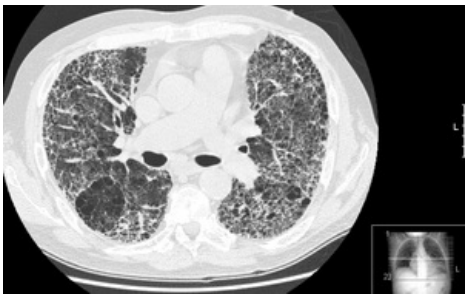
Interstitial pulmonary processes

Interstitial pulmonary processes (IPP, also *fibrotizing pulmonary processes*) are immunopathological processes at the level of the lungs interstitium, i.e. in the interalveolar region, in the alveoli and in the peribronchi. They prevent effective gas exchange on the alveolo-capillary membrane and lead to respiratory insufficiency.[1]

It is a group of diseases of different etiologies, which are characterized by varying degrees of inflammatory and/or fibrotic involvement of the lung parenchyma. Lung involvement is usually manifested by exertional dyspnea, weight loss, subfebrile conditions and more frequent respiratory infections. In the late stages cor pulmonale develops with signs of right-sided heart decompensation.[2]

Pulmonary fibrosis in general

Classification



Pulmonary fibrosis on HRCT, probably after interstitial pneumonia

1. **Diffuse lung processes from known causes**: exogenous allergic alveolitis (EAA), pneumoconioses, post-radiation pneumonia, drug-induced lung damage (e.g. with amiodarone and methotrexate);
2. **Idiopathic interstitial pneumonia**: idiopathic pulmonary fibrosis (IPF); nonspecific interstitial pneumonitis; lymphocytic interstitial pneumonitis; desquamative interstitial pneumonitis; interstitial lung disease associated with respiratory bronchiolitis; cryptogenic organizing pneumonia; acute interstitial pneumonitis;;
3. **Granulomatoses** − sarcoidosis, pulmonary histiocytosis from Langerhans cells, granulomatosis with polyangiitis and other vasculitides, etc.;
4. **Other**: eosinophilic pneumonia, lymphangioleiomyomatosis, alveolar proteinosis, etc.[2][1]

Pathogenesis

The deposition of fibrinalong the alveolar walls plays a role in the pathogenesis → so-called hyaline membranes are formed in the alveoli. This is followed by an inflammation phase with infiltration of neutrophils (later macrophages and lymphocytes), through which repair processes result in fibrosis. Another pathogenetic event is the proliferation of alveolar cells, the organization of fibrinous exudate, the deposition of collagen → repair / fibrosis.[3]

Consequences of interstitial lung diseases

- Hypoxemia (↓ p_aO_2) especially exertional already in the initial stages with hyperventilation with a tendency to respiratory alkalosis (↓ p_aCO_2);
- later resting hypoxemia (↓ p_aO_2) and hypoventilation;
- pulmonary hypertension → cor pulmonale.[3]

Common features

Common features include exertional and then resting **dyspnea**. ISTs are often accompanied by an **irritating cough'**. Reticulonodulations or **honeycomb lungs** may be visible on the skiagram. There may be **crepitations** in the listening findings.[1]

Examination

In laboratory diagnostics, we choose tests to rule out damage to other organs, basic immunological tests, tests for autoantibodies. In indicated cases, as part of screening to exclude glomerular involvement, calcium metabolism and serum angiotensin-converting enzyme in patients with suspected sarcoidosis. It is important to **examine lung functions** and parameters of respiration at rest, or during exercise if possible and a **skiagram of the chest in two projections'** (a negative finding, however, does not rule out IPP!). We also use high-resolution **computed tomography** (HRCT) in the diagnosis to assess the type and extent of pulmonary parenchymal involvement. From invasive examinations, **bronchoscopy** with bronchoalveolar lavage and transbronchial biopsy will help us, or surgical lung biopsy eventually. [2]

Therapy

We choose therapy according to the etiology (if known). The first step is to **stop exposure to harmful inhaled agents**.

Pharmacotherapy

- systemic corticotherapy in doses corresponding to the severity of the disability

    - indications: idiopathic non-specific interstitial pneumonitis (NSIP), severe exogenous allergic alveolitis (EAA), drug-induced lung disease, eosinophilic pneumonia, cryptogenic organizing pneumonia (COP), sarcoidosis with lung function impairment;
- systemic corticotherapy in combination with other immunosuppressants (e.g. methotrexate, azathioprine, cyclophosphamide)
    - systemic diseases of the connective tissue, other autoimmune syndromes;
- N-acetylcysteine – idiopathic pulmonary fibrosis (IPF),

proton pump inhibitors – IPF,

- inhalational bronchodilation – silicosis, angler pneumoconiosis,
- inhaled corticosteroids – sarcoidosis with bronchial hyperreactivity,
- macrolides – some forms of organizing pneumonia.[2]

Non-pharmacological treatment

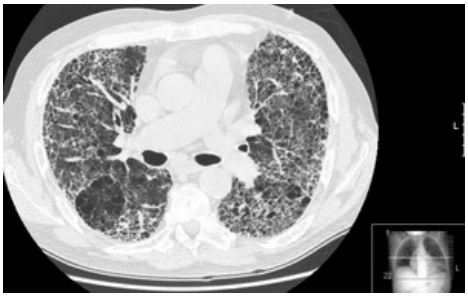
- oxygen therapy,
- balneotherapy,
- physiotherapy,
- lung transplantation.[2]

Prognosis

Idiopathic pulmonary fibrosis (IPF) has the most serious prognosis – lung transplantation, eventually treatment with pirfenidone[2] (immunosuppressant – suppresses fibroblast proliferation, production of cytokines and proteins associated with fibrosis and increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors).

Idiopathic pulmonary fibrosis (IPF)

It is a diffuse, primarily fibrotic lung process.



HRCT pulmonary fibrosis

Pathogenesis

This is probably a uniform pathological response of lung tissue to both infectious and non-infectious agents. These cause damage to the lining of the alveoli and thus result in progressive and uncontrollable scarring. The inflammatory reaction as such can occur only secondarily.

Epidemiology

- Patients are most often between the ages of 40 and 70.
- The incidence in women is 7.4 / 100,000 and in men 10.7 / 100,000.
- It occurs sporadically, is equally widespread in all localities, familial cases are rare.
- The disease is practically incurable, and even with adequate treatment, survival usually does not exceed 3-5 years.

Clinical picture

- Onset – rolonged unproductive cough in time with worsening exertiona dyspnea, fatigue, weight loss, tachypnoe;
    - on the bases of lungs late inspiratory crepitus similar to **Velcro opening**[4];
    - eventually chronic hypoxia with cyanosis develops.
- In 2/3 of the patients there are club-shaped fingers with nails in the shape of a watch glass.
- Image of COPD without obstructive defect, in the later phase restrictive lung damage - reduction of FVC.
- Despite the typically protracted progressively deteriorating course, acute exacerbations may occur in some patients:
    - sudden clinical deterioration;
    - decreased lung function;
    - radiological image of the so-called milk glass (indicating alveolitis).

Diagnostics

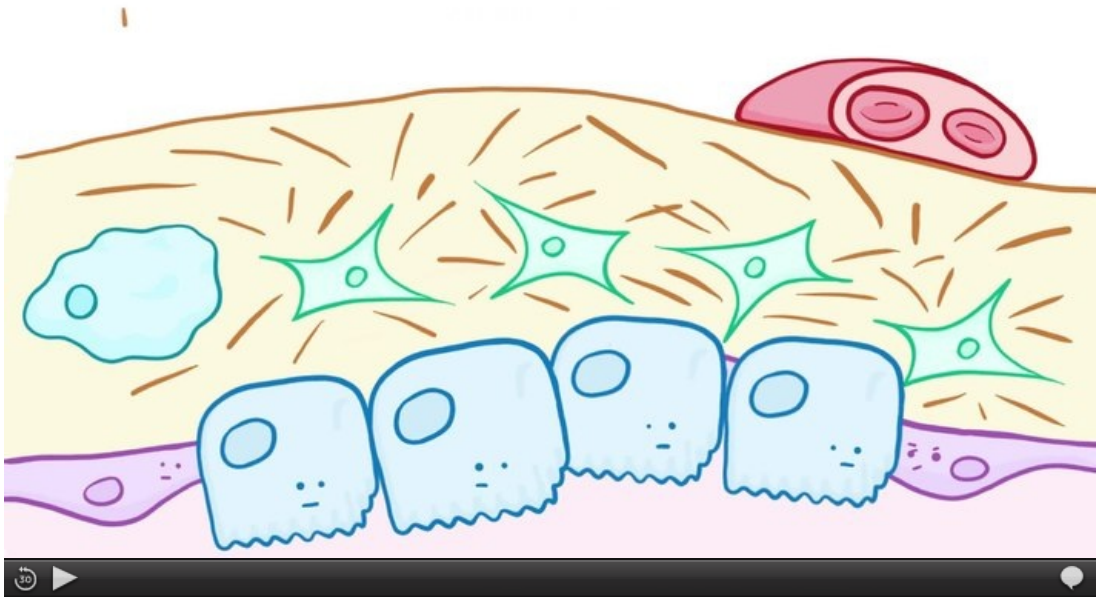
Here, HRCTs are crucial, and a typical clinical finding does not require a biopsy if systemic connective tissue diseases and an exogenous cause are excluded.

- **HRCT image of the lungs**: pulmonary fibrosis with an image of the honeycomb lung in the bases of the lungs and minimal areas of active changes.
- **Histology from a lung biopsy.**
- In patients unable to undergo surgical biopsy, X-ray and bronchoscopy must be sufficient.
- X-ray: increased lung drawing to reticulation - honeycomb lung.
- Functional examination: restrictive ventilation disorder, pulmonary compliance disorder.

Therapy

- Anti-inflammatory and immunosuppressive drugs are ineffective because the main pathological mechanism here is pathological fibroproduction, so they are not used in treatment today.
- Pirfenidon – inhibits fibrosis, indicated in patients with FVC 50-80%. Dosage 3x3cps - a total of 2403 mg.
- Nintedanib – a tyrosine kinase inhibitor on VEGFR, FGFR, and PDGFR
- **Early alveolar lesions**: **N-acetylcystein** 3 times 600 mg (antioxidant effect).
- **Acute exacerbations**: high doses of corticoids, anticoagulant therapy, and antibiotics. **PPI** (proton pump blockers) are given to prevent exacerbations.
- **Advanced diseases with hypoxemia**: long-term home oxygen therapy and consideration of lung transplantation.
- Corticosteroids in long-term therapy **are ineffective**, pbecause fibrotization is not induced by an inflammatory response. [5][6][7]

Summary video



Idiopathic pulmonary fibrosis (video in english)

Exogenous allergic alveolitis (EAA)

Exogenous allergic alveolitis (or hypersensitive pneumonitis, farmer's lung, pigeon's lung) includes a group of immunologically conditioned diseases (type III. hypersensitivity) with granulomatous inflammation in the bronchioles and alveoli. It is an interstitial pulmonary fibrosis caused by repeated contact with certain allergens. The most endangered group are workers of plant and animal production after repeated exposure to moldy hay, straw and grain. Exogenous allergic alveolitis also occurs while working with moldy malt, furs, moldy cheese, feather and bird excrement. It is rare in children and is most often caused by inhalation of organic dust from birds (pigeons, parrots, budgies).

Diagnostics

- Patient's history, laboratory signs of inflammation, precipitating antibodies (specific IgG) in serum against including antigen
- Chest X-ray: reticulonodular drawing with mottled volatile infiltrates
- BAL: usually lymphocytic alveolitis, ↓ CD4/CD8
- Chronic phase: X-ray + HRCT image of interstitial pulmonary fibrosis/honeycomb lung; restriction, lung diffusion capacity disorder, hypoxemia; lung biopsy.

Clinical picture

Acute

The acute form is reversible and develops within about 6 hours after intense antigen exposure. It expires within 48 hours. Physically, crepitus above the lung bases is demonstrable. The following characteristics are manifested:

- paroxysmal cough, fever, chill, malaise, myalgia, headache.

Chronic

If antigen exposure persists, a chronic form of exogenous allergic alveolitis develops. In case of repeated exposure, lower concentrations of the respective antigen are also sufficient. Irreversible interstitial lung fibrosis (restriction disorder) occurs. The symptoms are:

- weight loss, fatigue, cough, dyspnoea and cyanosis, cor pulmonale, clubbed fingers, respiratory failure.

Therapy

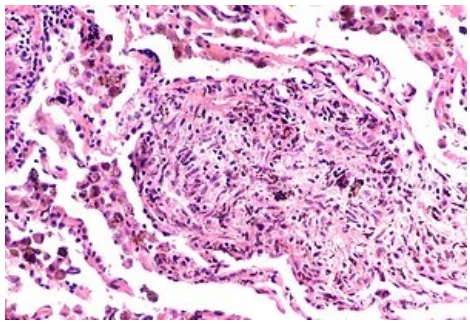
- Elimination of antigens – necessary permanent exclusion of the workers from exposure (for occupational diseases)
- corticoids
- oxygen therapy.[8][9][10]

Professional Pneumoconiosis

__Pneumoconiosis is **a group of occupational diseases** caused by long-term inhalation of air containing specific **inorganic particles**. The basis of lung changes is the response of immunocompetent cells to these particles, which leads to damage to the lung interstitium.

Types of diseases

Silicosis


Silicosis

- **Silicosis**
- **asbestosis**
- **pneumoconiosis**
- **berylliosis**
- **talcosis**- occurs after exposure to talc dust (during its mining and grinding), possible clinical manifestation of the disease:
  - nodular lesions,
  - diffuse interstitial fibrosis,
  - granulomatous reactions around foreign bodies,
- **pulmonary involvement during inhalation of heavy metals** - cobalt, tungsten, carbide, possible pictures of the disease:
  - chronic diffuse inflammation with pulmonary fibrosis,
  - acute and subacute interstitial disability with EAA or BOOP,
  - obstructive pulmonary disease resembling occupational asthma.

Nowadays, we encounter these diseases rather rarely (the incidence decreased due to prevention in the work environment).

Types of changes

The nature of the inflammatory changes depends on the shape and size of the inhaled particles, the length and intensity of the exposure. Inorganic particles can be divided into **fibrogenic** (silicosis, asbestosis) and **non-fibrogenic** (other) particles in terms of shape. In general, diseases caused by fibrogenic particles are worse because they do not respond to anti-inflammatory treatment and thus tend to progress permanently and their prognosis is very poor.

Manifestations of the disease

Gradual decrease in lung function, worsening cough, dyspnea, and development of respiratory insufficiency.

Diagnostics

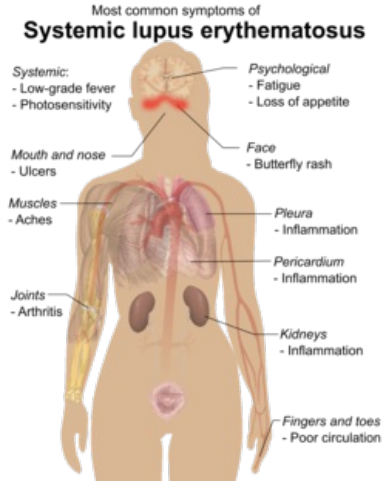
- History - symptoms (cough, shortness of breath), work and social history,
- X-ray of the lungs,
- functional lung examination (spirometry),
- BAL - if we need to identify the inorganic particles,
- biopsies are usually no longer performed.

Therapy

- Disease prevention (protective equipment, work environment limits),
- elimination of additional exposure,
- therapy of onset infections,
- long-term home oxygen therapy (DDOT),
- respiratory rehabilitation,
- lung transplantation (in indicated cases).[11]

Pulmonary manifestations in systemic connective tissue diseases

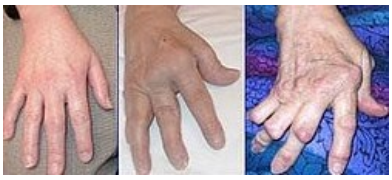
Systemic connective tissue diseases are autoimmune diseases with multiorgan impairment due to vasculitis; frequent arthritis, muscle and skin damage. The onset of *fibrosing alveolitis* is a response to immunocomplexes deposited in the pulmonary capillaries. The treatment is corticotherapy.[12]



Affected organs in lupus

Rheumatoid arthritis

- Interstitial damage in 1.5 to 4.5%;
- clinically and histologically identical to KFA;
- **prognosis**: unfavorable in case of pulmonary changes;
- **therapy**: glucocorticoids + immunosuppressants.[12]


Rheumatoid arthritis of the hand

Systemic lupus erythematosus

- Pulmonary impairment in 50 to 60%: most often pleurisy, ILD, rarely acute pneumonia;
- X-RAY: reticulonodular shadows with max. impairment of the lower lung fields;
- **therapy**: corticoids + penicillamine/cyclophosphamide;
- **survival** 10 to 14 years (cause of death renal failure, endarteritis or secondary pneumonia).[12]

Scleroderma (progressive systemic sclerosis)

- ILD in up to 80% of patients [12]

Polymyositis, dermatomyositis
Sjogren's syndrome
Bechterew's disease
Crohn's disease

Postradiation lung fibrosis

__**Pulmonary fibrosis** represents the final stage of postradiation lung changes.

- After irradiation of lung tissue with ionizing radiation at doses> 8 Gy in 30 weeks.
- Necrotic changes caused by ionizing radiation healed by a fibrotic scar.
- *Clinical manifestations:* dry cough, worsening dyspnea (restriction disorder with ↓ diffusion)
- *Diff. dg:* radiation pneumonitis (exudative alveolitis from pneumocyte + endothelial damage)
- *Therapy:* in small infiltrates, no treatment is necessary, in symptomatic individuals corticoids
- Risk factors: professional injury (radiologist, miner), poorly targeted radiotherapy[13]

Drug-induced pulmonary fibrosis

__**Drug-induced pulmonary fibrosis** is a development of an interstitial pneumonia and fibrosis due to hypersensitivity or toxic effets of drugs (Template:HVLP, MTX, amiodarone, nitrofurantoin[14], inhalation of O_2 in high concentrations):

- *hypersensitivity:* ATB (penicilin, ampicilin, nitrofurantoin), some cytostatics (MTX),
- *direct toxicity:* cytostatics (bleomycin, cyclofosfamidTemplate:HVLP) → cytostatic lungs.

It can manifest as an acute or chronic condition.[15]

Symptoms

- Dyspnea,
- Dry, irritating cough,
- X-ray: localised / diffuse interstitial damage, late honeycomb lung.

Therapy

- Discontinuation of the drug, glucocorticoids.[15]

Links

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