Ipertensione polmonare nelle PID non fibrosanti: cosa fare?

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WHO PPH Classifications

Geneva

Evian

Venice

Dana Point

Pathological

Clinical-Phatological

Therapeutic-based

1. Pulmonary Arterial Hypertension

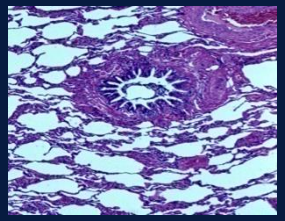
- Idiopathic PAH
- Heritable
  - BMPR2
  - ALK1, endoglin (with or without HHT)
  - Unknown
- Drugs and toxins induced
- Associated with:
  - connective tissue diseases
  - HIV infection
  - portal hypertension
  - systemic to pulmonary shunts
  - schistosomiasis
  - chronic hemolytic anemia

- PPHN

1' Pulmonary veno occlusive disease (PVO) and / or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension due to left heart disease

- Systolic dysfunction
- Diatolic dysfunction
- Valvular disease



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

- Chronic obstructive pulmonary disease
- **Interstitial lung disease**
- Other pulmonary diseases
- Sleep-disordered breathing
- Chronic exposure to high altitude
- Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

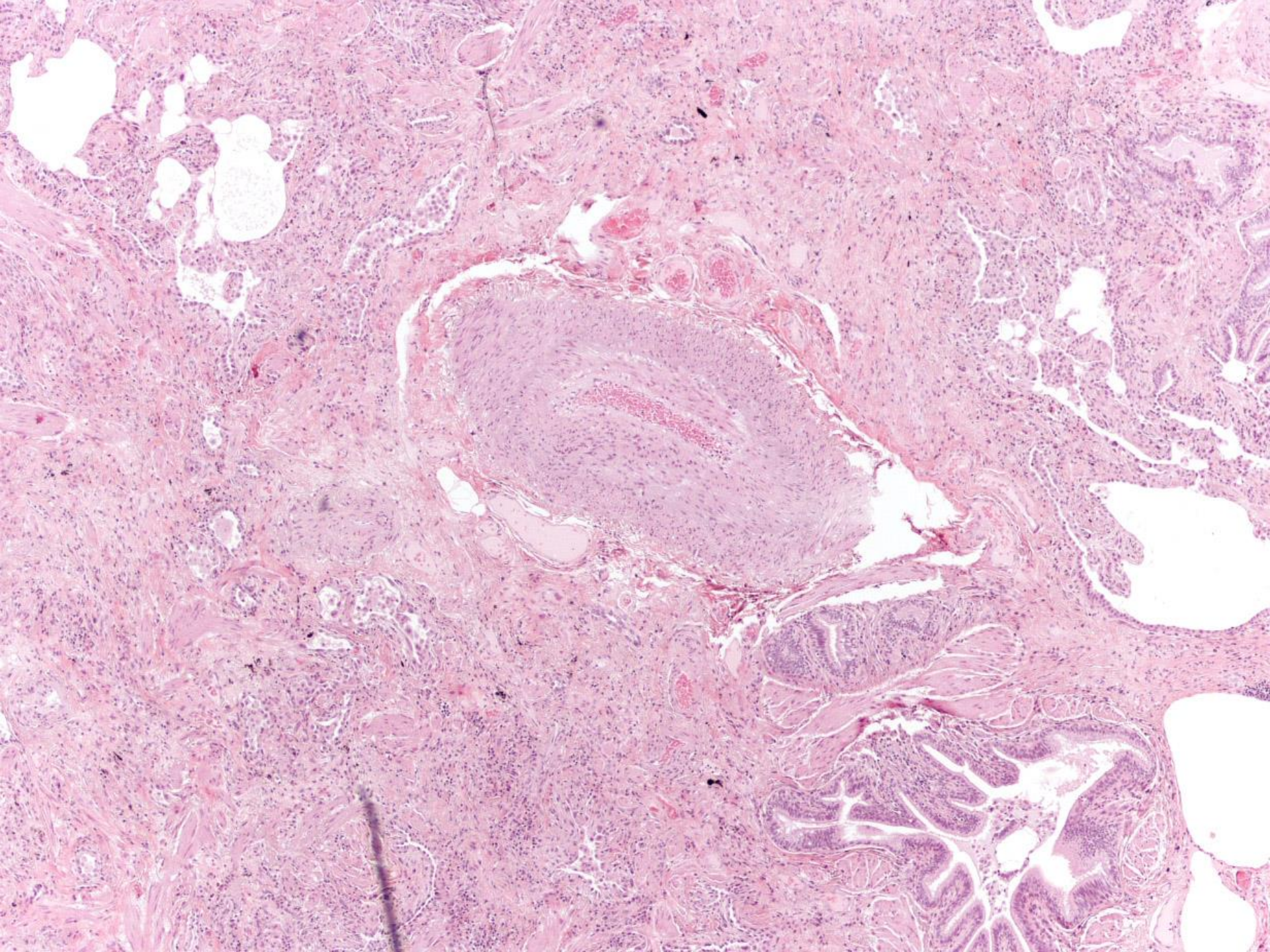
5. PH with unclear or multifactorial mechanisms

- Hematologic disorders, myeloproliferative disorders, splenectomy
- Systemic disorders: vasculitis, sarcoidosis, pulmonary Langerhans cell histiocytosis, LAM, neurofibromatosis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Congenital heart disease other than systemic to pulmonary shunt
- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, others

Disorders of the respiratory system and hypoxemia

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep disorders
- Alveolar hypoventilation
- Chronic exposure to high altitude
- Others...

- PH is generally mild or moderate (PAP < 30 mmHg), is not per se a predominant prognosis factor and not require specific therapeutic intervention (except oxygen therapy)
- Medial hypertrophy and mild intimal fibrosis



Treatment of hypoxic pulmonary hypertension

- Efficacy of vasodilators has never been demonstrated
- Long-term oxygen therapy improves survival in COPD

  24 H > 12 H (NOTT study 1981)

  15 H > 0 H (BMRC study 1981)

  survival improvement due to O_2 is associated with minor changes in PAP
- Beneficial effects of vasodilators in a subgroup of patients with severe PH ?

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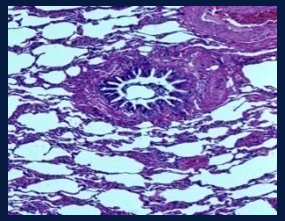

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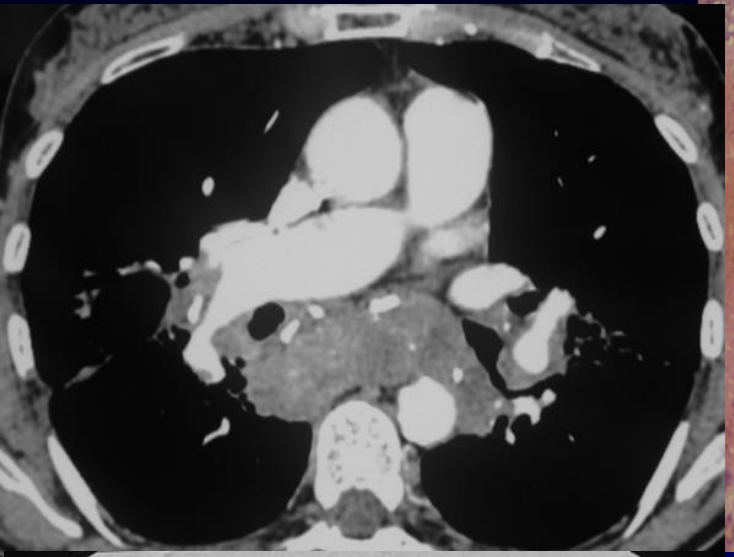
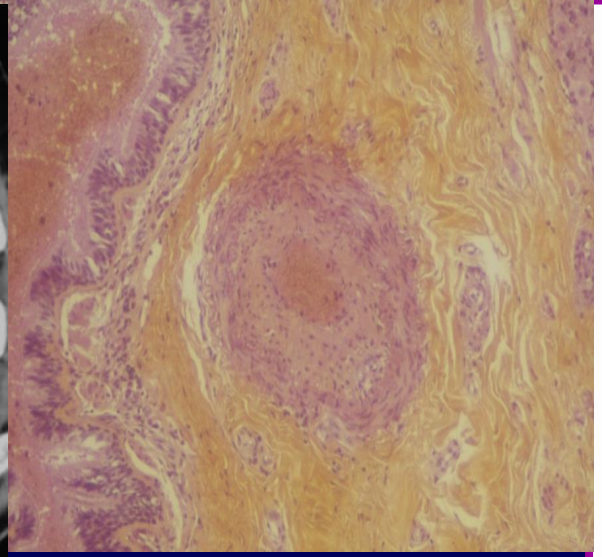
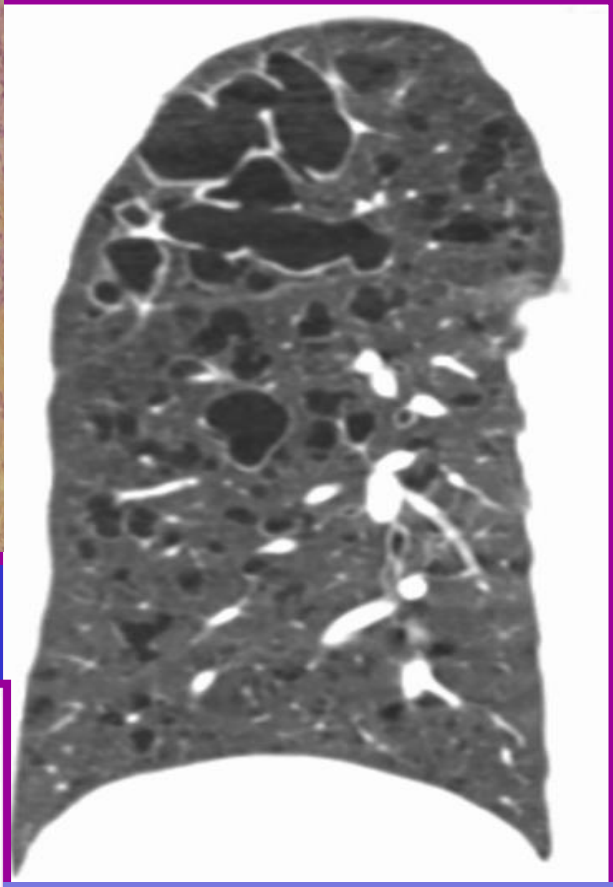
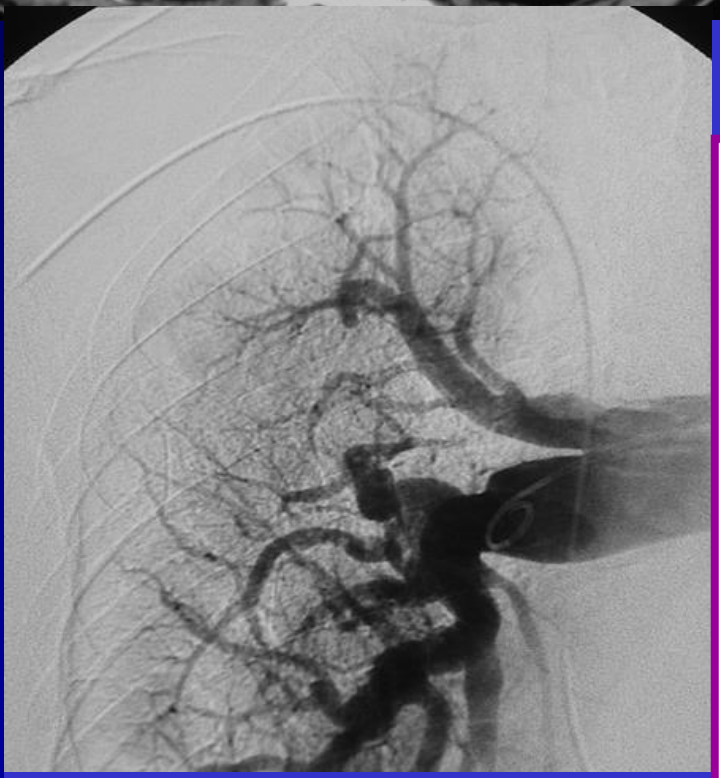




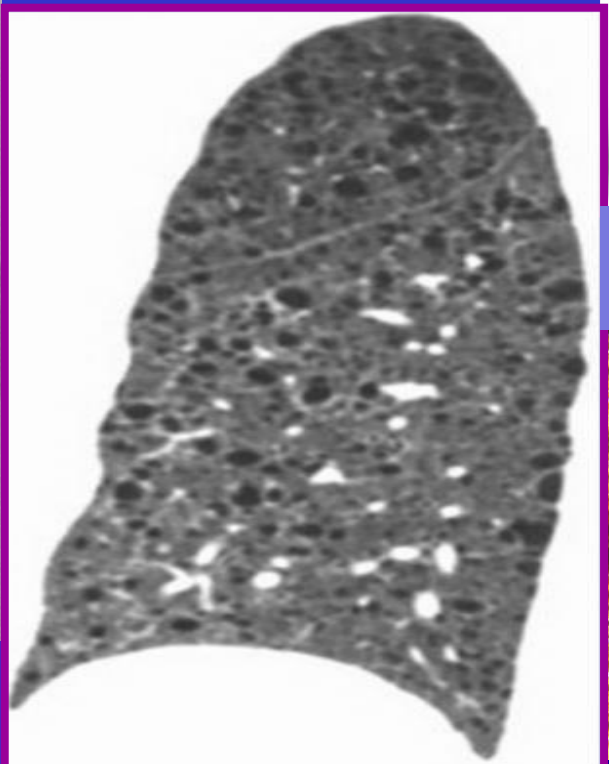
PLCH

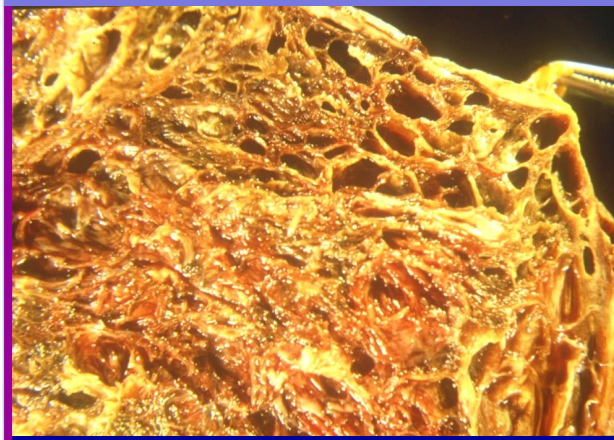


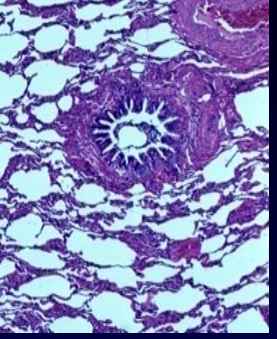
LAM



Sarcoidosis





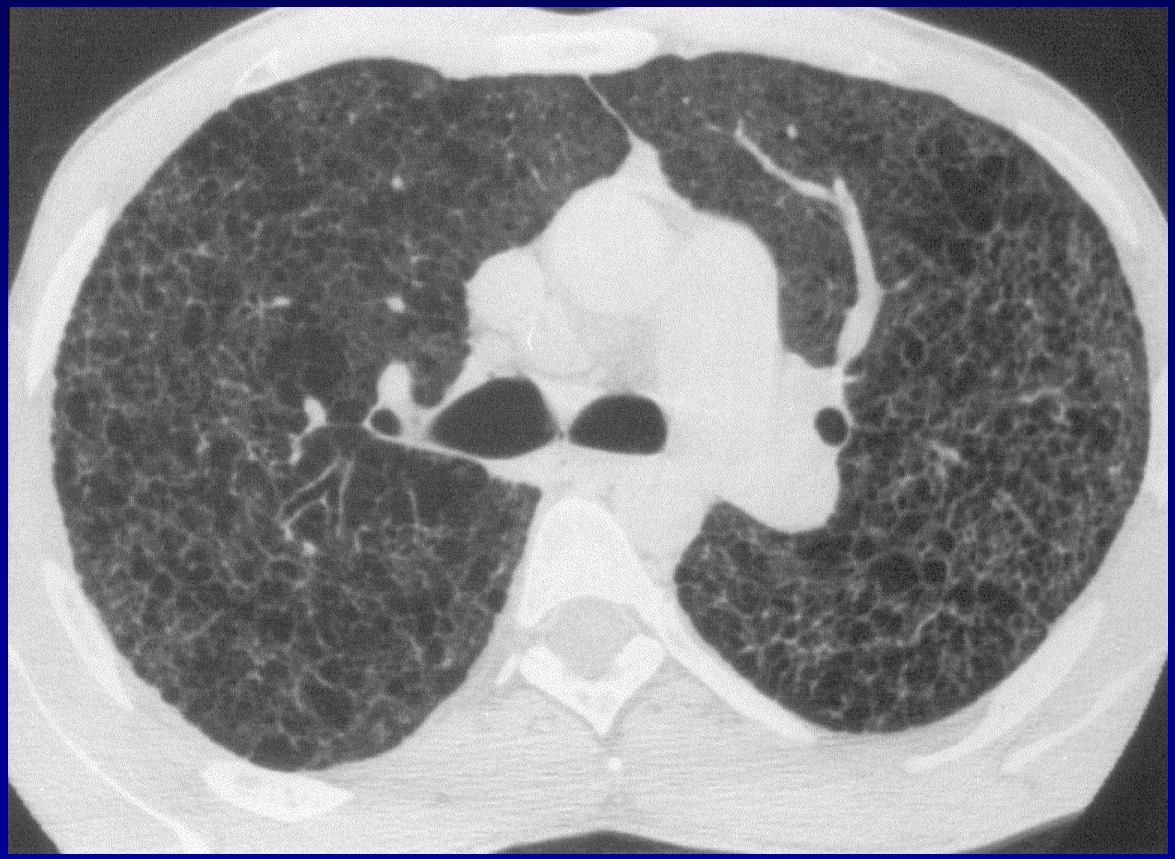


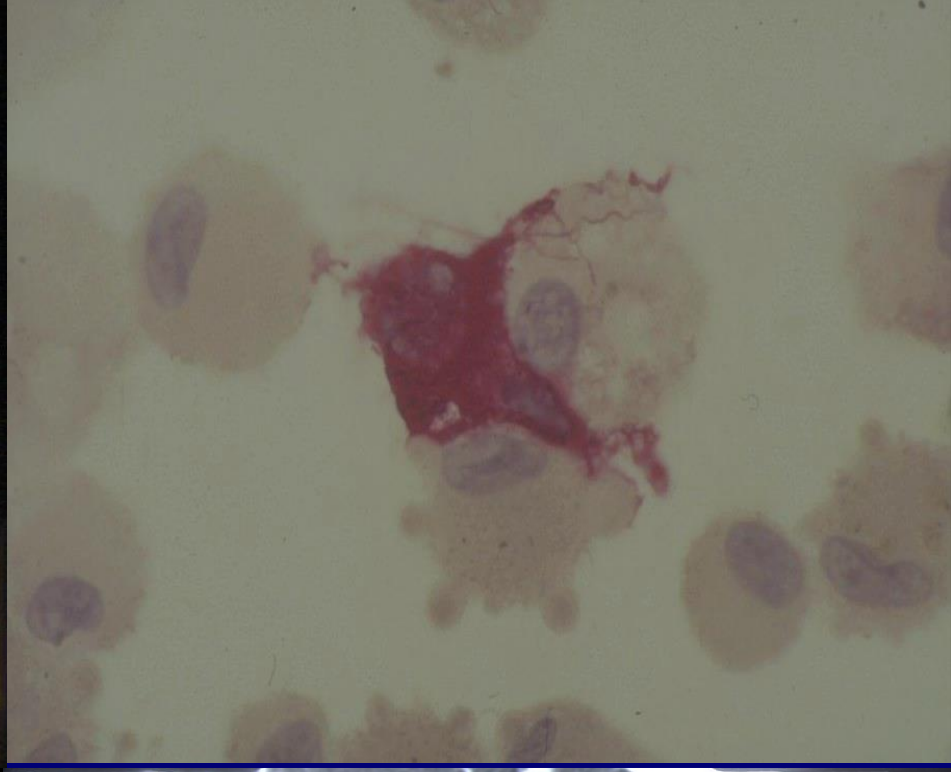
PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

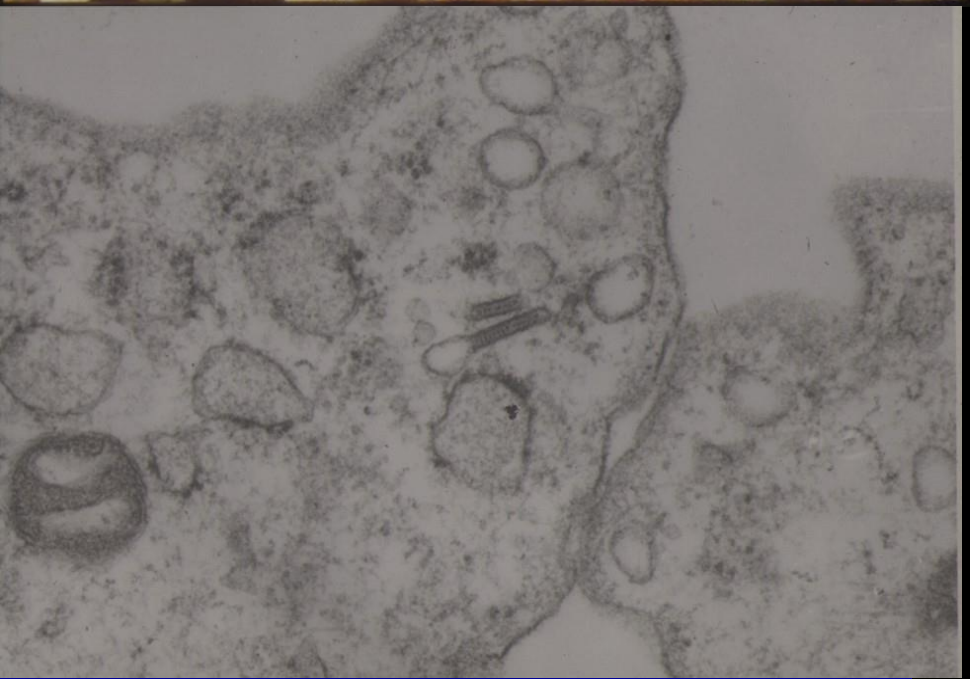
(updated 4th WSPAH-Dana Point 2008)

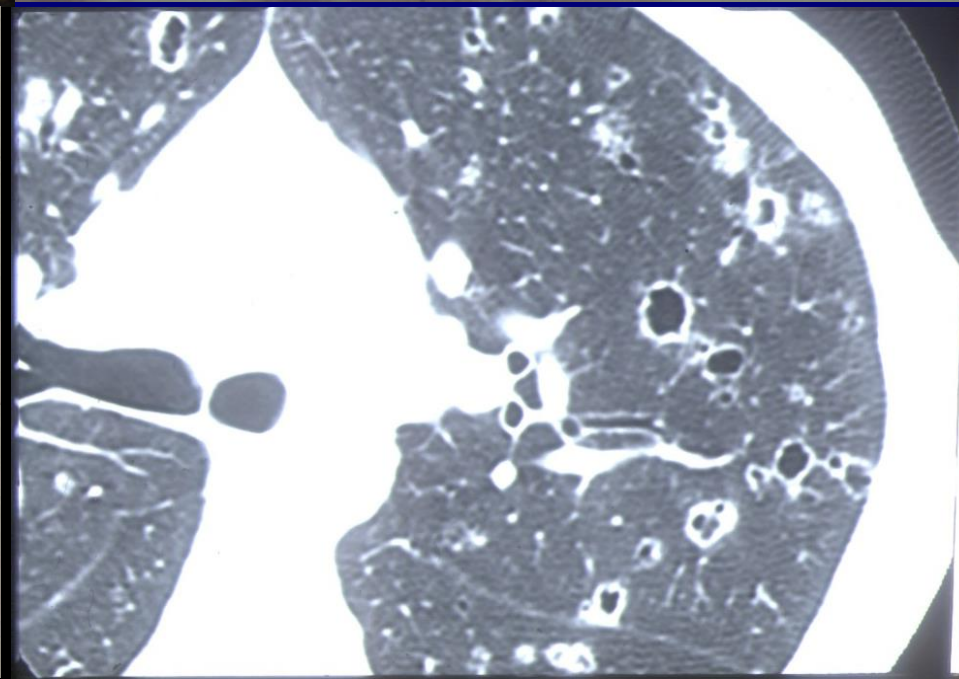
5. PH with unclear or multifactorial mechanisms

- Histiocitosis X







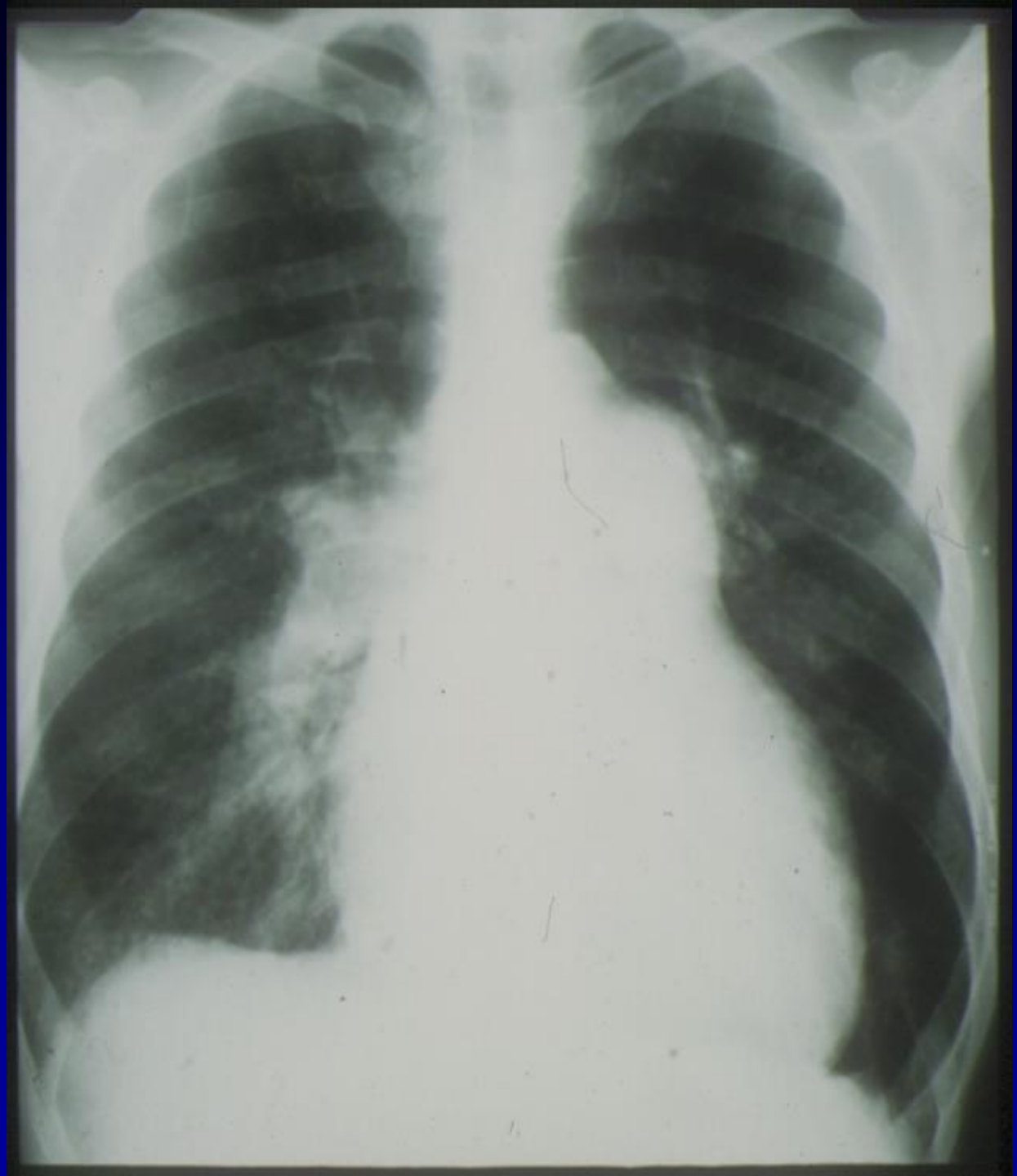


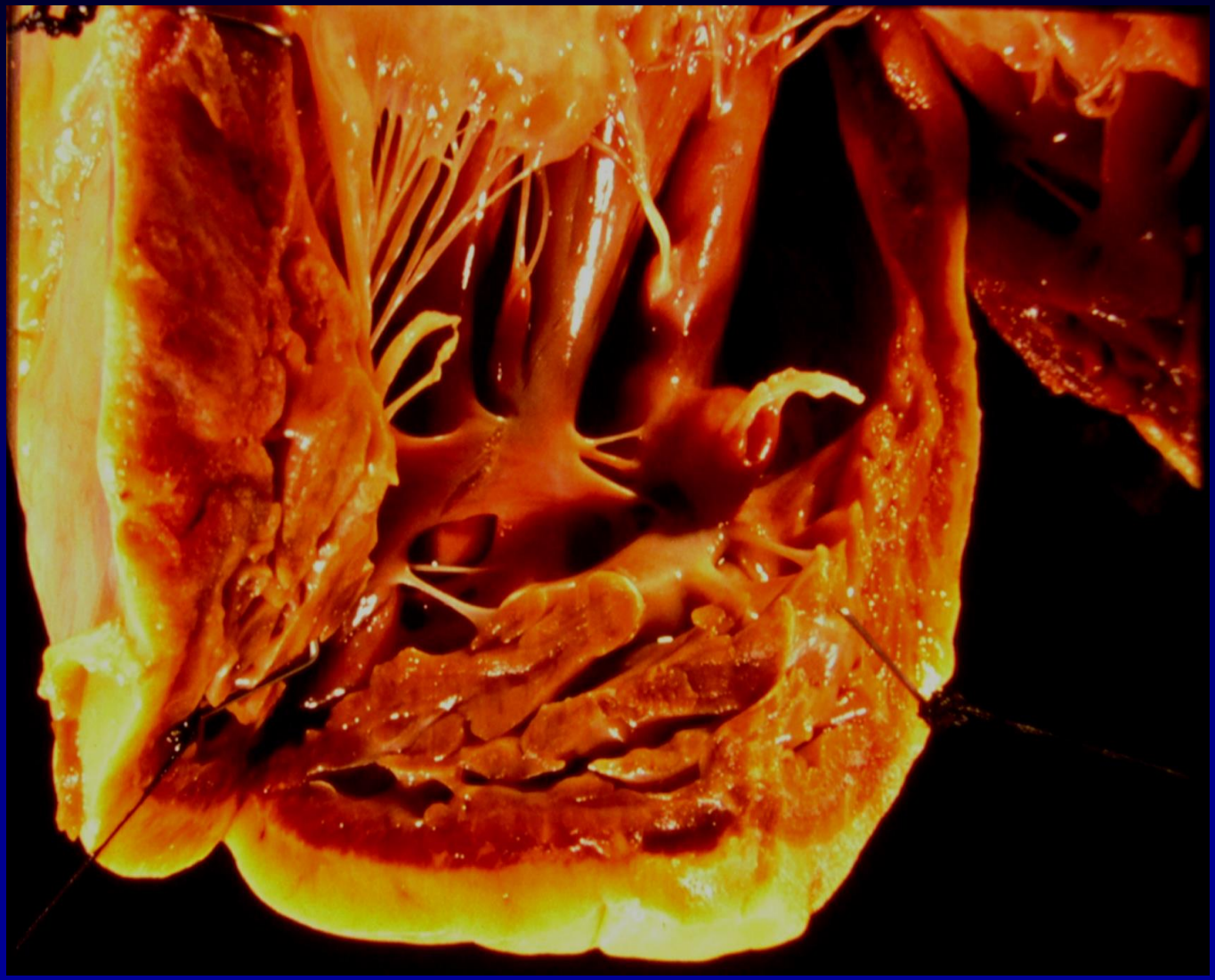
Advanced Pulmonary Hystiocitosis is Associated with severe pulmonary hypertesion

Harari S., Brenot F., Simmoneau G.
Chest 1997; 111: 1142-44

Pulmonary Vascular Involvement in Pulmonary Hystiocitosis x

Crausman RS, King TE
Chest 1997; 112 (6) : 1714





IS PULMONARY LCH A HYPERTENSIVE DISEASE?

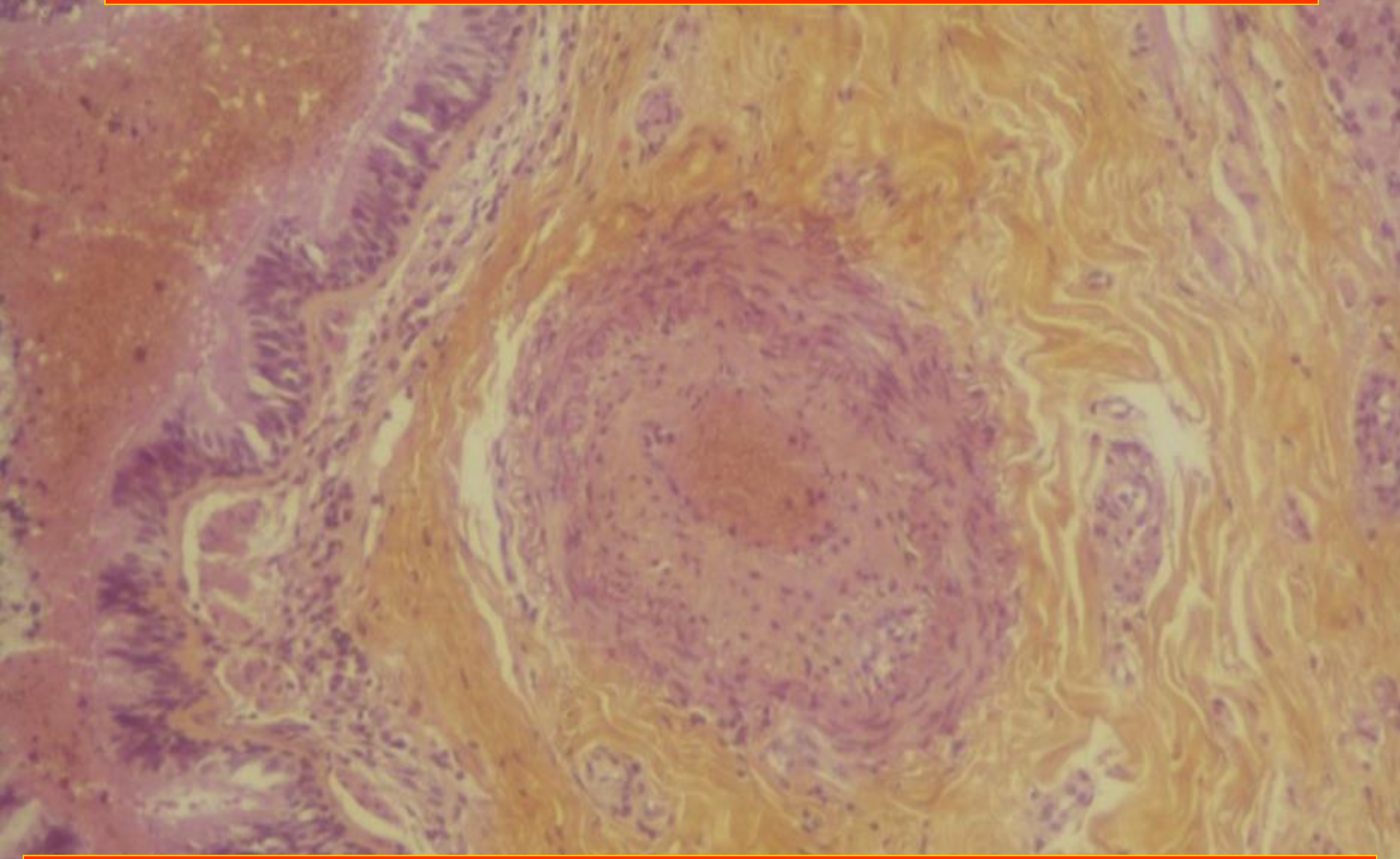
18 LCH PATIENTS

FEV1	**42.8% ± 15.5 S.D.**
TLC	**99.9% ± 18.8 S.D.**
Tiffenau	**55.4% ± 13.9 S.D.**
PaO2	**57.7 ± 10.6 S.D.**
PAPm	**55.9 ± 12 S.D.**
C.I.	**2.77 ± 0.71 S.D.**
PVRi	**17.6 ± 6.5 S.D.**

Harari S., Simonneau G. Brenot F. et Coll.

J Heart Lung Transplant 1997 Apr;16(4):460-463

PULMONARY HYPERTENSION IN PLCH



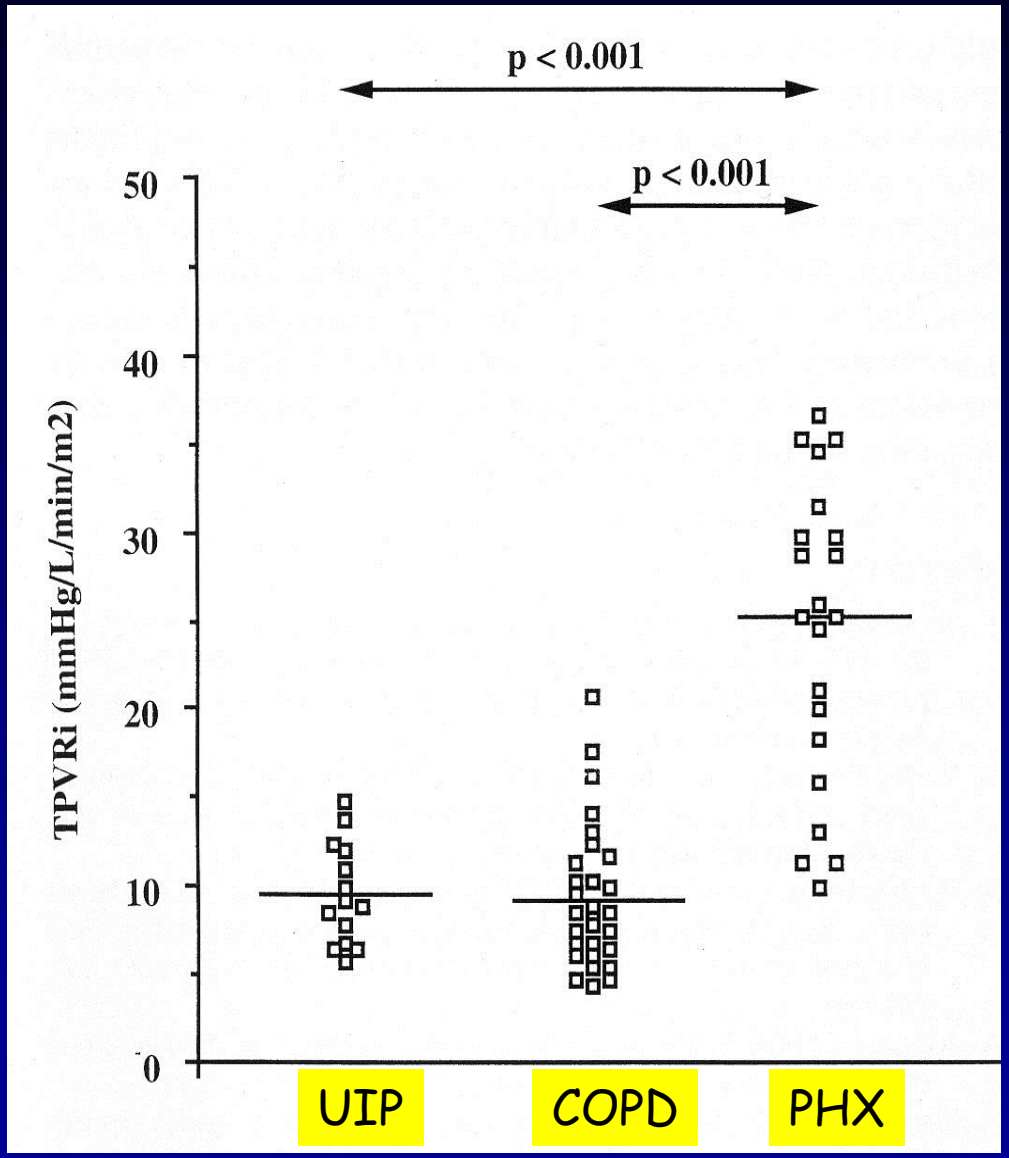
Occlusion of a vascular lumen by intimal hyperplasia and fibrosis

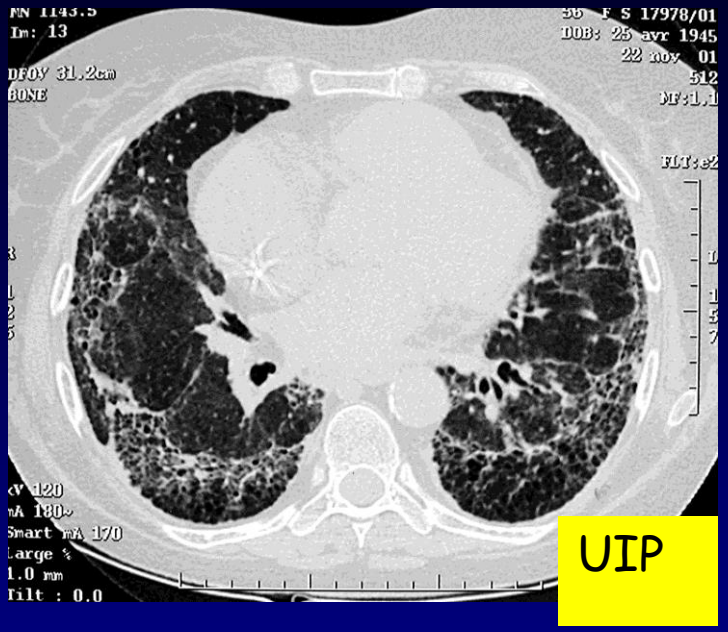
PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

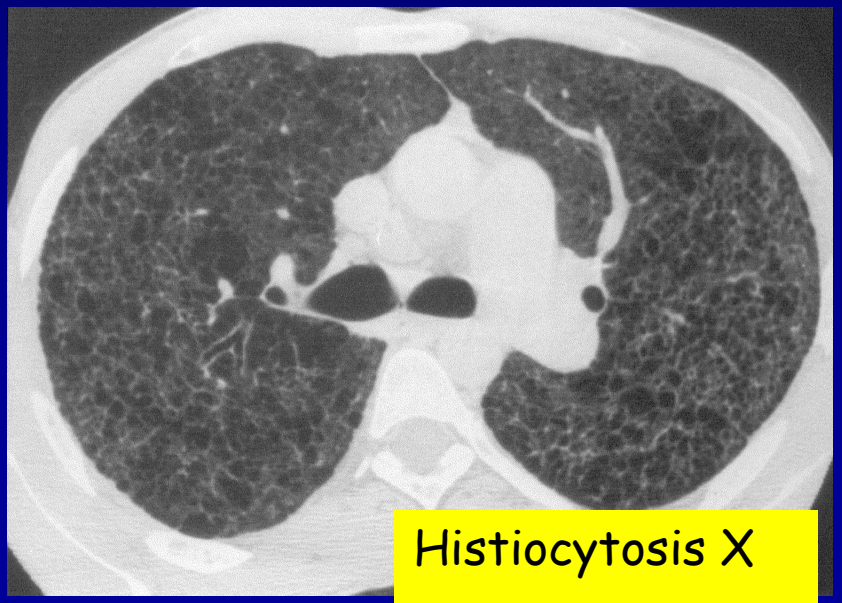
- 21 pts with advanced PLCH referred for LTx
- All of them had moderate-to-severe PH
- mPAP: 59 ± 4 mm Hg (range 36-74 mmHg)
- No correlation between mPAP and PFT
- Pathological findings (n = 12): intrinsic proliferative vasculopathy involving both small to medium-sized arteries and septal veins. VOD in 1/3 of pts

Fartoukh et al. Am J Respir Crit Care Med 2000; 161:216-23

PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X







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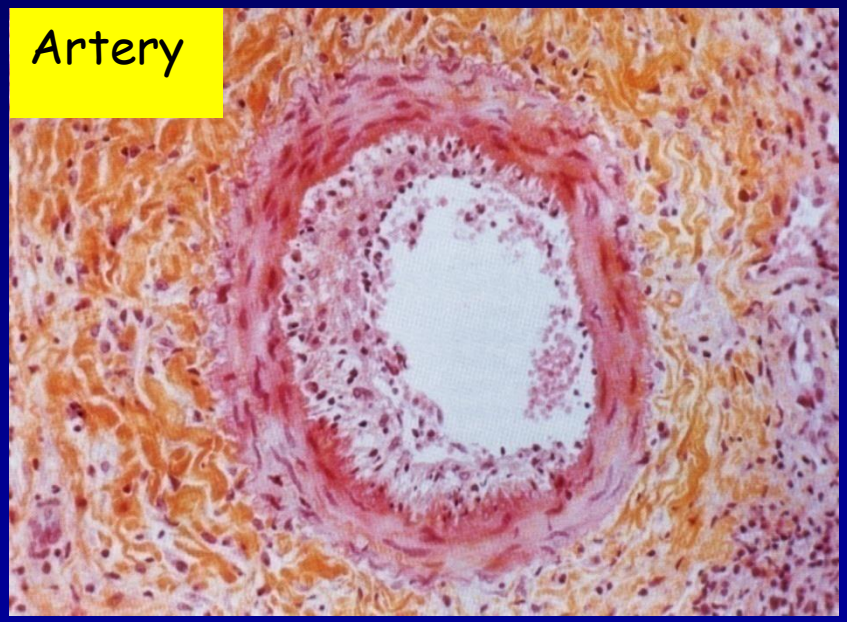
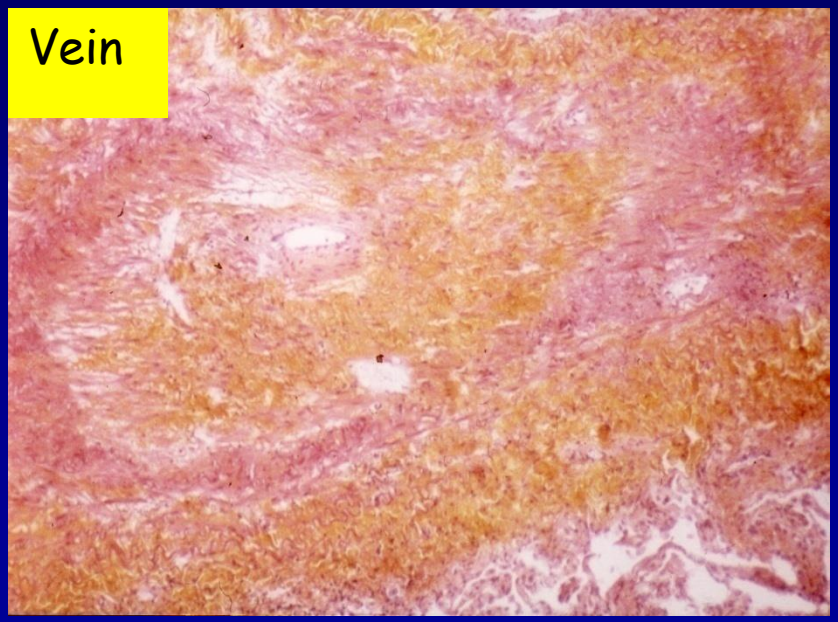
PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

- Pulmonary histiocytosis X = marked pulmonary vascular remodeling predominantly affecting pulmonary veins
- In patients with sequential histologies, this pulmonary vasculopathy was progressing with time (while parenchymal lesions were stable)
- A case of steroid-sensitive pulmonary hypertension has been reported (specific steroid-sensitive vasculopathy?)





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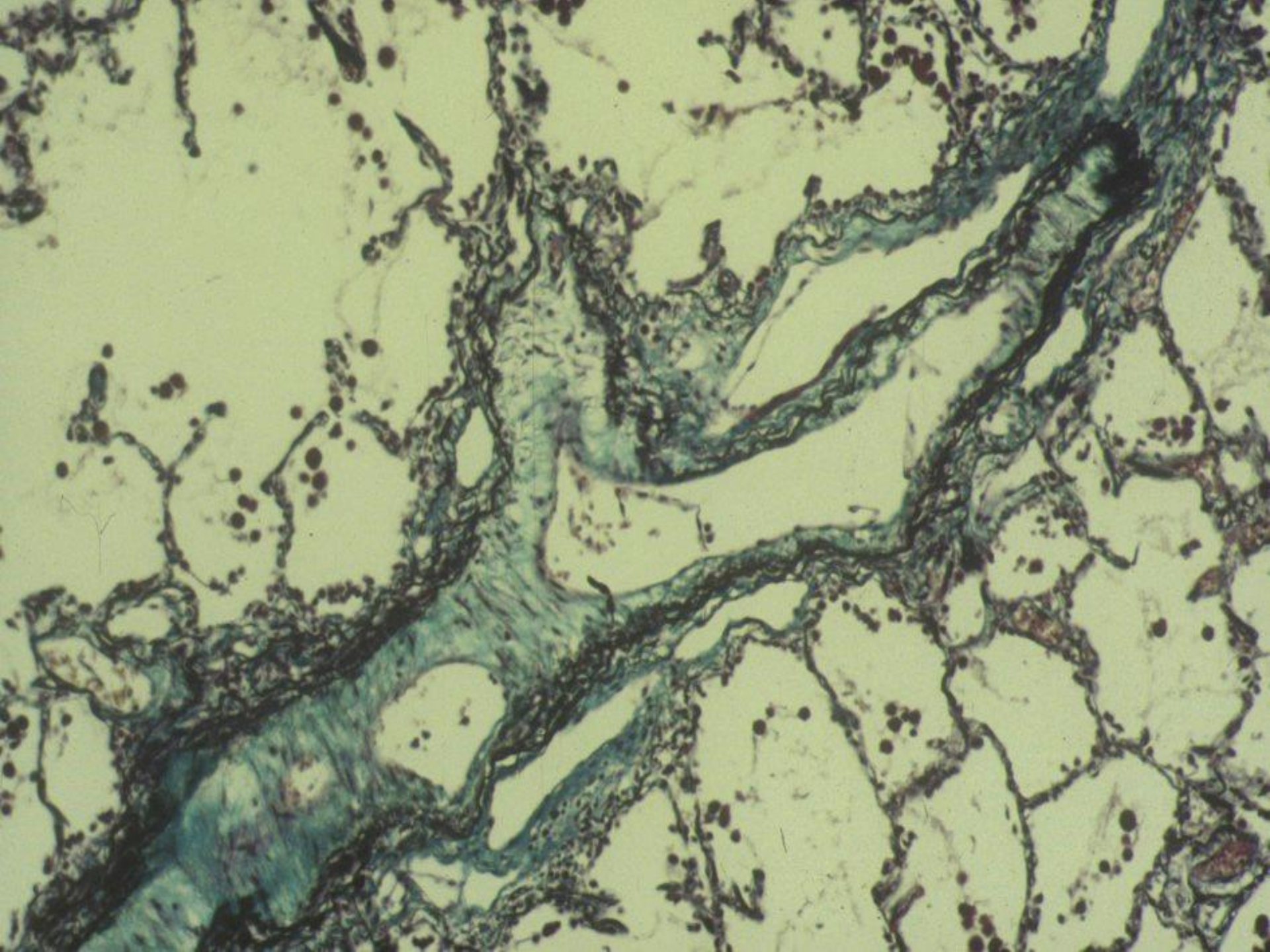
Benyounes et al. Chest 1996; 110:284-6



PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

- 39 pts who had LTx for PLCH at 7 centers in France
- PH (PAPm>25 mmHg): 92% of cases
- PAPm>35 mmHg: 72.5% of cases

G Dauriat et al, Transplantation 2006

PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

- PH is uncommon in pulmonary Langerhans'cell histiocytosis (PLCH)
- In advanced forms of the disease
  - PH is very frequent
  - When present, PH is most often moderate to severe

Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies

Le Pavec et al. Chest 2012; 142: 1150

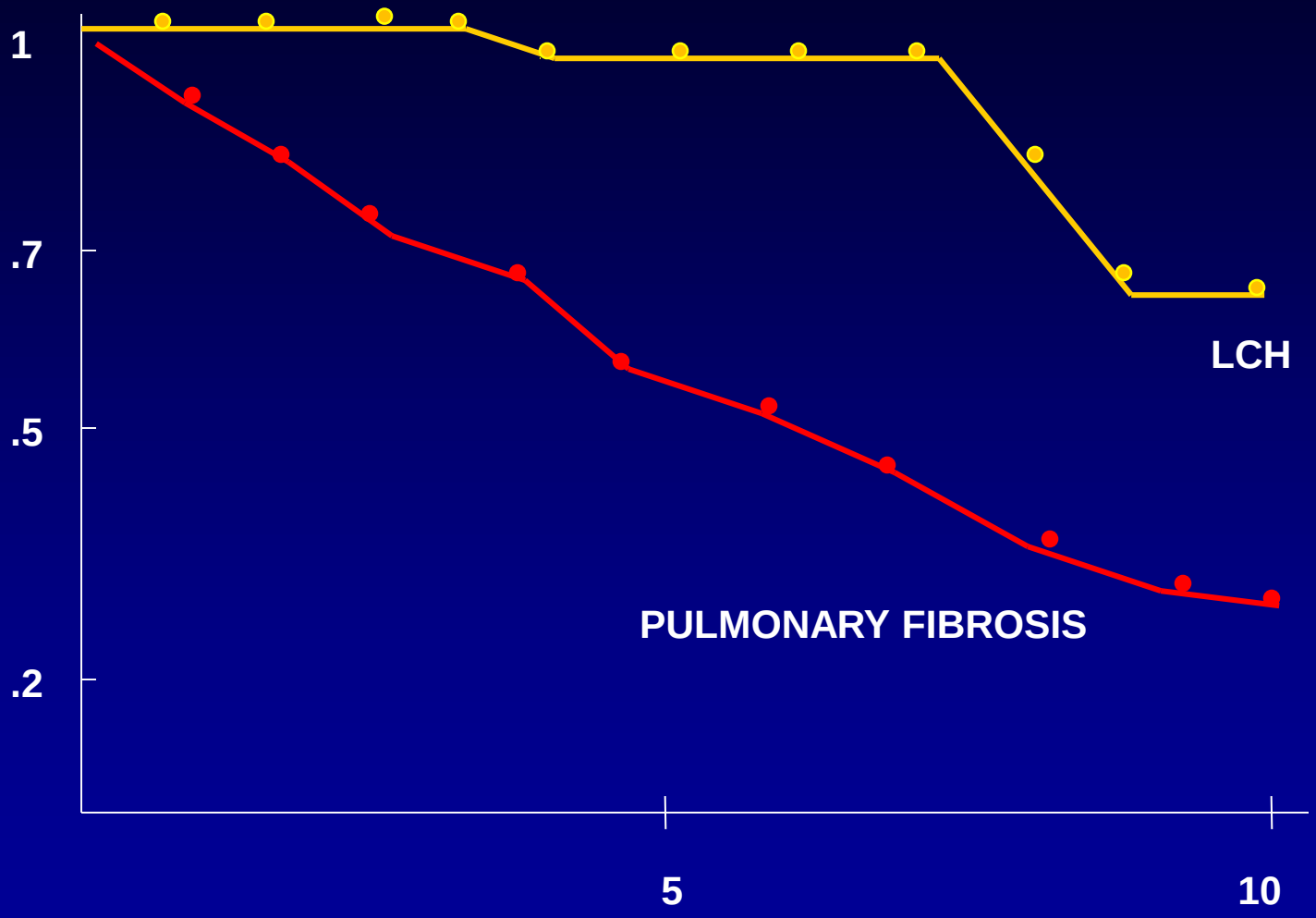
- 29 consecutive patients with PLCH and PH confirmed with RHC were included
- 83% of patients were in WHO functional class III to IV interval between PLCH and PH diagnosis of 9.2 ± 9.8 yrs
- Mean ± SD 6MWD: 355 m ± 95 m
- mPAP: 45 ± 14 mmHg
- Use of PAH therapy in 12 patients was followed by an improvement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

Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies

Le Pavec et al. Chest 2012; 142: 1150

- In this group of patients, PAH therapies improved hemodynamics without oxygen worsening or pulmonary edema
- WHO functional class was the only prognostic factor identified
- Prospective clinical trials focusing on this population of patients are warranted

LCH: SURVIVAL VERSUS PULMONARY FIBROSIS



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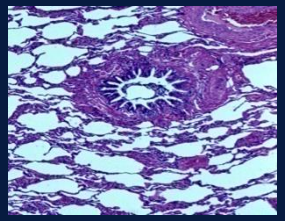

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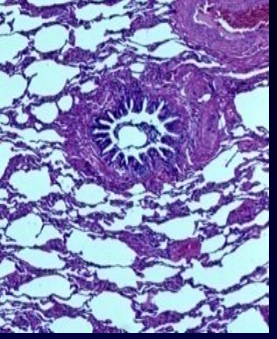

PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

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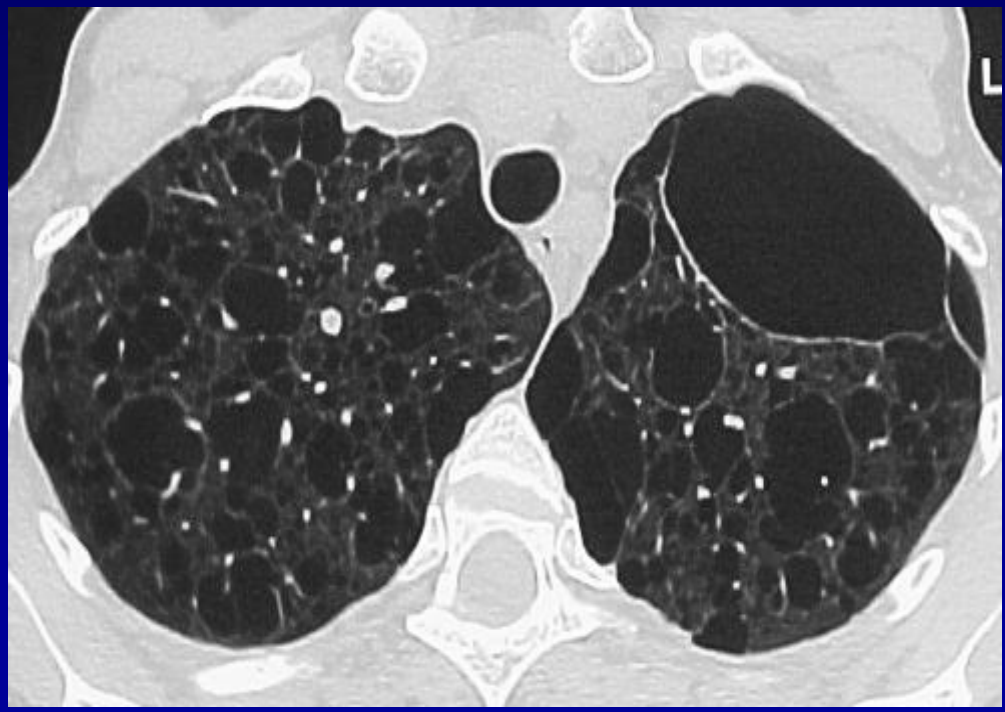

Pulmonary Artery Pressure in Lymphangioleiomiomatosis

An echocardiographic study

- 120 pts
- PFTs, exercise echocardiography, standard cardiopulmonary exercise testing were obtained in 95 pts

Taveira-Da Silva et al. Chest 2007; 132: 1573

Pulmonary Artery Pressure in Lymphangioleiomiomatosis

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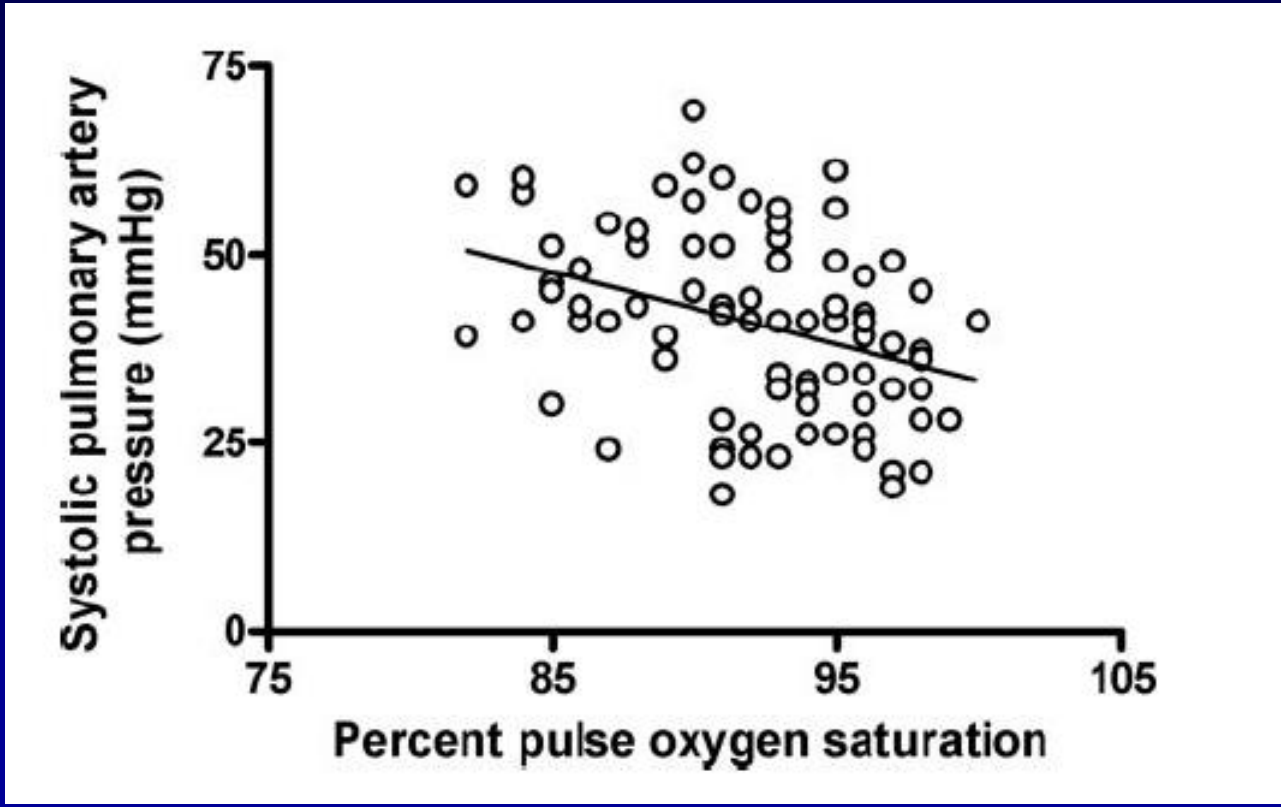


Taveira-Da Silva et al. Chest 2007; 132: 1573

Pulmonary Artery Pressure in Lymphangioleiomiomatosis

An echocardiographic study

- Resting PAP was 26 ± 0.7 mmHg (mean ± SEM)
- 8 pts had pulmonary hypertension (43 ± 3 mmHg) and 2 pts had right ventricular dilatation
- 95 pts exercised (room air, n= 64, oxygen, n= 31) to a power of 58 ± 2 W (49% of predicted)
- 61 pts had a decline in arterial oxygen saturation > 3% and 56 pts had an elevation in PAP > 40 mmHg

Taveira-Da Silva et al. Chest 2007; 132: 1573

Pulmonary Artery Pressure in Lymphangioleiomiomatosis

An echocardiographic study

- Pulmonary hypertension is rare in pts with LAM
- A rise in PAP at low exercise levels occurs frequently, in part related to exercise-induced hypoxemia
- Optimization of oxygen administration during activities of daily living should be undertaken in pts with LAM

Taveira-Da Silva et al. Chest 2007; 132: 1573

Pulmonary hypertension in lymphangioleiomyomatosis: hemodynamic characteristics in a series of 20 Pts.

Age, year, mean (range)	**49 ± 12 (33-73)**
FEV1	42 ± 25% (13-96%)
FVC	76±28 (27-121%)
Tiffenau	47±15 (22-75%)
DLCO	29±13 (14-57)
6MWT	340±84
mPAP	32±6 mmHg
C.I.	3.5 ± 1.1 L.min.m^{-2}
NYHA class I/II III IV	 10% 50% 40%

Cottin V. Eur Respir J. 2012 Sep;40(3):630-40

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 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

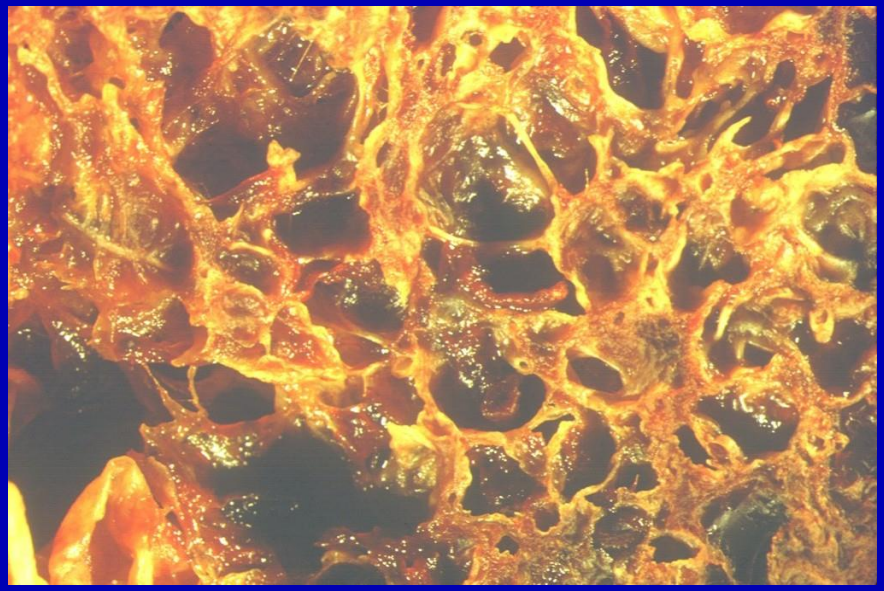
Pre-capillary PH of mild haemodynamic severity may occur in patients with LAM, even with mild pulmonary function impairment.
PAH therapy might improve the haemodynamics in PH associated with LAM.

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

Pulmonary hypertension in lymphangioleiomyomatosis: hemodynamic characteristics in a series of 20 patients

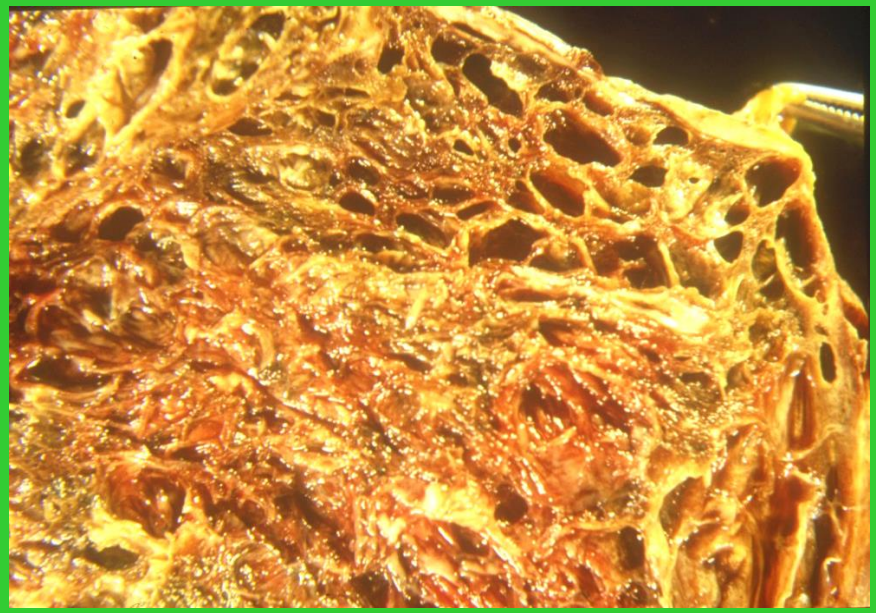
- The median delay between the diagnosis of LAM and PH was 6.2 years (range, 0-36 years)
- Precapillary PAH of moderate hemodynamic severity may occur in patients with LAM and severe pulmonary function impairment. Bosentan therapy might improve hemodynamic characteristics.

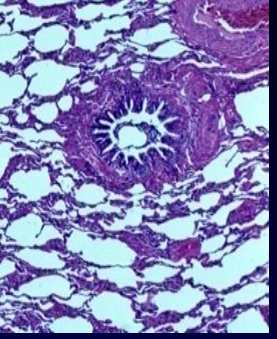
Cottin V. Eur Respir J. 2012 Sep;40(3):630-40



PLCH

LAM



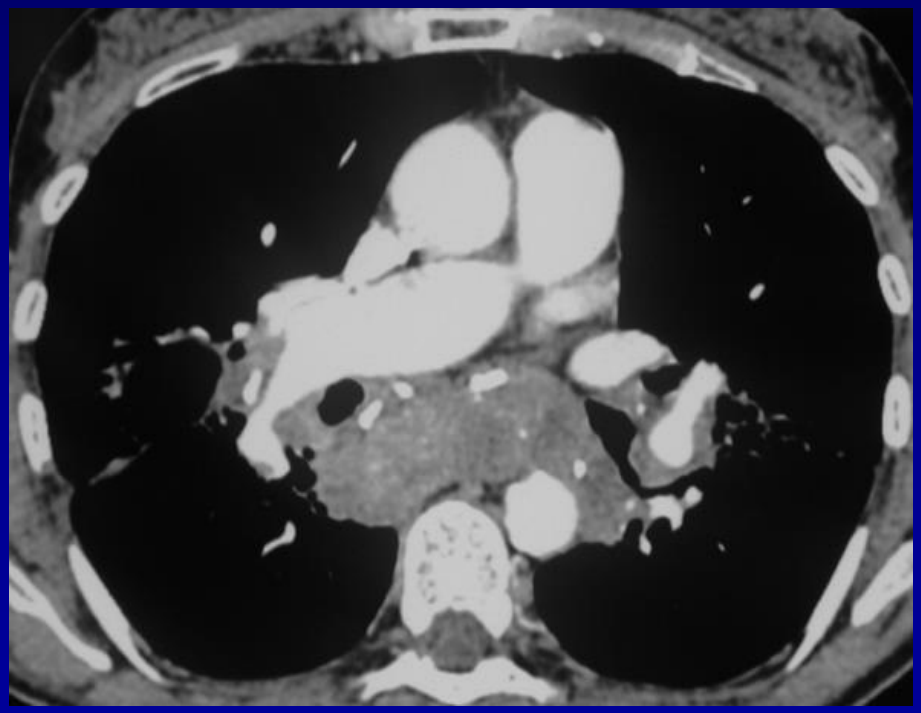


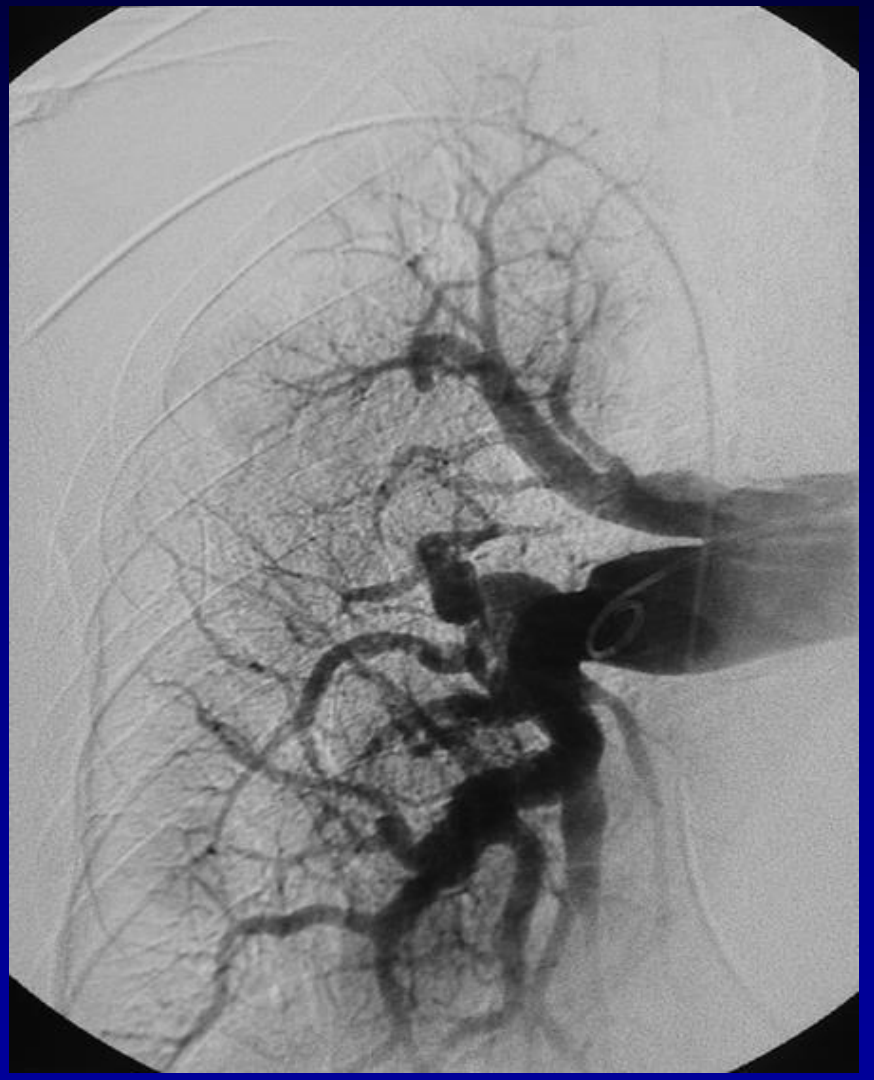
PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

(updated 4th WSPAH-Dana Point 2008)

5. PH with unclear or multifactorial mechanisms

- Sarcoidosis





PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

- 22 patients with biopsy-proven sarcoidosis and pulmonary hypertension

Gender, n (%)	
Men	16 (73)
Women	6 (27)
Age, yr	46 ± 13
Associated conditions, n (%)	
Appetite suppressants use	0 (0)
Portal hypertension	0 (0)
HIV positivity	0 (0)
Congenital heart-disease	0 (0)

Nunes et al. Thorax 2006

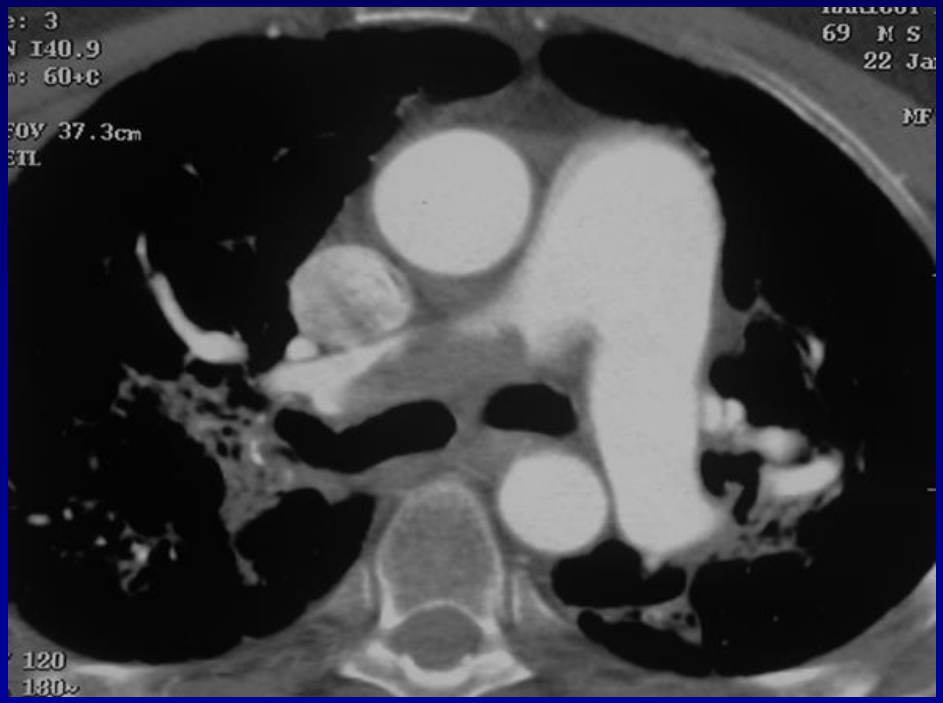
PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

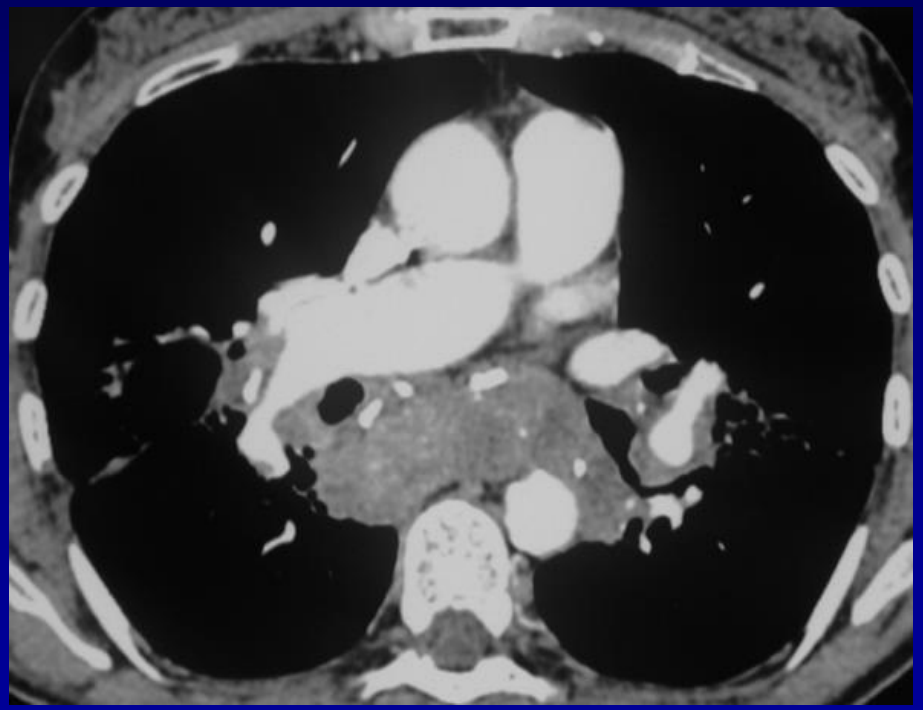
Chest X-Ray, n (%)	
Stage 0	2 (9)
Stage I	0 (0)
Stage II	4 (18)
Stage III	1 (5)
Stage IV	15 (68)

Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

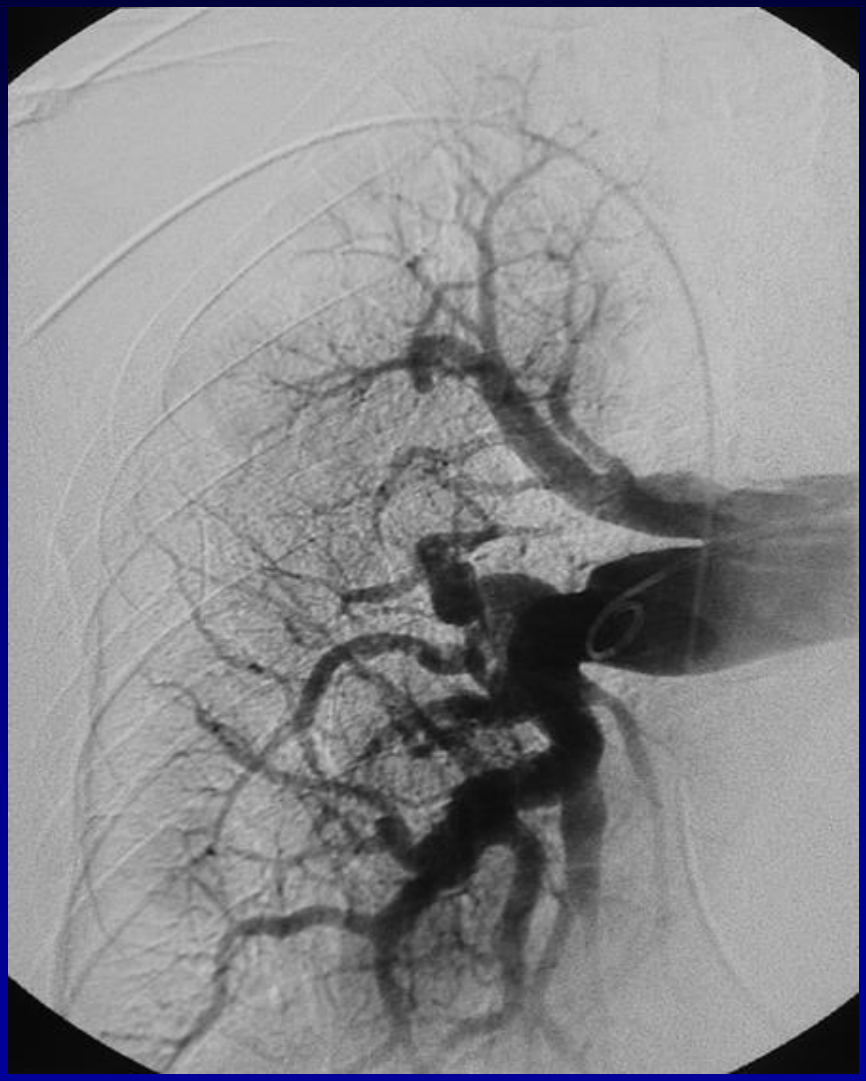
- Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis was detected in 4 out of 15 patients in stage IV





Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS



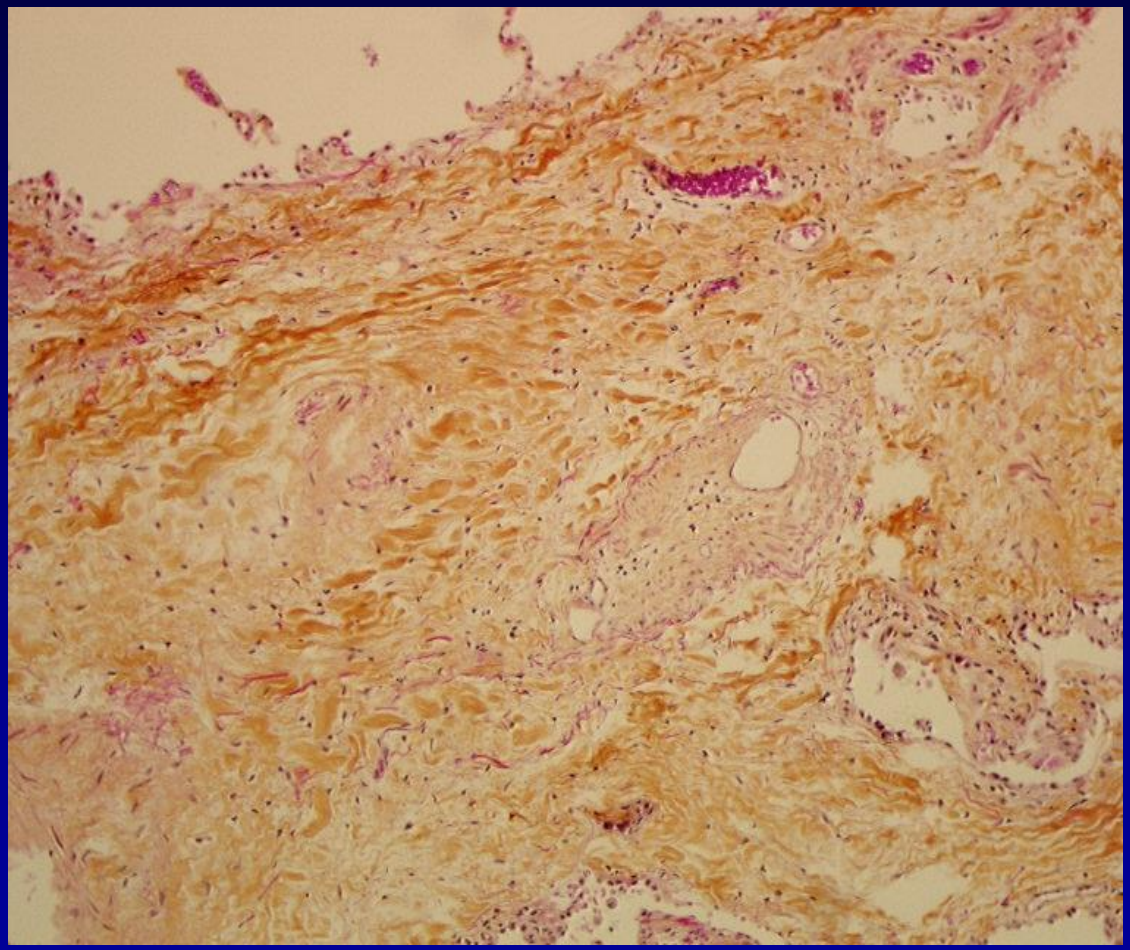
Pulmonary angiography

(9 patients)

➔ Vascular distorsion associated with extrinsic compression: n = 4 (stage IV in all the cases)

Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS



No correlation between mPAP, FEV1 and TLC

Pulmonary hypertension was out of proportion with alterations in lung function

➔ Specific pulmonary vasculopathy?

Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

	Stages 0-III	Stage IV
Base-line hemodynamics		
mRAP mm Hg	7.3 ± 4.2	6.4 ± 6.7
mPAP mm Hg	51.7 ± 16.0	40.1 ± 11.6
mPAP < 35 mmHg	1 (14.3)	7 (46.7)
PcWP mmHg	8.8 ± 2.3	8.1 ± 3.6
CI $l.min^{-1}.m^{-2}$	2.45 ± 0.69	3.26 ± 0.09
PVRI $IU.m^{-2}$	23.0 ± 10.4	14.6 ± 8.9
Pulmonary function tests		
FEV_1 % pred	75 ± 20	38 ± 18
FVC % pred	82 ± 18	50 ± 16
TLC % pred	84 ± 13	67 ± 13
DLCO% pred ‡	41 ± 29	58 ± 19

Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

- 10 patients were treated with steroids (0.5-1 mg/kg/day).
  - Stage 0 (n = 1)
  - Stage II (n = 5)
  - Stage IV (n = 4)

- Control of Doppler echocardiography at 3- 6 months.
  - No improvement in patients with stage IV disease
  - Some improvement observed in other patients

Nunes et al. Thorax 2006

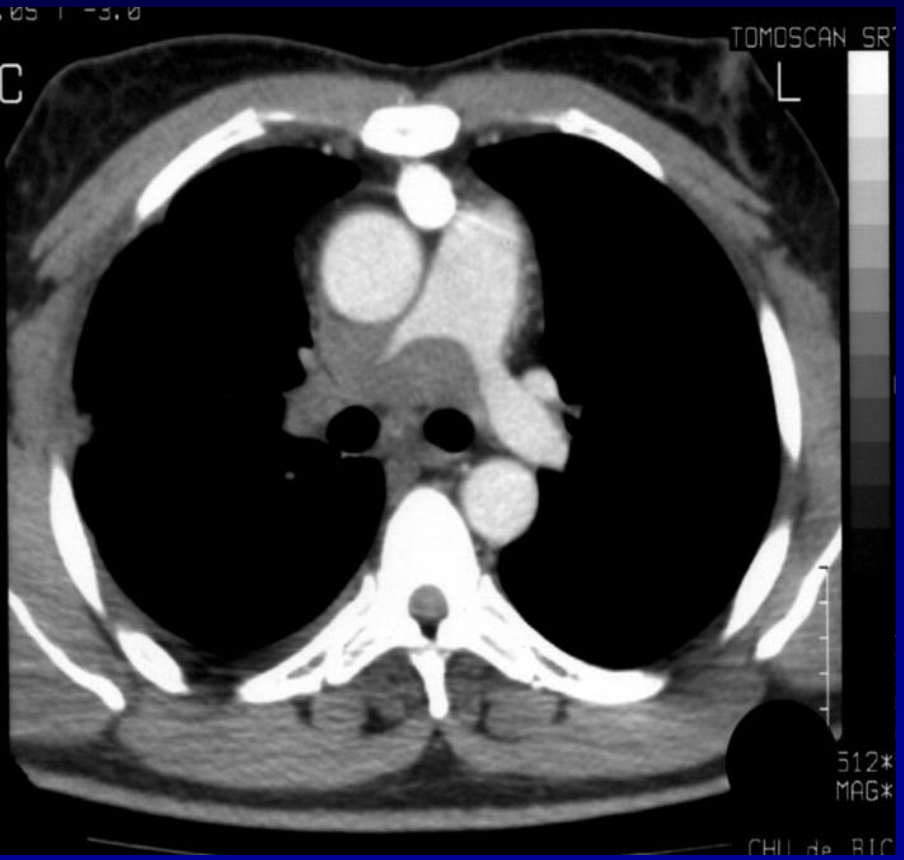
PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

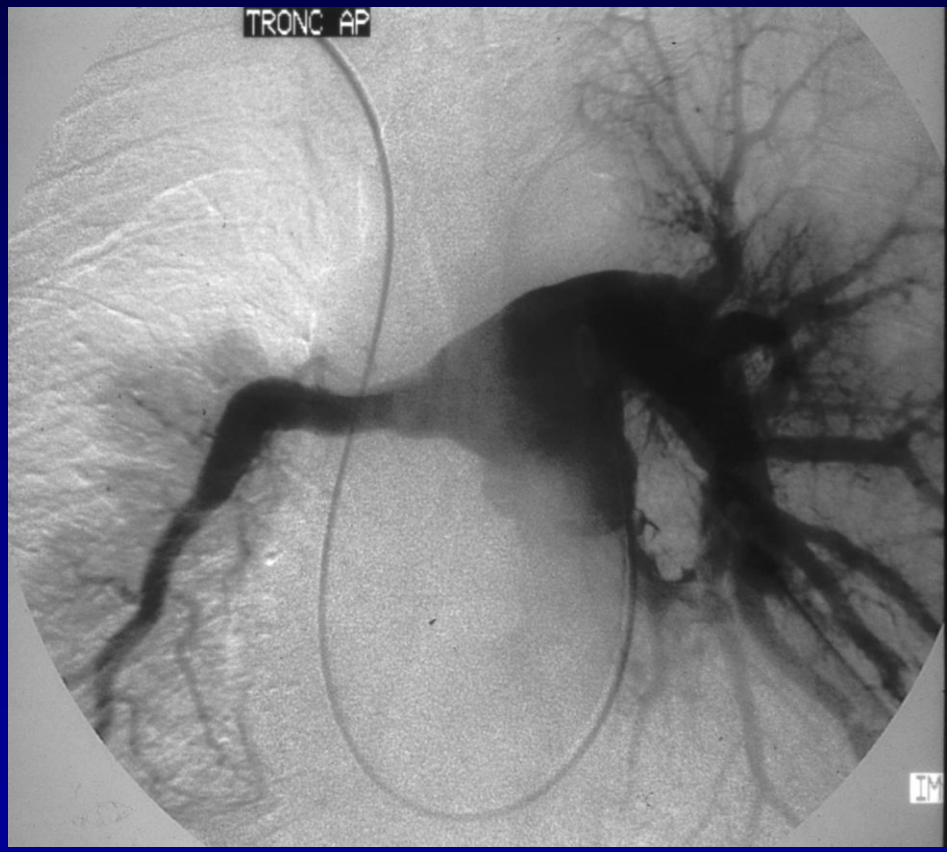
Precapillary pulmonary hypertension in the context of sarcoidosis may be due at least in part to:

- ➔ Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis
- ➔ Destruction of the distal capillary bed by fibrotic process and resulting hypoxia (stage IV)
- ➔ Specific vasculitis, with infiltration of the walls of pulmonary arteries and/or veins by granulomas (steroid sensitive ?)

Nunes et al. Thorax 2006

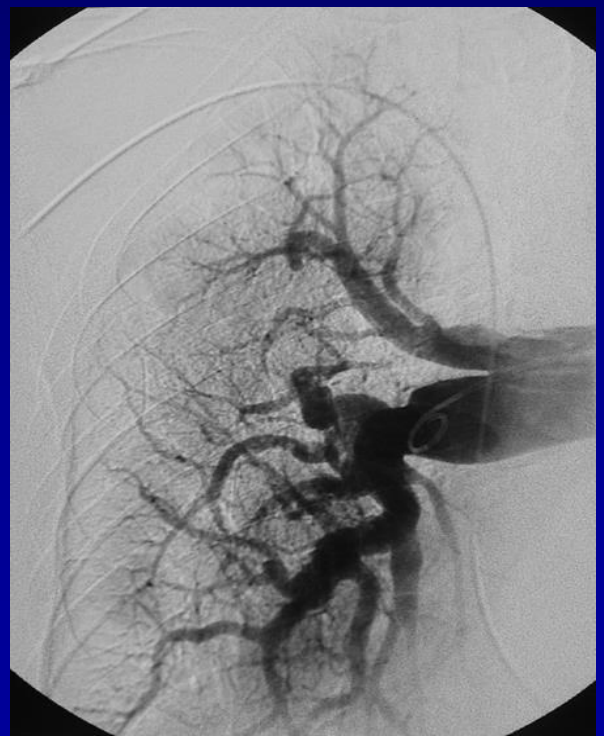
FIBROSING MEDIASTINITIS IS A CAUSE OF PULMONARY HYPERTENSION IN SARCOIDOSIS

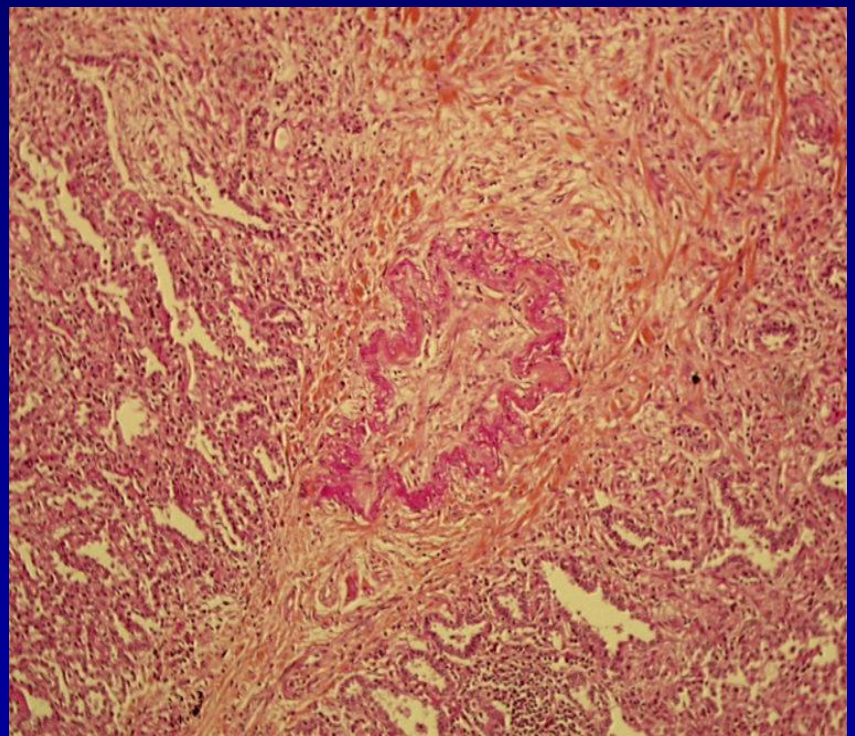




PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

- Pulmonary hypertension in sarcoidois occurs in two very different settings
- In the absence of pulmonary fibrosis, PH appears to be related to a specific vasculopathy and may be steroid-sensitive
- In case of pulmonary fibrosis, the mechanism of PH is complex, but certainly involves at least in part a specific vasculopathy as PH is out of proportion with alterations in lung fuction. In these patients, physicians have to consider lung transplantation sooner than they would have solely on the basis of lung function





Classification of pulmonary hypertension

Category	Treatment
Pulmonary arterial hypertension	prostanoids, ERA
Pulmonary arterial hypertension associated with PVOD and or PCH	risks in using VD lung transplantation as a first line treatment?
Pulmonary venous hypertension	diuretics, ACEI, ß-blockers
PH associated with hypoxemia	oxygen therapy
Proximal CTEPH	Thrombo-endarterectomy
PH with unclear mechanism	***A role for drugs ?***

Conclusions

- Drugs with proven efficacy in PAH are being increasingly used in other forms of PH, despite the virtual absence of clinical trials supporting this approach

- In selected cases of LAM, Hx and Sarcoidosis and moderate-severe PH it is conceivable a trial of therapy with drugs used in PAH