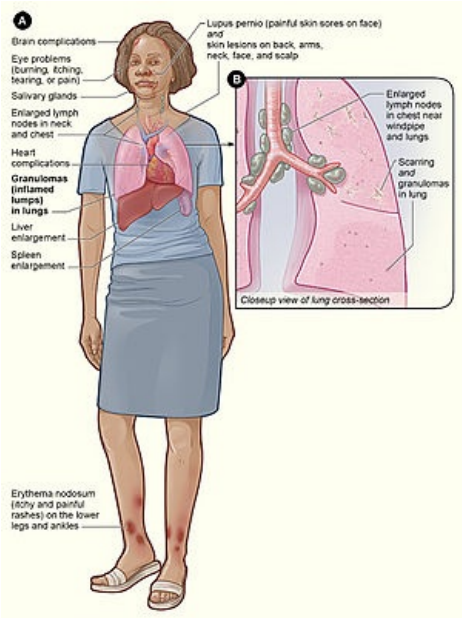
Sarcoidosis (internal)

Sarcoidosis is a **multi-system granulomatous disease** of unknown cause. It most often affects young and middle-aged people. It is often manifested by bilateral hilar adenopathy, pulmonary infiltrates and eye and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bone and other organs may also be affected. Diagnosis is made if radiological findings are supported by histological evidence classifying granulomas from epithelioid cells. Granulomas for known causes and local sarcoid reactions must be ruled out.[1]



Sarcoidosis signs and symptoms

Etiology

The etiology is unknown. Genetic factors, infectious agents, immunopathological processes are considered. Apparently, there is no specific agent or single discrete immunological defect causing sarcoidosis.

Granulomatous reactions are an "immunological backup position" in people who are unable to remove immunological agents more effectively. The onset of sarcoidosis is thus explained by the specific interaction between one or more exposures and one or more types of an immune response.

Possible triggers

- **Bacteria:** Mycobacterium tuberculosis, atypical mycobakteria, Propionibactertium acnes, Rickettsia, Borrelia, Mycoplasma, EBV.
- **Inorganic substances:** aluminium, zirconium, mineral fibres, silicon, clay, talc.
- **Organic substances:** pine pollen, starch.

Epidemiology

The incidence is 21.6 / 100,000 in women and 15.3 / 100,000 in men. The peak is between 35 and 45 years old.[2] There is a significant ethnic and racial heterogeneity of the presentation - in blacks more severe and more frequent uveitis, higher incidence of lupus pernio in Puerto Ricans, in the Caucasian race is a more common asymptomatic disease, in Japanese is more common eye and heart disease. The incidence of erythema nodosum varies by race in different studies. The mortality rate is 1-5%. Smokers are affected less often (21.9%).

Some epidemiological studies point to the seasonal occurrence, others to the possibility of interpersonal transmission and occupational exposure.

Associations with I HLA-A 188 and II HLA-DR3 in Caucasians have been found in genetic studies; HLA-DQB1 0201, HLA-DRB1 0301 in Lofgren's syndrome; HLA-DQB1 1501, HLA-DQB1 0602 in patients with chronic sarcoidosis and up to five times higher incidence of sarcoidosis in individuals with a sick parent or sibling.

Pathogenesis

Macrophages appear to have increased expression of HLA II molecules due to antigen-IFN-gamma interaction and present the putative antigen to Th1-type CD4 cells and, through IL 12 production, cause further accumulation of CD4 cells and their differentiation into Th1-type with subsequent IFN-gamma production. These activated T cells release IL-2 and chemotactic factors causing the accumulation of monocytes and macrophages at the site of disease activity and the expansion of various T cell clones. IFN-gamma further activates macrophages and transforms them into epitheloid and multinucleated giant cells, which form the basis of the granuloma and produce ACE. Macrophages produce TNF-alpha, a key cytokine for granuloma integrity. Lymphocytes CD4, CD8 and smaller numbers of B-lymphocytes then form a border around the granuloma.

Already in the early stage of granuloma formation, in some individuals, due to increased production of macrophage fibrogenic cytokines (TGF-beta, PDGF, IGF-I) or because the antigen is presented by a different HLA class, cytokine production is shifted to the Th2 phenotype (IL-4). , IL-6, IL-B, IL-15,). This response does not lead to the elimination of the pathogen and results in the continuous formation of granuloma with chronic disease. For unclear reasons, in some cases, this cluster of cells begins to envelop the dense band of fibroblasts, mast cells. collagen fibres and proteoglycans. This fibrotic response can cause substantial, often irreversible organ destruction and physiological dysfunction.

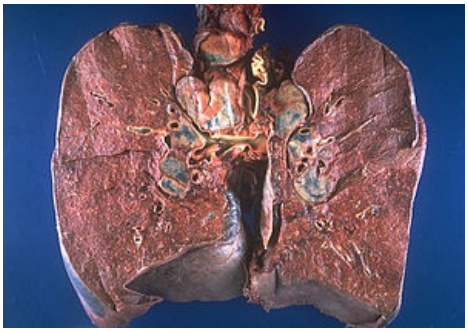
General symptoms

General symptoms include **fever** (mostly subfebrile), **exhaustion**, **fatigue**, **weight loss** (2-6 kg over 10-12). weeks before the event), sometimes also **night sweating**. General symptoms are generally more pronounced in blacks and Indians.

Pulmonary impairment

Pulmonary involvement occurs in more than 90% of patients. It manifests with **shortness of breath, dry cough, *chest pain*. The pain is manifested only by pressure on the chest but it can also mimic anginal pain. Influenza and hemoptysis are rare; however, hemoptysis can be fatal.** Bilateral hilar lymphadenopathy **occurs in about 3/4 of patients.**

It is also possible to find bronchial hyperreactivity, endobronchial granulomas, abnormal functional examination of the lungs, pleural effusion, pneumothorax, thickening or calcification of the pleura, or cavitation.



Bilateral hilar lymphadenopathy

Scadding's 1961 radiographic classification of pulmonary sarcoidosis **(it relates only to the classic ZP skiagram, not to the HRCT finding)**	
stage	**X-ray finding**
0	normal chest x-ray
I	bilateral hilar lymphadenopathy (BHL)
II	BHL + pulmonary infiltrates
III	pulmonary infiltrates (without BHL)
IV	pulmonary fibrosis with evidence of honeycomb, retraction of hils, bul, cysts and emphysema

Tendency to spontaneous remission	
stage	**(%)**
I	85 %
II	70 %
III	37 %
progression into st. IV	less than 5 %

Extrapulmonary sarcoidosis

Outside the lungs, sarcoidosis can affect the eyes, nerves, lymphatic system, heart, liver, musculoskeletal system, endocrine system, kidneys, gastrointestinal tract, parotid glands or reproductive organs. Furthermore, sarcoidosis can cause metabolic disorders (hypercalcemia, hypercalciuria) and hematological abnormalities (anemia, leukopenia, lymphopenia).

Up to 20% of patients with sarcoidosis have an associated autoimmune disease - hypothyroidism, Graves' disease, CVID (Common Variable Immuno-deficiency).

Diagnostics

⚠ Only patients with Lofgren's syndrome do not require a biopsy if the disease resolves rapidly and spontaneously.

Laboratory

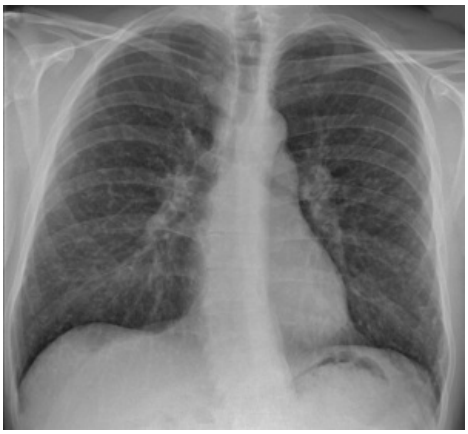
Non-specific laboratory tests are elevation of serum angiotensin-converting enzyme (*'S-ACE'*). Its increase below twice the upper limit of the standard is never diagnostic. If increased more than twice, a diagnosis of sarcoidosis is likely. However, other granulomatous diseases (TB, Gaucher's disease) and hyperthyroidism must be ruled out.

RTG

The most characteristic finding is *'BHL'* (occurs in 50-80% of patients with sarcoidosis; patients with sarcoidosis make up 74% of all patients with BHL). BHL may also be a sign of malignancy (lymphoma, bronchogenic carcinoma, extracorporeal tumors).

In 25-50% of patients, we find **infiltrative changes**, which are mostly bilateral, symmetrical, with a predilection for the central areas and upper lobes, especially posterior and apical segments in the form of *reticular, reticulonodular or focal alveolar opacities* '. Diffuse miliary disability or diffuse image of milk glass is a unique finding.

Later, destruction of the lung parenchyma can lead to architectural distortion, hil retraction, loss of upper lobe volume, wide and coarse septal bands, honeycomb and bullous changes. Enlarged pulmonary arteries and bronchiectasis may be present in advanced stages III and IV. Pleural effusion or cavitation observable on a simple skiagram is rare in patients with sarcoidosis.



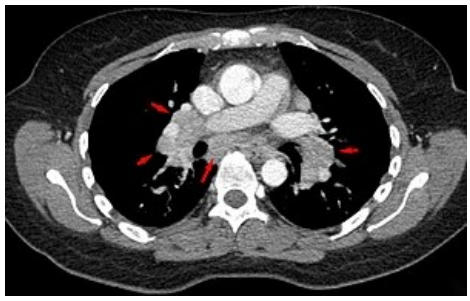
Chest X-ray of sarcoidosis nodules

Biopsy

Biopsy and subsequent histopathological and immunohistochemical examination.

🔎 *For more information see Sarcoidosis (pathology).*

CT

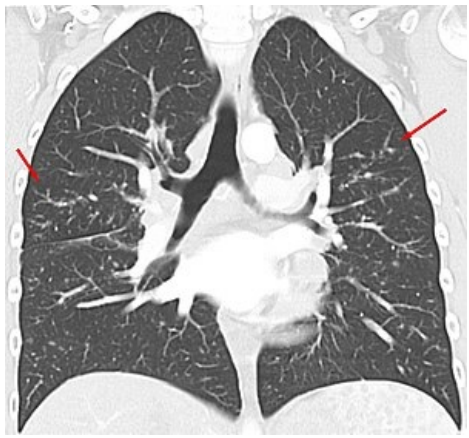


Chest CT scan: mediastinal lymphadenopathy (arrows) in a patient with sarcoidosis

- **Reversible changes:** intrathoracic lymphadenopathy (hilar, mediastinal, paraaortic, subcarcinoma) with predilection in the upper and middle lungs with perihilus distribution.
- Lesions are deposited along the bronchovascular bundles and lymphatic vessels.
- Nodules (microscopic, macroscopic, usually 1-2 mm in diameter with a blurred border).
- Consolidation (mass-mimicking lesions, confluent alveolar opacity), milky glass opacity, strengthening of bronchovascular bundles and interlobular septa, unseptic lines, subpleural linear opacity.

Chronic changes: bronchiectasis, bronchioloectasia, cysts, bullae, paracicatrial emphysema, anatomical distortion, volume loss (especially in the upper lobes and hilt retractions), mycetomas in pre-existing cavities, calcified nodes. If honeycomb lungs are present, it is usually in the upper lobes or perihiliously.

NMR



Coronary CT scan: sarcoidosis

In the case of pulmonary sarcoidosis, it has a lower resolution than CT examination, so it has its place in this area only in patients with contraindicated administration of iodine contrast agent. However, gadoline-enriched NMR is a sovereign method in the diagnosis and monitoring of neurosarcoidosis. In cardiac sarcoidosis, the NMR sensitivity is 75-100%, but it cannot be used in patients with a pacemaker.

PET

It cannot distinguish between sarcoidosis and lymphoma. It is used for diagnosis and monitoring of cardiac sarcoidosis, where it has a sensitivity of up to 100%, but with low specificity (35%).

Ga-scintigraphy

The image of **panda** in the facial part (lacrimal glands and parotid glands) and **lambda** in the whole body image (bilateral hilar and paratracheal nodes) only supports the diagnosis of sarcoidosis or is an indication for a more invasive examination. This classic picture is present in only a small number of patients. The lambda pattern itself is highly nonspecific and has been observed in patients with lymphoma. In addition, a negative test does not rule out the presence of granulomas in any organ.

Ga-scintigraphy is not useful for predicting the prognosis and indication of treatment, with the exception of cardiac sarcoidosis, where in combination with T1-scintigraphy it allows predicting the response to corticosteroids.

At present, indications for Ga-scintigraphy are limited to patients with normal or equivocal chest X-ray and clinical picture of extrauterine sarcoidosis, to determine the location of extracorporeal biopsy in clinically silent diseases, to distinguish active lung disease as signs of relapse in patients with fibrotic changes and to determine activities before organ transplantation.

Tl-scintigraphy, Tc-scintigraphy

Tl-scintigraphy is useful for the diagnosis of heart disease, myocardial examination by Tc-scintigraphy has a higher sensitivity.

Bronchoalveolar lavage

Lymphocytosis with an increased CD4 / CD8 immunoregulatory index (IRI) above 3.5 has a specificity of 50% for sarcoidosis when considering the differential diagnosis of lung disease in general, which increases to 94% if only interstitial lung disease is considered. The sensitivity of BAL is 53%.

An increase in IRI also occurs in berylliosis, asbestosis, TB, Crohn's disease, RA, which can be ruled out based on other factors. A low value does not rule out the diagnosis of sarcoidosis, as normal values occur in 30% of patients, reduced values in 10% of patients at the time of diagnosis.

Kveim's test

At present, performing the Kveim test is considered unethical. *'Not done'*.

Kveim's test (Kveimův-Nickersonův kožní test, Kveimův-Siltzbachův test[3]) is a previously used **test for diagnosing sarcoidosis**. It is based on subcutaneous injection of splenic or lymph node homogenate [4] sarcoid patient with evidence of **granulomatous skin reaction** at the application site. The test is evaluated in 4-6 weeks. [4]

In patients with sarcoidosis, small dark red nodules are formed at the application site, biopsies and subsequent histopathological examination from this site show the presence of sarcoid granulomas. [4]

It may be indicated for normal X-ray and CT findings, for uveitis of unknown origin, hypercalciuria, hepatic granulomatous involvement, suspected neurosarcoidosis or recurrent erythema nodosum. However, it is difficult to access, difficult to implement, experience in its interpretation is necessary and there is a risk of transmission of infectious agents, including prions (bovine spongiform encephalopathy).[5]).

The test was named after the Norwegian pathologist Morten Ansgar Kveim.[6]

Histological differential diagnosis

- TB, atypical mycobacteriosis, brucellosis, toxoplasmosis, granulomatous histiocytic necrotizing lymphadenitis, cat-scratch disease.
- Sarcoid reactions in cancer, Hodgkin's disease, non-Hodgkin's lymphoma.
- GLUS syndrome (**g**ranulomatous **l**esions of **u**nknown **s**ignificance).

Forecast

The prognosis is worse in blacks, in patients over 40 years of age, in the duration of symptoms longer than 6 months, in the absence of erythema nodosum, in splenomegaly, in more than 3 organ systems and III. stages of pulmonary involvement.

If spontaneous remission does not occur within two years, the probability of transition to chronic or persistent form is high.

Mortality is 1-5%. The cause of death is respiratory insufficiency, CNS involvement or myocardial involvement.

Tracking

The most intensive monitoring should be in the first two years of the disease. Monitoring should continue for at least 3 years after the end of treatment.

- Stage I - every 6 months.
- In stages II, III and IV - every 3-6 months.

We monitor the clinic and functional tests. We perform X-rays only in case of their deterioration, during the development of cardiomegaly or newly in stage IV. We determine the activity of the disease - the number of lymphocytes in BAL, S-ACE. Ga-scintigraphy or CT scans can identify active diseases but do not predict the prognosis, response to treatment, presence and intensity of inflammation - it is not clear whether such a proven active disease requires treatment.

Treatment

- **Glucocorticoids** (side effects: increased appetite, diabetes, osteoporosis, gastroduodenal ulcer).
- **Cytostatics:** methotrexate (hepatotoxicity, pneumotoxicity), azathioprine (myelotoxicity, carcinogenicity), cyclophosphamide (myelotoxicity, marked carcinogenicity).
- **Antimalarials:** chloroquine, hydrochloroquine (ocular toxicity).
- **Anti TNF:** infliximab / Remicade® / (risk of infection including TB, carcinogenicity - lymphoma), thalidomide (constipation, abdominal pain, rash, drowsiness, peripheral neuropathy).

Treatment of pulmonary sarcoidosis

Because ethical asymptomatic patients should not be exposed to the side effects of long-term systemic corticosteroid therapy and symptomatic patients with severe functional impairment should be left untreated, the possibilities for controlled studies are limited. There is currently no convincing evidence of improved lung function in systemic corticosteroid therapy or its effect on long-term disease progression, and there is limited evidence of the efficacy of immunosuppressive and cytostatic therapy.

Opinions on when to start corticosteroid treatment vary, according to most authors, due to low mortality and potentially serious side effects of systemic corticosteroids, treatment should be reserved for symptomatic patients or patients with rapidly progressing X-ray changes.

For drug-induced remission, the relapse rate is up to 76% vs. 2-8% in spontaneous remissions.

Chronic pulmonary sarcoidosis is defined as persistent symptoms lasting more than 2 years, but not all of these patients have active inflammation. Chronic symptoms of sarcoidosis may also be due to fibrosis or factors unrelated to sarcoidosis (eg shortness of breath in overweight after corticosteroid treatment). ⚠

Due to the complex effect of corticosteroids on inflammatory processes in sarcoidosis and the fact that corticosteroids can be completely discontinued in more than 25% of patients and only 20% of patients require more than 10 mg prednisone daily, some authors recommend chronic administration of 5-10 mg prednisone daily in mono therapy.

Other authors argue for minimal improvement in lung function and X-ray changes at more than 50% of corticosteroid side effects and prefer the use of methotrexate (10 mg / week), azathioprine (200 mg / day) or infliximab (3 mg / kg every 2 weeks). as a steroid-saving or completely replacement drug. However, infliximab has shown only a static, not a biological, effect in pulmonary sarcoidosis (Baughman). The effect of etanercept has not been demonstrated[7], therefore, this treatment is not routinely recommended. In case of insufficient control of sarcoidosis with corticoids or case of their unbearable side effects, the BTS (British Thoracic Society) recommends methotrexate as the drug of first choice.[8]

References

Related articles

- **Extra-pulmonary sarcoidosis** • Sarcoidosis / lymphatic system • Sarcoidosis / heart • Sarcoidosis / liver • Sarcoidosis / kidneys • Sarcoidosis / eyes • Sarcoidosis / eyes] • Sarcoidosis / skin • Sarcoidosis / nerves • Sarcoidosis / musculoskeletal system • Hypercalcemia of sarcoidosis • Sarcoidosis / blood
- Sarcoidosis (pathology)
- Interstitial lung processes
- Pulmonary manifestations in systemic connective tissue diseases
- Tuberculosis (pneumology)

Resources

ANTON, Jan. Materials for the lecture "Sarcoidosis". (abbreviated)

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