findings	Multiple nodules of varying attenuation, random. Nodules abut cyst walls Masses (Amyloidosis) Lymph node enlargement

Extrapulmonary manifestations

LIP/FB	- Sjögren syndrome - Other CTDs - HIV - Common variable immunodeficiency
Amyloidosis	- Systemic amyloidosis - Sjögren syndrome - Other CTDs - MALT lymphoma
LCDD	- Lymphoproliferative disorders (75% of cases in multiple myeloma or macroglobulinemia) - Renal failure

Cisti in altre patologie polmonari



Patologia polmonare diffusa, con aspetto patchy, caratterizzata da presenza di opacità ground-glass, minimi aspetti di distorsione fibrotica e multiple cisti aeree, presenti nelle zone di ground-glass, con diametro variabile da pochi mm a circa 1 cm…

...Successiva diagnosi di alveolite allergica estrinseca

Dati demografici/clinici/laboratorio

	LAM	PLCH	BHD	LIP/FB	Amiloidosi	LCDD
Smoking		X				
Gender	Female					
Lab	*Serum VEGFD*	Diabetes insipidus	*FLCN mutations*	autommune Immunodeficit	autoimmune Systemic amyloidosis	Linfoprolif. diseases Renal failure
Family history	*Possible TSC*		*Possible BHD*			
PNX prevalence	XX	X	X			
Recurrent PNX	XX	X	XX			
Chylous effusions	X					