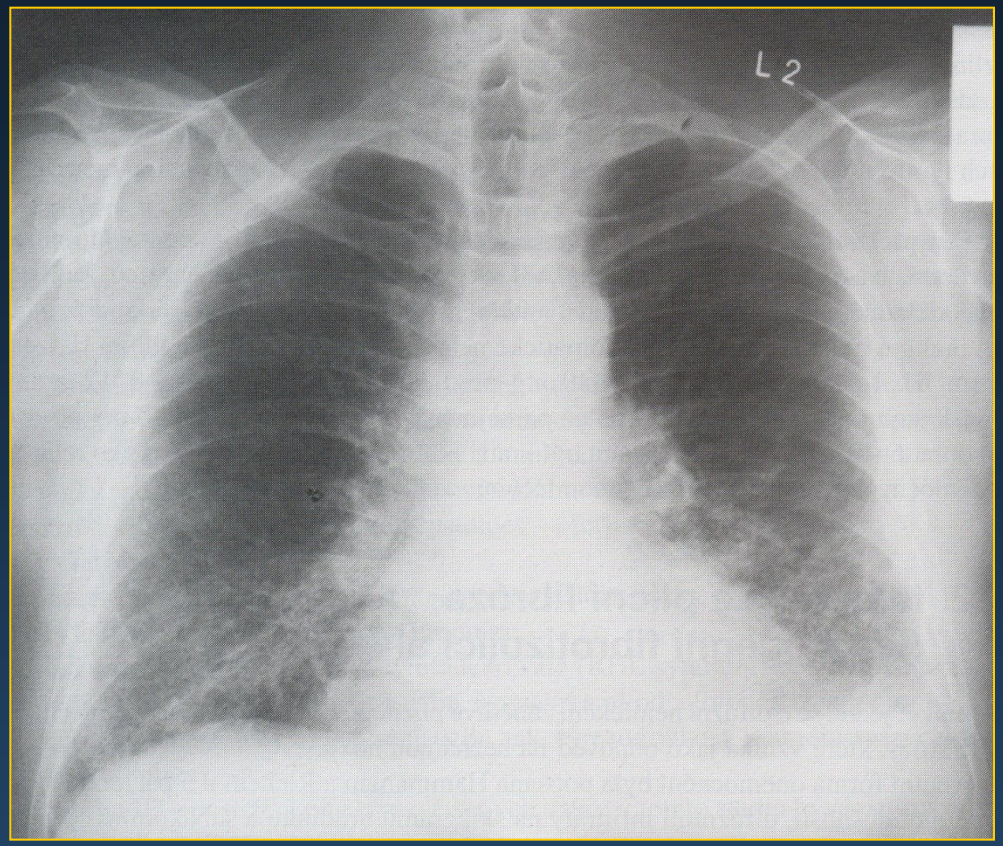



# Interstitial lung diseases

Martina Doubková

# Definition

**Diffuse parenchymal lung diseases (DPLDs), also called interstitial lung diseases (ILDs), are a large (comprise 200 entities) and heterogeneous group of acute and chronic lung disorders.**

**ILDs are characterized by a variable degrees of inflammatory and fibrotic changes affecting the interstitial spaces, airspaces, and alveolar walls.**

# Classification of DPLDs according to histology

- ✓ **Granulomatous process (reverzible process):** sarcoidosis, silicosis, collagen – vascular/connective tissue diseases, hypersensitivity pneumonitis

- ✓ **Process with the terminal lung fibrosis (nonreverzible process):** idiopathic pulmonary fibrosis, collagen vascular disease

- ✓ **Process with the presence of granuloma and fibrosis:** hypersensitivity pneumonitis

# Classification of DPLDs by etiology

**ILDs of known cause**

- ✓ lung infections (bacterial, fungal, viral, protozoal)
- ✓ postirradiation damage (external irradiation)
- ✓ inhalation causes (occupational exposure, organic and inorganic dusts)
- ✓ haemodynamic causes (congestive heart failure, uremia)
- ✓ neoplasia (lymfangitis carcinomatosis)
- ✓ inheredited cause (neurofibromatosis, tuberous sclerosis)
- ✓ drug causes (busulfan, amiodaron…) www.pneumotox.com
- ✓ metabolic causes (m. Gaucher, m. Crohn...)

**ILDs of unknown cause** (idiopathic pulmonary fibrosis, sarcoidosis, collagen vascular disease)

# Classification of DPLDs by frequency of occurrence

- frequent ILDs (IPF, sarcoidosis)
- less frequent ILDs (drug damage, hypersensitivity pneumonitis)
- rare ILDs (lymphangioleiomyomatosis, pulmonary Langerhans´s cell histiocytosis)

# Classification of ILDs

| Group | Clinical entitis |
|---|---|
| **Idiopathic interstitial pneumonias** | IPF - UIP, NSIP, BOOP, DIP, AIP, LIP, RBILD |
| **DPLD of known cause** | Pneumoconiosis<br>Hypersensitivity pneumonitis |
| **Granulomatous DPLD** | Sarcoidosis<br>Histiocytosis X<br>Vasculitis |
| **Other forms of DPLD** | Lymphangioleiomyomatosis<br>Alveolar proteinosis |

# Diagnosis of DPLD

History – searching for etiology, symptoms, duration of symptoms

Physical examination – dyspnea, cough, fatigue, end-inspiratory fine crackles on auskultation, clubbing, skin lesions, cyanosis..

Blood tests and other tests - antibody, angiotensin-converting enzyme,..

Imaging – chest radiography (X-ray), high-resolution computed tomography (HRCT) + other imaging methods

Pulmonary function tests – restrictive picture, obstructive or a combination, reduced gas transfer

Bronchoscopy with bronchoalveolar lavage (BAL) – a physician takes samples from inside the lungs: biopsies, fluid (BAL) or endobronchial brushing.

Lung biopsy – transbronchial lung biopsy, open thoracotomy or preferentially by video-assisted thoracoscopy

# Sarcoidosis

# Definition

**Descriptive definition:**

Sarcoidosis is **a multisystem disorder of unknown cause(s).** It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved.

# Definition

**The definition by morfology:**

The characteristic lesion of sarcoidosis is a discrete, compact, **noncaseating epithelioid cell granuloma**. The epithelioid cell granulomas consist of highly differentiated **mononuclear phagocytes** (epithelioid cells and giant cells) and **lymphocytes**. **Sarcoid granulomas may develop fibrotic changes.**

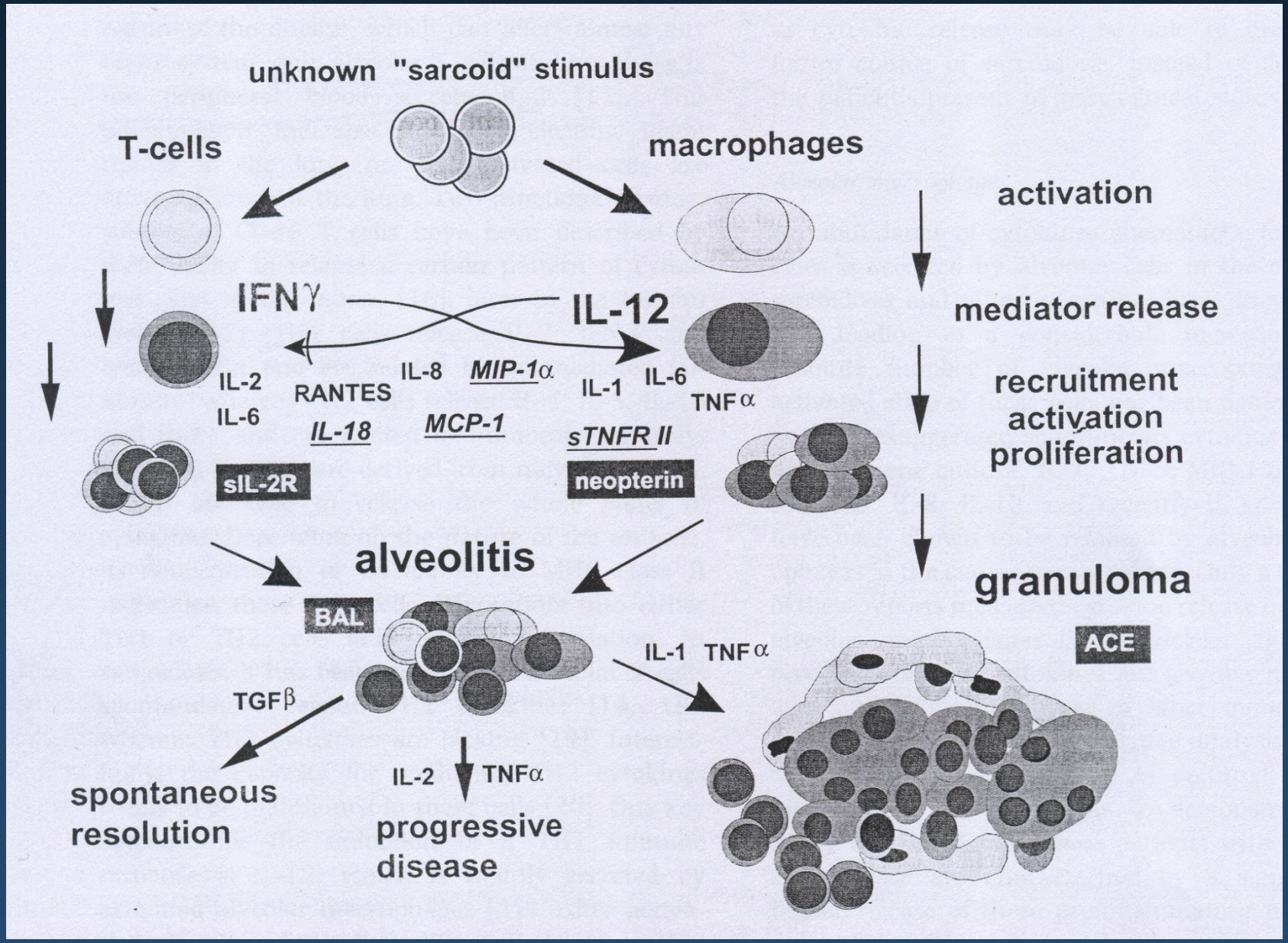
# Epidemiology and etiology of sarcoidosis

**Epidemiology:** prevalence in the CR 63,1/100 000
incidence in the CR 3,7/100 000
rate women:men 2:1

**Etiology:** infection (viruses, mycobacteria, other infectious agens), hypersensitivity, immunity, an exposure to an antigen – inorganic materials in a genetically predisposed, susceptible host. Sarcoidosis is a polygenetic disorder. Several alleles were associated with susceptibility (HLA DR2, 11, 12, 14, 15, 17) or protective effects (HLA DR1, DR4) for sarcoidosis.

A genetic predisposition may explain the heterogeneity in disease presentation and severity among different ethnic and racial groups.

# Immunopathogenesis of sarcoidosis



# Immunopathogenesis of sarcoidosis

Immunopathogenesis: immunological abnormalities are characterized by the accumulation of actived CD 4+ T cells of the Th 1 type and macrophages at sites of ongoing inflammation. Cytokines and other mediators produced by these cells contribute to granuloma formation.

# Clinical presentation of sarcoidosis

## Acute sarcoidosis

- ✓ Lofgren's syndrome – bilateral hilar adenopathy on X-ray, erythema nodosum, fever, arthralgia or arthritis, negativ tuberculin skin test.
- ✓ Heerfordt's Waldensröm syndrome: fever, uveitis, parotid enlargement, and facial nerve palsy.
- ✓ sarcoid infiltration of scars

## Chronic sarcoidosis

- ✓ Sarcoidosis lasting at least 2 years
- ✓ Respiratory involvement and other organs is graver
- ✓ Chronic or progressive course is observed 10% - 30% of patients
- ✓ Progressive sarcoidosis can lead to death in 1 – 5% of cases

# Clinical presentation of sarcoidosis. Pulmonary sarcoidosis

- ✓ Involvement of intrathoracic organs, i. e. lymph nodes, lung parenchyma or pleura occurs in 90% of all cases
- ✓ Dyspnea, cough, chest pain similar to cardiac angina occur most frequently

# Clinical presentation of sarcoidosis. Extrapulmonary sarcoidosis

- ✓ **Sarcoidosis of lymph nodes and spleen**
- ✓ **Sarcoidosis of eyes –** iridocyclitis, conjunctivitis, uveitis
- ✓ **Sarcoidosis of skin** – erythema nodosum, lupus pernio
- ✓ **Musculoskeletal sarcoidosis** – arthritis, arthralgias, myalgias, myopathy
- ✓ **Neurosarcoidosis** – CNS or PNS
- ✓ **Sarcoidosis of heart**
- ✓ **Sarcoidosis of other organs**

# Diagnosis of sarcoidosis

- ✓ History, physical examination - exposure, symptoms
- ✓ Laboratory and immunological tests – whole blood count, metabolic panel (electrolytes, calcium, liver enzymes, creatinine, blood urea nitrogen), urinalysis, angiotensin-converting enzyme, sIL-2r, neopterin, hypercalcemia, hypercalciuria
- ✓ Radiology, imaging – chest X-ray: bilateral hilar adenopathy, upper lobe infiltrates, HRCT scan: peribronchial thickening, gallium scan: uptake in mediastinum and parotids
- ✓ Pulmonary function tests – spirometry and diffusion capacity for carbonmonooxide (DLCO)
- ✓ Bronchoscopy with BAL – lymphocytic alveolitis with a CD4/CD8 – ratio > 3.5 – 10, TNF alfa
- ✓ Examination of impairment organs - eye (ophthalmological examination), heart (electrocardiography)
- ✓ Biopsy – lung biopsy (endobronchial, transbronchial, videothoracoscopy) and other biopsy sites (lymph nodes, skin)

# Diagnosis of sarcoidosis

- ✓ **The need for biopsy:**

  **If sarcoidosis is suspected the diagnosis should be made with biopsy whenever possible – except for the cases of typical presentation of a Lofgren's syndrome**

# Chest radiograph stages of sarcoidosis

**0** … Normal chest radiograph

**I** … Bilateral hilar lymphadenopathy (**BHL**)

**II** … BHL + diffuse pulmonary infiltration

**III** …Difuse pulmonary infiltration, but without hilar lymphadenopathy

**IV** … Pulmonary fibrosis

# Differential diagnosis of sarcoidosis

- ✓ **Autoimmune diseases –** Churg - Strauss syndrom, Wegener's granulomatosis
- ✓ **Exposures –** aluminium, beryllium, talc, titanium, zirconium
- ✓ **Infections -** brucellosis, coccidioidomycosis, histoplasmosis, mycobacterial infection, syphyllis, toxoplasmosis
- ✓ **Malignancy -** lymphoma
- ✓ **Other –** hypersensitivity pneumonitis**,** methotrexate toxicity

# Overview of therapy for pulmonary sarcoidosis

- ✓ A large number of patients undergo spontaneous remission or have a benign clinical course
- ✓ There is no easy way to assess disease activity and severity, so that predicting the course and prognosis of the disease is difficult.
- ✓ The marked variability in presentation and clinical course make it difficult to develop treatment guidelines.
- ✓ The cause of the disease is unknown; consequently, no specific treatment exists.

# Indication for systemic therapy

| Absolute | Relative |
|---|---|
| Neurologic | Symptomatic pulmonary disease |
| Cardiac | Arthritis |
| Hypercalcemia | Hepatic |
| Ocular – when topical therapy has failed | |
| Other life – or organ – threatening disease | |

SIRS: systemic inflammatory response system

# Current pharmacological treatment options for sarcoidosis

| Substance (mechanism) | Proposed use in sarcoidosis | Side effects |
|---|---|---|
| **Corticosteroids: Prednisone 0.5 mg/kg/day, prednisolone** (IL-2, TNF α) | Use for all forms of sarcoidosis, topical application, inhalation | Osteoporosis, DM, hypertension, insomnia |
| **Chloroquine, hydroxychloroquine** | Skin disease, neuro-, steroid-sparing, hypercalcaemia | Ocular toxicity, nausea |
| **Methotrexate** (IL-2,TNF α) | Acute, chronic sarcoidosis, steroid-sparing | Nausea, neutropenia, hepatotoxicity, pulmonary fibrosis |
| **Azathioprine** (IL-2, TNF α) | Few data for chronic sarc., steroid-sparing | Nausea, neutropenia |

# Current pharmacological treatment options for sarcoidosis

| | | |
|---|---|---|
| **Pentoxifylline** (influence on lymphocytes, TNF α) | Efficacy for acute (mild-moderate) disease | Gastrointestinal intolerance |
| **Thalidomide** (IL-12, TNF α) | Useful for chronic skin disease, no effect on pulmonary disease, anti-angiogenic | Somnolence, teratogenic, constipation, peripheral neuropathy |
| **Cyclophosphamide** | Because of toxicity only for refractory cases | Neutropenia, nausea, cystitis, carcinogenic |
| **Cyclosporine** (IL – 2, T-cell activation) | Possible effect for neurosarcoidosis, no clinical improvement, no steroid-sparing effect | Renal failure, hypertension, can cause lymphoma |
| **TNFα antagonists**: **infliximab** (monoclonal antibody), **etanercept** | Limited data about effectiveness and dosage, possible use for refractory disease. No good evidence for effect | Increased rate of tuberculosis, allergic reaction, possibly carcinogenic |

# Chest radiograph stratification (Scadding scale)

| Stage | Description | Rate of spontaneous resolution |
|---|---|---|
| Stage 0 | Normal radiograph | ? |
| Stage 1 | BHL | 60% - 90% |
| Stage 2 | Difuse pulmonary infiltrates and BHL | 50% - 60% |
| Stage 3 | Diffuse infiltrates only | < 30% |
| Stage 4 | Fibrotic lundg disease | 0% |
| Stages do not represent sequential steps in disease course and are based only on the posterior –anterior chest radiograph | | |

# Idiopathic pulmonary fibrosis (IPF, KFA)

# Idiopathic pulmonary fibrosis (IPF, KFA)

- ✓ **IPF**, known in Europe as cryptogenic fibrosing alveolitis, is a clinical term that describes a chronic fibrosing interstitial pneumonia with no known cause.

- ✓ **IPF** is a progressive and lethal pulmonary fibrotic lung disease. IPF is the most common of the idiopathic interstitial pneumonias (IIP) and the one that is unresponsive to treatment.

# Epidemiology and etiology of IPF

**Epidemiology:** incidence 7 – 11 cases per 100 000

prevalence 13 – 20 cases per 100 000

more males 1.4 : 1, between 40 and 70 years of age

median survival from the diagnosis of IPF: 2 – 4 years

**Etiopathogenesis:** the etiological agent(s) in IPF has not been elucidated, two key features, alveolar epithelial cell injury and dysregulation of fibroblasts appear to be pivotal in the pathogenesis of UIP/IPF.

**Risk factors are associated with IPF:** cigarette smoking, exposure to commonly prescribed drugs, chronic aspiration, environmental factors (metal dust, wood dust), infectious agents (EBV), genetic predisposition (familial IPF – 0,5 – 3 per cent of cases of IPF)

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# Diagnosis of IPF

**History** - symptoms, duration of symptoms, …

**Physical examination** – shortness of breath (dyspnea), cough, fatigue, on auskultation there are end-inspiratory crackles and are most prevalent in the lung bases, clubbing, cyanosis, cor pulmonale

# Clinical symptoms

- ✓a progressive shortness of breath, or dyspnoea: 90%
- ✓chronic nonproductive cough: 74%
- ✓end-inspiratory crackles : 80%
- ✓clubbing: 50 - 60%

-

# Diagnosis of IPF

**Laboratory and serological tests** are nonspecific

**Chest radiograph, High resolution CT scanning** + others imaging

**Pulmonary function tests** – restrictive lung volumes and capacities, reduced the carbon monooxide transfer factor (DLCO), hypoxemia with widened alveolar-arterial oxygen gradient that increases with exercise

**Bronchoscopy with BAL** – differential diagnosis of fibrosing interstitial pneumonias but is not diagnostic of IPF

**Lung biopsy** – open thoracotomy or preferentially by video-assisted thoracoscopy

# Radiographic findings of IPF

**Conventional chest radiograph** – diffuse bilateral interstitial or reticulonodular infiltrates with a predilection for basilar and peripheral (subpleural) regions

**High resolution thin section CT scan** – reticular densities (interlobular and intralobular septal lines), traction bronchiectasis, honeycomb change, minimal or no ground glass opacities; predilection for peripheral (subpleural) and basilar regions

# Treatment of IPF

- ✓ This disease progress slowly or rapid to respiratory failure.
- ✓ Specific idiopathic pulmonary fibrosis treatment options include: **antifibrotic agent pirfenidone or nintedanib**
- ✓ Other medications: oxygen therapy, pulmonary rehabilitation, lung transplantation.

# Treatment of IPF

- **Lung transplantation (LTx)** may be considered for patients with end-stage pulmonary fibrosis (who are not benefiting from medicines, and who have no other serious medical problems). Two-year survival following SLT ranges from 60 to 80 per cent, 5-year survival is 40-60 per cent.

**Thank you for your attention.**