Pulmonary Langerhans cells hystiocitosis: new trends

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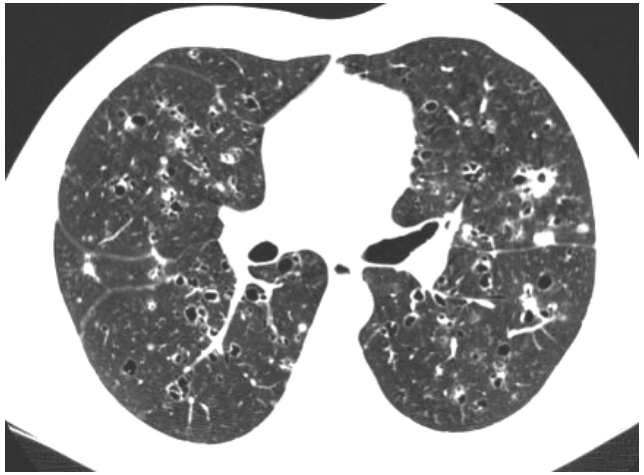
Langerhans cell histiocytosis

It is a rare histiocytic disorder of unknown origin, affecting 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

The types of lung lesions vary with disease duration. In early disease, nodules and cavitated nodules are more numerous than lung cysts, while more advanced disease is often cystic in appearance



Role of smoking

Smoking interactions on gene mutations has not been investigated, so far, in PLCH

Children with extra-pulmonary LCH who subsequently develop PLCH during adolescence or adulthood are often smokers
(Bernstrand C. Acta Ped 2000)

Smoking induce CD1a+ cell accumulation even in lungs of healthy smokers stimulate local production of different chemokines and promotes the survival of dentritic cell via anti-apoptotic mechanism

Osteopontin seems to play a role in PLCH. Large quantities has been found in BAL of PLCH pts compared to smoker controls.

BRAF-V600E and LCH

BRAF-V600E mutation has been described in the sample of the lesions of:

- 38 to 69% of LCH patients (Badalian-Very G *Blood* 2010, Satoh *Pediatric Disease* 2012, Sahm *Blood* 2012, Hervier *Blood* 2014)
- 30-50% of patient with PLCH (Rodean *Am J Sur Pat* 2014)
- 54% to 82% of patients with Erdheim Chester Disease (Haroche *Blood* 2012, Hervier *Blood* 2014)

In children with severe systemic forms of LCH, the presence of the $BRAF^{V600E}$ mutation was not only present in tissue lesions (somatic mutation), but also in circulating and sometimes bone marrow precursors of dendritic cells infiltrating LCH granulomas

(Barres et al. *The Journal of experimental medicine* 2015)

PLCH: Clinical Presentation

Three main manifestation:

1) Respiratory symptoms: usually cough and dyspnea less frequently associated to fever, malaise and loss of weight
2) Acute presentation with a spontaneus pneumothorax
3) Incidental finding in a routine Chest X-Ray (5-25% of cases)

Vassallo R , Harari S, Tazi A. Thorax 2017

PLCH: Clinical assesment

The primary goal of clinical assesment is:

1) To determine to degree of functional and pulmonary impairment
2) To assess for complications
3) To evaluate for extrapulmonary manifestation

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 Multi Medica, via San Vittore 12, 20123 Milano, Italy

Characteristics of patients at time of diagnosis.

	Patients
Gender (m/f)	18/22
Age (years)	40 ± 14
Years from symptoms	2 ± 3.7
Number of cigarettes smoked (pack/year)[a]	25 ± 15
FEV1 (L)	2.6 ± 0.99
FEV1 (%)	79.65 ± 24.18
FVC (L)	3.59 ± 1.08
FVC (%)	92.84 ± 20.45
FEV1/FVC	71.61 ± 14.78
DLCO (%)	60.56 ± 24.30

[a] Pack/years = (no cigarettes smoked × years of smoking) / 20.

Eur J Intern Med 2015

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

Elia D. et al. Eur J Int Med 2015

Original Article

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Pulmonary function pattern at the presentation.

Pulmonary function pattern	Number of patients
Normal	22
Obstructive	16
Restrictive	2

Extra-pulmonary manifestations.

Manifestation	Number of patients
Bone lesions	7
Diabetes insipidus	5
Skin	1

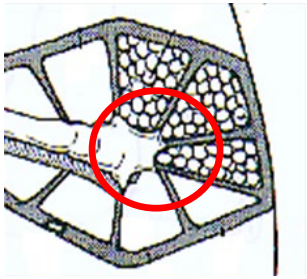
Elia D. et al Eur J Intern Med 2015

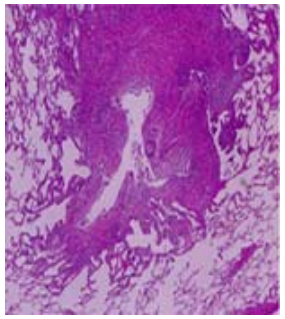
Pulmonary function at diagnosis

		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

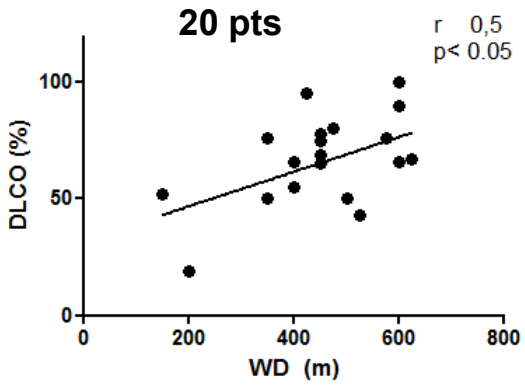




Exercise evaluation at diagnosis

6 minute walking test

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



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

Exercise limitation may be ascribed to vascular impairment

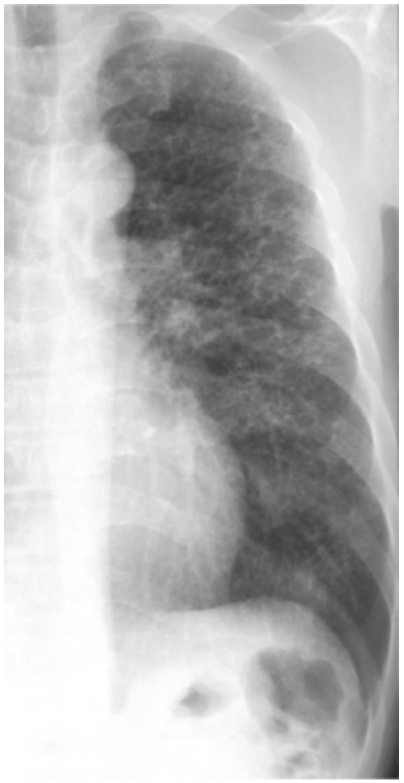
Crausman RS, AJRCCM 1996

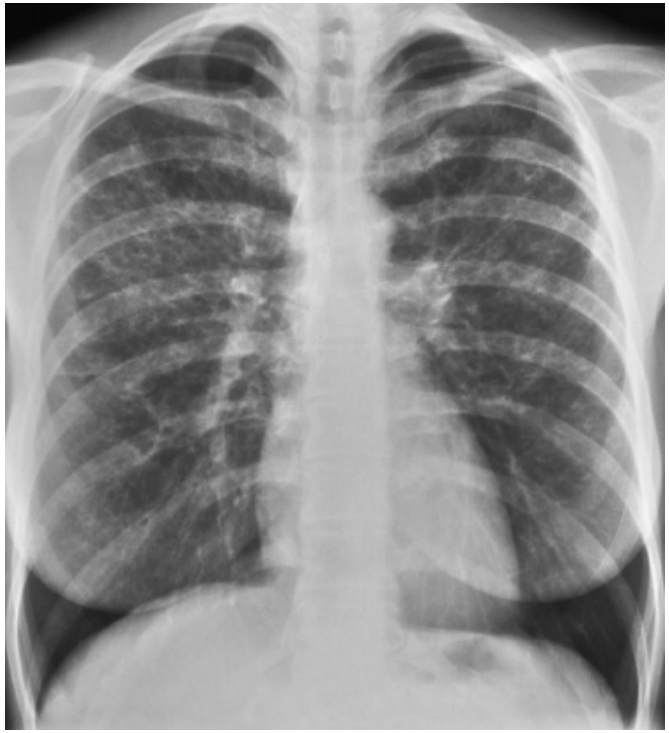
Radiological Imaging: Chest X-ray

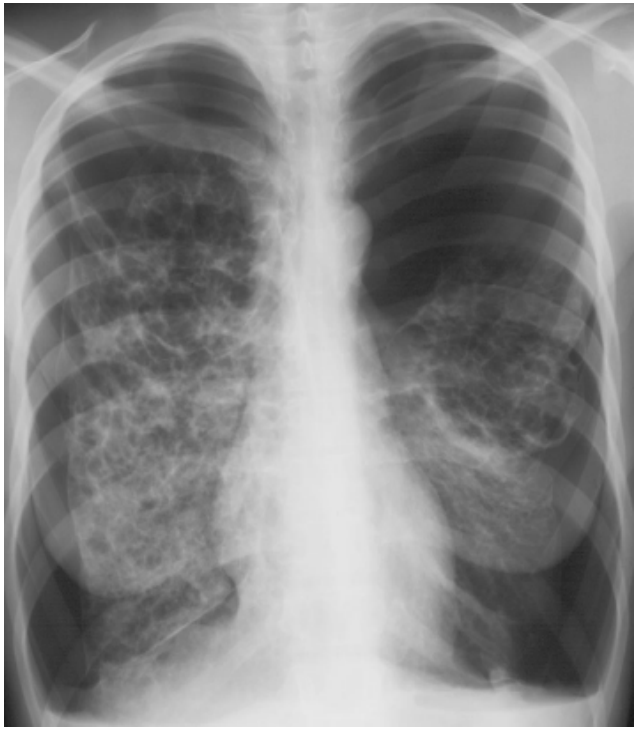
Rarely it is normal

Often shows bilateral, and generally symmetric, reticulo-micronodular changes, in which cysts may sometimes be identified, predominantly involving the upper and middle lung fields

Occasionally, chest radiography may reveal a pneumothorax, or rarely, a lytic lesion of a rib



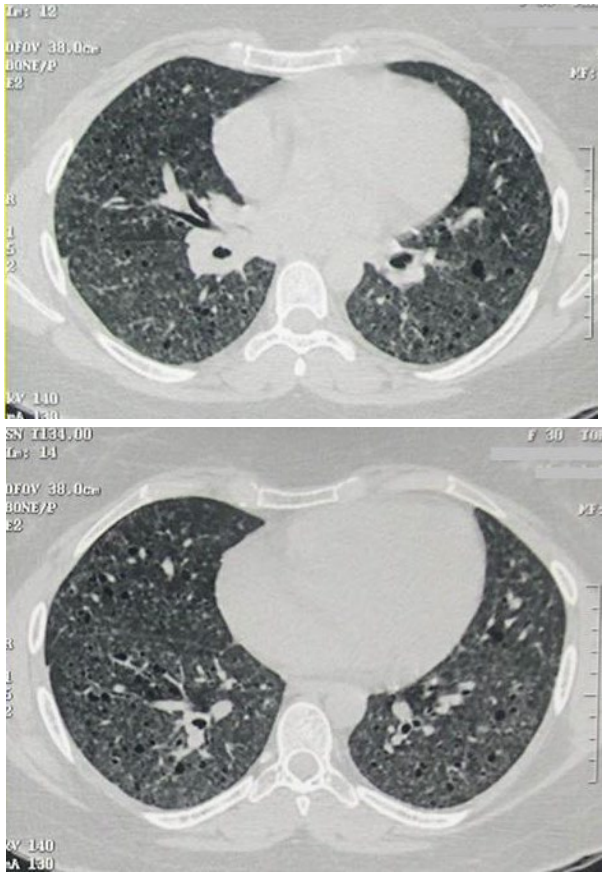




Radiological Imaging: HRCT scan

It is characterized by the presence of a combination of nodules, cavitating nodules and irregular shape cysts.

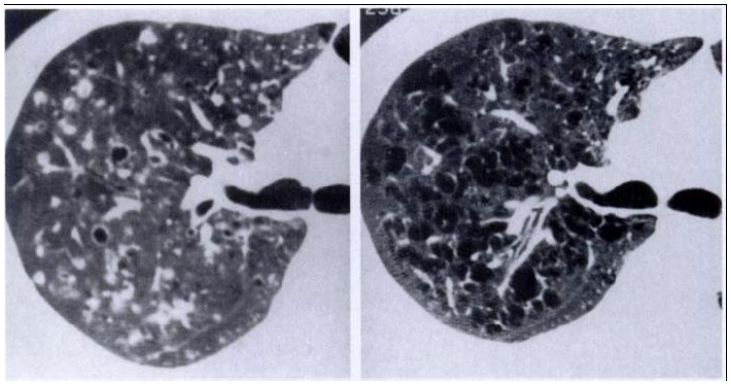
A predominant involvement of upper and middle lung is observed with a basal sparement



PLCH: evolution of lesions on CT scans

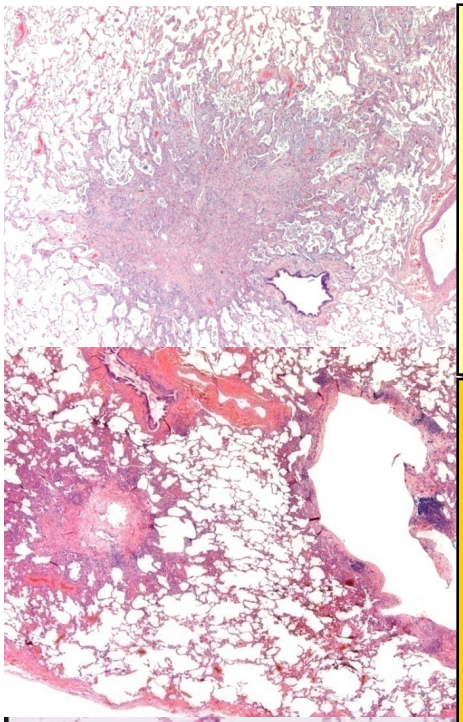
Longitudinal observation of CT features suggest the following evolutionary sequence for pulmonary lesions of PLCH:

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



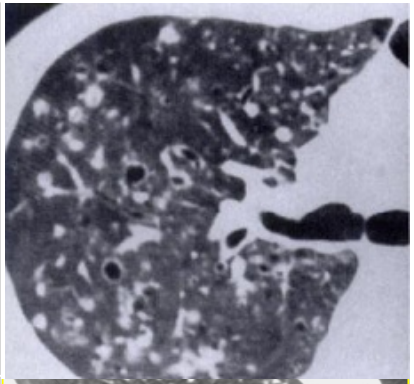
Brauner et al. Radiology 1997

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



- *Early stage:*

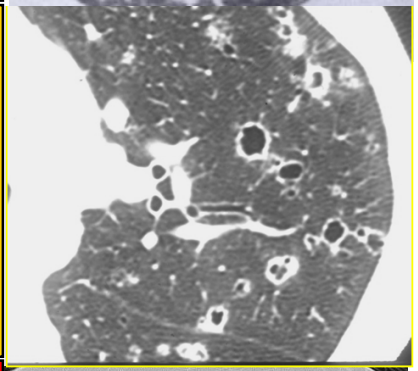
Infiltrates invade the bronchiole, destroying the bronchiolar wall in an eccentric fashion and forming **nodules**

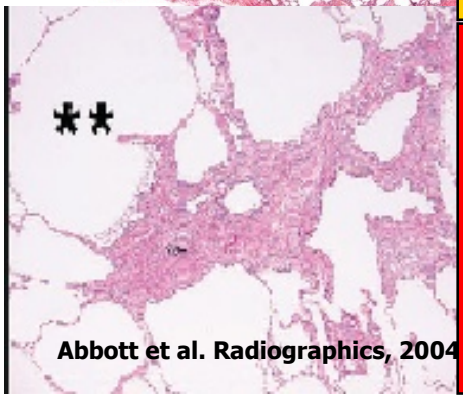


- *Disease progression:*

Increasing numbers of nodules and **cavitary nodules**

Appearance of **fibrotic scars**

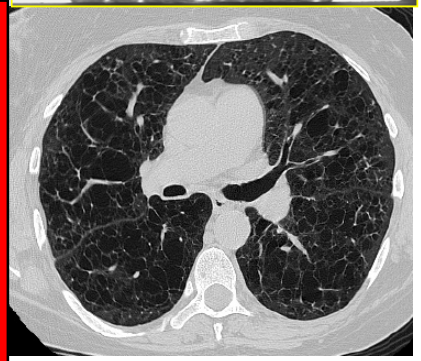




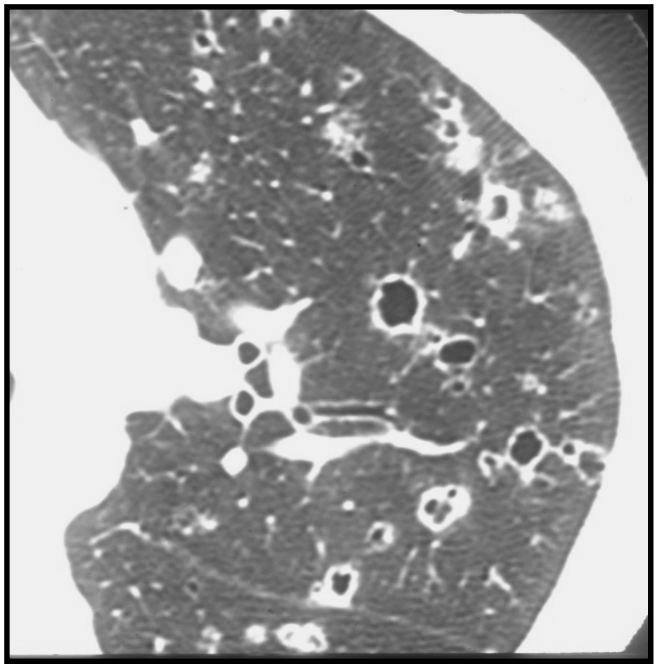
Abbott et al. Radiographics, 2004

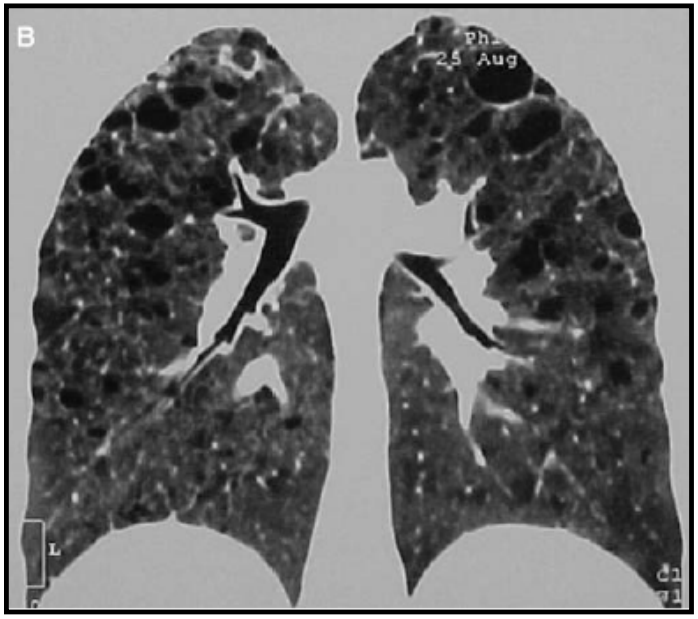
- *End stage:*

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



PLCH – Radiological features

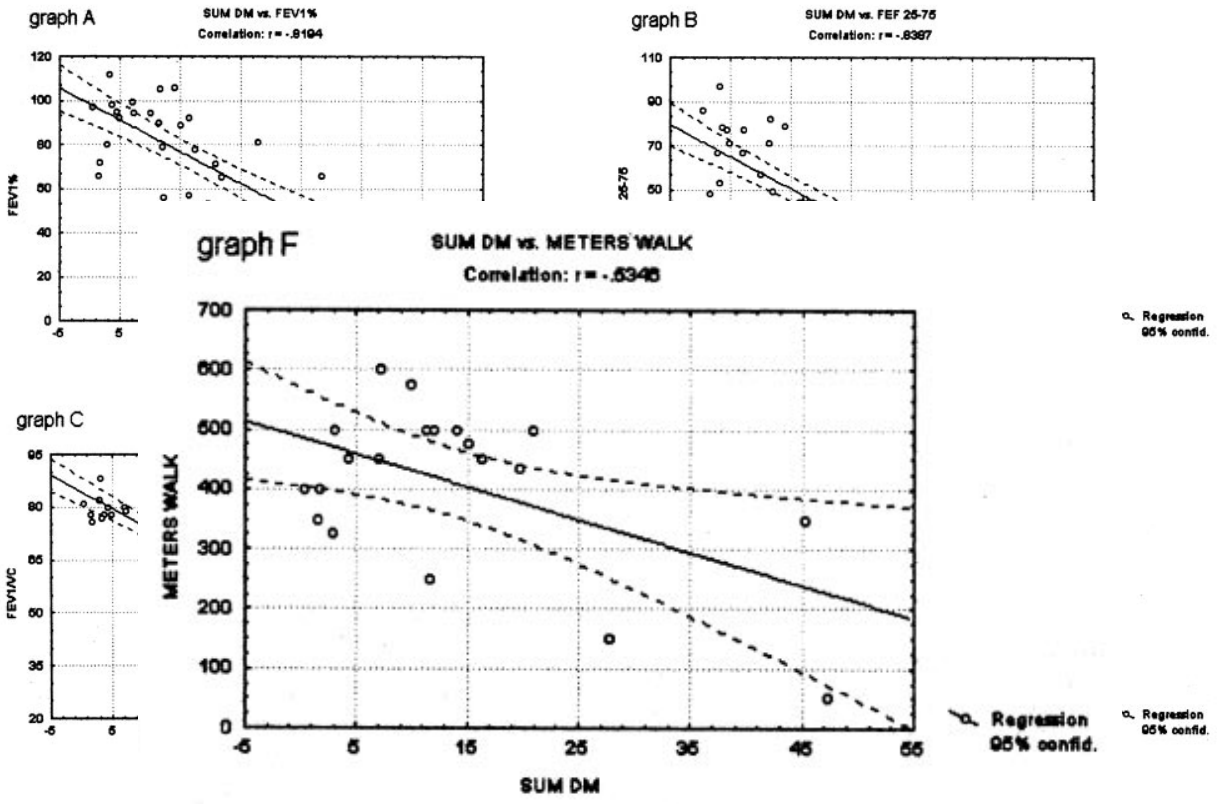




The combination of multiple cysts and nodules with a mid to upper zone predominance and sparing of lung bases in a young smoker is so characteristic that may be diagnostic

Harari S et al. Proc Am Thorac Soc. 2006

Diffuse Cystic Lung Diseases: Correlation between Radiologic and Functional Status



The severity of airflow limitation on lung function testing correlates with the extend of cystic lesions on HRCT

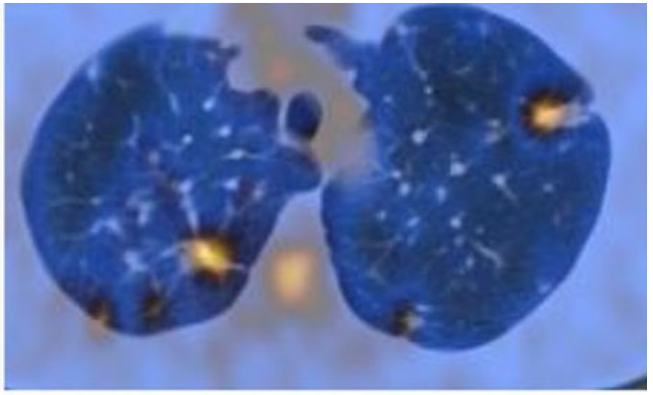
Paciocco G et al. Harari S Chest 2004

Does CT-PET play a role?

It is not well defined

As the nodules can be hypermetabolic, the presence of a superimposed lung cancer must be excluded

It is predictive of the disease course or response to treatment, expecially in multisystemic forms involving the bones



Obert J Eur J Nucl Med Mol Imaging 2017

Bronchoscopy

BAL is usefull to support the diagnosis of PLCH in the presence of a number of CD1a+ cells >5%, associated to a typical CT scan pattern

TBB is rarely usefull due to the focal nature of the lesions

Cryobiopsy could increase the diagnostic yield but is probably associate to a higher risk of pneumothorax

Harari S. et al Respir Med 2012,
Baquir M. et al. J Bronchol Interv Pulminol 2013,
Fruchter et al Respirology 2014

Bronchoscopy

Records of 452 patients with the presumptive diagnosis of interstitial lung disease were reviewed; 67 had a clinical-radiological diagnosis of either LCH (27) or LAM (n 40).

Of 16 patients with LCH who underwent BAL, four specimens (25%) contained cells which had positive immunoreactivity for CD1a.

Of three patients with negative BAL fluid who had TBB, only one had a positive tissue diagnosis.

Ten LCH patients were diagnosed by surgical lung biopsy of which five had negative BAL fluid.

The remaining 12 patients were diagnosed by clinical and radiologic features.

Harari S et al. Respiration 2012

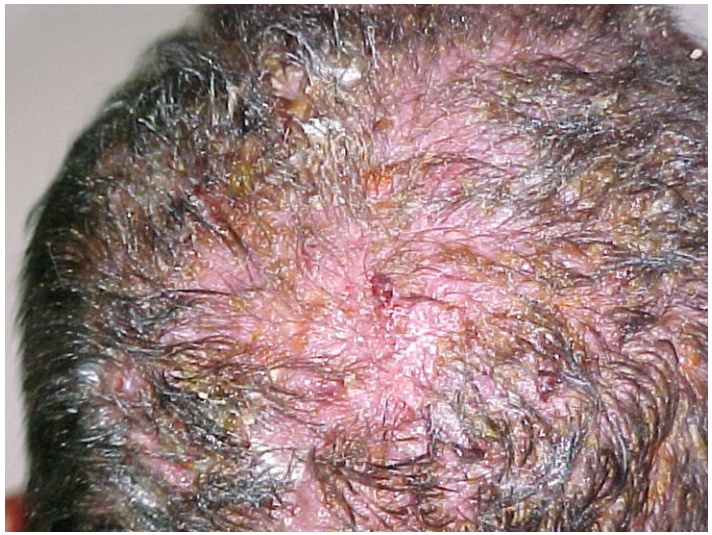
Management of extra-pulmonary manifestations in PLCH

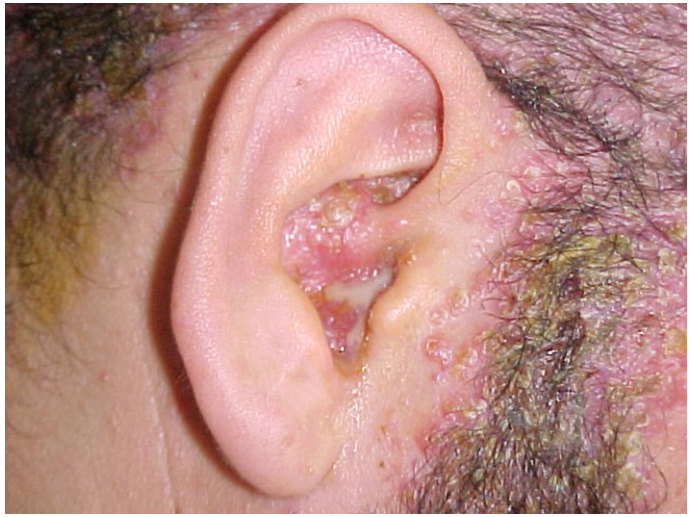
Although PLCH occurs as a single organ disease, approximately 10-20% of adults may show extra-pulmonary manifestations.

The management of diabetes insipidus, endocrine, skin and bone involvement often require a multidisciplinary approach with other specialists experienced in the management of LCH

Among 40 patients referred to our center in 10 years 7 showed bone involvement (3 of the femur, 1 petrous bone, 1 of the jaw and 2 in the arm bones); 5 were affected by *diabetes insipidus*, 1 presented another endocrine dysfunction and 2 showed skin lesions

Elia D. et al. J Intern Med 2015





Extrapulmonary manifestation: How can I find them?

Table 1

Symptoms, Causes, and Recommended Clinical Tests for Common Extraskeletal Manifestations of Langerhans Cell Histiocytosis

Symptom	Cause	Recommended Clinical Tests
Thirst, polyuria	Diabetes insipidus (pituitary involvement)	Head MRI, urine and plasma osmolality, water deprivation testing
Decreased energy, weight gain, lethargy, cold intolerance	Hypothyroidism (thyroid or hypopituitary axial involvement)	TSH, free T4, head MRI
Lethargy, pallor, history of bleeding disorders, tachycardia	Pancytopenia, anemia, (marrow infiltration, associated malignancy)	Anemia studies, marrow aspirate
Enlarged lymph nodes	Lymph nodal involvement	Biopsy, CT-CAP or PET-CT
Cough, dyspnea, tobacco use	Pulmonary involvement	Smoking cessation (if applicable), chest radiograph and CT-CAP, pulmonary function tests
Purpuric rashes/mucosal lesions	Skin involvement	Skin biopsy
Diarrhea, weight loss, malabsorption symptoms or hematochezia	Gastrointestinal involvement	Endoscopy with biopsy or capsule endoscopy, stool studies
Hearing impairment, chronic otorrhea	Mastoid involvement	Head MRI, formal hearing assessment

CT-CAP = CT of chest, abdomen, and pelvis with oral and intravenous contrast, PET-CT = positron emission tomography CT, TSH = thyroid stimulating hormone, T4 = thyroxine

Di Caprio R J AM Act Ort Sur 2014

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]

European Journal of Internal Medicine 51 (2018) 61–67

18 adult patients (7M/11F) were evaluated for:

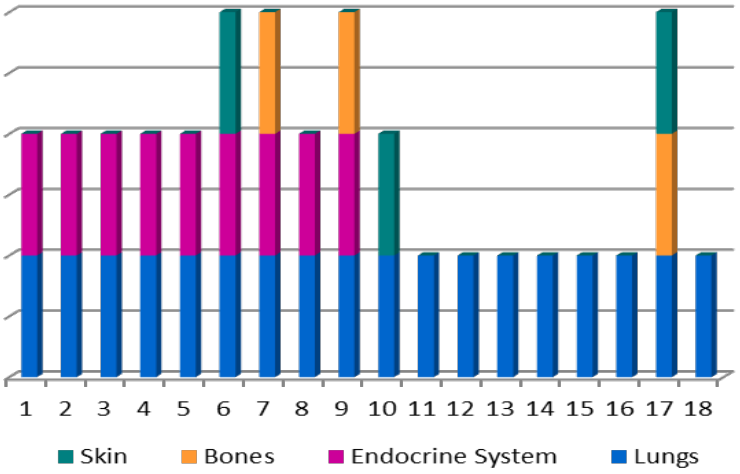
-Endocrine involvement: basal (early morning plasma and urine osmolarity, serum cortisol, fT4, fT3, TSH, PRL, GH, IGF-I, LH, FSH and in men total testosterone, albumin and SHBG) and dynamic endocrine lab tests (1 mcg ACTH test, Arg+GHRH test),

-Glucose metabolism: (basal and post-OGTT glucose levels, HbA1c, fasting and post load insulin levels, HOMA-I, BMI, hypertension and lipid metabolism).

-Thyroid involvement: US thyroid scan, AB Tg, AB TPO.

Results

9 pts (50%) showed endocrine involvement:



- 9 DI
- 5 Growth Horm. Defic.
- 5 Gonadotropines Defic.
- 4 hypothyroidism
- 1 hypoadrenalism

Moreover
- 2 Hyperprolactinemia
- 2 Hypothalamic syndrome

5 of the 10 brain MRI performed had abnormalities (hyper-intense focal lesion, empty sella or thicker hyperintense pituitary gland).

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European Journal of Internal Medicine 51 (2018) 61–67

Results of the Metabolic evaluations

	LCH population	General population (35-45 years , ISTAT DATA 2009)
Obesity	39%	7,7%
Glucose alterations (IFG/IGT)	28%	11,7%
Diabetes	5%	0,9%
Metabolic Syndrome	39%	22%

Results: Thyroid evaluations

12 patients thyroid US scan:
5 structure inhomogeneity without focal lesions
2 multinodular goiter, one underwent e thyroidectomy with the finding of a papillary multifocal micro-carcinoma BRAF-V600E mutation positive

Bone involvement

- Bone involvement is known to occur in PLCH as demonstrated in several retrospective analysis. Nevertheless, in these studies is not clear if X-rays were performed consequently to the occurrence of specific symptoms or signs or as a routinary follow up.

- Tazi et al. evaluated 51 PLCH pts at the time of diagnosis with a skeletal X-ray: bone involvement was found in 2 pts asymptomatic and stable over 2 years . Of 47 pts who received dental panoramic, 3 showed abnormalities not related to the disease (no presence of mandibulary/maxillary lesions).

- A complete clinical history and a comprehensive physical examination to search for extrapulmonary involvement in adult PLCH patients is important. However, in the absence of symptoms or signs suggestive of bone LCH involvement, the systematic use of specific imaging does not appear informative.

Tazi et al. Orphanet Journal of Rare Diseases 2016

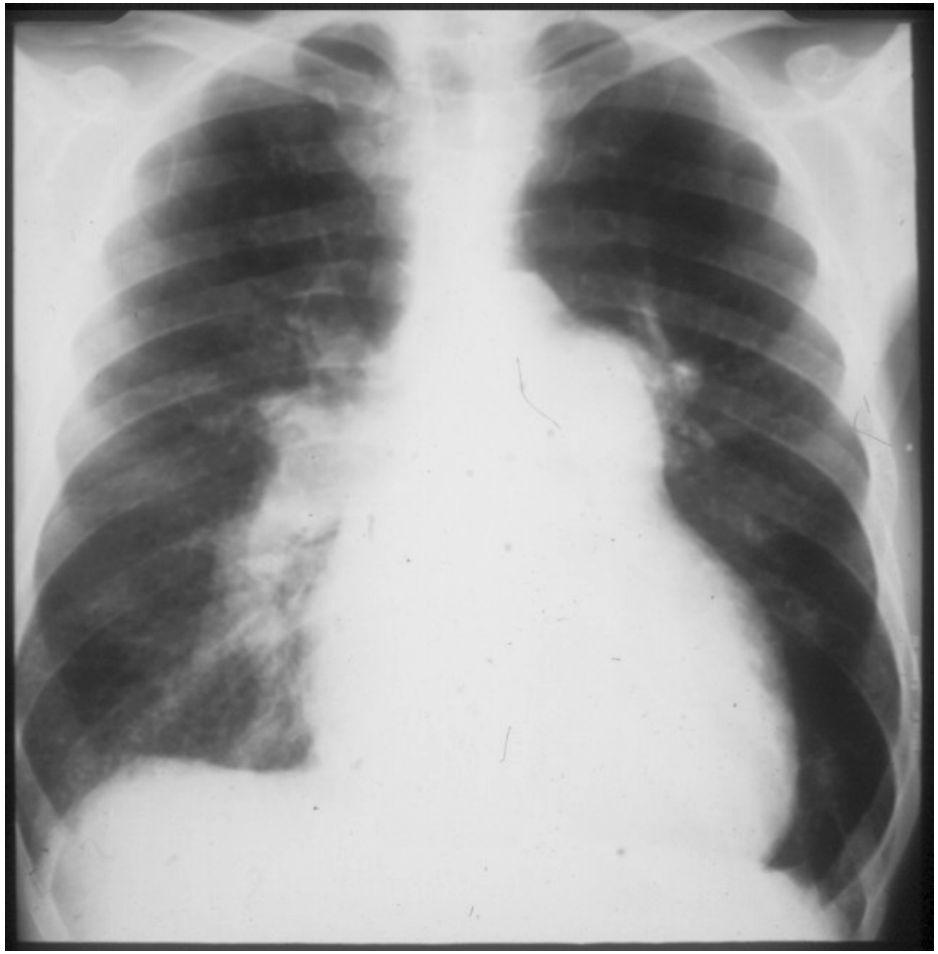
PLCH and Pulmonary Hypertension

It is more frequent in advanced disease and is related to an intrinsic pulmonary vascular disease in which pulmonary circulation is involved independently from small airways and lung parenchyma involvement

It is more frequently moderate-severe (PAPm ≥ 35mmHg)

It may also develop independently from the stage of the disease

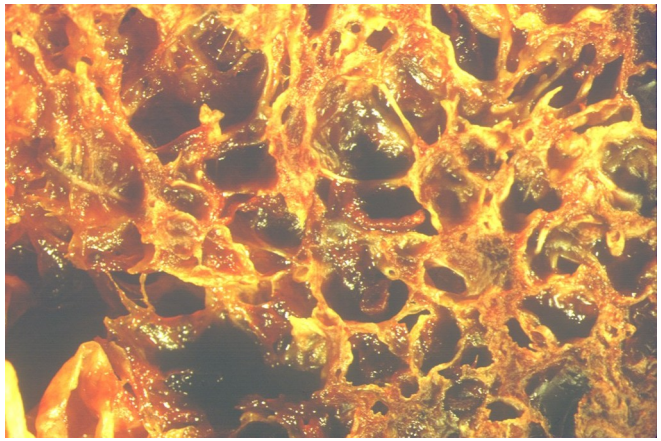
Harari S Chest 1997;
Harari S J Heart Lung Trans 1997;
Dauriat G Transpl 2016



Hemodynamic and spirometric findings in patients with chronic ILD referred for lung or heart-lung transplantation

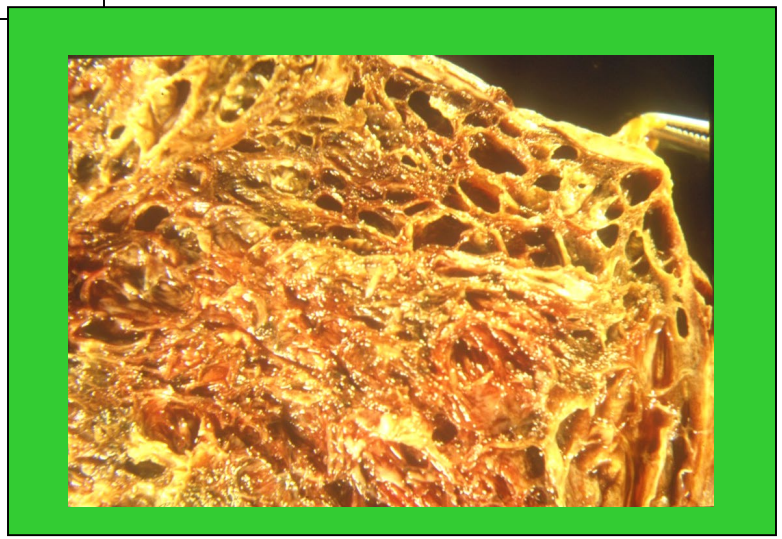
Hemdynamic data respiratory function values	43 IPF (mean ± sd)	18 PLCH (mean ± sd)	6 LAM (mean ± sd)	t Test results		
				IPF/Hx	IPF/LAM	Hx/LAM
FEV_1	43.6 ± 13.8	42.8 ± 15.5	31.1 ± 14.5			
TLC	52.3 ± 21.7	99.9 ± 18.8	97.1 ± 14.5	p <0.0005	p <0.0005	
Tiffenau	93.7 ± 18.7	55.4 ± 13.9	48.5 ± 15.0	p <0.0005	p <0.0005	
PaO_2	56.8 ± 21.3	57.7 ± 10.6	63.1 ± 11.2			
$PaCO_2$	40.1 ± 66.7	37.9 ± 6.22	45.3 ± 17.9			
PAPs	53.5 ± 18.6	83.9 ± 18.3	40.0 ± 15.3	p <0.0005		p <0.0005
PAPd	23.1 ± 8.14	40.2 ± 10.6	15.0 ± 5.15	p <0.0005	p <0.005	p <0.0005
PAPm	33.6 ± 10.6	55.9 ± 12.0	26.0 ± 2.52	p <0.0005	p <0.0005	p <0.0005
CI	3.18 ± 0.82	2.77 ± 0.71	3.94 ± 0.72		p< 0.05	P<0.005
WP	9.20 ± 5.70	8.36 ± 3.30	4.23 ± 0.55		p< 0.0005	p< 0.0005
RVPi	8.30 ± 4.8	17.6 ± 6.50	3.71 ± 0.67	p< 0.0005	p< 0.0005	p< 0.0005

Harari S., et coll. JHLT 1997 Apr;16(4):460-463



PLCH

LAM



1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
  1.2.1 BMPR2 mutation
  1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
  1.4.1 Connective tissue disease
  1.4.2 Human immunodeficiency virus (HIV) infection
  1.4.3 Portal hypertension
  1.4.4 Congenital heart disease (Table 6)
  1.4.5 Schistosomiasis

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1′.1 Idiopathic
1′.2 Heritable
  1′.2.1 EIF2AK4 mutation
  1′.2.2 Other mutations
1′.3 Drugs, toxins and radiation induced
1′.4 Associated with:
  1′.4.1 Connective tissue disease
  1′.4.2 HIV infection

1″. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

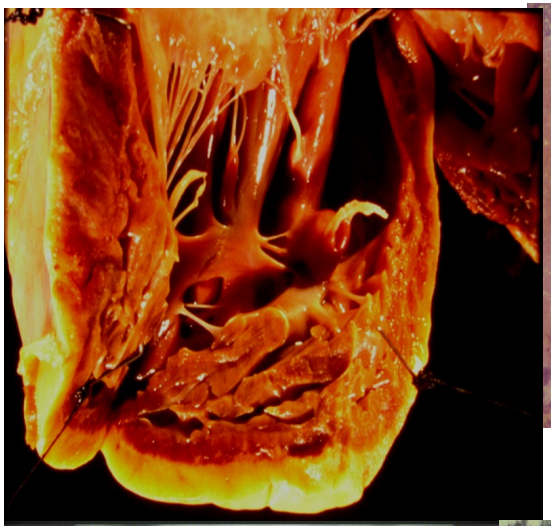
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
  4.2.1 Angiosarcoma
  4.2.2 Other intravascular tumors
  4.2.3 Arteritis
  4.2.4 Congenital pulmonary arteries stenoses
  4.2.5 Parasites (hydatidosis)

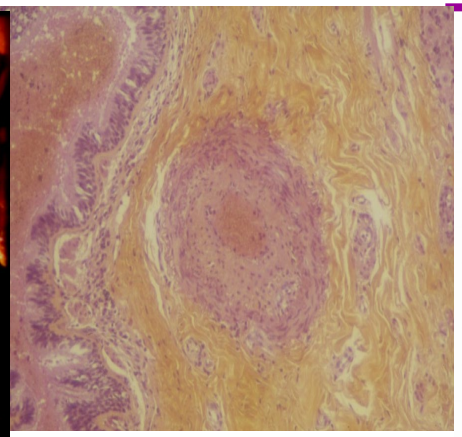
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

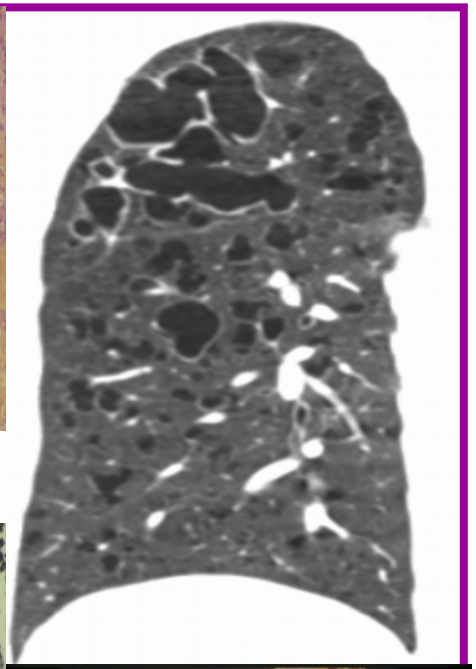
PLCH is in group 5 PH

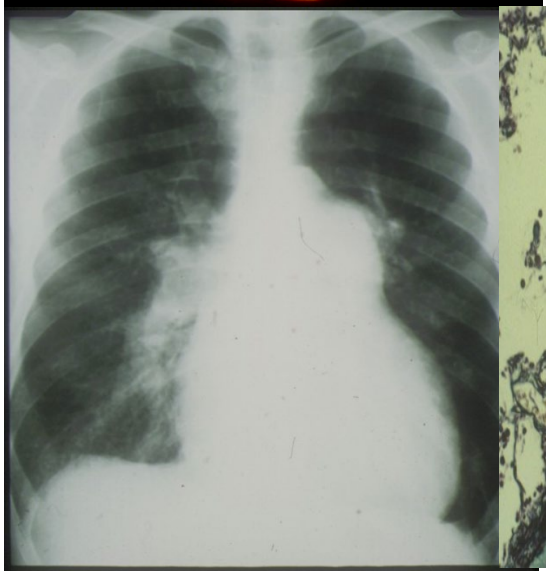
ESC/ERS Guidelines 2015

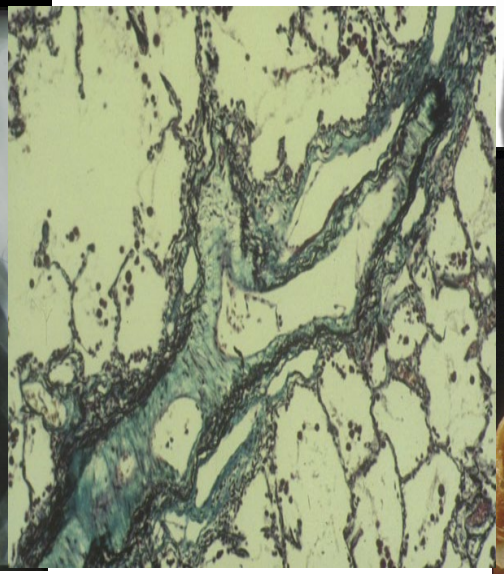


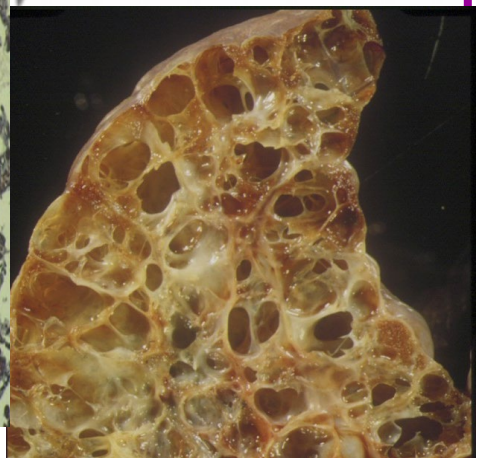


PLCH









Pulmonary Langerhans Cell Histiocytosis-Associated Pulmonary Hypertension

Clinical Characteristics and Impact of Pulmonary Arterial Hypertension Therapies

Jérôme Le Pavec, MD, PhD; Gwenaël Lorillon, MD; Xavier Jaïs, MD; Colas Tcherakian, MD; Séverine Feuillet, MD; Peter Dorfmüller, MD, PhD; Gérald Simonneau, MD; Marc Humbert, MD, PhD; and Abdellatif Tazi, MD, PhD

- 29 consecutive patients with PLCH and PH confirmed with RHC were included
- 83% of patients were in WHO functional class III to IV; interval between PLCH and PH diagnosis of 9.2 ± 9.8 yrs
- Mean ± SD 6MWD: 355 m ± 95 m
- mPAP: 45 ± 14 mmHg
- Use of PAH therapy in 12 patients was followed by an improvement in mPAP (56 ± 14 mmHg and 45 ± 12 mmHg, p> 0.05) between baseline and follow-up evaluations

Chest 2012; 142; 1150-1157

Recommendation for PH due to lung diseases

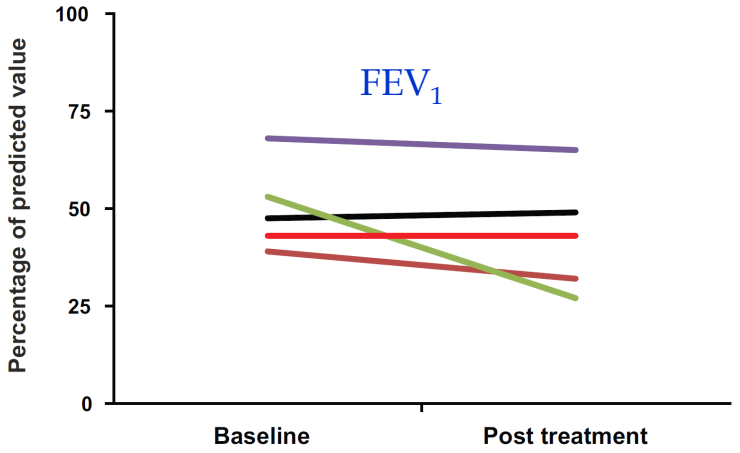
Statement	Class#	Level*f*
Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases	I	C
The optimal treatment of the underlying lung disease including long-term O2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases	I	C
Patients with "out of proportion" PH due to lung diseases should be enrolled in RCTs targeting PAH specific drugs	IIa	C
The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases	III	C

Systemic treatments in PLCH

- Corticosteroids
  - no convincing data on the improvement of lung function
  - even correlated with worth outcome in a retrospective study

  Delobbe et al. Eur Respir J 1996

- Vinblastine
  - Virtually no effects on lung function

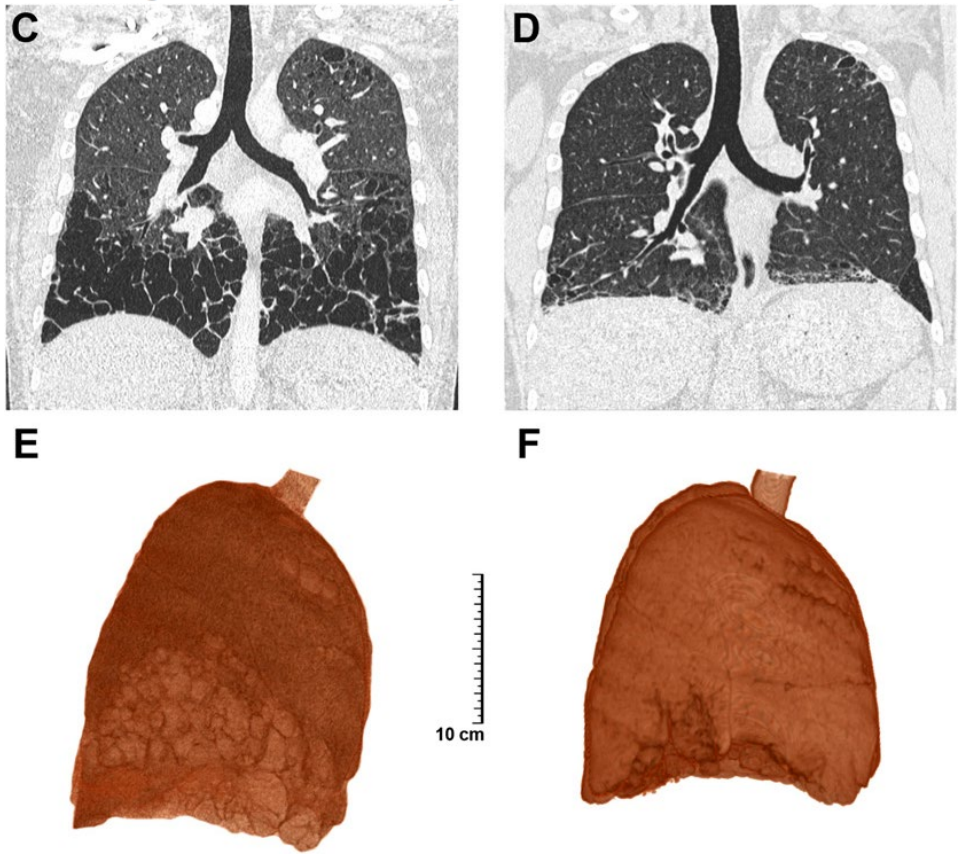


Tazi et al. Orphanet J Rare Dis 2017

Cladribine in PLCH

- 2-CDA: purine analogue
- Toxic for resting monocytes and lymphocytes
- Highly immunosuppressive (prolonged lymphopenia)
- Second-line treatment for MS LCH
- Several cases reports on cladribine efficacy in PLCH
  - *Aerni et al. Respir Med 2008*
  - *Lazor et al. Thorax 2009*
  - *Lorillon et al. Am J Respir Crit Care Med 2012*
  - *Grosbost et al. Orphanet J Rare Disease 2014*
  - *Epaud et al. Eur Respir J 2015*
  - *Nasser et al. ERJ Open Res. 2018*

Cladribine Is Effective against Cystic Pulmonary Langerhans Cell Histiocytosis

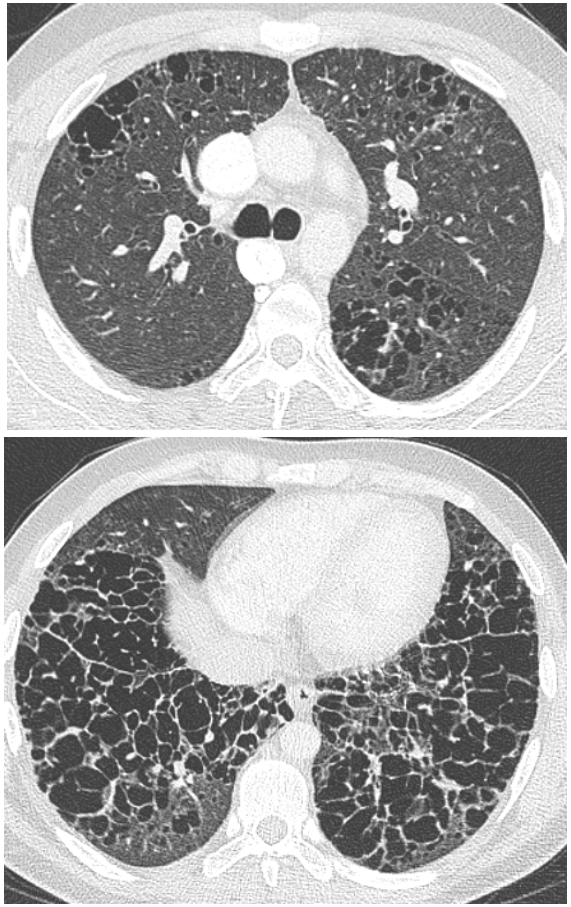


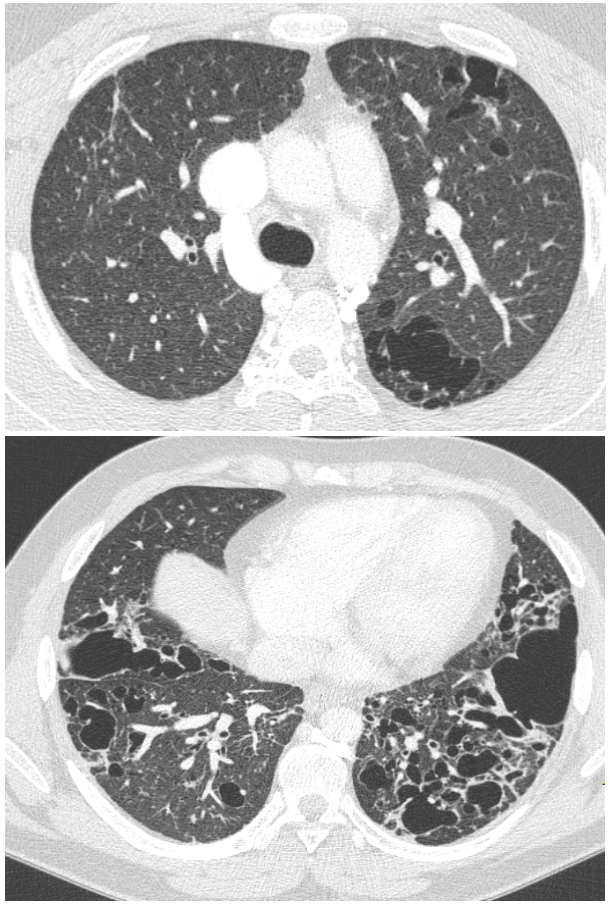
Lorillon et al. AJRCCM 2012

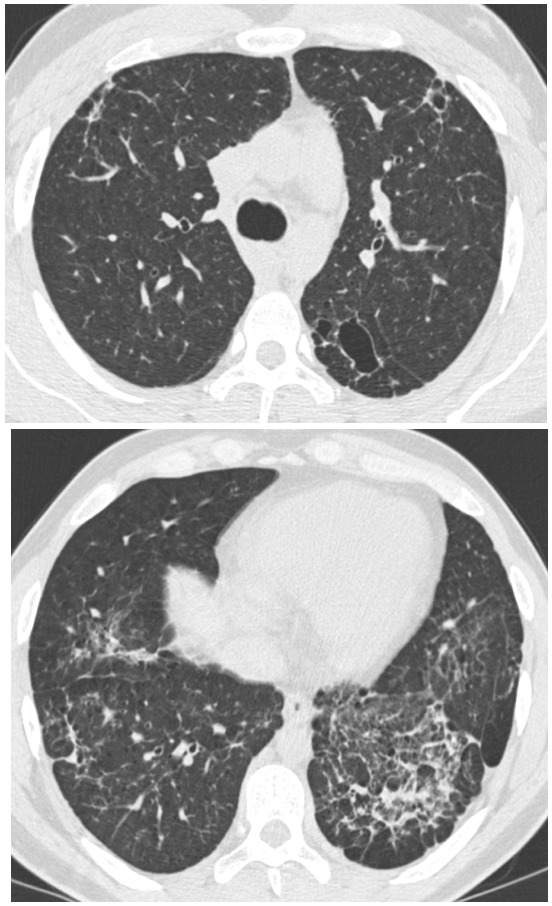
Before treatment

6 months after treatment

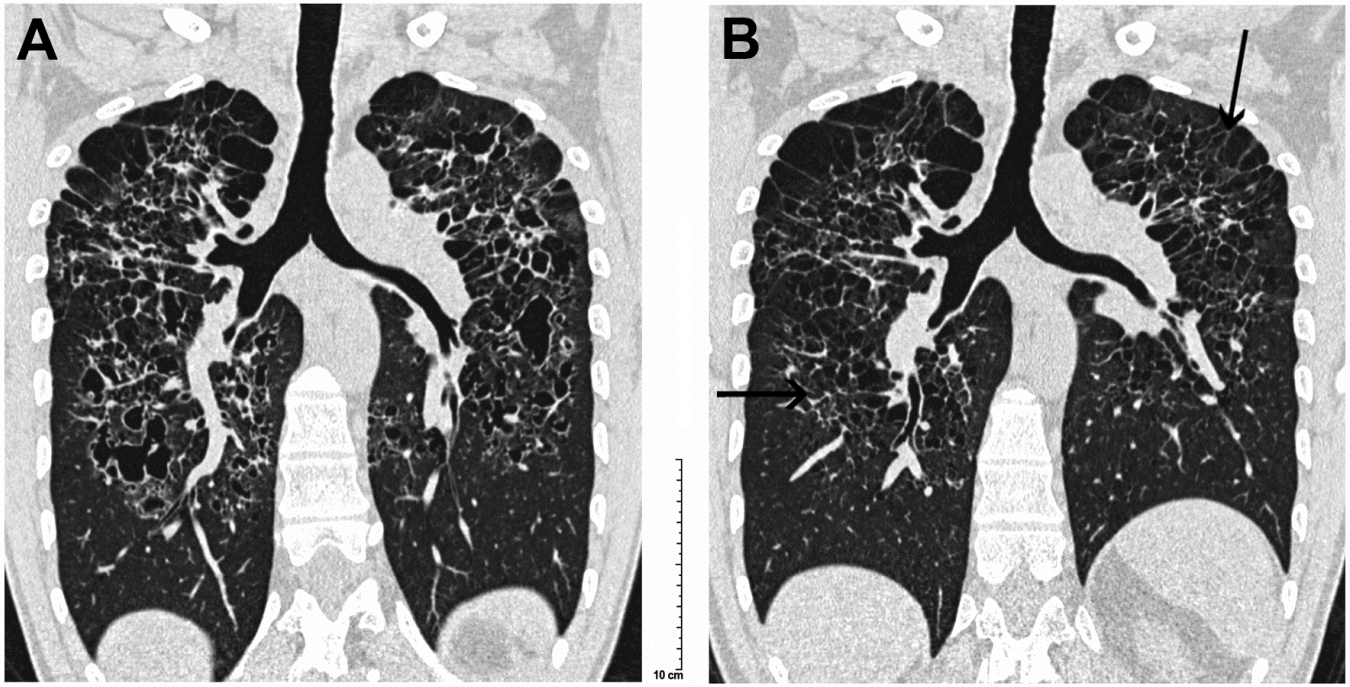
4 years after treatment







Courtesy A. Tazi



Courtesy A. Tazi

	Patient 1				Patient 2				Patient 3			
PFTs	M0	M6	M12	M48	M0	M6	M21*	M48	M0	M6	M16	M-48
TLC	6360	6800	7130		7240	6810	7260	7820	5000	4170	4980	4940
%	73	78	83		93	88	93	100	80	67	79	78
VC	3830	4320	4700		4610	3920	3850	3380	3060	2660	3030	3450
%	57	65	71		80	69	68	60	63	55	63	72
RV	2520	2470	2430		2630	2890	3530	4440	1930	1510	1950	1520
%	133	130	126		134	146	181	217	128	100	129	97
FEV_1	2520	3090	2940	3000	3790	2700	2470	2180	1840	2300	2550	3030
%	42	53	51		78	56	52	46	46	57	63	78
FEV_1/VC	66	72	63		82	67	64	58	73	86	84	88
DL_{CO} %	22	23	26		24	35	35	35	53	53	45	61

*2 additional courses of cladribine

Courtesy A. Tazi

Evaluation of Efficacy and Tolerance of Cladribine in Symptomatic PLCH (ECLA study "NCT01473797")

- Phase II non-randomized pilot study (n=10); age >16 and ≤ 55 years

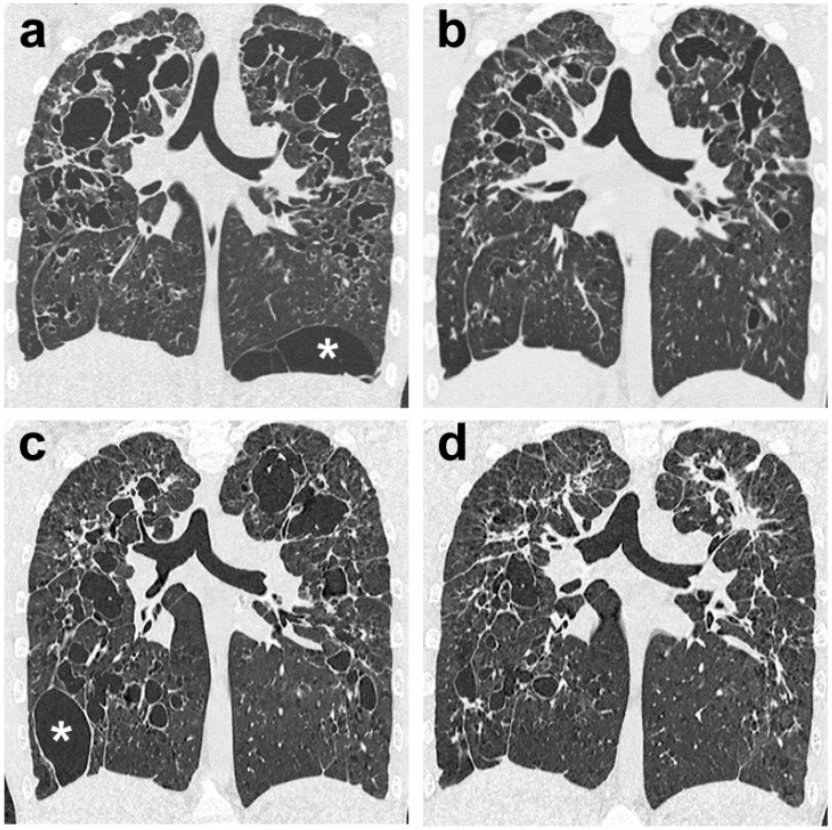
- Symptomatic PLCH (NYHA class ≥2)
  - $FEV_1/FVC<70\%$ and postβ2 FEV_1=30-70% of predicted
  - and/or decrease ≥15% in FEV_1, FVC or DLCO in the year before inclusion
  - without respiratory failure or PH

- Cladribine (Litak®)
  - 5 sc consecutive injections (0.1 mg/kg/d)
  - 4 monthly cycles
  - prolonged infection prophylaxis

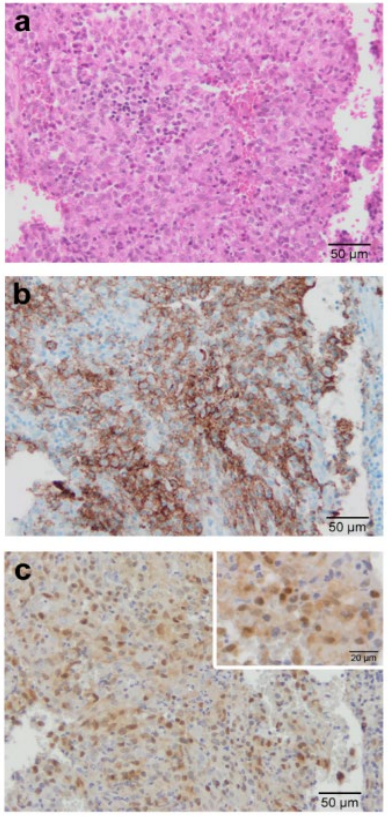
- Primary outcome : cumulated incidence of response at 6 months
  - ≥10% improvement of FVC
  - and/or ≥10% improvement of post β2 FEV_1 and ≥200ml
  - evaluation at M3,6,9,12,18,24….M48

Response to Trametinib of a Pulmonary Langerhans cell Histiocytosis Harboring a MAP2K1 deletion

cladribine



trametinib



HES

CD1a

p-ERK1/2

Lorillon et al. AJRCCM 2018

Summary

- Better knowledge of short- and middle-term natural history
- Progress:
  - patients' monitoring
  - treatment
- Smoking cessation essential (difficult)
- Need for better knowledge of long term outcome (ongoing)
  - identification of robust predictive factors (biomarkers)
- Pathogenesis of LCH
  - myeloid neoplasia of variable severity with inflammation
  - MAPK pathway++
  - animal model++
  - etiology?
- MAPK-targeted treatments (BRAF, MEK inhibitors, combination)
  - selected patients progressive refractory disease
  - duration? side effects++

Follow-up

- During the first years after the diagnosis a complete evaluation with PFT and other tests, if clinically required, every 3-4 month is recommended

- After that an annual follow up for minimum 5 years is recommended

- The role of repeated CT scan imaging is not clear, and decisions must be taken by the clinician case by case

Vassallo R , Harari S , Tazi A Thorax 2017

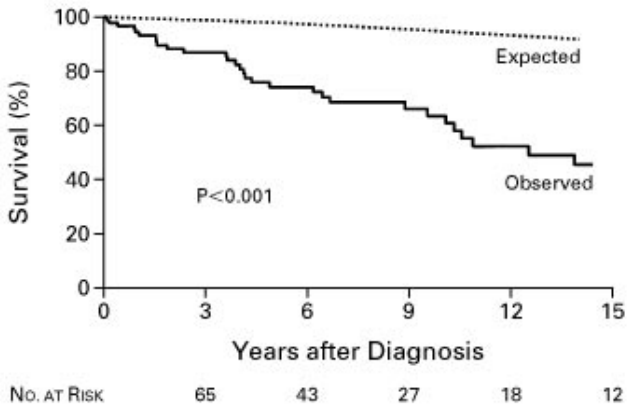
PLCH and cancer

- The diagnosis of lymphoma, multiple myeloma, adenocarcinoma and othe solid tumors before, after or at the same time of the PLCH diagnosis has been described.
- Due to small numbers of patients described and the retrospective nature of the studies, a definite conclusion about the relative risks of different cancers, expecially myeloprolifertive disorders, cannot be drawn
- Cigarette smoking, prior treatment with chemotherapeutic agents, and chromosomal or genetic abnormalities are factors that may confer a predisposition to the development of malignant neoplasm in patients with PLCH

Vassallo R. NEJM 2002
Egeler RM Hematol Oncol Clin North Am 1998

PLCH - Prognosis

Survival of adults with PLCH



Vassallo, NEJM 2002

In an 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) **Delobbe J ERJ 1996**

Table 5. Factors That Are Associated With Poor Outcome in Patients With Pulmonary Langerhans Cell Histiocytosis[a]

Extremes of age
Prolonged constitutional symptoms
Multiorgan involvement
Extensive cysts, honeycomb changes
Severe decrease in diffusing capacity
Obstructive lung function
Prolonged treatment with steroids
Pulmonary hypertension

[a] Data derived from Vassallo et al.[2]

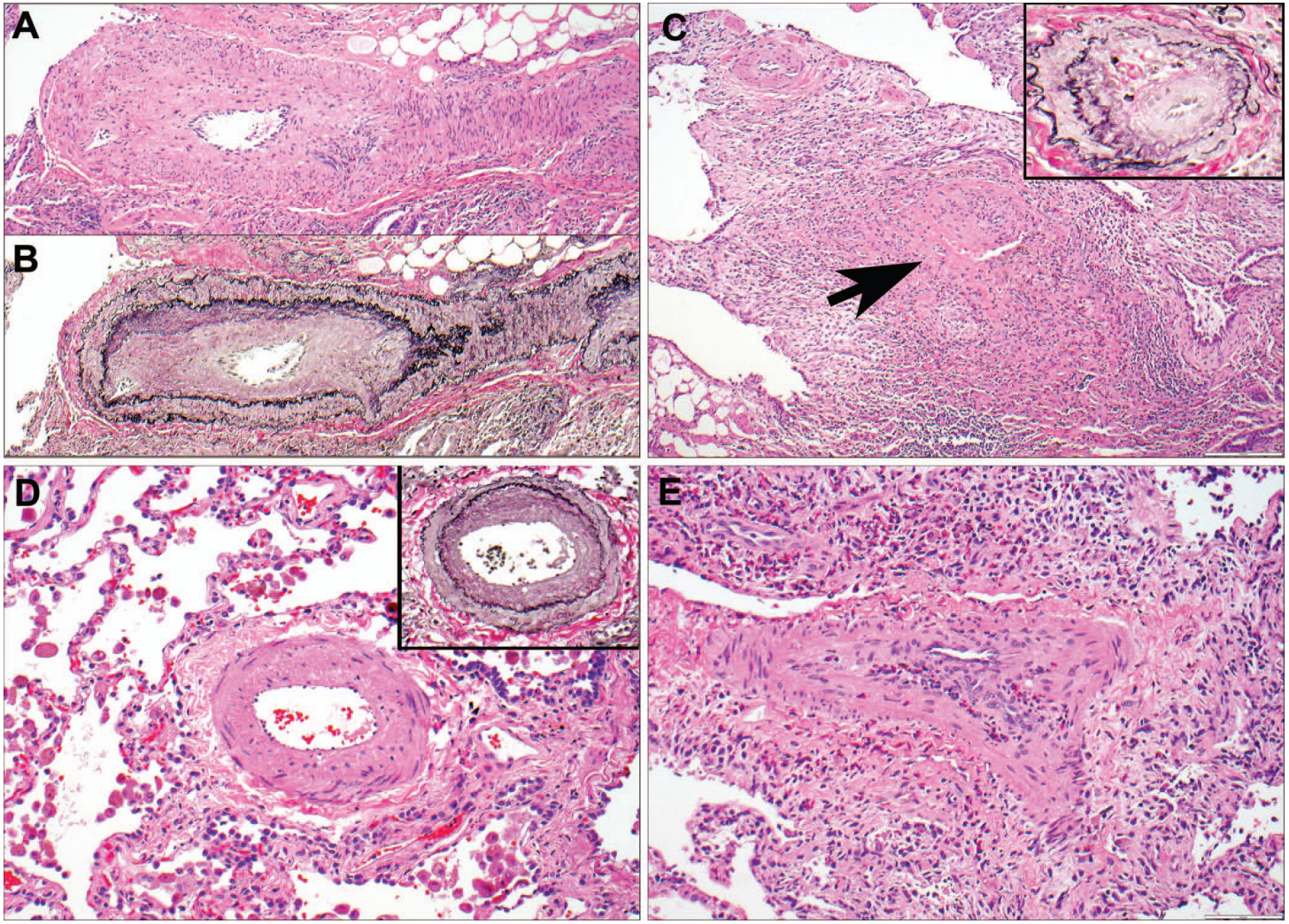
Take Home Messages

- A careful medical and clinical history assessment must be performed, with particular attention to ENT, dental, cardiac, pulmonary, lymphonodal and endocrine system (complete blood count analysis, serum electrolytes, liver function studies, and urine osmolality testing).
- In selected patients, when extra-pulmonary disease is suspected because of focal symptoms (bone pain, etc) or constitutional symptoms (weight loss, fevers, sweats, extreme fatigue), imaging with a PET scan may provide evaluation of disease extent (staging) with high sensitivity.

Take Home Messages

- PH should be considered in PLCH patients when a level of oxygen desaturation higher than expected during 6MWT or CPET is associated to a DLCO decline.
- Clinicians should take in consideration the possibility of the development of malignancies in patients affected by PLCH. Although a high rate of lymphoma has been described, an increased incidence of primary lung cancer (related to smoking history), and various other types of malignant tumours, has been reported

Back up slides

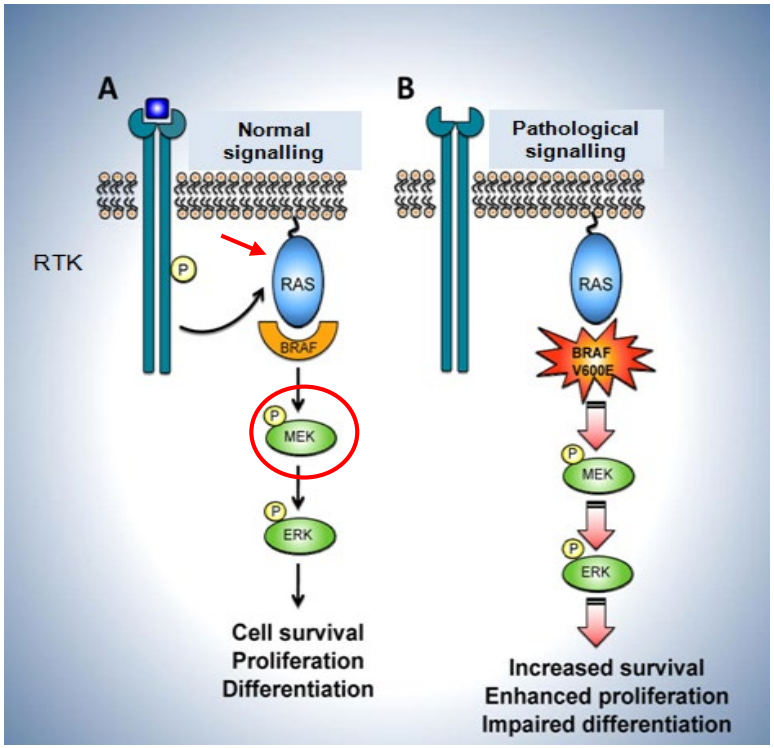


Arch Pathol Lab Med. 2016;140:230–240

Recurrent *BRAF* mutations in Langerhans cell histiocytosis

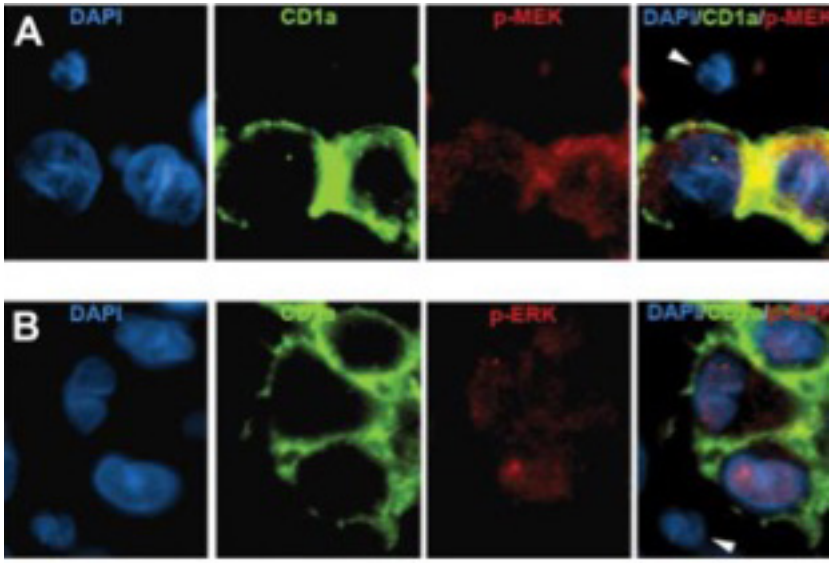
Gayane Badalian-Very,[1-3] Jo-Anne Vergilio,[4,5] Barbara A. Degar,[6-8] Laura E. MacConaill,[9] Barbara Brandner,[1-3] Monica L. Calicchio,[4] Frank C. Kuo,[5,10] Azra H. Ligon,[5,10,11] Kristen E. Stevenson,[12] Sarah M. Kehoe,[9] Levi A. Garraway,[1-3,9,13] William C. Hahn,[1-3,9,13] Matthew Meyerson,[1,2,9,13] Mark D. Fleming,[4,5] and Barrett J. Rollins[1-3]

Blood 2010



Nichols KE and Arceci RJ Blood 2010

p-MEK



p-ERK

Brown et al. Blood 2014
Chakraborty et al. Blood 2014

Yousem et al. Chest 2013

Chilosi et al. Leuk Lumphoma 2014

Roden et al. Am J Surg Pathol 2014

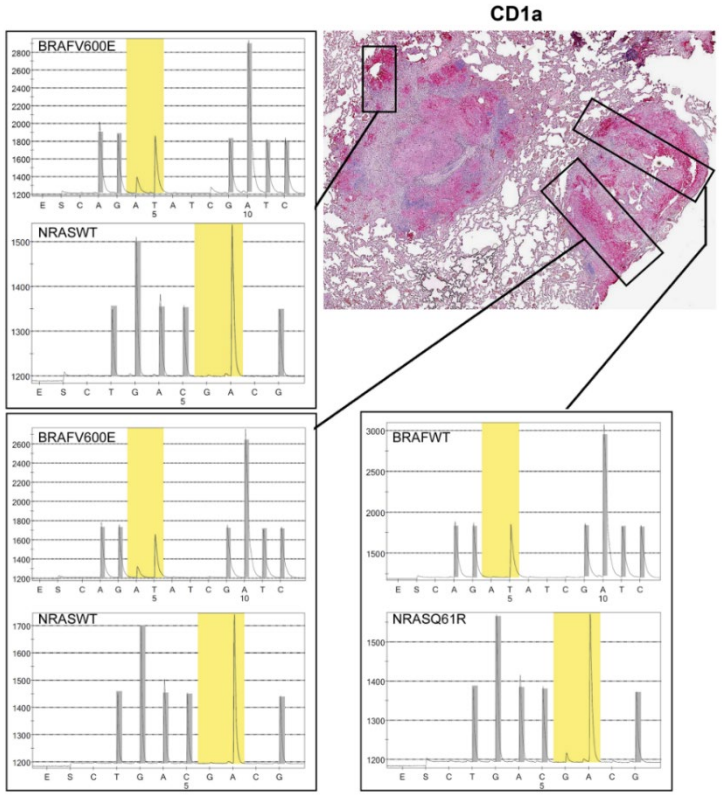
Kamionek et al. Histopathology 2016

Zeng et al. Hematol Oncol 2016

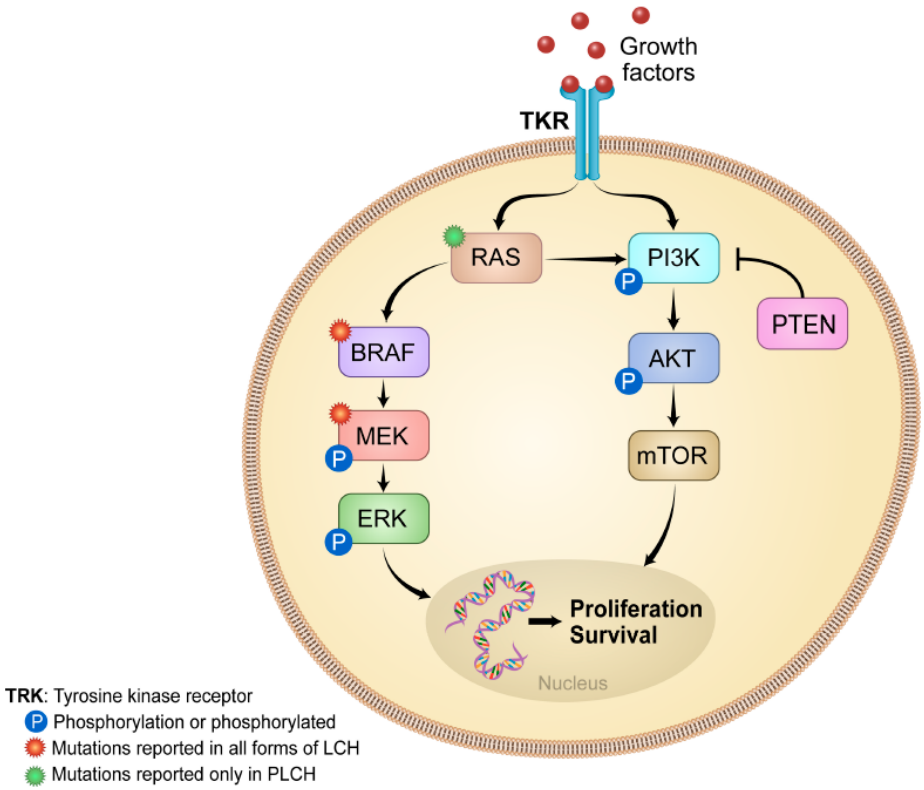
Alayed et al. Human Pathol 2016

Mourah et al. Eur Respir J 2016

Recurrent *NRAS* mutations in pulmonary Langerhans cell histiocytosis



Mourah et al. Eur Respir J 2016



Vassallo R, Harari S, Tazi A. Thorax 2017