

PULMONARY

ALVEOLAR

PROTEINOSIS

Pulmonary Alveolar Proteinosis (PAP)

- Rare cause of chronic interstitial lung disease in children
- **Characteristic:** Intra-alveolar accumulation of surfactant components and cellular debris
- **Epidemiology**
 - Prevalence: 3.7 per million of population
 - Median age: 40 years
 - M>F ~ 3:1
 - In adult: $\frac{3}{4}$ of male patients have smoking

Pulmonary Alveolar Proteinosis (PAP)

- **Pathogenesis:** acquired or genetic dysfunction of alveolar macrophages that impair catabolism of surfactant lipids and proteins
- Gas exchange impairment and respiratory symptoms of variable severity

Surfactant

- Surfactant

1. Lipids (90-95%): phosphatidylcholine,
phosphatidylglycerol

2. Proteins (5-10%): SP-A, SP-B, SP-C, SP-D

- *Type II pneumocytes* responsible for production and storage of surfactant

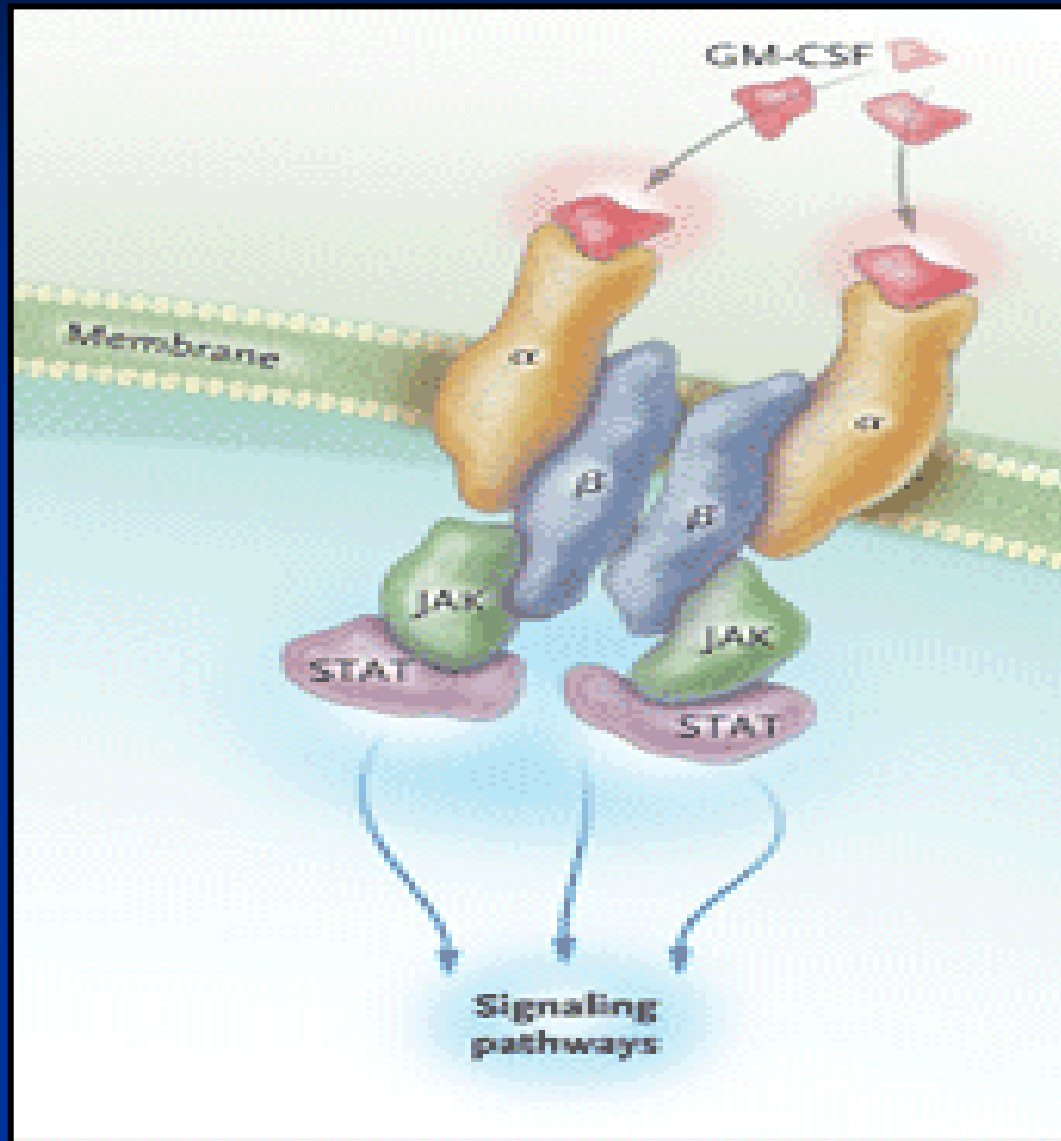
- Surfactant cleared or catabolized by *alveolar macrophages*

- *Granulocyte-macrophage colony-stimulating factor (GM-CSF)* activates the alveolar macrophages

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

- Potent capacity to augment the proliferation and differentiation of neutrophilic and monocyte - macrophage hematopoietic lineages
- **GM-CSF receptor** is on the cell surface of hematopoietic cells and alveolar macrophages
 - composed of 2 parts
 1. **α chain** (binding unit)
 2. **Common β_c chain** (signal transduction unit)

GM-CSF receptor



GM-CSF receptor

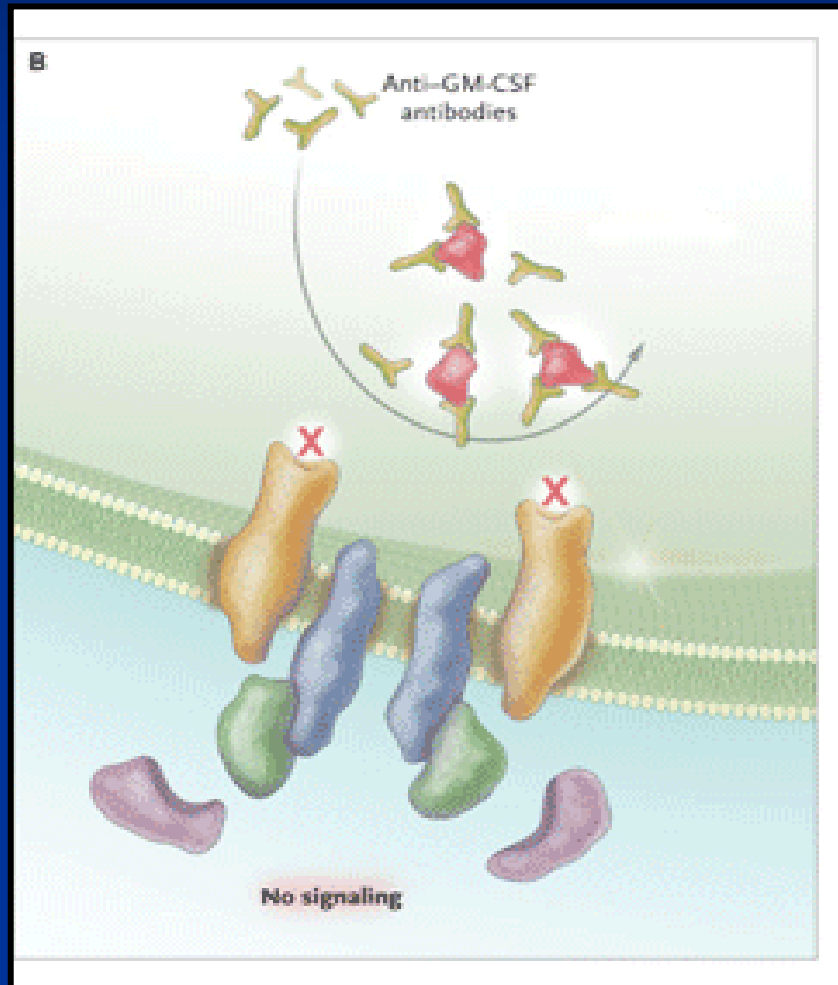
1. α chain (binding unit)
2. Common β_c chain (signal transduction unit)

Pulmonary Alveolar Proteinosis (PAP)

■ 3 forms:

1. Congenital (2%)
2. Primary or idiopathic (>90 %)
3. Secondary (<10%)

Idiopathic PAP



- The most common form of PAP (>90%)
- Pathogenesis:
 - A specific Ab against GM-CSF (anti- GM-CSF autoantibody) in the lungs may be related to a decreased GM-CSF pathway activity

Secondary PAP

1. Hematopoietic disorders

(myelogenous leukemia, acute lymphoid leukemia, lymphoma, myelofibrosis, aplastic anemia, myelodysplasia, thrombocythemia, ITP, myeloma)

2. Environmental and industrial materials

(silica, cement dust, aluminium dust, fibrous insulation fibers, titanium dioxide, nitrogen dioxide)

Secondary PAP

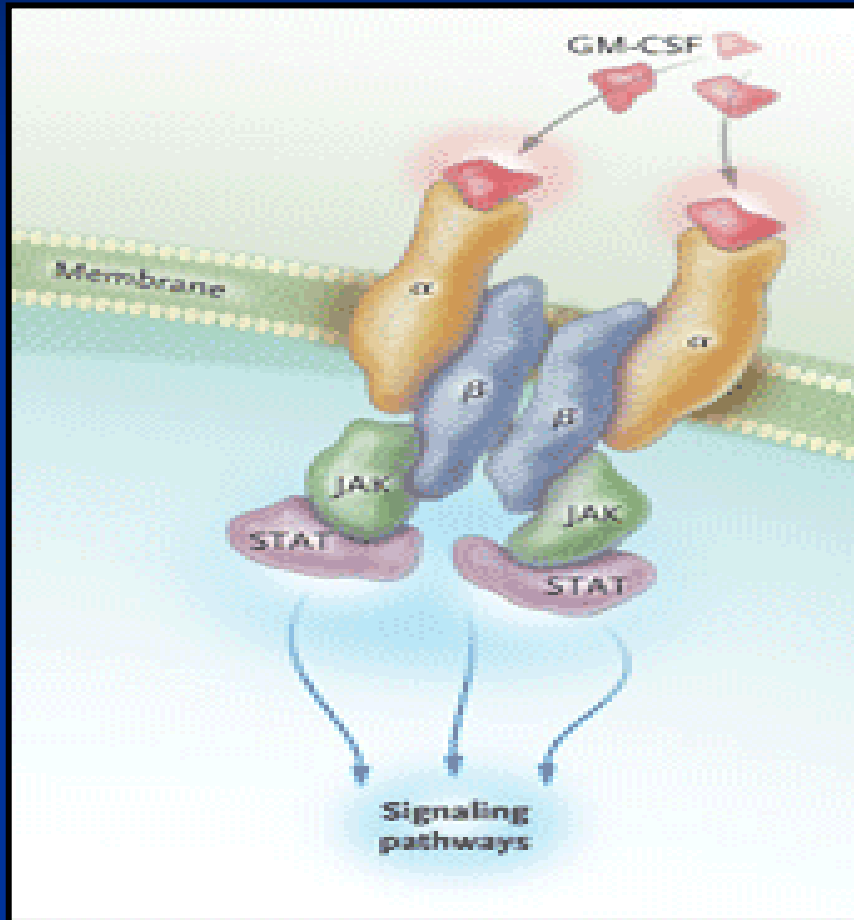
3. Infections

(mycobacteria, CMV, PCP, Aspergillus, cryptococcus, *Histoplasma* spp., *Norcadia* spp., anerobes)

4. Immunodeficiency disorders

(thymic alymphoplasia, IgA deficiency, neutropenia post transplantation, HIV infection)

Congenital PAP



■ Caused by

- Primary abnormality in β_c chain of the GM-CSF receptor

Clinical presentation of PAP

- Variable and nonspecific
- May lead to months or years until diagnosis
- Insidious onset of progressive exertional dyspnea
- Nonproductive cough

Clinical presentation of PAP

- Less common symptoms include fatigue, weight loss, and low-grade fever
- PE: crackles, cyanosis and clubbing
- Hemoptysis & chest pain < 20%
- Pneumothorax & Cor pulmonale - rare

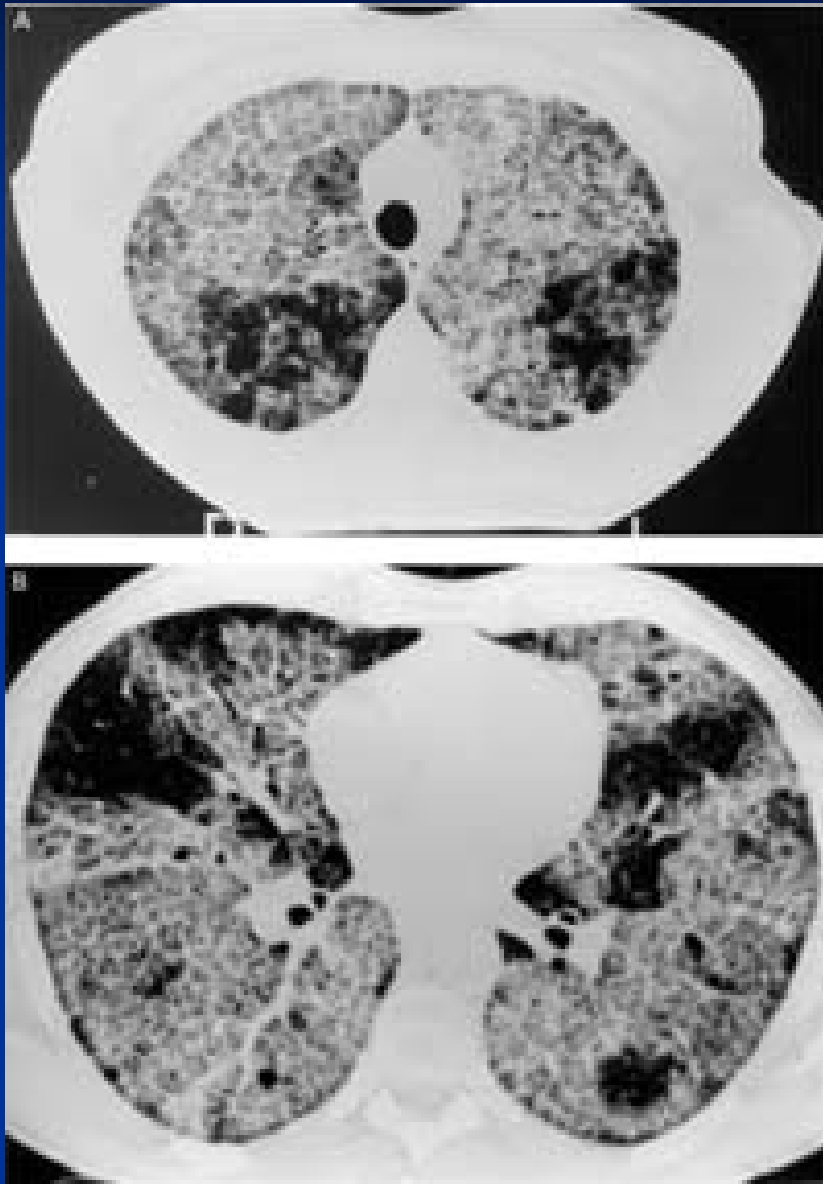
Investigation: imaging studies of PAP

CXR



- Bilateral, symmetrical alveolar-type infiltration
- Perihilar opacities extending into the periphery, more pronounced in the lower lobes **“Butterfly” distribution**
- Sparing the costophrenic angles

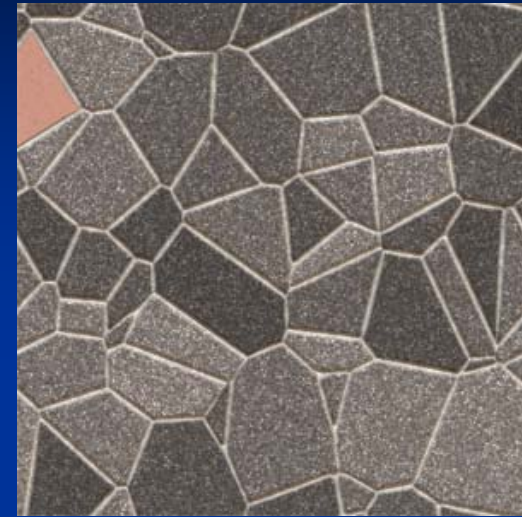
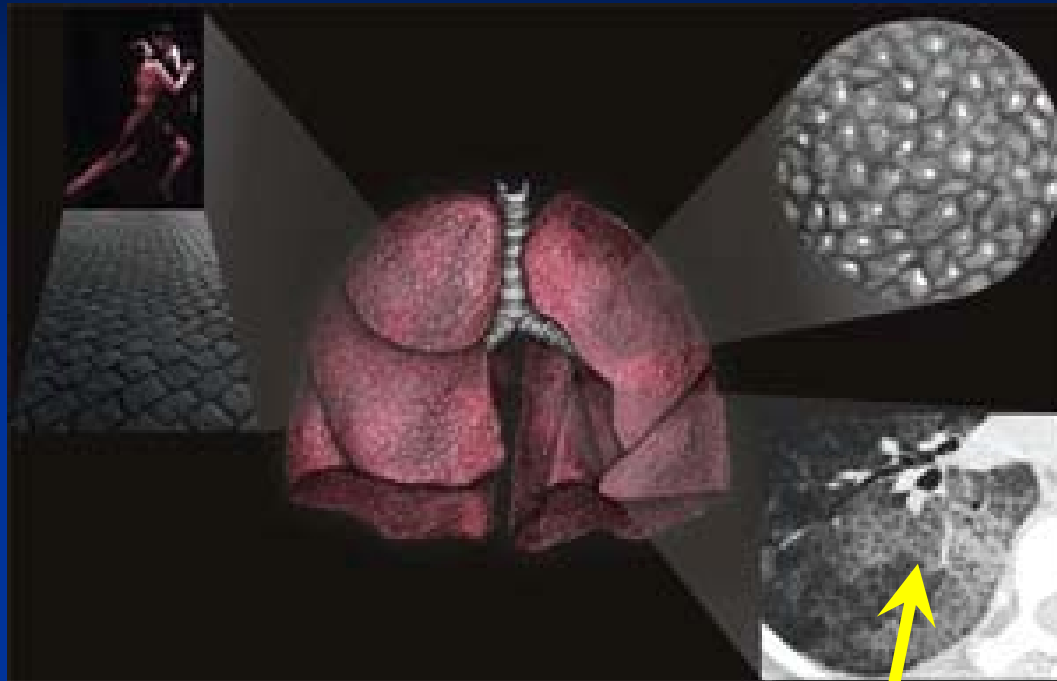
Investigation: imaging studies of PAP



HRCT Chest

Ground-glass opacifications with
interlobular septal and
intralobular thickening
“ Crazy paving ” pattern

“ Crazy- paving” pattern



Laboratory investigations

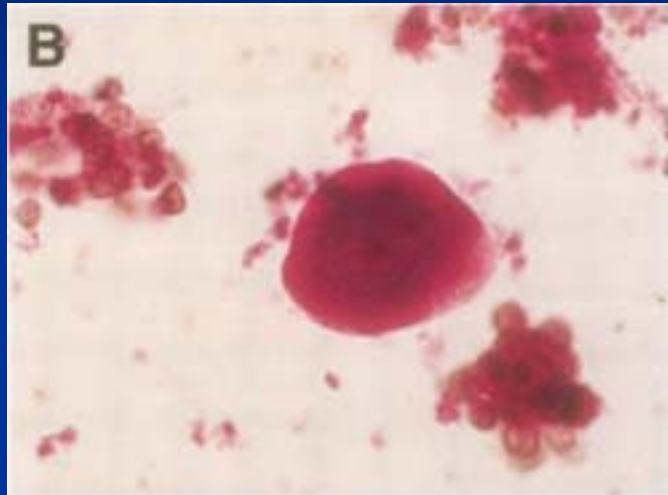
■ Bronchoalveolar lavage (BAL)

- Milky appearance



Laboratory investigations

■ Bronchoalveolar lavage (BAL)



PAS



PAS

LM:

Dirty appearance - large amounts of granular, acellular eosinophilic lipoproteinaceous material

Periodic acid Schiff (PAS) - positive, Diastase resistance

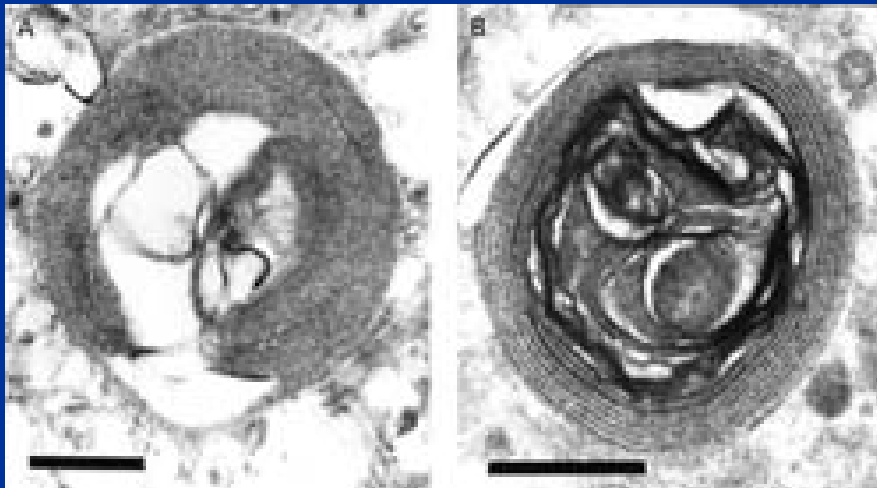
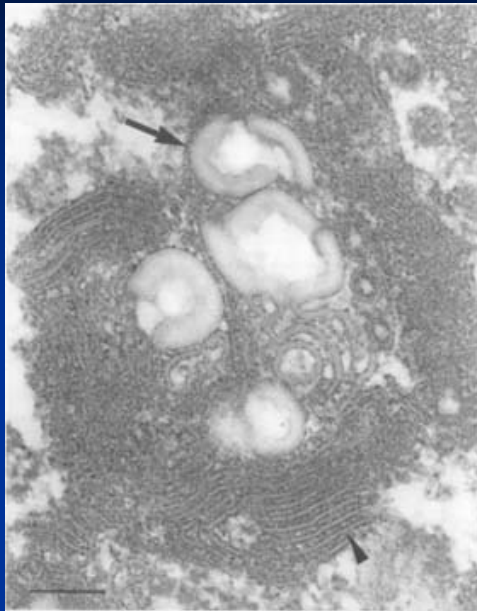
Laboratory investigations

- Bronchoalveolar lavage (BAL)

EM:

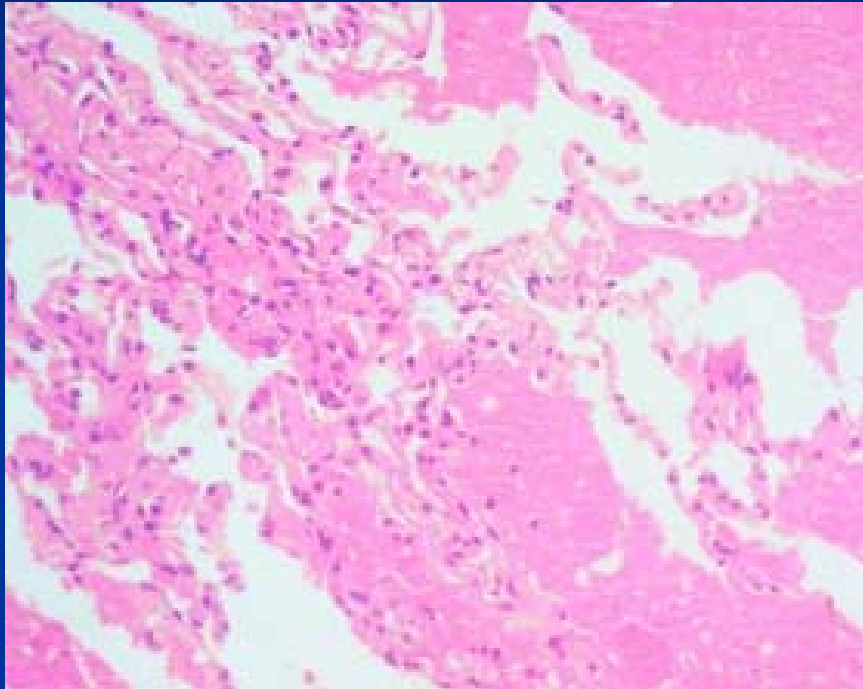
Concentrically laminated structures
called

'lamellar bodies'



Laboratory investigations

Lung biopsy



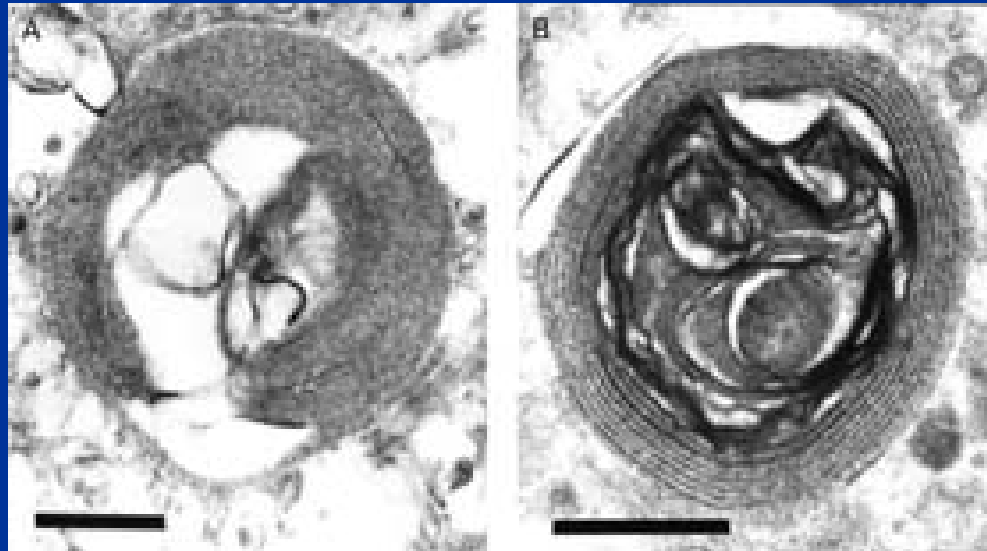
LM:

- intra-alveolar and terminal bronchioles filling with PAS positive material
- alveolar and interstitial architecture usually well preserved, except for late pulmonary fibrosis

Laboratory investigations

■ Lung biopsy

- **EM:** multilamellated structures within the alveolar material



Investigation: functional evaluation

- Restrictive ventilatory defect
- Hypoxemia
- Elevated alveolar-arterial gradient
- Carbon monoxide diffusing capacity (DLCO) ↓

Other investigations

- CRP ↑
- LDH ↑
- Carcinoembryonic antigen (CEA) ↑
- Krebs von den Lungen-6 (KL-6) in serum ↑
- **Anti-GM-CSF antibody** are increasingly used as a diagnostic tool in PAP (idiopathic form)

Management

■ Depend on the causes

1. Primary or idiopathic PAP

: whole-lung lavage, GM-CSF or plasmapheresis

2. Secondary PAP

: treatment of underlying condition or

whole-lung lavage to remove offending agent

3. Congenital PAP

: supportive, lung transplantation

Progression & Prognosis

- The clinical course of idiopathic PAP falls into 3 categories
 1. Persistent symptoms
 2. Progressive deterioration
 3. Spontaneous improvement
- Overall, disease-specific survival rates >80% at 5 years
- Death in PAP mainly related to infections (~20%),
respiratory failure (~70-80%)

Progression & Prognosis

■ Secondary infection

- Community- and hospital- acquired lung infection

: *Streptococcus, Klebsiella, Haemophilus, Staphylococcus, Pseudomonas, Proteus, and Escherichia*

- Unusual or opportunistic infection

: *Nocardia, Mycobacterium, Pneumocystis, Aspergillus, Cryptococcus*

THANK YOU

Whole-lung lavage (WLL)

- A method of physically removing the excess alveolar lipoproteinaceous material
- Repeated dilution with saline solution
- The bulk removal of anti GM-CSF Ab and other possible immunologic effects on the effector cells

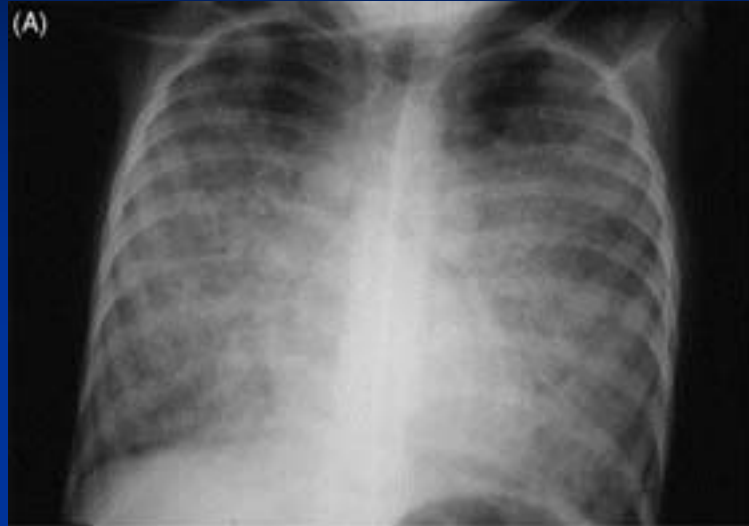
Whole-lung lavage (WLL)

■ Result of WLL

- FVC, TLC, PaO₂ (at rest and with exercise), diffusing capacity of carbon monoxide (DLCO) increased markedly
- Alveolar-arterial gradient and shunt fraction decreased significantly
- Improved ventilation/perfusion matching
- Gradual radiographic clearing

Severe pulmonary alveolar proteinosis in a 5-year-old boy

(PAEDIATRIC RESPIRATORY REVIEWS 2004 : 5, 316–22)



before therapeutic lung lavage



after 12 therapeutic lung lavages

GM-CSF therapy

- A positive effect of GM-CSF has been shown in idiopathic PAP
- Many important questions remain:
 - the optimal dose ?
 - the optimal duration of treatment ?
 - the relation to the anti-GM-CSF titers ?

GM-CSF therapy



Before treatment



CXR following 3 mo. of treatment

Pulmonary alveolar proteinosis: a complete response to GM-CSF therapy

Hereditary Surfactant Protein C Deficiency

- Lung disease in older children
- AD
- SP-C mutation
- Onset and clinical presentation vary widely
- Lung histopathology: elements of both nonspecific interstitial pneumonitis and usual interstitial pneumonitis and pulmonary fibrosis

Hereditary Surfactant Protein B Deficiency

- AR
- Onset: 12-24 hours after birth
- Histologic appearance of SP-B deficiency has features in common with PAP
- Most infants die within 6 months