UNCOMMON INTERSTITIAL LUNG DISEASES

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Pulmonary Langerhans Cell Histiocytosis

Definition

- Forms part of a spectrum of diseases characterized by monoclonal proliferation and infiltration of organs by **Langerhans' cell**s
- Lung involvement may occur either in isolation or as part of a multiorgan disease: bone, skin, pituitary gland, liver, lymph nodes, and thyroid.
- PLCH refers to disease in adults that affects the lung, in isolation or in addition to other organ systems

Epidemiology

- Afflicts predominantly whites, uncommon in Asian
- 20-40 yrs
- Initial reports: males: recent studies females
- Incidence:

❖ 5% surgical biopsy series (N=502)

❖ 6.6% Italian registry of ILD (N=1382)

- Rare cases of LCH have been reported following Hodgkin disease treated with chemoRx and radioRx

Relationship to smoking

- Epidemiological: >90% smokers
  smoking precipitates PLCH in pts with LCH
- Experimental observation: ↑ dendritic cells
  Nonclonal proliferation of Langerhans cells
- Clinicopathologic observation:

➢ ↑Langerhans cells in asymptomatic smokers
➢ Bronchiolocentric distribution of lesions
➢ Recurrence of disease in post-transplant
➢ Regression of after smoking cessation

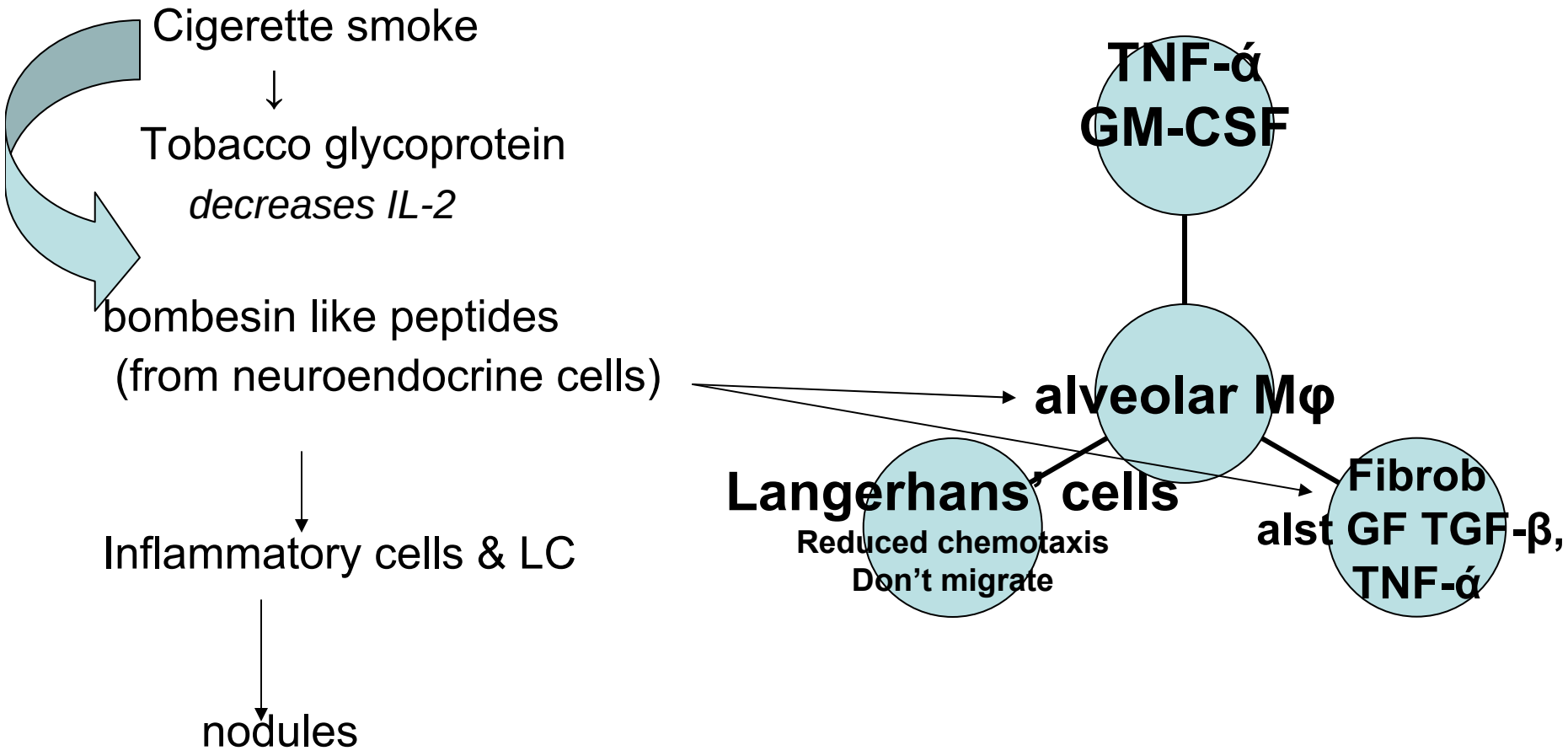
Langerhans’cells

- Type of dendritic cells
- Site: beneath the tracheobronchial tree,

Functions: serve as a primary line of defense surveying the inhaled antigens

- Inflammatory response
- tolerance

Pathogenesis



Pathogenesis

Uptake of cigarette-smoke antigens by alveolar Mφ or Langerhans' cells

↓

promote local expansion of T cells and further inflammation

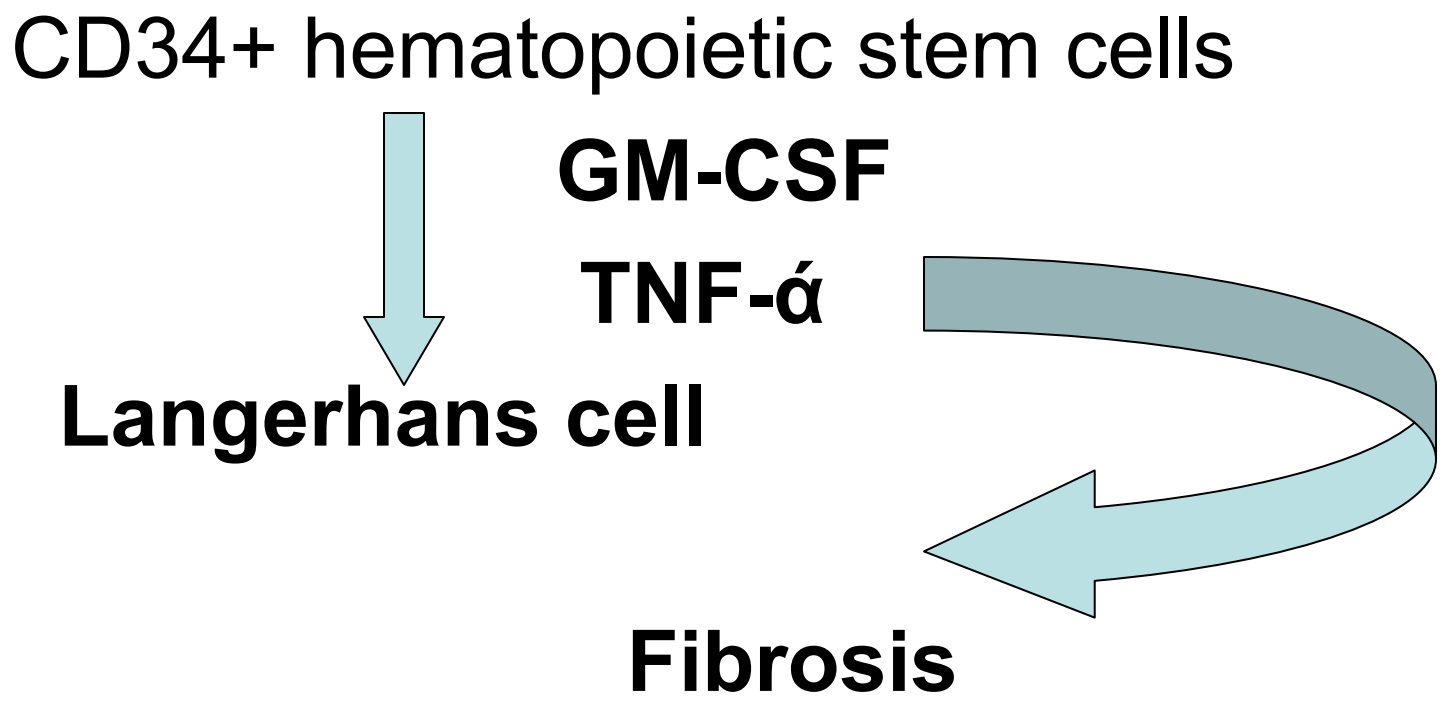
↓

stimulate B-lymphocyte

↓

Ab and Ag-Ab complexes

Role of GM-CSF & TNF-ά

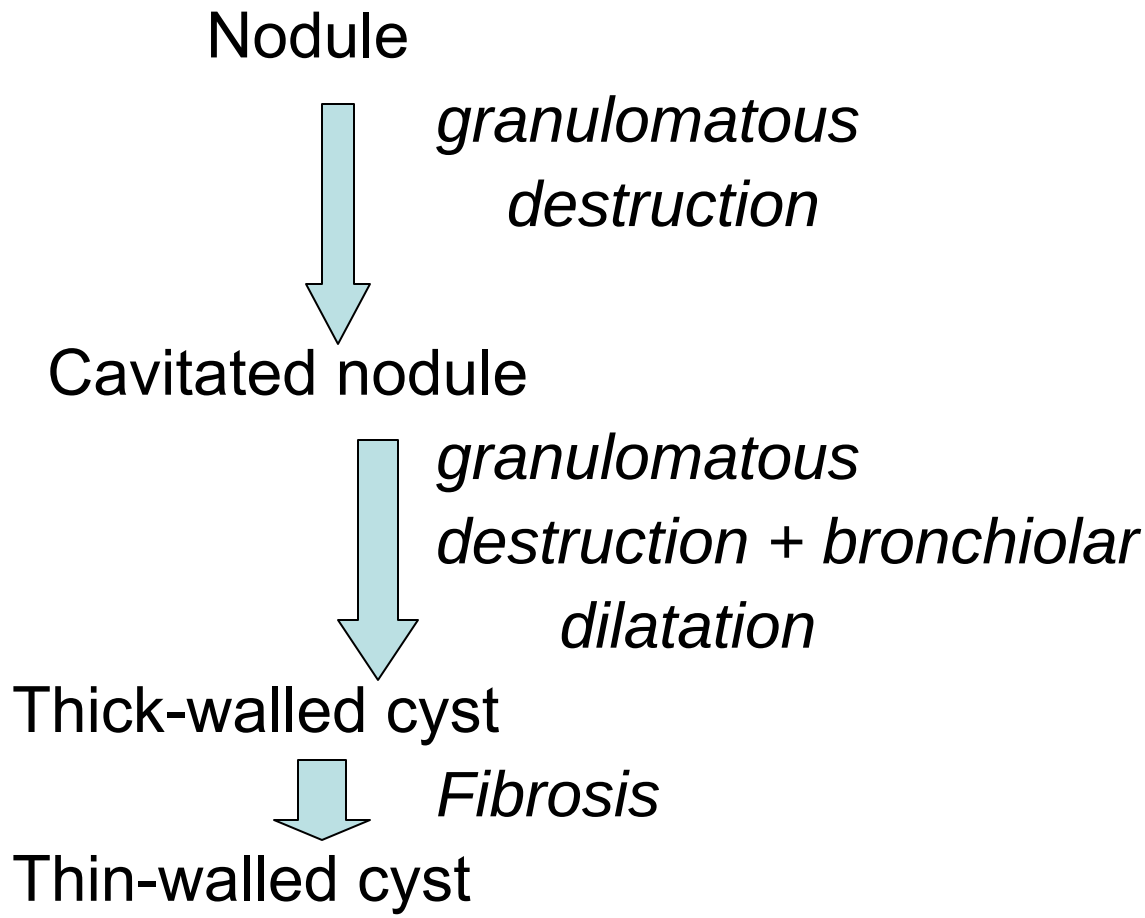


Role of IL-2

- IL-2 inhibits histiocyte proliferation
- relative lack of IL-2 favors local proliferation of Langerhans' cells in the lung

Clinical remission of Langerhans'-cell histiocytosis in a child treated with intravenous interleukin-2.

Mechanism of cyst formation



Increase in cyst size

- traction bronchiolectasis
- ball-valve effect in partially obstructed bronchioles

- Confluence of cysts: honeycombing

Pathology

- Histologic diagnosis:

identification of typical lung lesions +

reliable demonstration of ↑ no. of Langerhans' cells

- Symmetric stellate lesions: Centripetal replacement of granulomatous nodular infiltrates by fibroblasts
- Respiratory bronchiolitis
- Emphysema

Identification of Langerhans' cells.

- **Birbeck granules**: pentalaminar, rod-shaped intracellular structures
- **CD1a antigen** on cell surface
- S-100
- Langerin (CD207)
- Folded nucleus
- Pale cytoplasm

Clinical features

- Asymptomatic: 25%
- Weight loss, fever, night sweats, and anorexia: 33%
- Spontaneous pneumothorax 10-15%
- Hemoptysis: <5%
- Involvement of other organs: 5-15%

❖ DI
❖ Rash
❖ Lymphadenopathy
❖ Hepatosplenomegaly
❖ Bone cysts

Pulmonary Vasculopathy

- Pulmonary hypertension far out of proportion to indices of ventilatory or gas-exchange limitation
- Intimal fibrosis, medial hypertrophy, or luminal obliteration with occasional infiltration into vessel walls by lymphocytes and/or eosinophils
- Both venules and arteries are affected.
- Limited value of PFT and physical examination in predicting an individual's disease course

HRCT Chest

- **Cysts (80%) and/or nodules (60 to 80%);**
  - Thin walled cyst<10mm
  - Upper lobe predominance in size & no.
  - Larger cyst in > 50% cases, but only some are > 20mm
  - Nodules: centrilobular
  - <3mm: 47%
  - 3mm-10mm: 45%
  - >10mm: 8%

HRCT Chest

- Ill-defined nodules and curvilinear/reticular opacities
- Upper-lobe involvement
- Costophrenic angles generally spared
- LV generally preserved or increased

Uncommon HRCT findings

- Mediastinal adenopathy
- Presentation as a solitary pulmonary nodule
- Consolidative opacities
- Pleural effusions

PFT

- Most common: ↓ Dlco 60-90%
- Obstruction:
  - Peribronchiolar distribution of the inflammatory and fibrotic lesions
  - Coexistant emphysema
  - Predominantly cystic and bullous disease in some patients
- Restriction: late; due to fibrosis

Role of bronchoscopy & TBLB

- Patchy disease
- BAL CD1a+ cells> 5%

May be ↑ in active smokers

- Low diagnostic yield 10-40%
- Used mainly for exclusion of other diseases

Natural History

- Records of 102 adults with histopathologically confirmed PLCH
- Median follow-up period:4 years (range: 0 to 23)
- Deaths 33, Attributable to respiratory failure: 15
- Hematologic cancers: 6
- The overall median survival: 12.5 yrs
- Variables predictive of shorter survival
  - older age
  - ↓ FEV1
  - ↑ RV
  - ↓ FEV1/ FVC
  - ↓ DLco

NEJM 2002

Poor prognostic factors

- Extremes of age
- Multi-system involvement
- Prolonged constitutional disturbance
- Extensive cysts & honeycombing
- ↓FEV_1/FVC ratio
- ↓↓DLCO
- Corticosteroid therapy at F/u
- Severe PAH

Malignancies

- Lymphoma
- Myeloproliferative disorders
- Epithelial cancers
- Bronchogenic Ca: does not appear to be scar carcinoma

Treatment

- Smoking cessation
- F/u: 3-6 mo PFT
- Pleurodesis: recurrence rate of pneumotx=50%
- 2-Chlorodeoxyadenosine
- ? IL-2, Vinblastine, Methotrexate, Cyclophosphamide, Etoposide, Etanercept, Anti TNF-ά
- Lung Tx: may recur if smoking is contd

Steroids

- Persistent pulmonary or constitutional symptoms
- Progressive decline in lung function
- Complicated by pulmonary hypertension
- Dose: 0.5 mg/kg/d

Lymphangioleiomyomatosis

Introduction

- Characterized by an unusual type of muscle cell: grow uncontrollably and obstruct

❖airways,

❖lymphatic system

❖blood vessels of the lungs

Global perspective

	France	Japan	UK	NHLBI
N	69	46	22	230
Females	100%	100%	100%	100%
Age at diagnosis	39.3 ±9.6	undetermined	35.5	41.0 ± 0.65
Age at onset of symptom	36.3 ±9.6	32.0 ± 8.9	30.7	38.9 ± 0.73
Intervel b/w onset of symptom & Δ	3.0 ± 4.5	undetermined	4.72	2.1 ±0.08
Source	*Medicine 1999;*	*AJRCCM 1995*	*New York: Marcel Dekker 1999*	*AJRCCM Sep 2005*

Other associations

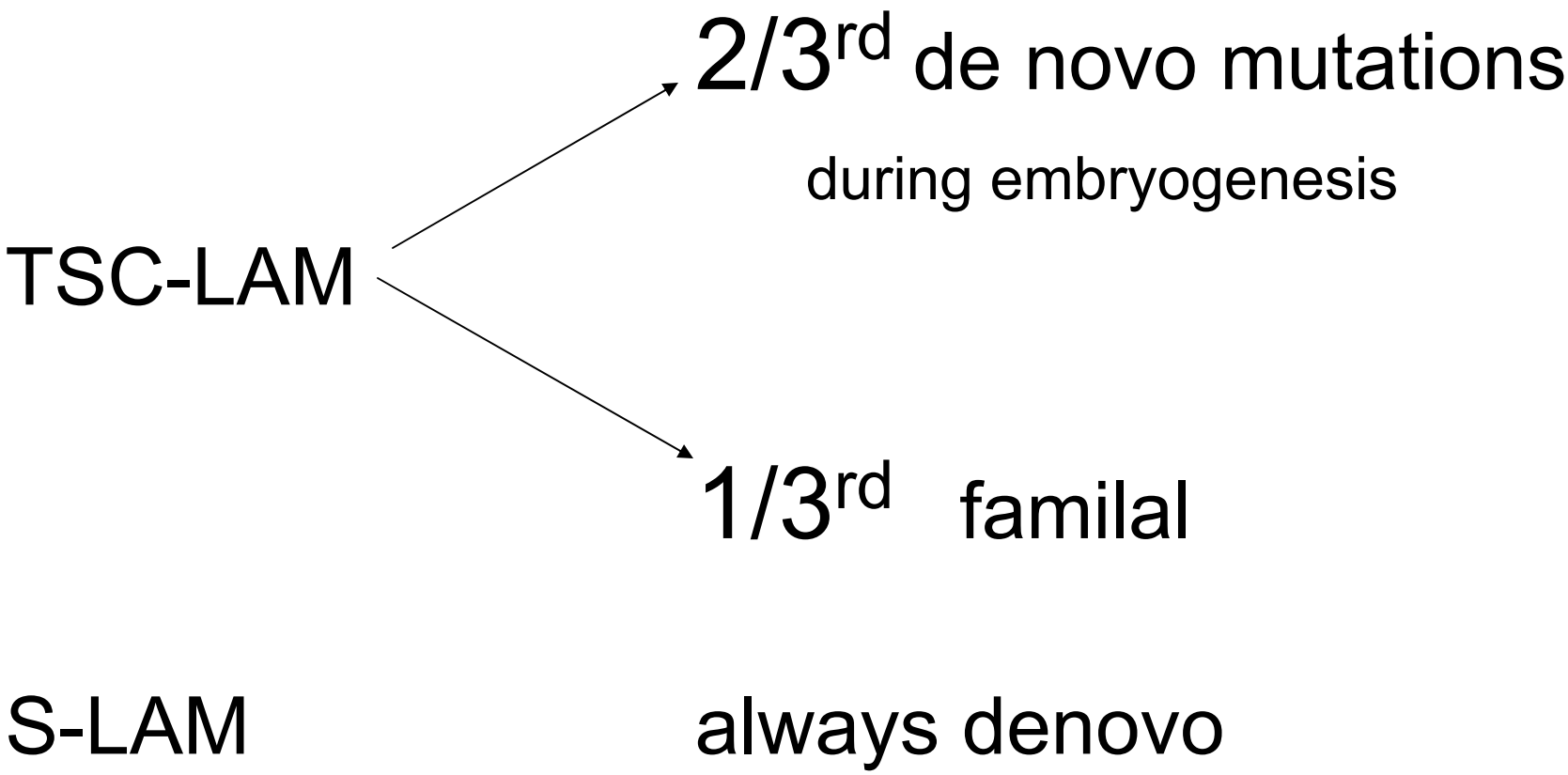
LAM has been reported to occur in patients with

- Tuberous sclerosis complex (TSC)
- ά-1 antitrypsin deficiency
- Langerhans' cell histiocytosis
- Thyroid carcinoma
- Bronchoalveolar carcinoma
- In association with renal angiomyolipomas (AMLs)

Lymphangioleiomyomatosis

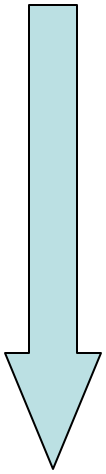
- Two settings: with TSC/Sporadic: S-LAM
- TSC: autosomal dominant; associated with development of hamartomas and dysplastic lesions in several organs
- S-LAM: only angiomyolipomas and cysts in the kidney, and smooth muscle infiltration of the lymphatic system

Inheritance



Inheritance

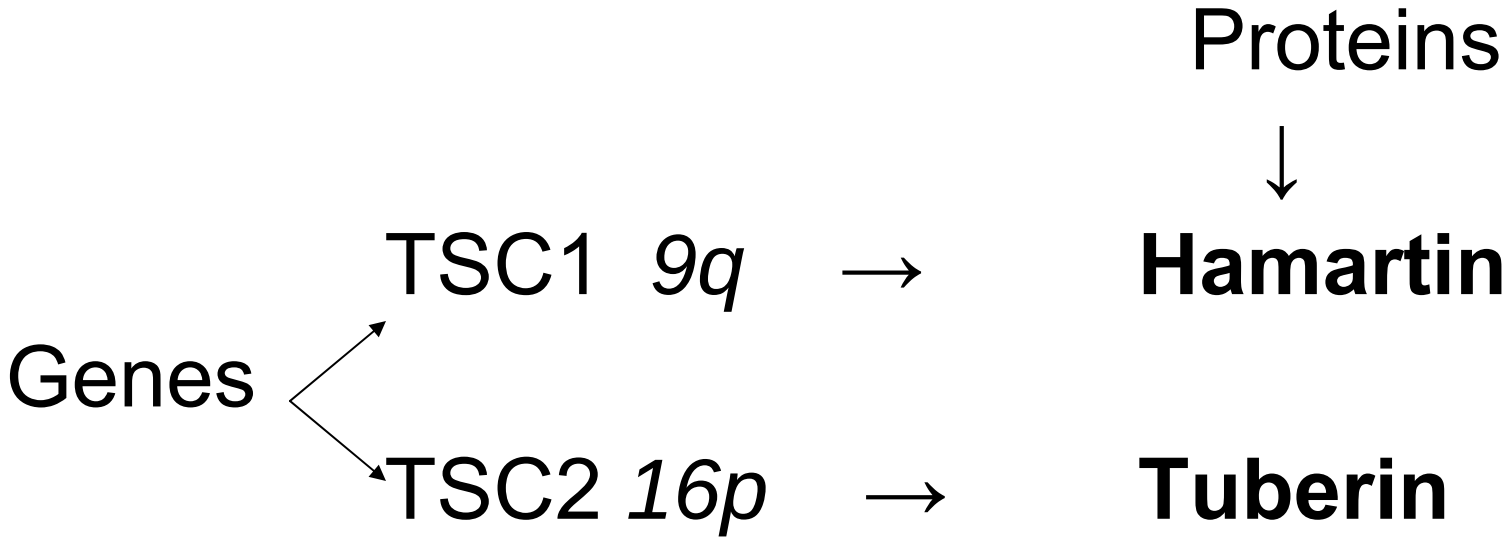
Germline mutation in one of two genes
(TSC1 or TSC2)



2^{nd} somatic mutation (or hit):
k/a loss of heterozygosity (LOH)

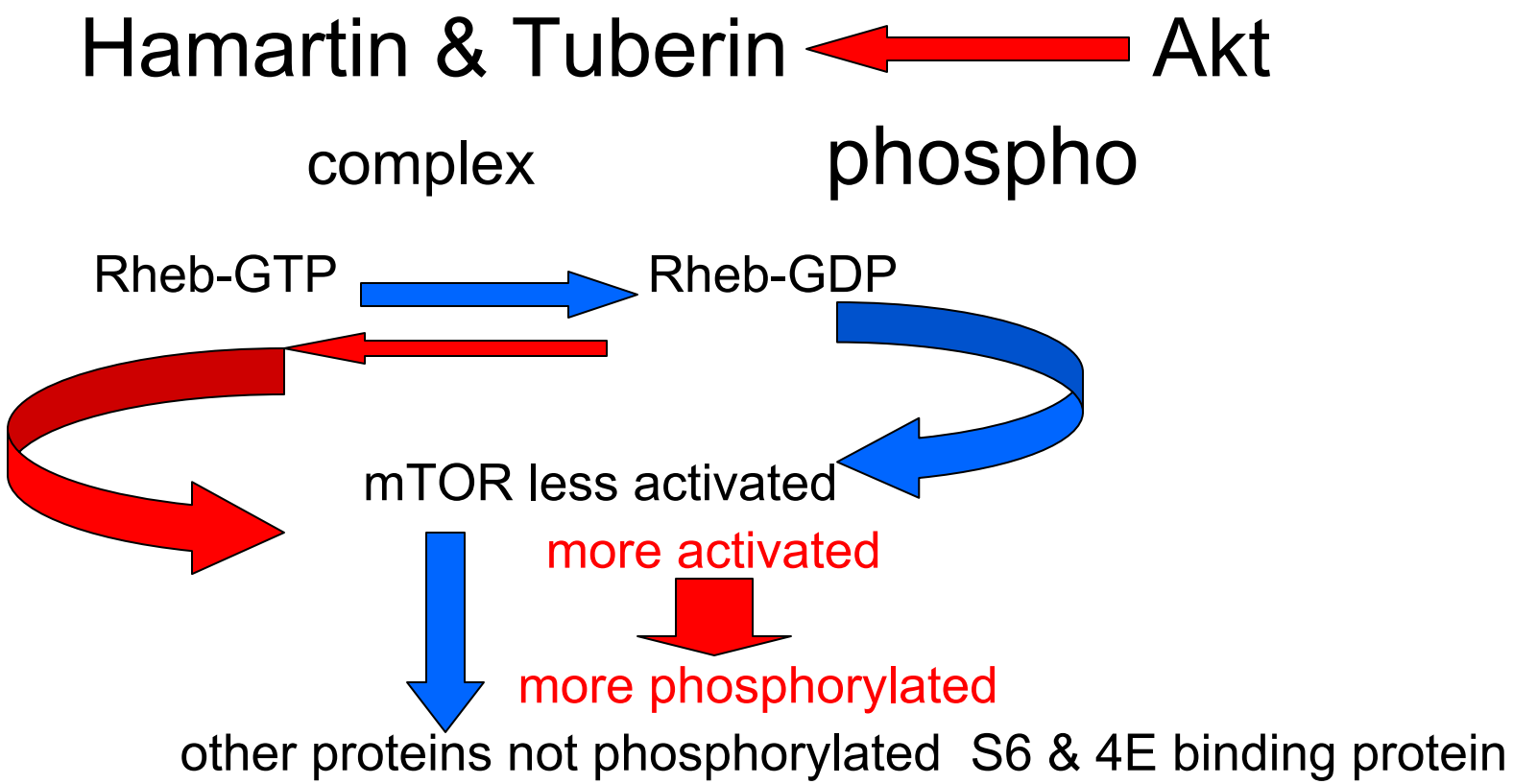
loss of protein function (hamartin or tuberin)
in that cell

Pathogenesis



Suppress inappropriate cell growth
(tumor suppressor activity)

Pathogenesis



Pathogenesis

Activated mTOR (kinase)
More phosphorylation of downstream products
↓
inappropriate stimulation of
protein synthesis,
cell motility
cell growth
Sirolimus inhibits mTOR

Estrogen in LAM

Estrogen promotes growth through estrogen receptor

- increased expression and activation of PDGFR-beta
- Modulate signaling through Akt pathway
- PR and ER are localized mainly in the nuclei of large epithelioid LAM cells
- down-regulated by hormonal therapy

AJRCCM Mar 2000

Mechanism of Cyst formation

- airflow obstruction due to smooth muscle cell infiltration
- protease imbalance: up-regulation of matrix metalloproteinases 2 and 9 and down-regulation of tissue inhibitor of metalloproteinase-3

Diagnostic criteria for TSC

MAJOR

- Facial angiofibromas or forehead plaque
- Non-traumatic ungual or periungual fibroma
- Hypomelanotic macules (more than three)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- *Cortical tuber*
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- **Lymphangiomyomatosis**
- **Renal angiomyolipoma**

MINOR

- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter migration lines
- Gingival fibromas
- Non-renal hamartoma
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts

Definite: 2 major/ 1major+2 minor

Probable: 1 major + 1 minor

Possible: 1 major/≥2minor

	TSC-LAM	**S-LAM**
Estimated pts	250,000	50,000
Reported in males	+	-
Germline TSC mutation	+	Double hit
Inheritable	+	-
TSC1/TSC2 mutations	33%/66%	0%/100%
Angiomyolipomas	80% multiple, B/L	40%, single U/L
MMPH	+	very rare
CNS/skin/eye/cardiac	+	-
Chylothorax	Less	33%
Pneumothorax	Less	66%
Adenopathy thoracic/RPLN	+	+

Complications

- **Pneumothorax**:
  - rupture of subpleural blebs triggered by progressive degradation of connective tissue matrix
  - airflow obstruction and overdistention of distal air spaces
- **Chylous complications**: obstruction of lymphatic channels due to infiltration by smooth muscle cells.
- **Angiomyolipomas**: composed of fat, smooth muscle, and abnormal blood vessels, may occur in any location in the chest and abdomen
- Blood vessels in angiomyolipomas are tortuous and aneurysmal, composed of cells *TSC* mutations

HRCT

HRCT more sensitive than PFT

- Symmetric distribution
- Intervening parenchyma: normal
- Reticulation: uncommon may be seen at the margins of cyst
- linear densities (29%), ground-glass opacities (12%), nodular densities (11%), hilar or mediastinal lymphadenopathy (9%), pleural effusion, pneumothorax, lymphangiomyomata, and dilated thoracic duct

HRCT

- Cysts: 2mm-5cm
  - thin walled: faintly perceptible-4mm
  - clear margins
  - rounded
  - diffusely distributed
- Nodules: small; upper lobe
- Multinodular pulmonary disease: defined as > 10 nodules

MMPH

- In TSC nodular densities on high-resolution CT represent multifocal micronodular pneumocyte hyperplasia (MMPH): clusters of hyperplastic type II pneumocytes
- MMPH may be present in men or women with TSC, very rare in patients with S-LAM
- No known physiologic or prognostic consequences

PFT

- Normal spirometry:42%
- Obstructive physiology: 35% (25% sig BDR)
- Restrictive physiology:14%
- Combined obstructive and restrictive:9%
- DLCO: is the most sensitive functional abnormality
- Poor exercise performance:

➢ airflow obstruction and

➢ increased dead space ventilation, caused by pulmonary vascular disease or extensive cystic change

OLB

- Successful bronchoscopic diagnosis, using TBLB with appropriate immunohistochemical staining: exception
- OLB: Most definitive way. HMB-45(monoclonal Ab against premelanosomal protein gp 100)

Indications of OLB:

- Cystic pulmonary change without corroborating features of known TSC or angiomyolipomata
- In smokers, to distinguish LAM from emphysema and Langerhans cell histiocytosis

Treatment

Progestins (oral/IM): at doses sufficient enough to suppress estrogen

suprapharmacologic intramuscular progesterone: undesirable side effects

✓ Retrospective study N=50

In premenopausal patients: significant reduction in decline in both FEV1 and DLCO

AJRCCM Aug 1999

➢ progesterone therapy does not slow the decline in FEV1 and DLCO (N=348)

Chest 2004

Treatment

- GnRH agonist: unproven benefit
  induction of early menopause is distressing
- Steroids
- Immunomodulatory cytotoxic agents
- Ovarian irradiation
- Ovariectomy

Lung Transplant

- 34 patients:27 single-lung transplants; 6 B/L transplants; and 1 a heart–lung transplant.
- Age at transplantation: 40 ± 9 years (range:24-55)
- Interval between the onset of symptoms and transplantation: 11 ± 6 years (range:3-24)
- Survival : 69 % after 1 year and 58 % after 2 years

NEJM 1996

Management

- Stop smoking
- Stop all estrogen-containing medications
- Counsel regarding pregnancy
- Inform patient of symptoms of pneumothorax, chylothorax
- Refer large angiomyolipomas (>4 cm diameter) for possible embolization
- Refer for transplantation evaluation for FEV1 <30%
- Yearly Influenza and Pneumovax

Management

- High-resolution CT of the chest (follow every 1–2 yr)
- Pulmonary function testing (follow every 6–12 mo)
- Abdominal CT or ultrasound for angiomyolipoma (follow every yr)
- Rule out TSC with head CT or MRI, dermatologic, and ophthalmologic exams
- Oximetry with rest, sleep, exercise
- Bone densitometry

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis

Filling of lung alveoli with

- periodic acid-Schiff-positive, lipid-rich material
- preservation of normal lung architecture
- paucity of inflammation or fibrosis

Classification

syndrome of heterogeneous group of diseases resulting from failure to clear surfactant

- Idiopathic PAP: Occurring in the presence of circulating anti-GM-CSF
- Neonatal or congenital PAP
- In the setting of a systemic inflammatory disease or malignancy
- In association with specific exogenous or occupational exposures

Surfactant metabolism

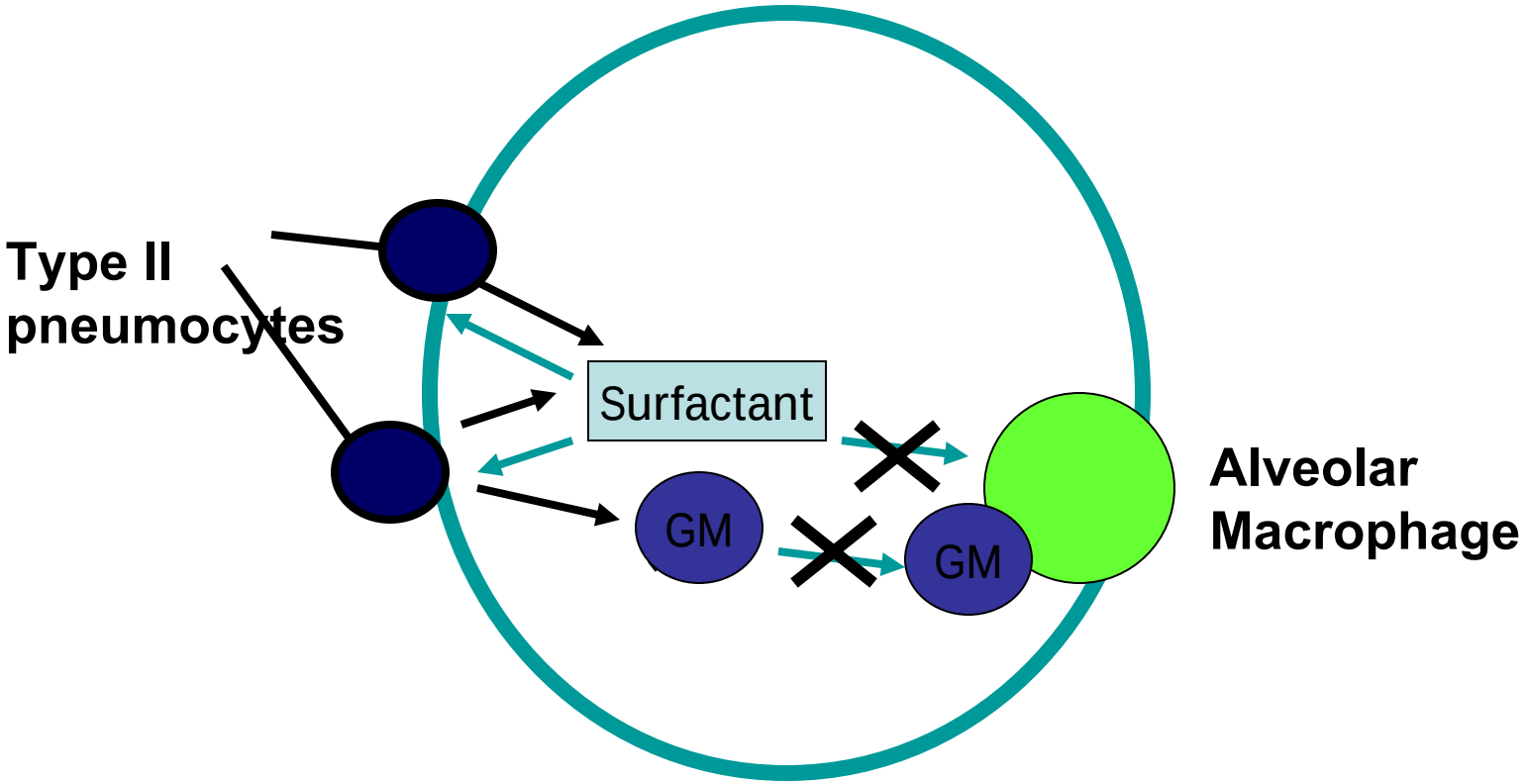
Type II alveolar cells → surfactant lipid

Type II cells + Clara cells →SPs

Catabolism by alveolar Mφ (GM-CSF helps)

Reuptake and catabolism by alveolar type II cells

Surfactant metabolism



Pathogenesis

- Interruption of GM-CSF signaling in the alveolar Mφ
- ↓ catabolism of surfactant
- Intracellular buildup of membrane-bound, concentrically laminated surfactant aggregates.
- Expansion of the extracellular surfactant pool & accumulation of cellular debris
- Filling of the alveoli, reducing the size of the available gas-exchange surface

ANTI-GM-CSF AUTOANTIBODY

- Main mechanism for idiopathic PAP
- Neutralizing and polyclonal, and composed of IgG1 and IgG2
- Serum anti-GM-CSF assay for diagnosis of Idiopathic PAP

sensitivity 100%,

specificity (titer of 1:400 & +) 100%.

- Anti-GM-CSF titer correlates

➢ disease activity as well as

➢ likelihood of response to GM-CSF therapy

Nuclear transcription factor

- ↓**PU.1** in alv Mφ
- decreased maturation, differentiation, and surfactant catabolism

❖ promotes the growth and differentiation of myeloid progenitors

❖ required for the production of Mφ

- ↓ **Peroxisome proliferator-activated receptor-γ (PPAR-γ)**
- GM-CSF regulates surfactant metabolism through PPAR-γ-dependent pathways in alveolar Mφ.

Congenital PAP

Autosomal recessive

- Surfactant protein (SP) B deficiency:
  - ➢ frame shift mutation in codon of SP-B gene.
  - ➢ SP-B gene is responsible for the formation of tubular myelin
- IL-3, IL-5, GM-CSF receptor β_c chain abnormality

Secondary causes of PAP

- Acute lymphocytic leukemia
- Acute myeloid leukemia
- Aplastic anemia
- Chronic lymphocytic leukemia
- Chronic myelogenous leukemia
- Myelodysplastic syndromes
- Multiple myeloma
- Non-Hodgkin's lymphoma
- Waldenström's macroglobulinemia
- Adenocarcinoma
- Glioblastoma
- Melanoma
- Acquired immunodeficiency syndrome
- Amyloidosis
- Congenital lymphoplasia
- Fanconi's syndrome
- Hypogammaglobulinemia
- Idiopathic thrombocytopenic purpura
- Juvenile dermatomyositis
- Renal tubular acidosis
- Subacute combined immunodeficiency disease
- Cytomegalovirus
- *Mycobacterium tuberculosis*
- *Nocardia*
- *Pneumocystis jirovecii*

Occupational exposures

- Agricultural dust
- Aluminum dust
- Bakery flour dust
- Cement dust
- Chlorine
- Cleaning products
- Fertilizer dust
- Gasoline fumes
- Nitrogen dioxide
- Paint
- Petroleum
- Sawdust
- Silica
- Synthetic plastic fumes
- Titanium
- Varnish

2^0 PAP

- Leukemic cells lack expression of the βc chain of the GM-CSF receptor
- Effect of chemotherapy and radiation on macrophage number and function
- Steroid  ↑ production of phospholipids

Clinical features

- 500 cases reported
- Median age at diagnosis: 39 yrs
- Median duration of symptoms before diagnosis: 7 months
- M:F 2.6:1
- 72% smokers
- No male predominance among nonsmokers

CXR

- B/L airspace disease
- With an ill-defined nodular or confluent pattern
- Perihilar predominance

HRCT

- B/L GGO
- Smooth interlobular septal thickening in areas of GGO= Crazy-paving
- Consolidation
- A patchy or geographical distribution
- superimposed interlobular septal thickening and intralobular lines

Investigations

- Hypoxemia
- ↓DLCO
- mild to moderate restrictive abnormality
- ↑CEA, cytokeratin-19, mucin KL-6
- Slight to moderate ↑ of LDH (82%)
- Elevated serum levels of SP-A, B & D: correlate with disease activity
- Monocyte chemoattractant protein (MCP-1) increased in BAL

BAL

A diagnosis of alveolar proteinosis is considered to be established if the gross appearance of lavage fluid is opaque and/or milky and microscopic evaluation reveals

(I) few alveolar macrophages,

(2) large acellular eosinophilic bodies against a background of small eosinophilic granules and amorphous debris, and

(3) on combined Alcian blue periodic acid-Schiff stain, there is predominant periodic acid schiff staining of the proteinaceous material with a lack of significant Alcian blue staining

ATS Statement

Indications for WLL

- Dyspnea affecting a patient's daily activities
- PaO2 below 60 mmHg
- Shunt fraction above 12%

Whole Lung Lavage

- Total I/V anaesthesia: Propofol+ fentanyl+ atracurium
- Non invasive monitoring
- Left sided double-lumen endotracheal tube
- Single lung ventilation for non lavage lung: PC FiO_2 1.0 PEEP 10-12
- Lavage is done with NS warmed to 37° C in 500 mL to 1 L aliquots

Effects of WLL

- ↑ in FVC, TLC, pO2 at rest and with exercise, and diffusing capacity,
- ↓ in alveolar- arterial O_2 gradient and shunt fraction
- gradual radiographic clearing
- ↓ LDH
- ↑ventilation, perfusion & V/Q matching on scintigraphy and improved AM migration
- Overall survival higher at 5 years

GM-CSF Therapy

- 7 studies, total 44 patients
- Dose: 5-25 mcg/kg
- Duration: 1-12 mo
- About 50% of the patients obtained an objective clinical improvement.
- Lag time of greater than 8 weeks from start of therapy to observed clinical response.
- There is a uniform lack of hematopoietic response to GM-CSF.
- There is a ↓ in anti-GM-CSF titer in both serum and BAL fluid with GM-CSF therapy
- GM-CSF therapy is not curative, and some patients relapse after discontinuing therapy.

Other treatment

- Lung transplantation
- Bone marrow transplantation
- Anti-interleukin-10 antibody: enhances GM-CSF production
- Immunosuppression
- Plasmapharesis

Natural History

- In the 3 most recent case series, 54 to 75% of patients received at least one lavage
- Spontaneously remission: 8%
- About 54 to 62% required repeat WLL
- 5 yr survival: 75%
- Deaths
  - Respiratory failure: 72%
  - Infections: 20%

Complications

- Infection: 13%

  Nocardia most common
- Interstitial pulmonary fibrosis: Isolated 3 reports

Pulmonary Alveolar Microlithiasis

Pulmonary Alveolar Microlithiasis

- Inborn error of calcium metabolism confined to the lung
- Concretions collect in alveolar spaces
- Composed of calcium and phosphorus
- Alveolar walls become fibrotic
- Microliths may appear in other tissues: kidneys, prostate, sympathetic chain & gonads

Clinical features

- 3rd- 5th decades
- Familial association: > 50% (usually in siblings)
- Among familial cases: female > male
- Sporadic cases: M=F
- Cough and dyspnea: late
- Expectorated microliths

CXR

- Fine sand-like opacification throughout the lungs, described as a "sandstorm
- The individual microliths are well defined and usually < 1 mm in diameter
- No. of microliths increases in the lower lung fields
- Pneumothorax, pleural thickening, and pericardial calcifications can also occur. Presence of bullae at the lung apices, a zone of hyperlucency between lung parenchyma and the ribs (black pleura sign)

Diagnosis

- Diffuse bilateral calcific infiltrate with predilection for the lower lung
- Alveolar infiltrate, producing air bronchograms & obliteration of the heart borders
- TBLB : confirmation
- PFT: normal or only slightly impaired for a prolonged period
- 99mTc diphosphonate scan: to confirm diffuse calcifications in PAM

Other uncommon ILDs

Gaucher's ds

- Hepatosplenomegaly, anemia, thrombocytopenia, long-bone erosions, and an increase in serum acid phosphatase
- Pulmonary involvement: 1/3rd

serious pulmonary disease seems to occur preferably in children with a more severe course of GD

- Gaucher cells can fill:

alveolar spaces

inter- and intralobular septa→ ILD

- No acute or chronic inflammatory cells and there is no interstitial fibrosis
- prevalence of asthma is higher than in the normal population (23% versus 15%, respectively)

- Pulmonary vascular disease: more common:

➢ vascular plugging by Gaucher cells

➢ intrapulmonary shunts related to the hepatopulmonary syndrome

➢ hepatosplenomegaly and spinal deformities → to small lung volumes and to changes of the pulmonary vascular bed

➢ secondary hypoventilation

HERMANSKY-PUDLAK SYNDROME

- Autosomal recessive
- Accumulation of a chromolipid ceroid related to lipofuscin in the reticuloendothelial system
- Oculocutaneous albinism
- Qualitative platelet defect
- Granulomatous colitis
- Diagnosed on the basis of oculocutaneous albinism and a storage-pool deficiency (the absence of platelet dense bodies on electron microscopy

Pulmonary involvement

- ILD:
  - more likely to occur in women
  - develops during the 2nd through 4th decades.
- Pulmonary fibrosis: accumulation of ceroid-lipofuscin in alveolar Mφ

CXR

- Normal: 79%
- Reticulonodular pattern: 12%
- Perihilar fibrosis: 5%
- Pleural thickening: 9%
- Interstitial infiltrates: 9%

HRCT

- Earlier stages: septal thickening, ground-glass pattern, and mild reticulation
- Advanced stages: moderate to severe reticulation, bronchiectasis, subpleural cysts, and peribronchovascular thickening
- Fairly even distribution throughout the lungs among the upper, middle, and lower zones, with a slight predilection for the middle and lower zones
- Periphery → center

Neurofibromatosis

- ILD in 25% of NF-1
- Dyspnea 3rd-6th decade
- Lower zone radiographic interstitial infiltrates are the rule, and bullous changes eventually appear in the upper zones
- Restrictive ventilatory impairment
- obstructive lung disease later on: involvement of small airways.
- Scar carcinoma

NIEMANN-PICK DISEASE

- Hepatosplenomegaly
- Hemostatic defects
- Platelet dysfunction
- cerebellar ataxia: occasionally
- ILD: appears as diffuse nodular infiltrates on CXR: usually asymptomatic