Istiocitosi X e Limfangioleiomiomatosi

Sergio Harari

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

XIII Disease's Management in Medicina Respiratoria
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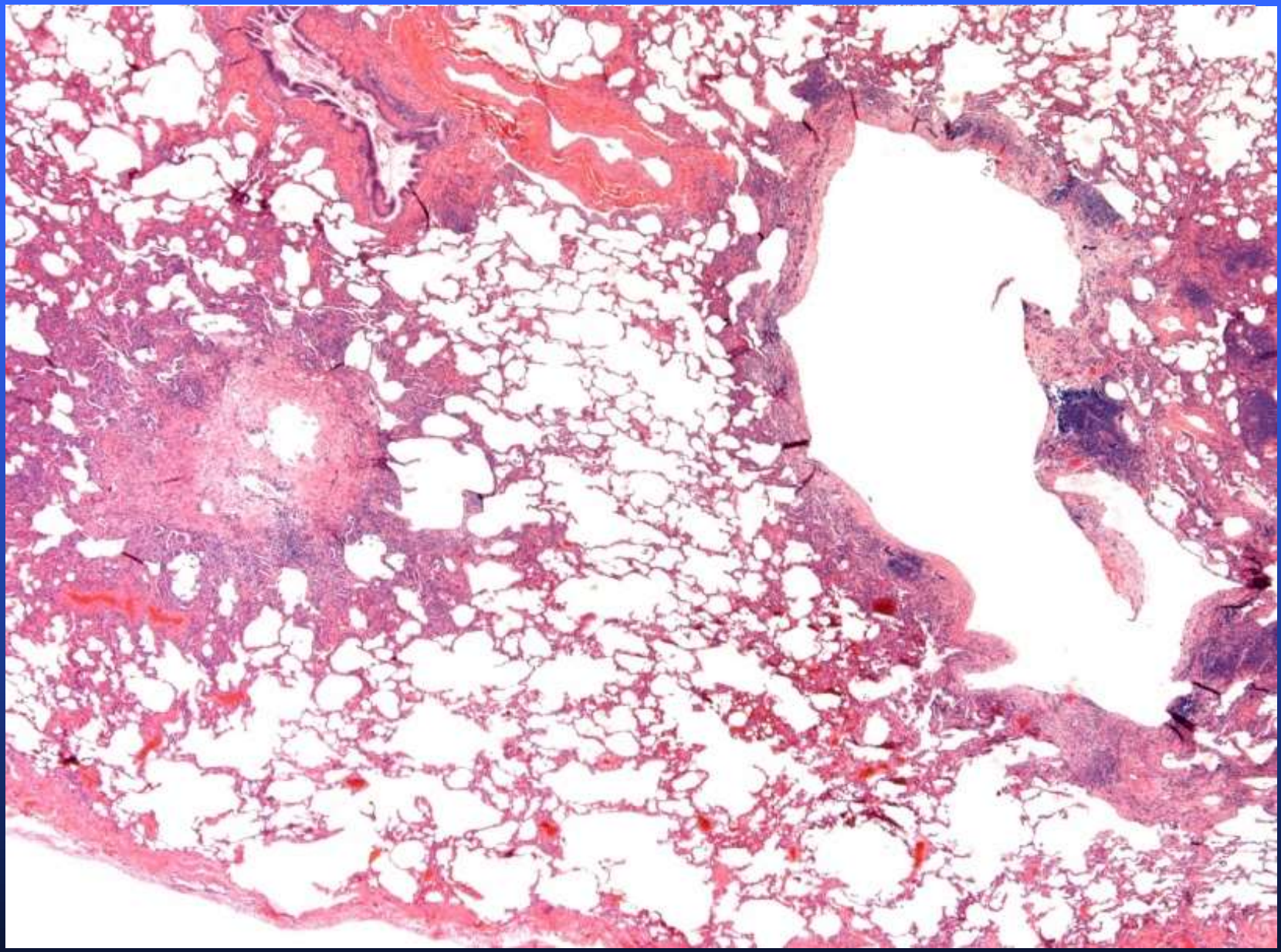
Pulmonary Langerhans' cell Histiocytosis (PLCH)

- 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 0,27/100000 Females 0,07/100000	

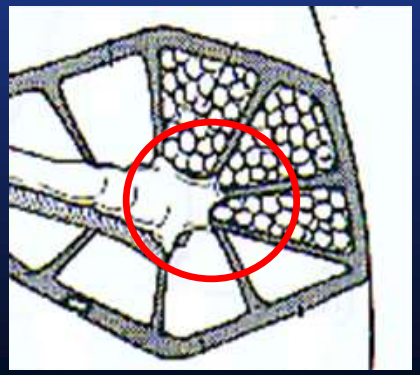
A similar proportion of males and females, or even a slight predominance of females, was observed

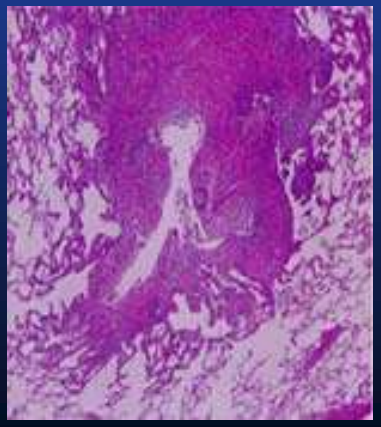
PULMONARY FUNCTION AT DIAGNOSIS

		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	Unpub.	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

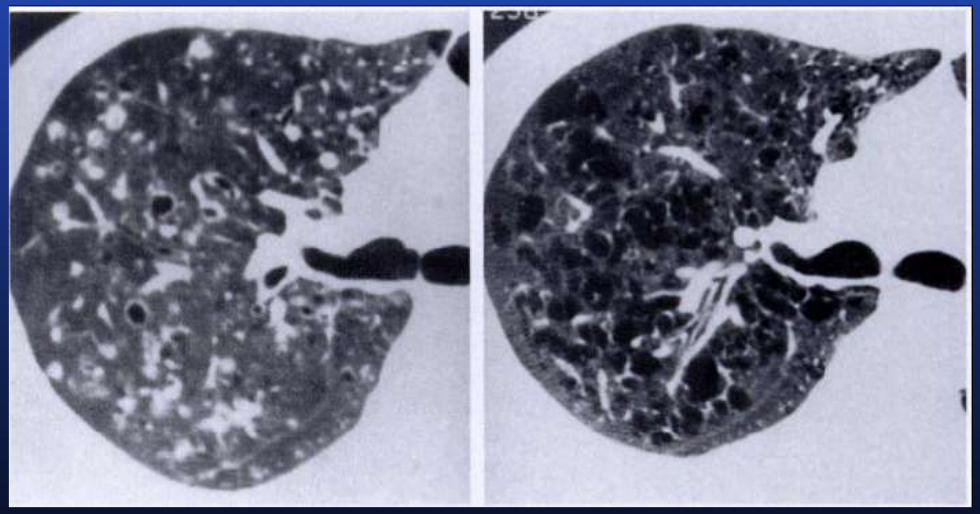




PLCH: evolution of lesions on CT scans

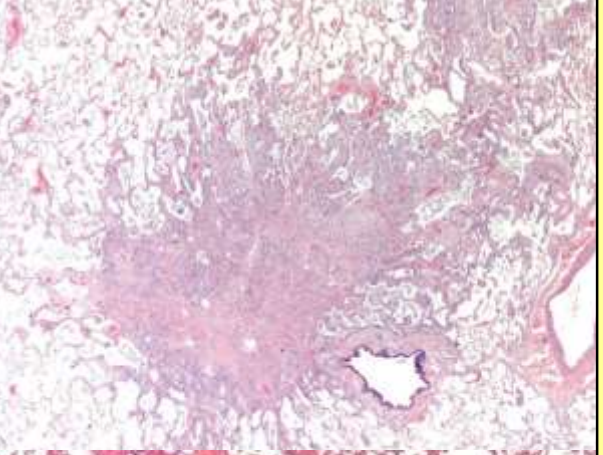
Longitudinal observation of CT features suggest the following evolutionary sequence for pulmonary lesions of PLCH:

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



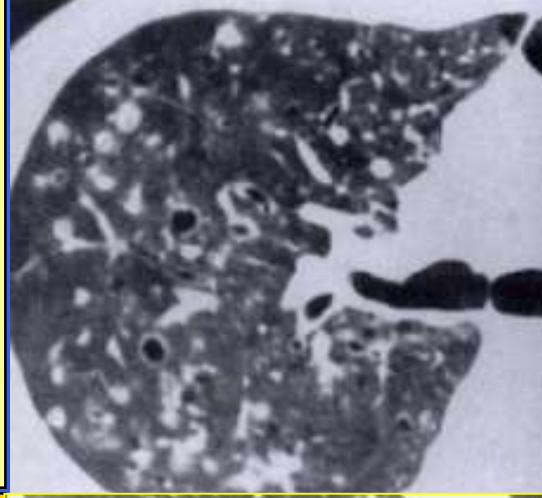
Brauner et al. Radiology 1997

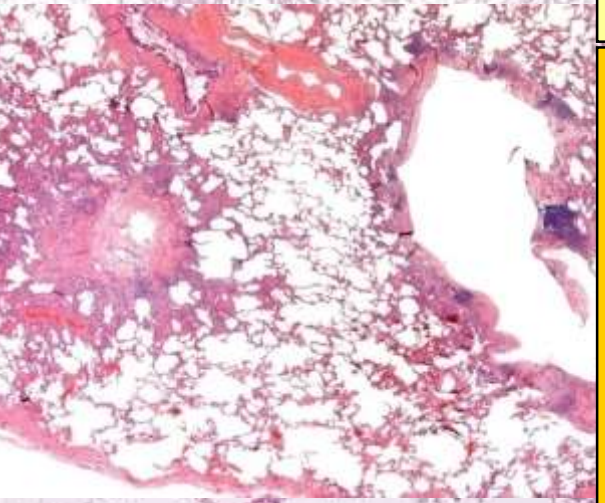
Harari et al. AJRCCM 1997;155 (4) A 329



➢ *Early stage:*

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

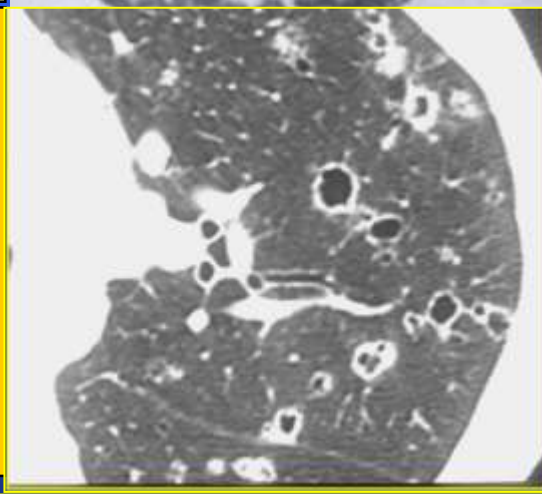


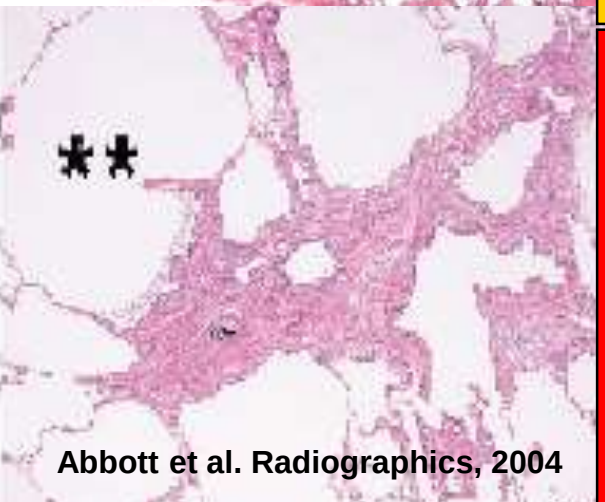


➢ *Disease progression:*

Increasing numbers of nodules and **cavitary nodules**

Appearance of **fibrotic scars**

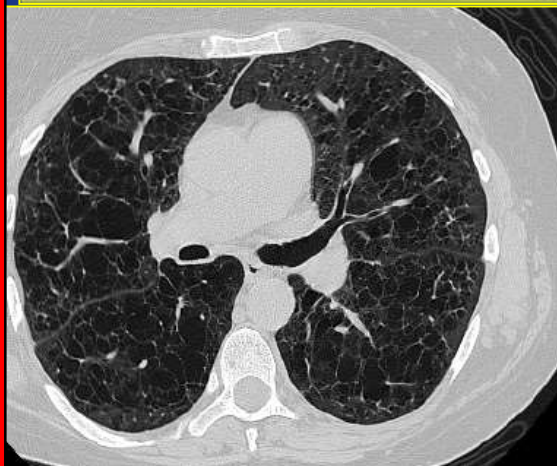




Abbott et al. Radiographics, 2004

➢ *End stage:*

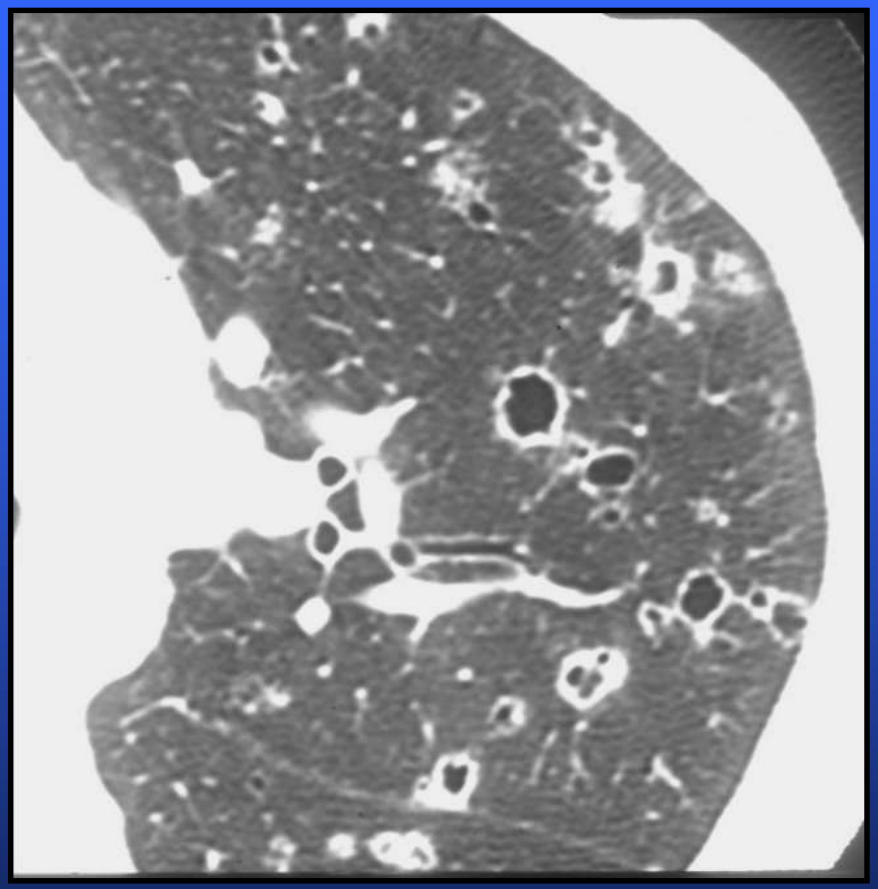
Prominent fibrotic scars surrounding **cystic spaces** of variable diameter and paracicatricial enphysema

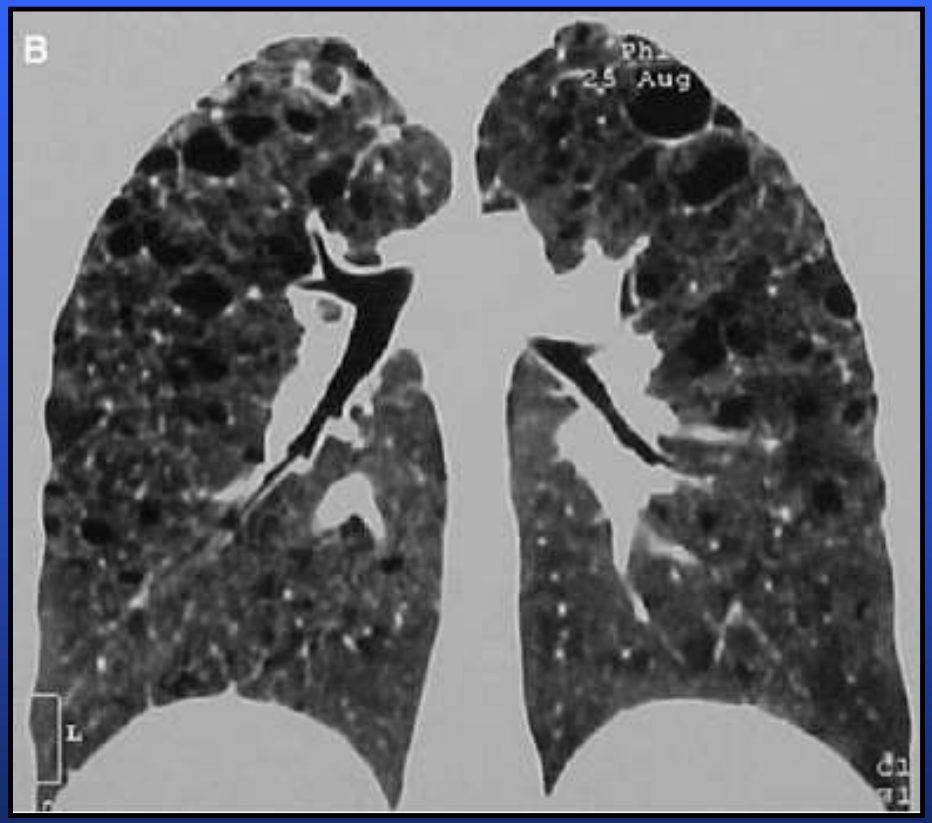


PLCH - Symptoms

Dyspnea	40-87%
Cough	56-70%
Chest Pain	10-21%
Hemoptysis	13%
Pneumothorax	25%
Chylothorax	0%

PLCH - RADIOLOGYCAL FEATURES





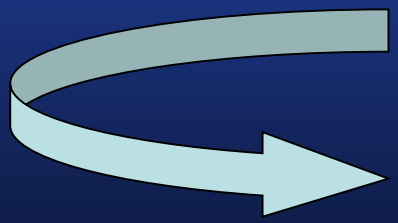
The combination of multiple cysts and nodules with a mid to upper zone predominance and sparing of lung bases in a young smoker is so characteristic that may be diagnostic

Harari et al. Proc Am Thorac Soc, 2006

DIAGNOSIS

- medical history
  clinical setting
  radiological features (HRCT)

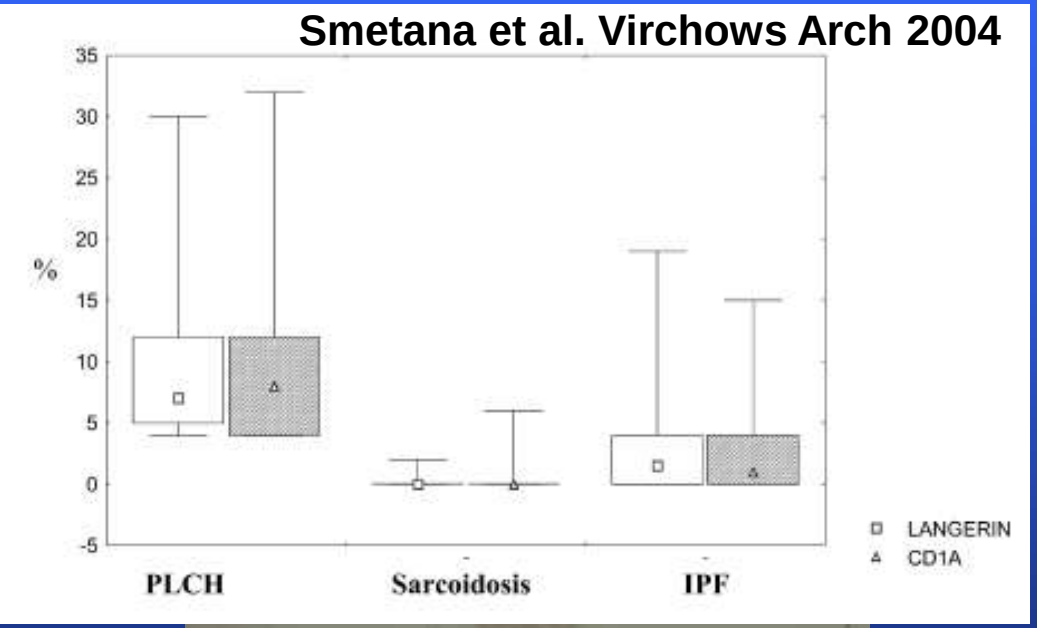
- morphologic confirmation

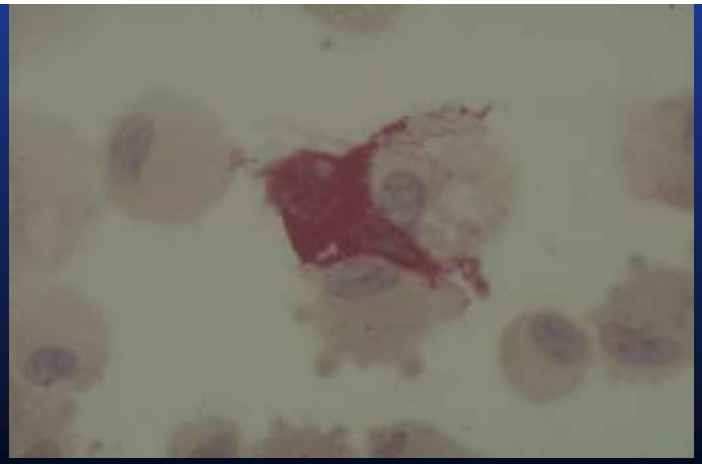


- **Surgical lung biopsy**
- ***TBB***
- ***BAL***

BAL and TBB in PLCH

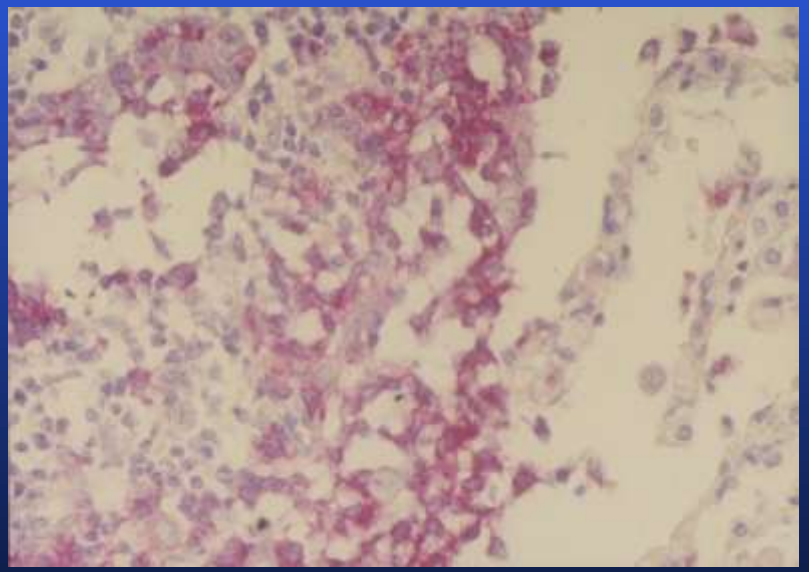
BAL





TBB

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



PLCH

CASES FROM 1997 TO 2008

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

- ***7 pts → extrapulmonary involvement***
  - **3 pts with pulmonary involvement and bone granuloma**
  - **3 pts with pulmonary and diabetes insipidus**
  - **1 patient with pulmonary and skin involvement**
- ***2 pts → severe respiratory failure and pulmonary hypertension***

Harari S et al, Respir Med. 2012

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

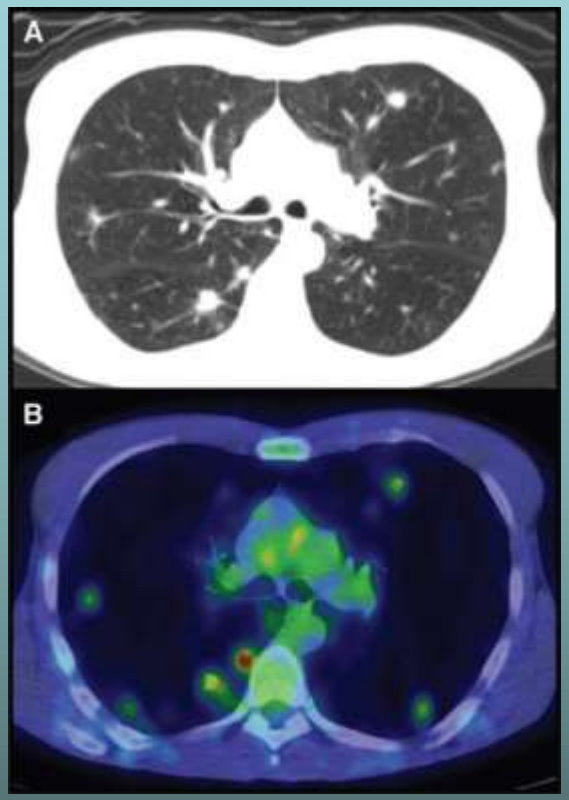
THE ROLE OF SURGICAL LUNG BIOPSY

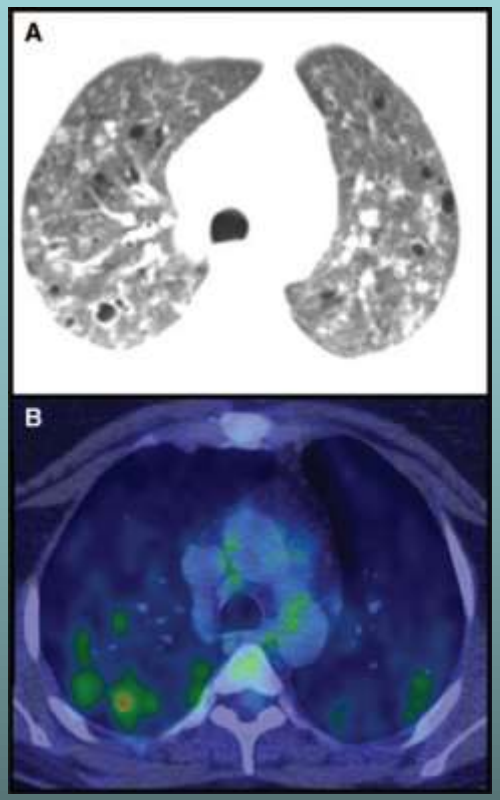
The decision to perform a surgical (VATS or open) lung biopsy depends on

- 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.

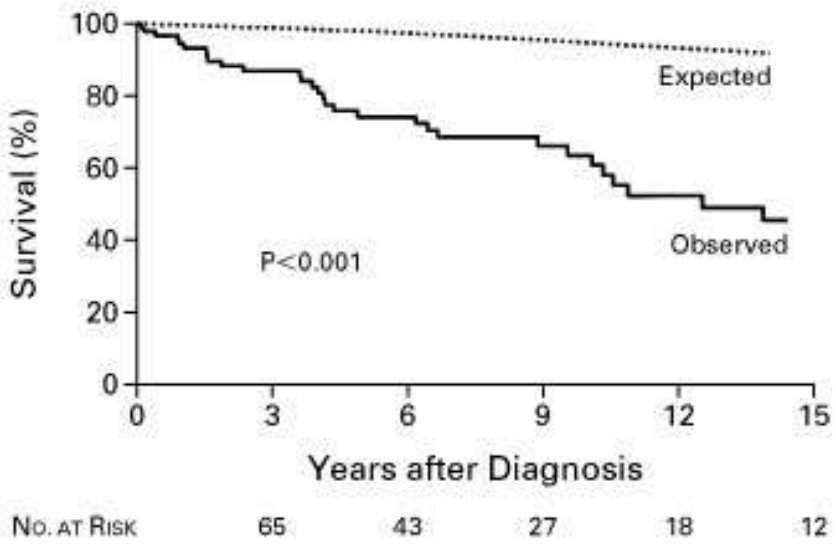
Friedman et al. Medicine 1981
Schonfeld N, et al. Respiration 1993

- 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 DLCO(p=0.001)**

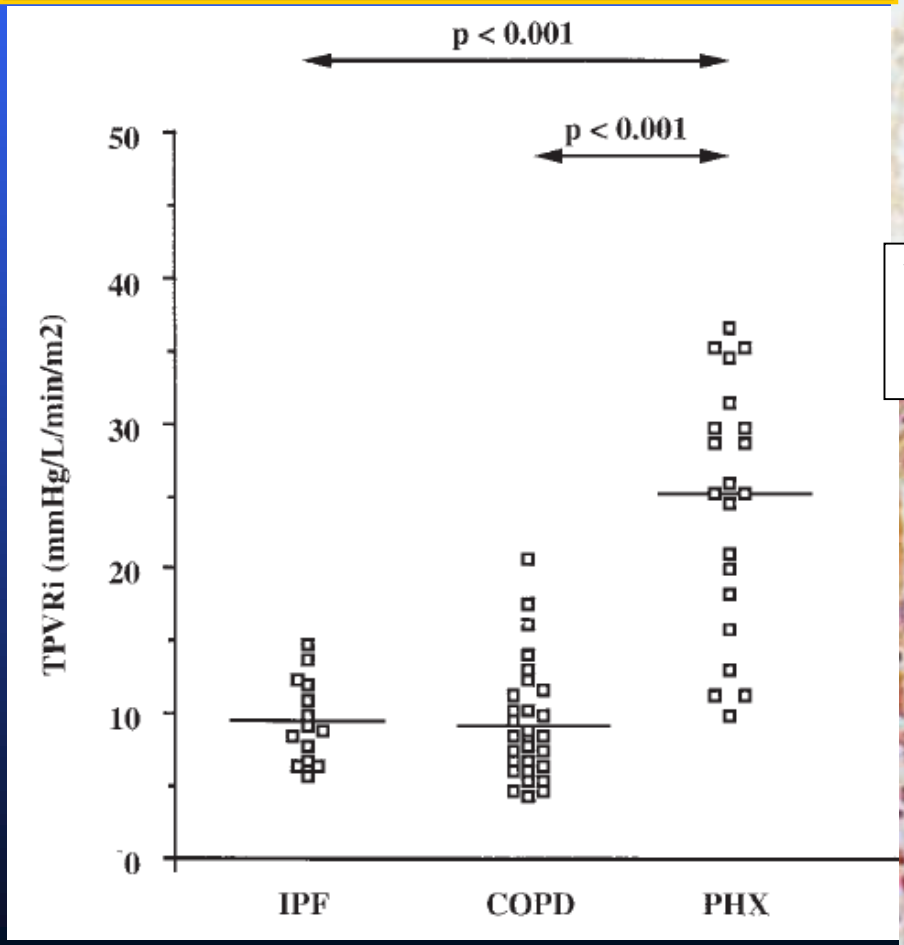
- Chemotherapeutic agents such as vinblastine, cyclophosphamide, chlorambucil, methotrexate, etoposide, and cladribine have been used in patients with progressive disease that is unresponsive to corticosteroids or in those with multiorgan involvement but none has clearly improved the course of the disease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

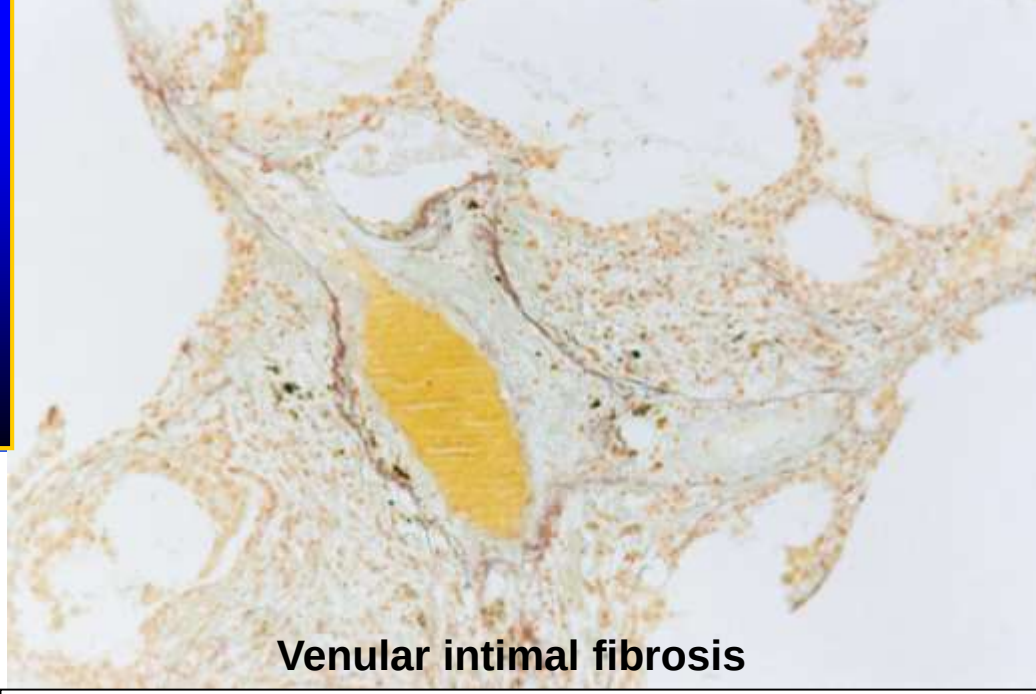
These drugs should be reserved as salvage therapy for patients with progressive disease that is unresponsive to both smoking cessation and a trial of corticosteroid therapy

- Pleurodesis may be needed in patients with recurrent pneumothoraces.

Severe PH in Histiocytosis X

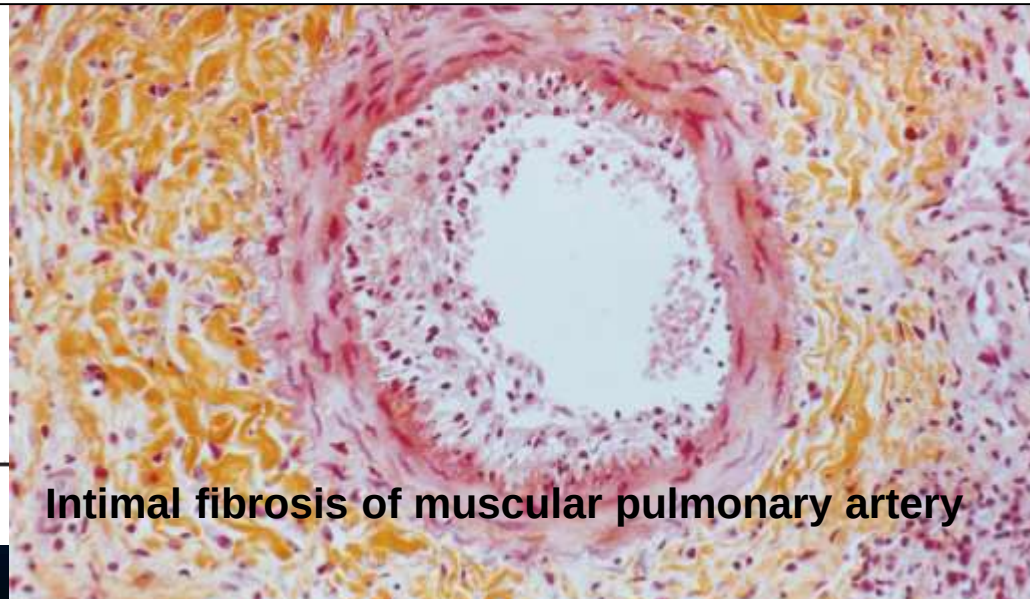
Fartoukh, AJRCCM 2000





Venular intimal fibrosis

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



Intimal fibrosis of muscular pulmonary artery

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

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

TABLE 1 Overview of clinical, functional and haemodynamic features

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

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

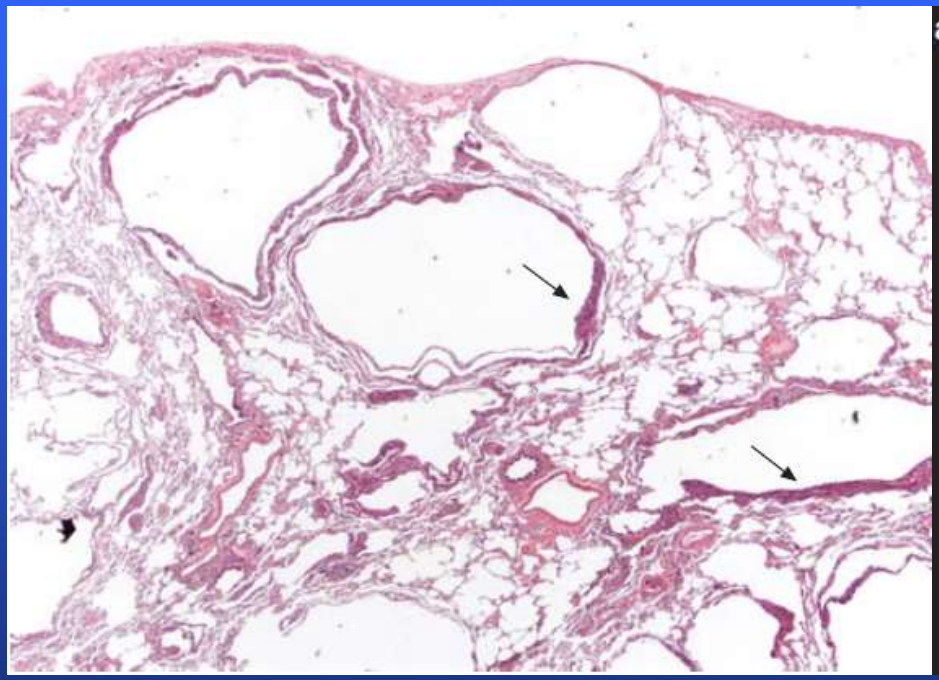
- Recurrence of the disease in the transplant within the first year has been reported, with possible risk factors being resumption of smoking and extrapulmonary involvement

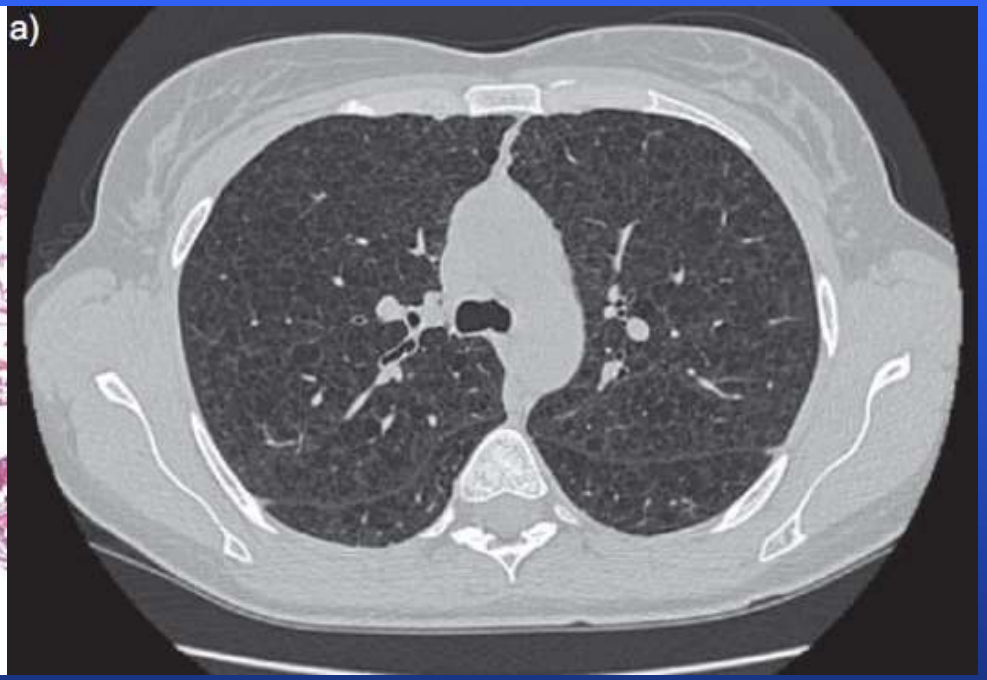
PLCH and NEOPLASMS

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.

Lymphangioleiomyomatosis (LAM)





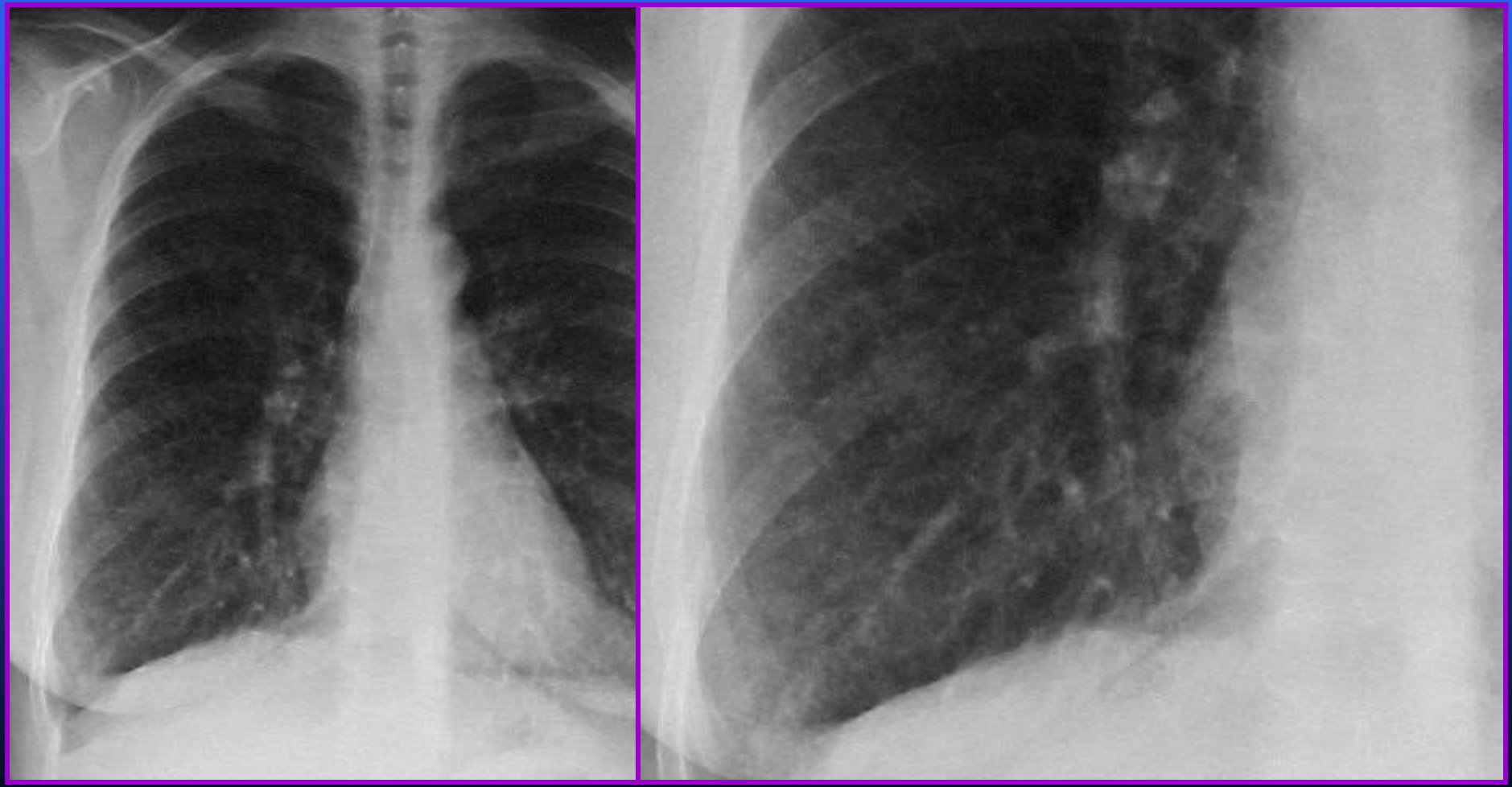
Lymphangioleiomyomatosis (LAM) is a rare multisystem disorder affecting predominantly young females in their reproductive years.

It is characterised by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumours (e.g. angiomyolipomas)

Lymphangioleiomyomatosis (LAM)

- The abdominal tumors and lung cysts are composed of abnormal smooth muscle cells (LAM cells) that express melanoma antigens.
- LAM occurs in patients with and without evidence of tuberous sclerosis complex, a syndrome resulting from mutations in the *TSC1* or *TSC2* tumor suppressor genes.

LAM - Radiology

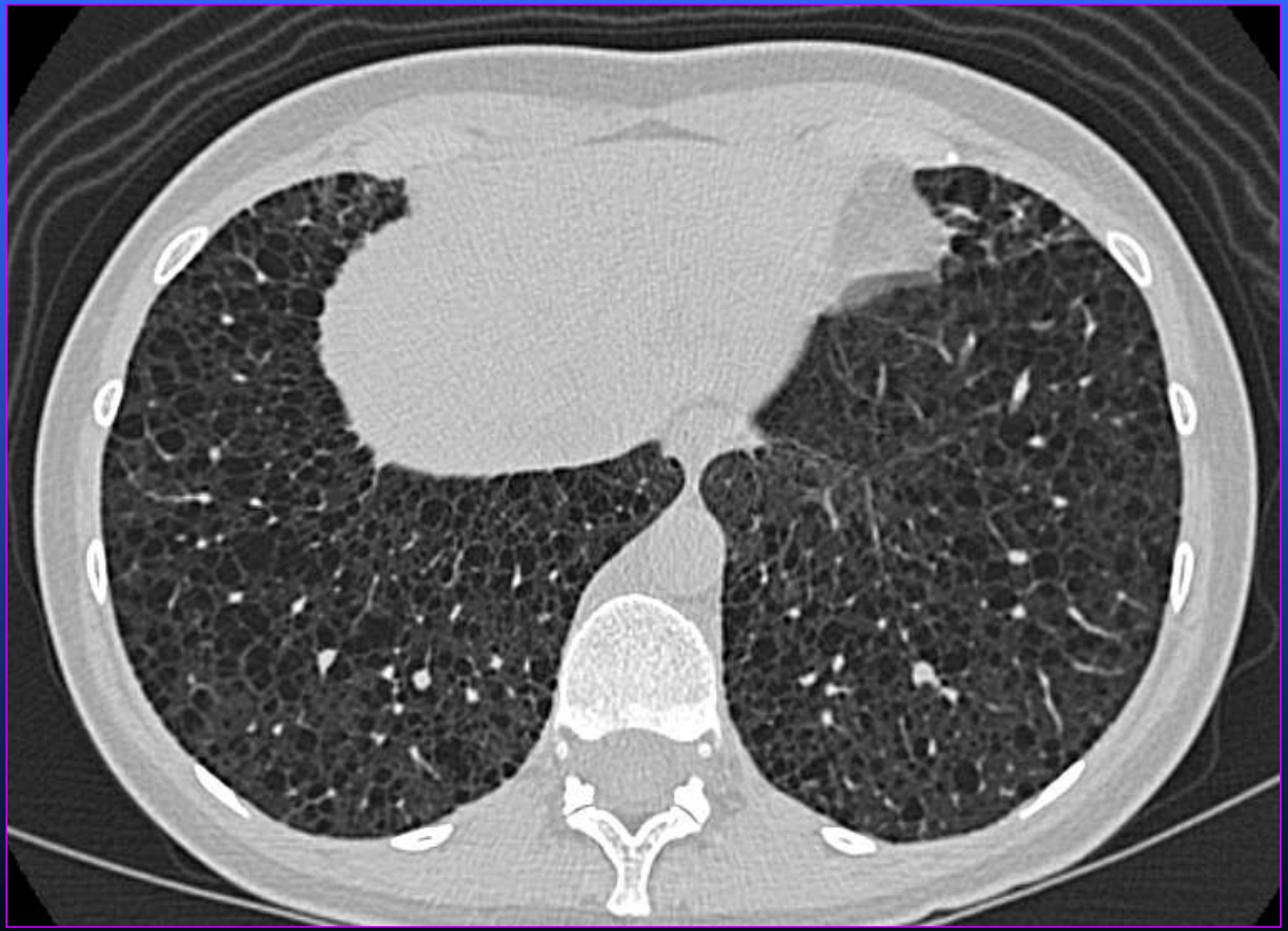


LAM – HRCT findings

- Numerous thin-walled lung cysts
- These cysts usually range from 2 mm to 5 cm in diameter
- Their size tends to increase with progression of the disease
- The cysts are distributed diffusely throughout the lungs and no lung zone is spared

- In some cases a slight increase in linear interstitial markings, interlobular septal thickening, or patchy areas of ground-glass opacity are also seen

LAM – HRCT findings



LAM - Symptoms

Dyspnea	42-87%
Cough	20-51%
Chest Pain	14-34%
Hemoptysis	14-22%
Pneumothorax	43-65%
Chylothorax	12-28%

LAM - Diagnosis

Lung biopsy, either transbronchial or surgical, has been the gold standard for diagnosis in most studies

Recent ERS guidelines define the diagnostic criteria for LAM

According to these criteria, lung biopsy is not necessary for a definite diagnosis if specific extrapulmonary manifestation are present.

Diagnosis – ERS guidelines

Definite LAM	characteristic lung HRCT + any of the following - angiomyolipoma - thoracic or abdominal chylous effusion, - lymphangioleiomyoma - biopsy-proven lymph node involved by LAM, - TSC
Probable LAM	characteristic lung HRTC + compatible clinical history compatible lung HRTC + angiomyolipoma or chylous effusion
Possible LAM	characteristic or compatible lung HRTC alone

Characteristic HRCT: multiple (more than 10) thin-walled round well-defined air-filled cysts with no other significant pulmonary involvement (with the exception of MMPY in TSC)

Compatible HRTC: few (more than two and fewer than 10) typical cysts

Johnson SR et al, ERJ 2010

Diagnosis

The past…

- ✓ TBB
- ✓ Lung biopsy

And the future…

- ✓ Detection of LAM cells in body fluids
- ✓ Serum VEGF-D

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

BAL

- No diagnostic relevance in LAM
- High percentage of pigment-laden macrophages likely due to microscopic pulmonary hemorrhages

TBB

- Higher diagnostic role than in PLCH
- Immunohistochemical staining (HMB-45) improve the diagnostic yield of TBB

Harari S et al, Respir Med. 2012

LAM cells in body fluids

LAM lesions are marked by proliferation of abnormal-appearing smooth muscle-like cells (LAM cells) that have loss of heterozygosity (LOH) and inactivating mutations in one of the two TSC genes

The presence of circulating LAM cells from lung, kidney, or lymphatic sites may identify patients at risk of disease progression or spread.

Analyses of the genetic abnormalities in samples of blood or urine or chyle could be a relatively inexpensive and noninvasive means for early diagnosis of disease, as well as perhaps for following its progression and/or response to potential therapy.

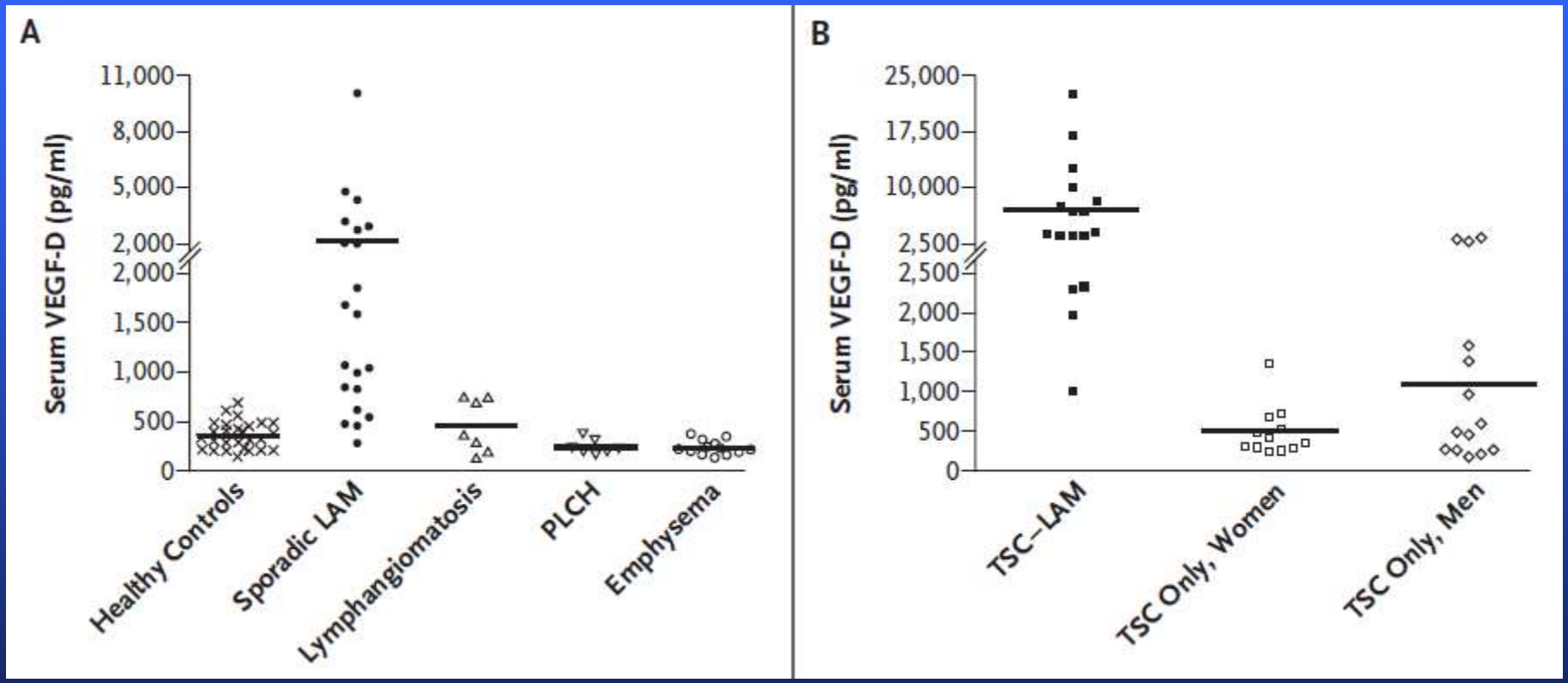
Crooks DM et al, PNAS 2004

Serum VEGF-D

Vascular endothelial growth factors C (VEGF-C) and D (VEGF-D) are ligands for the lymphatic growth factor receptor VEGFR-2 and VEGFR-3/Flt-4 that induce formation of lymphatics and promote the spread of tumor cells to lymph nodes in mouse models and in humans.

Serum levels of VEGF-D, but not VEGF-C, are elevated in patients with S-LAM in comparison with normal controls.

Serum VEGF-D



McCormack FX, NEJM 2008

Serum VEGF-D

Serum VEGF-D may be a useful biomarker for differential diagnosis and prognostic evaluation of LAM

It has been considered as a diagnostic criteria in clinical trials for therapy (everolimus)

The past: hormonal theraphy

- ✓ Oophorectomy
- ✓ Anti-oestrogen therapy

Controversial effects
No objective evidence of improvement

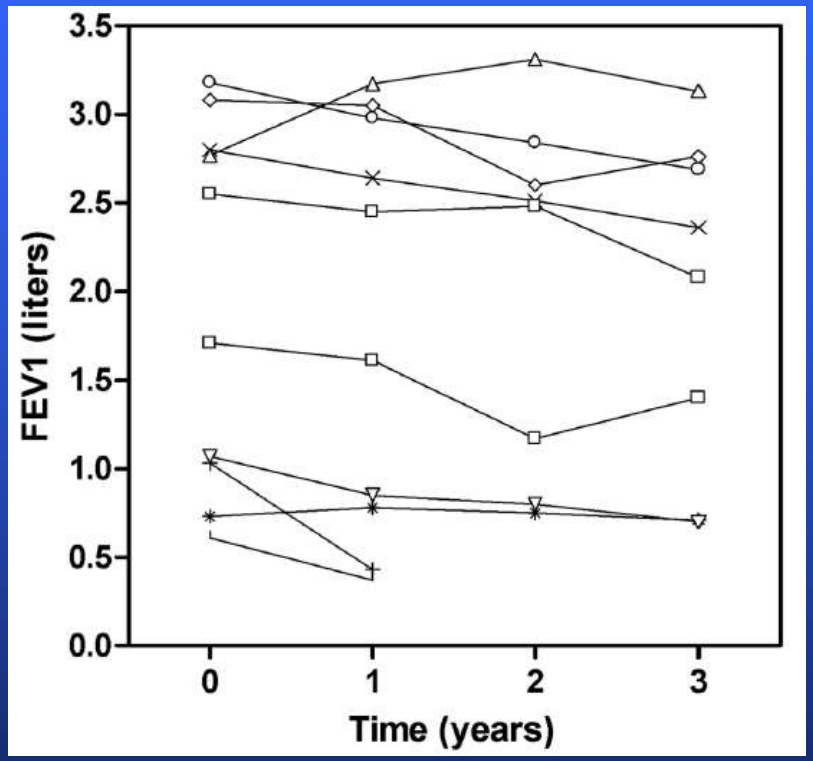
- ✓ Gonadotrophin-releasing hormone (GnRH) analogues

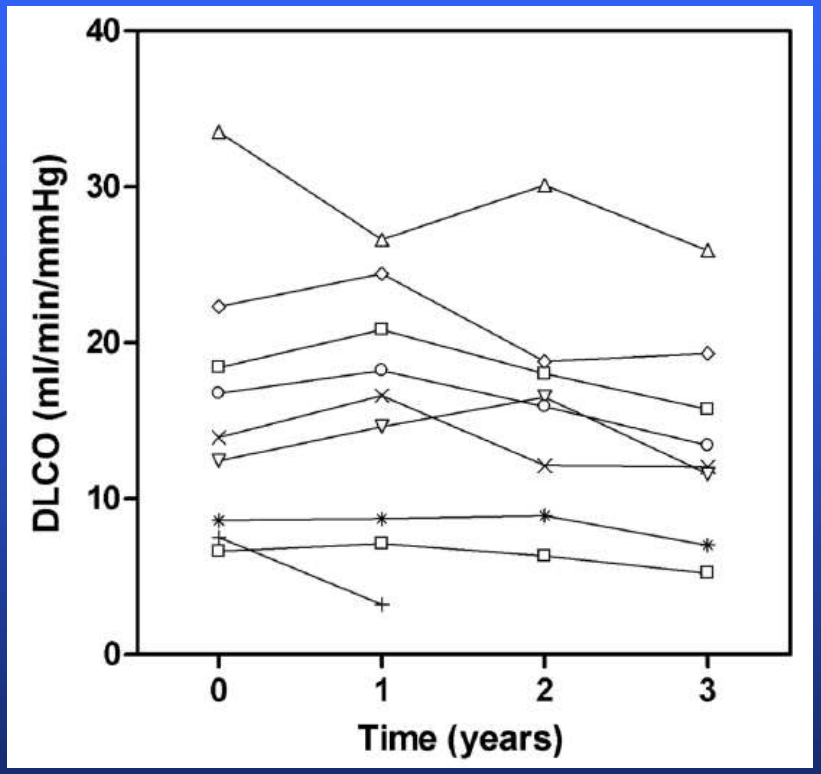
Case reports
Retrospective studies
A prospective study showing no effects on lung function

- ✓ Progesterone

Case reports
Retrospective studies

The past: hormonal theraphy Triptorelin





Changes in FEV1 (10 pts) and DLCO (9 pts) in patients with LAM who were treated with triptorelin

Harari S et al, Chest 2008

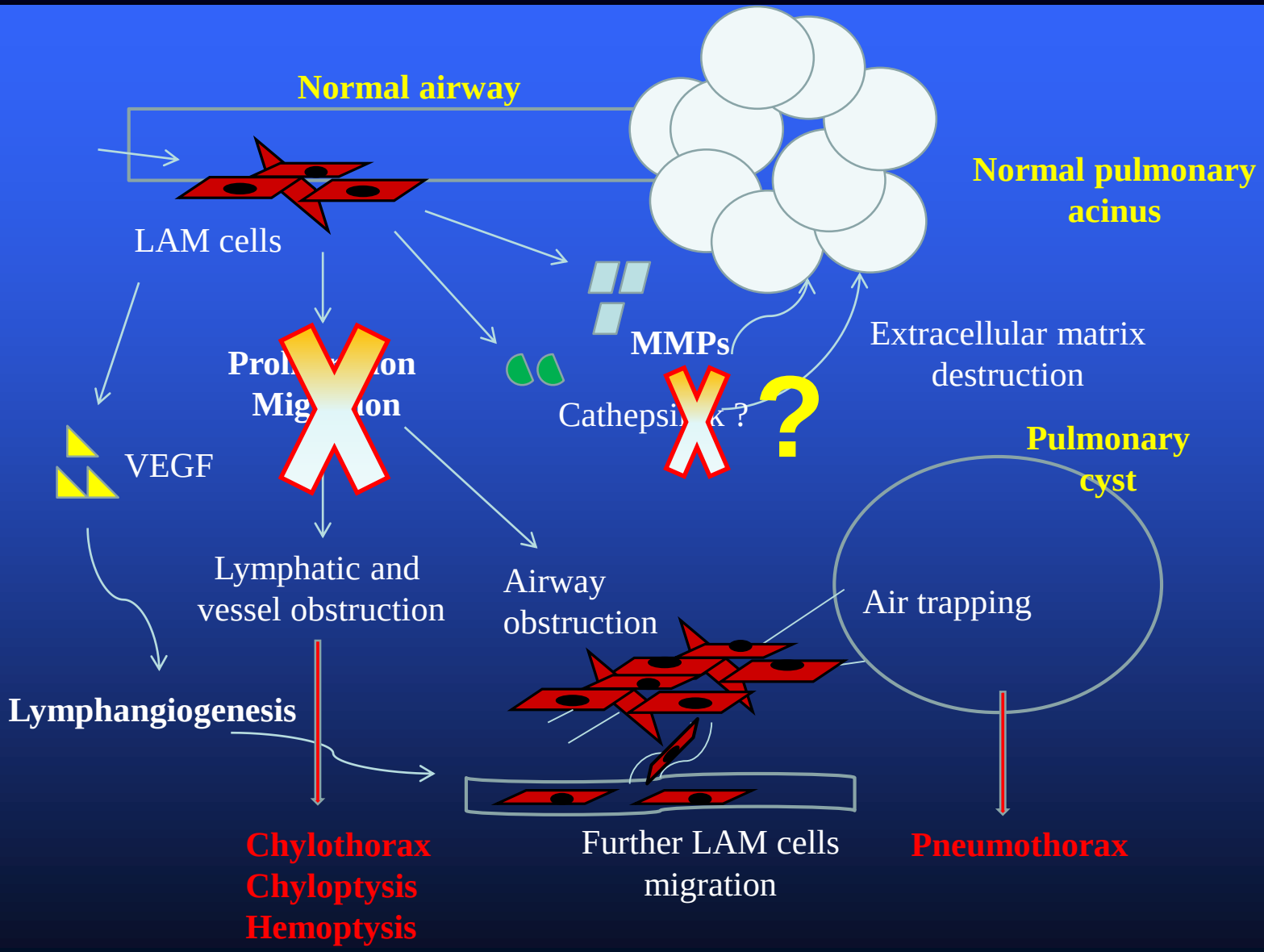
New therapies

- ✓ mTOR inhibitors
  - Sirolimus
  - Everolimus
- ✓ Doxycycline

Future issues

- ✓ *Chloroquine*
- ✓ *Vaccines*

Sirolimus


Normal airway
Normal pulmonary acinus
LAM cells
MMPs
Extracellular matrix destruction
Cathepsin K ?
VEGF
Pulmonary cyst
Lymphatic and vessel obstruction
Airway obstruction
Air trapping
Lymphangiogenesis
Chylothorax
Chyloptysis
Hemoptysis
Further LAM cells migration
Pneumothorax

Sirolimus

- In a group of patients with TSC or sporadic LAM and angiomyolipomas, sirolimus has been shown to decrease tumor size by almost 50% after one year of therapy

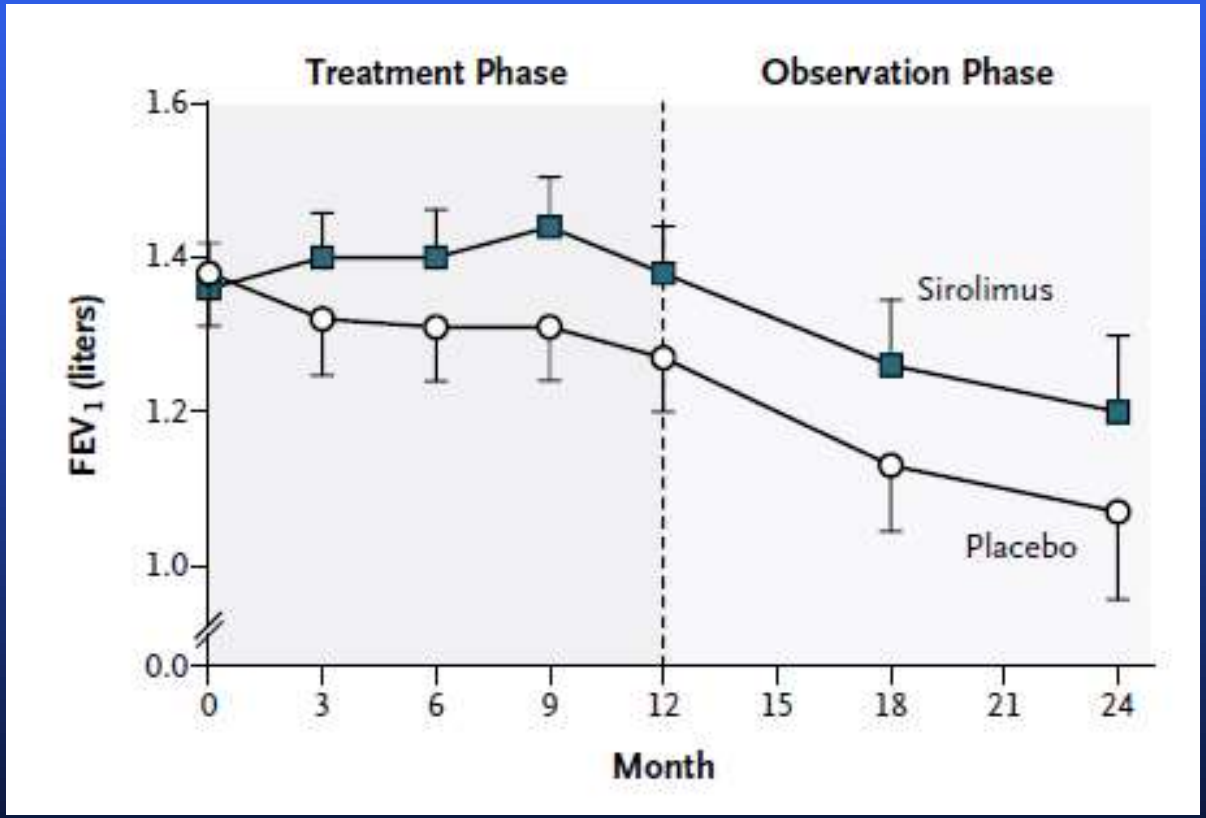
- Lung function improved in some patients

- However angiomyolipomas partially regained size following withdrawal of therapy

Bissler JJ et al, NEJM 2008

Efficacy and Safety of Sirolimus for Treating Lymphangioleiomyomatosis (MILES trial)

A 12-month randomized, double-blind comparison of sirolimus with placebo, followed by a 12-month observation period



McCormack FX et al, NEJM 2011

Everolimus for angiomyolipoma associated with TSC or sporadic LAM (**EXIST-2)**

multicentre, randomised, double-blind, placebo-controlled

- Primary endpoint: the proportion of patients with a confirmed angiomyolipoma response
- Secondary key endpoints: time to angiomyolipoma progression and skin lesion response rate.

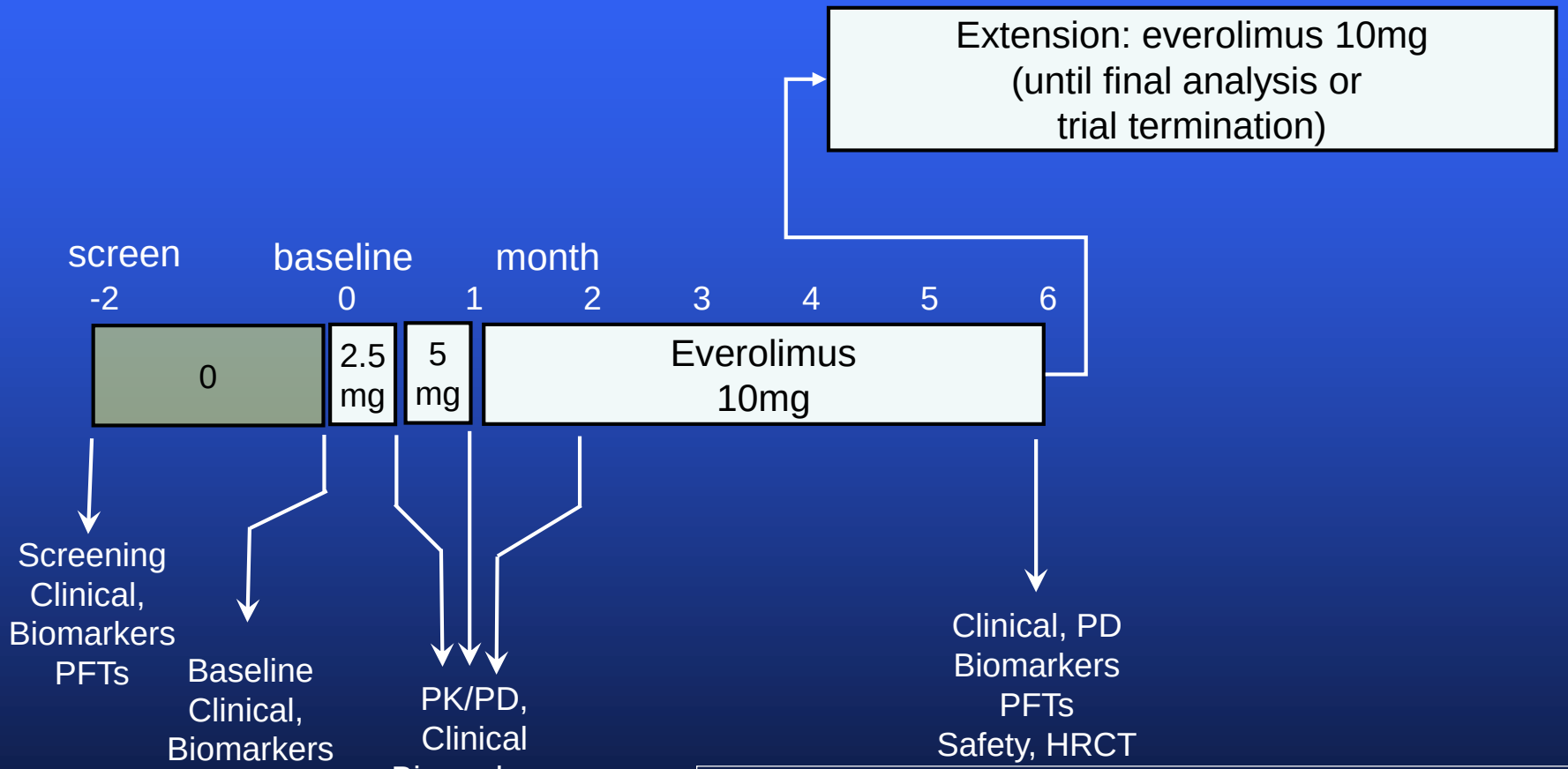
- Lung function in patients with LAM and sporadic LAM on everolimus showed slightly less deterioration during the study than did patients in the placebo group

- Interpretation of this *exploratory endpoint* was limited because of the short duration of treatment exposure and the low number of patients.

Bissler JJ, Lancet 2013

Everolimus in LAM - Study Design

Open-label, non randomized, within-patient multiple dose escalation



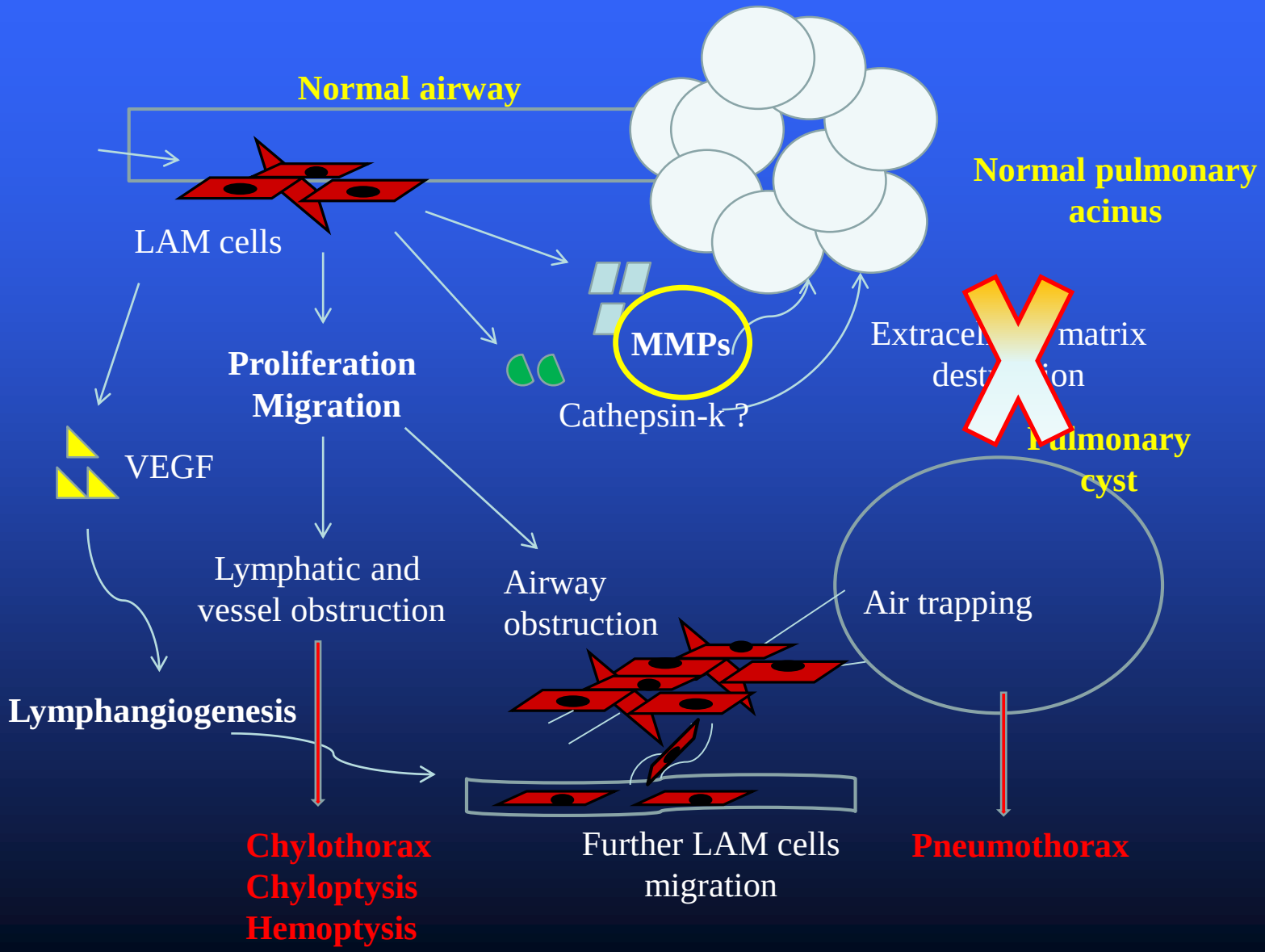
PoC Interim Analysis
18 patients reach 26-weeks

Final Analysis
all subjects (last patient completes 26-weeks)

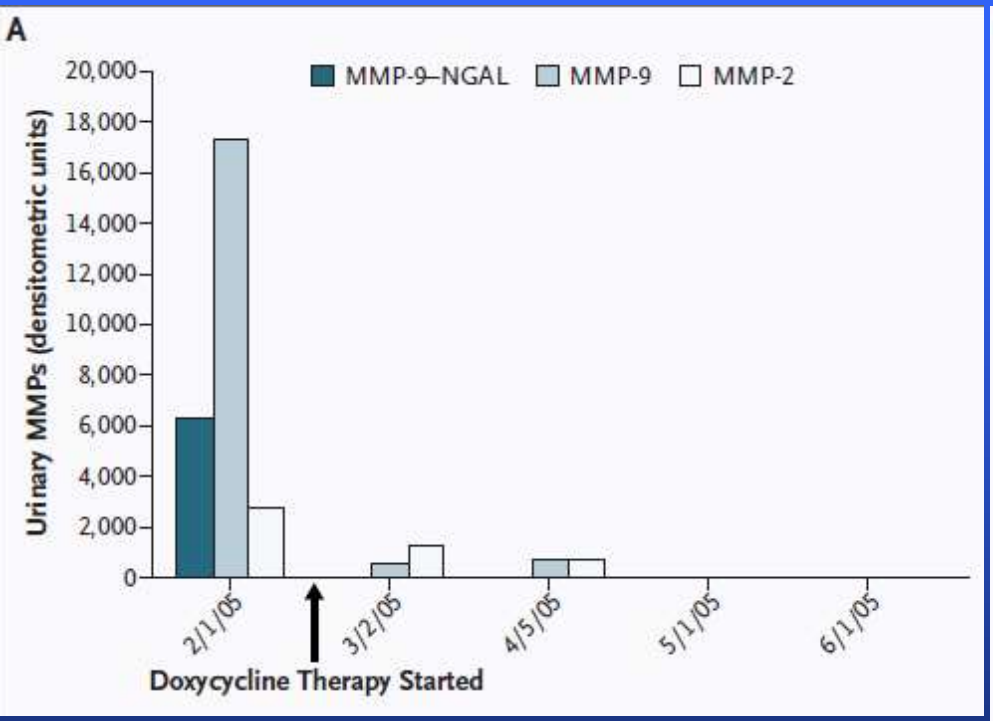
Conclusions

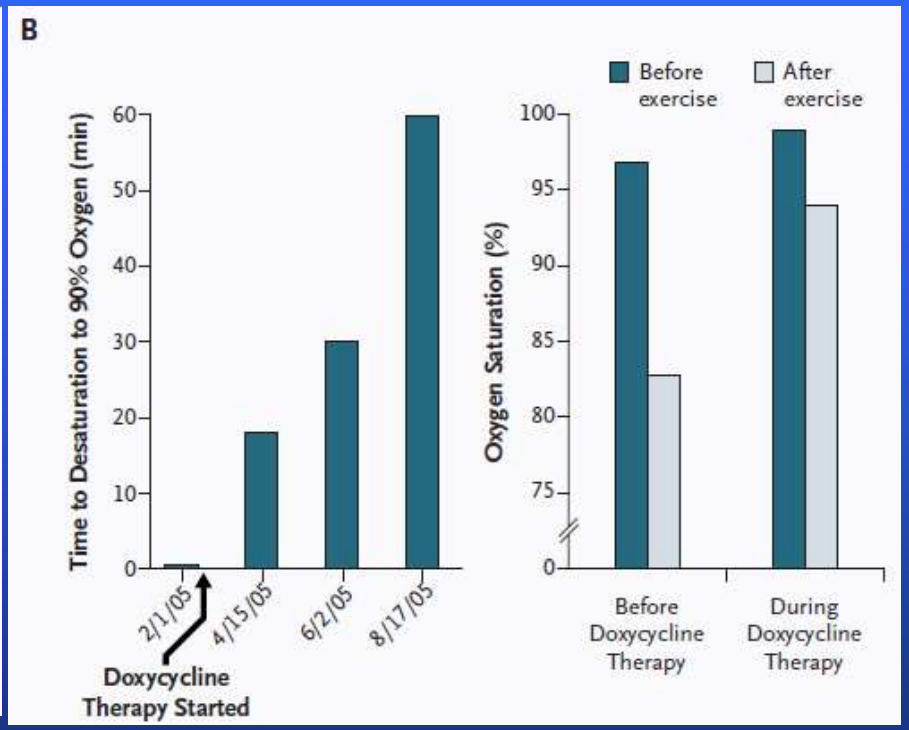
- In patients with LAM, RAD001 treatment was associated with improvements in FEV_1, FVC, and 6-MWD.
- AEs were frequent and consistent with the known toxicity profile of mTORC1 inhibitors.
- Treatment with RAD001 may be useful in selected patients with LAM.

Doxycycline



Doxycycline - Case report 2006





Urinary MMPs

Clinical improvement

Moses A et al, NEJM - 2006

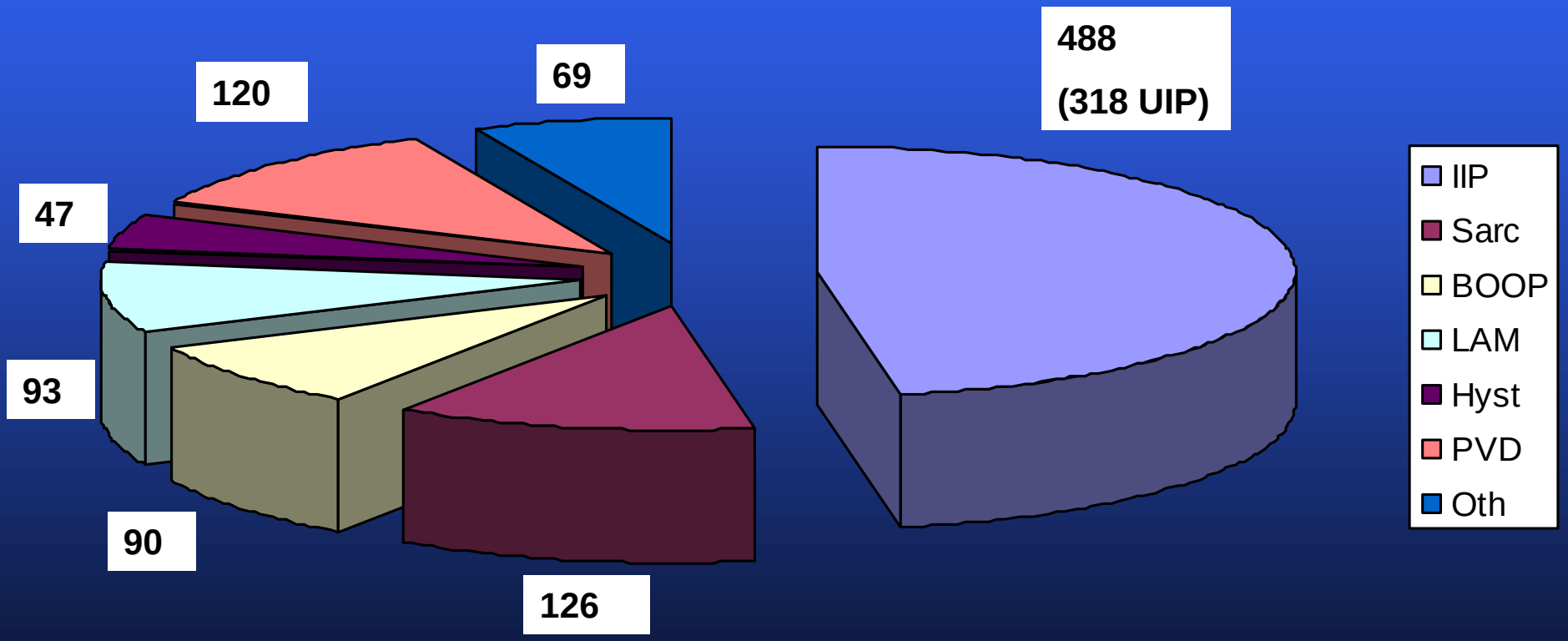
Doxycycline

A potential role of doxycycline in the treatment of LAM is being investigated in a placebo-controlled trial (UK)

Rare Lung Diseases

Ospedale San Giuseppe Experience (2001- 2013)

Tot. 1033 pts



LAM
San Giuseppe dal 2001 ad oggi

93 LAM, di cui 16 con TSC
(13 decedute, 14 perse al follow-up)

- 10 trattate con Decapeptyl in 3 anni: una stabile, 9 peggiorate
- 8 trattate con doxiciclina: tutte peggiorate
- 23 in sirolimus, di queste 10 con valutazione a 12 mesi (6 stabili, 3 migliorate, 1 peggiorata)
- 8 hanno partecipato allo studio everolimus e 7 lo hanno portato a termine con stabilità di malattia e lo continuano in modalità compassionevole
- 5 trapiantate di cui 3 decedute a due anni dal trapianto, 1 ora viva a 8 mesi dal Tx e una persa al follow-up

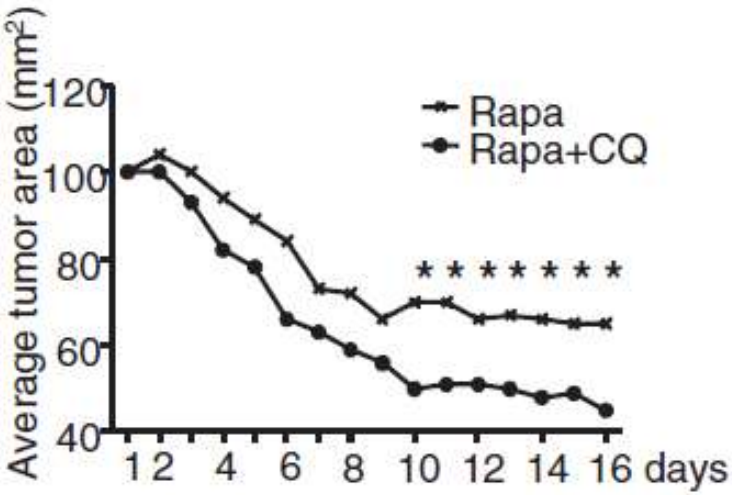
Immunotherapeutic Treatment Options

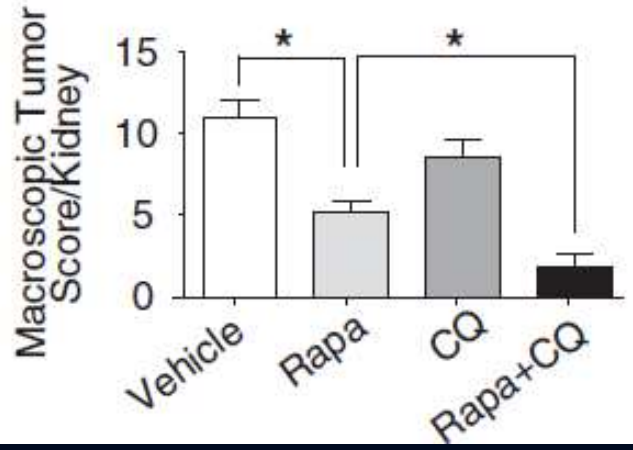
- LAM cells express markers associated with melanocytic differentiation, including gp100 MART-1 and other melanocytic markers
- The same proteins are targeted by T cells infiltrating melanoma tumors, and these antigens are regarded as relatively immunogenic. Vaccines have been developed for melanoma targeting these and other immunogenic melanocyte differentiation proteins
- Preliminary data showing susceptibility of LAM cells to melanoma derived T cells suggest that vaccines targeting melanosomal antigens may be successful in treating LAM.

Dilling DF, PNAS 2012

Autophagy and TSC tumorigenesis

Autophagy has been recently shown to be a critical component of TSC tumorigenesis





The combination of mTORC1 and autophagy inhibition (using rapamycin and chloroquine) is more effective than either treatment alone in inhibiting the survival of tuberin (TSC2)- null cells, growth of TSC2-null xenograft tumors, and development of spontaneous renal tumors in Tsc2+/− mice

Thus dual inhibition of mTORC1 and autophagy is a potential therapeutic strategy for TSC and LAM patients.

Parkhitko A et al, PNAS 2011

Pulmonary Hypertension in Lymphangioleiomyomatosis: Characteristics in 20 patients

- This retrospective, multicenter study evaluated patients with LAM and pre-capillary PH by RHC
- Mean ± SD age: 49 ± 12 years and mean ± SD time interval between LAM and PH diagnosis of 9.2 ± 9.8 yrs
- All, except for one patient, were receiving supplemental oxygen
- Mean ± SD 6MWD: 340 m ± 84 m
- mPAP: 32 ± 6 mmHg
- mPAP > 35 mmHg in only 20% of cases
- Mean ± SD FEV1: 42 ± 25%; DLCO 29 ± 135

Cottin V , Harari S et al. Eur Respir J 2012; 40: 630

Pulmonary Hypertension in Lymphangioleiomyomatosis: Characteristics in 20 patients

- In six patients who received oral PAH therapy , the PAP decreased from 33 ± 9 mmHg to 24 ± 10 mmHg

Pre-capillary PH of mild haemodynamic severity may occur in patients with LAM, even with mild pulmonary function impairment.
PAH therapy might improve the haemodynamics in PH associated with LAM.

Cottin V , Harari S et al. Eur Respir J 2012; 40: 630