Definition of Sarcoidosis

- Sarcoidosis (Behnier-Beck-Shauman's disease) is a systemic disease characterized by the development of productive inflammation with the formation of epithelioid-cell granulomas without necrosis with the outcome of resorption or fibrosis.

- Sarcoidosis is characterized by the formation of noncaseating granulomas in one or more organs and tissues; the etiology is unknown. Most often the lungs and lymphatic system are affected, but sarcoidosis can affect any organ. Symptoms of sarcoidosis of the lungs vary from total absence (limited disease) to shortness of breath when exercising and, rarely, respiratory or other organ failure (a common disease).

Stages of chronic sarcoidosis

Chronic sarcoidosis	Chest x-ray findings
Stage 0	Normal findings
Stage I	**Bilateral hilar lymphadenopathy** (reversible)*
Stage II	Bilateral reticular or ground-glass opacities with hilar lymphadenopathy → disseminated, reticulonodular infiltrates
Stage III	Bilateral reticular or ground-glass opacities without hilar lymphadenopathy
Stage IV	Lung fibrosis
* In most cases, the disease resolves spontaneously at this stage.	

Etiology of Sarcoidosis

1. **Genetics**

Studies have shown that a mutation of the gene **BTNL2**, as well as the **HLA-DQB1 variant of the gene HLA**, are associated with an increased risk for the disease.

2. **Infectious agents**

The major implicated infectious agents include: mycobacteria, fungi, borrelia, and rickettsia.

Mycobacterium tuberculosis infection.

M.Tuberculosis catalase – peroxidase has been identified as a possible antigen catalyst of sarcoidosis.

The disease has also been reported by transmission via organ transplants.

3. **Autoimmune**

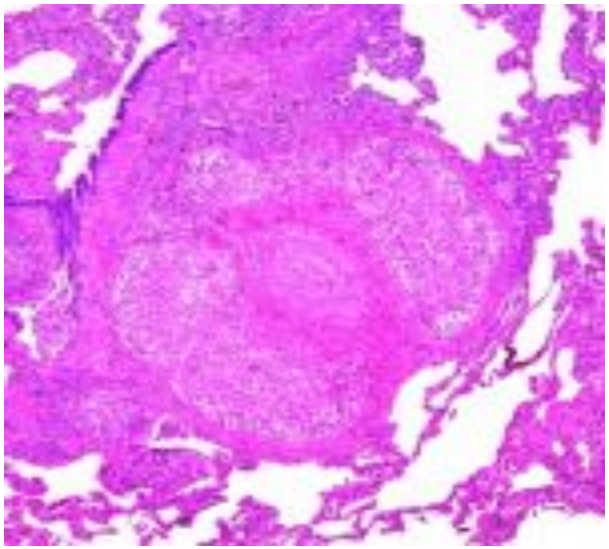
Association of autoimmune disorders has been frequently observed. The exact mechanism of this relation is not known, but some evidence supports the hypothesis that this is a consequence of Th1 lymphokine prevalence

Risk factors

- While anyone can develop sarcoidosis, factors that may increase your risk include:
- **Age.** Sarcoidosis can occur at any age, but often occurs between the ages of 20 and 60 years. Women are slightly more likely to develop the disease.
- **Race.** People of African descent and those of Northern European descent have a higher incidence of sarcoidosis. African-Americans are more likely to have involvement of other organs along with the lungs.
- **Family history.** If someone in your family has had sarcoidosis, you're more likely to develop the disease.

Pathology and pathogenesis of sarcoidosis

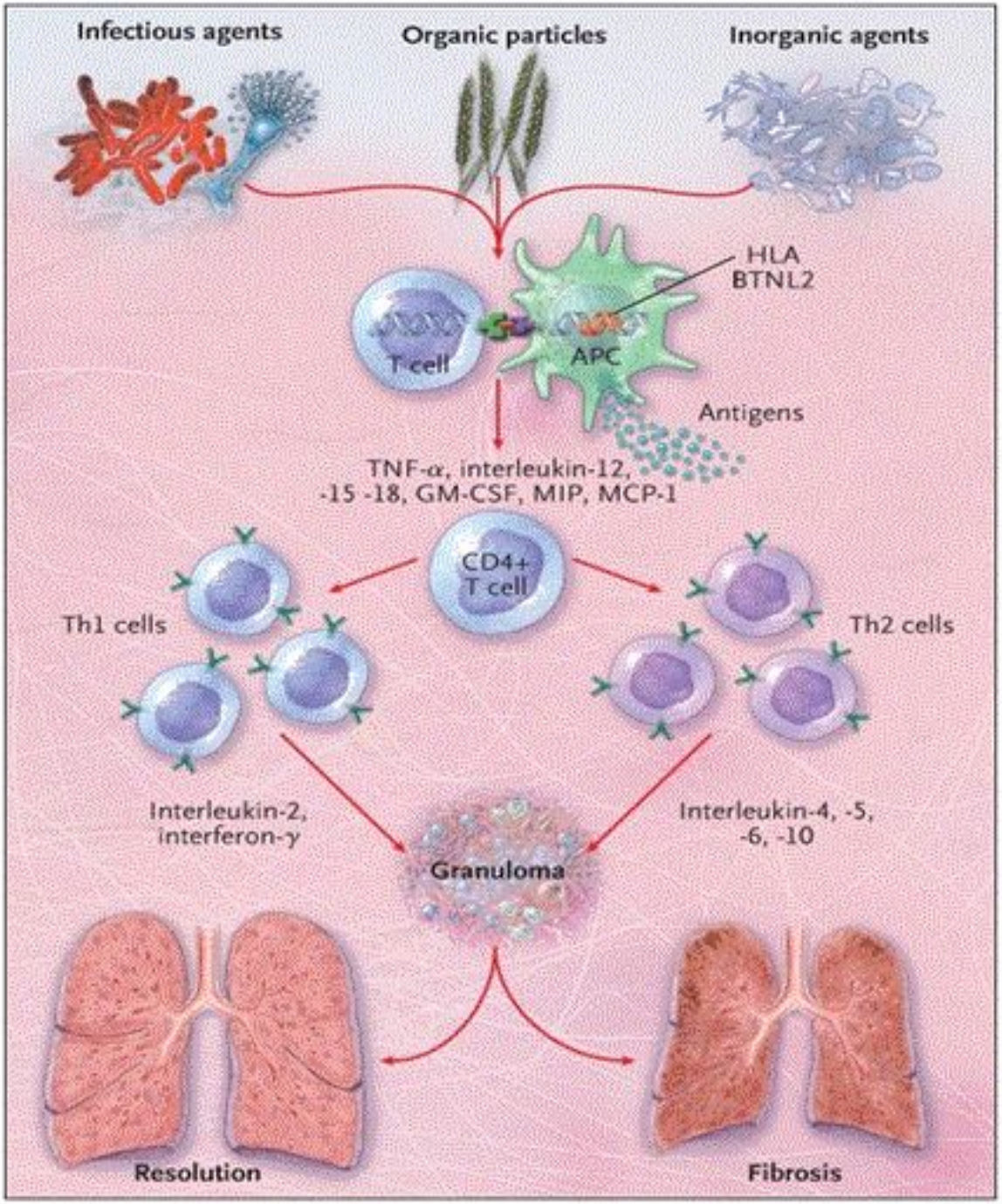
Immunological hyperactivity occurs caused by a **disturbance of T cell function** and **increased B cell activity.** Macrophages accumulate locally and release mediators, which, in turn, cause those macrophages to change into **epithelial cells**. Some of these epithelial cells merge into **giant Langerhans cells**. Lymphocyte accumulation occurs, i.e. they are surrounded by lymphocytes, and this is referred to as **'granuloma'**. The granulomas occurring within the scope of sarcoidosis do not show signs of **necrosis in their center**, which is why they are referred to as **'non-caseating granulomas.**



Sarcoidosis on a Cellular Level

. While this information may not be as relevant for the exam, one may come across this in clinical practice where a patient may want to know about this in more detail. Within the aforementioned giant cells, shell-shaped calcified inclusions can be found here and there, the so-called '**Schaumann bodies**'. These were named after J. N. Schaumann, who was the first to recognize that sarcoidosis is a systemic disease that can attack several organs and not only the skin, which had been the theory until that time.
Note: Histologically, in cases of sarcoidosis, non-caseating granulomas are present, while in cases of tuberculosis, the granulomas are caseating

Sarcoidosis is a multisystem disease that involves the lungs in 90 percent of cases. It has a predilection for the upper lobes of the lung and bronchovascular bundles more than other lung compartments, although it can affect any area. Lung involvement is often associated with hilar and mediastinal lymphadenopathy.
On histopathology, classic sarcoid granulomas are non-necrotizing with a tightly packed central area composed of macrophages, epithelioid cells, multinucleated giant cells, and T lymphocytes that are CD4 positive. The central areas are surrounded by CD8 and CD4 positive T lymphocytes, B lymphocytes, monocytes, mast cells, and fibroblasts, which in turn are surrounded by lamellar rings of hyaline collagen. The proportions of lymphocytic infiltrate and fibrosis surrounding the granulomas vary depending on the patient and disease duration. Additional histopathologic features of sarcoid granulomas that may be present include asteroid bodies, Schaumann bodies, and birefringent crystalline particles (calcium oxalate and other calcium salts.


Infectious agents
Organic particles
Inorganic agents
HLA
BTNL2
T-cell
APC
Antigens
TNF-α, interleukin-12,
-15 -18, GM-CSF, MIP, MCP-1
CD4+
T cell
Th1 cells
Th2 cells
Interleukin-2,
interferon-γ
Interleukin-4, -5,
-6, -10
Granuloma
Resolution
Fibrosis

C L I N I C A L M A N I F E S T A T I O N S

The presentation of sarcoidosis ranges from patients who are asymptomatic to those with organ failure.

Acute sarcoidosis and chronic sarcoidosis are two distinct manifestations of the disease, where acute sarcoidosis does not necessarily precede chronic sarcoidosis.

Acute sarcoidosis (approx. ⅓ of cases)-typically has a sudden onset and remits spontaneously within approx. 2 years

Chronic sarcoidosis (approx. ⅔ of cases)-in rare cases, preceded by acute sarcoidosis

- **Respiratory complaints including**

cough **and** ***dyspnea*** **are the most common presenting symptoms. In many cases, the patient presents with a 2- to 4-week history of these symptoms.**

- **Symptoms related to cutaneous and ocular**

disease are the next two most common complaints. Skin lesions are often nonspecific.

- **Nonspecific constitutional symptoms include**

fatigue, fever, night sweats, and weight loss. Fatigue is perhaps the most common constitutional symptom that affects these patients.

Lung symptoms

Lung involvement occurs in >90 % of sarcoidosis patients and may cause lung problems, such as:

- **Persistent dry cough is a very common symptom.** Airway hyperreactivity, as determined by methacholine challenge, will be positive in some of these patients.
- **Shortness of breath**
- **Wheezing**
- **Chest pain**
- **Pulmonary arterial hypertension** is reported in at least 5% of sarcoidosis patients. Either direct vascular involvement or the consequence of fibrotic changes in the lung can lead to pulmonary arterial hypertension.

Skin symptoms

Skin involvement is eventually identified in over a third of patients with sarcoidosis.

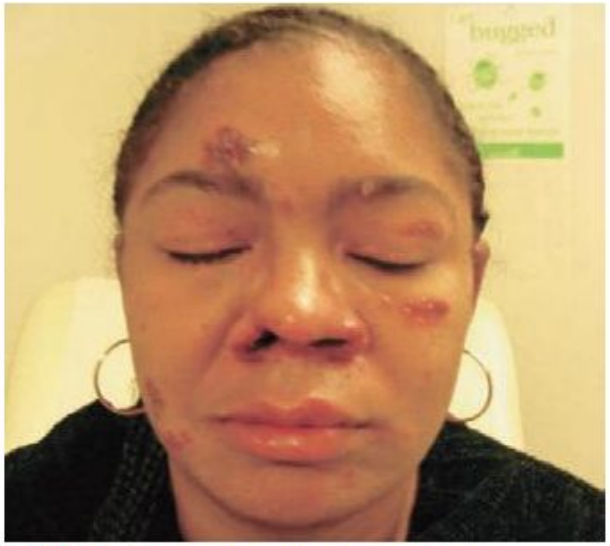


FIGURE 390-4 **Chronic inflammatory lesions** around nose, eyes, and cheeks, referred to as lupus pernio.

The classic cutaneous lesions include erythema nodosum, maculopapular lesions, hyper- and hypopigmentation, keloid formation, and subcutaneous nodules. A specific complex of involvement of the bridge of the nose, the area beneath the eyes, and the cheeks is referred to as lupus pernio and is diagnostic for a chronic form of sarcoidosis.

The maculopapular lesions from sarcoidosis are the most common chronic form of the disease and they are not painful and indurated. They can become confluent and infiltrate large areas of the skin. With treatment, the color and induration may fade.

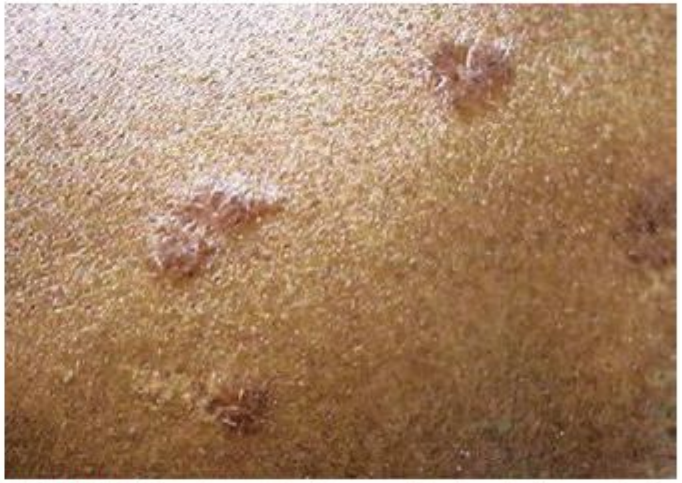


FIGURE 390-5 **Maculopapular lesions on the trunk** of a sarcoidosis patient.

Eye symptoms

- **Blurred vision**
- **Eye pain**
- **Burning, itching or dry eyes**
- **Severe redness**
- **Sensitivity to light**

Heart symptoms

- **Chest pain**
- **Shortness of breath (dyspnea)**
- **Fainting (syncope)**
- **Fatigue**
- **Irregular heartbeats (arrhythmias)**
- **Rapid or fluttering heart beat (palpitations)**
- **Swelling caused by excess fluid (edema)**

Sarcoidosis can also affect calcium metabolism, the nervous system, the liver and spleen, muscles, bones and joints, the kidneys, lymph nodes, or any other organ.

Laboratory diagnostics

In case of suspicion, the patient is prescribed a **General** and **biochemical blood test**, a **urine test.**

Preparation for laboratory diagnostics:

***Alcohol and smoking are excluded 24 hours before the study;**

***blood and urine sampling is performed in the morning before meals;**

***some medications are canceled within a few days.**

General blood test:

The changes observed in the General analysis of blood:

*decrease in the concentration of red blood cells;

*increase in white blood cells, less often their decrease;

*increased eosinophils;

*increased lymphocyte count;

*the increased level of monocytes;

*moderate increase in ESR.

Biochemical analysis

Specific changes:

*Angiotensin-converting enzyme. The level is significantly increased, the norm is from 17 to 60 units/l. Venous blood is taken for the study.
*Calcium. Granulomas in the disease actively produce vitamin D, which affects the exchange of calcium. The level of the substance increases significantly, the deviation is considered to be higher than 2.5 mmol/l.
*Tumor necrosis factor alpha. The substance takes part in the formation of granulomas. In the exchange of this substance, macrophages and monocytes are involved, the number of which increases significantly with the disease. Patients have a General increase in the concentration of this protein.
*Test Kveim-Sulzbach. The analysis confirms the disease. The patient is subcutaneously injected with infected lymphatic tissue. When the disease occurs, a bubble appears above the skin.
*Tuberculin test. In sarcoidosis, this test is negative in 90% of people. The drug is administered subcutaneously. If the result is positive.
*Copper. With pathology, the level of this substance increases. At the same time, the level of ceruloplasmin rises.

Acute sarcoidosis:

↑ Inflammatory markers

Findings typical for sarcoidosis are absent (e.g., ↑ ACE, ↑ IgG, ↑ calcium)

Chronic sarcoidosis:

↑ Calcium due to elevated levels of 1,25-(OH)2-vitamin D3

↓ CD4+ T cells: T helper cells are consumed during granuloma formation → CD4+ levels are low in serum and high in bronchoalveolar lavage.

↑ IgG (approx. 50% of patients)

↑ Angiotensin-converting enzyme (ACE) blood levels; may be used to monitor disease activity and therapy

↑ Inflammatory markers, possible lymphopenia

Urine analysis: hypercalciuria

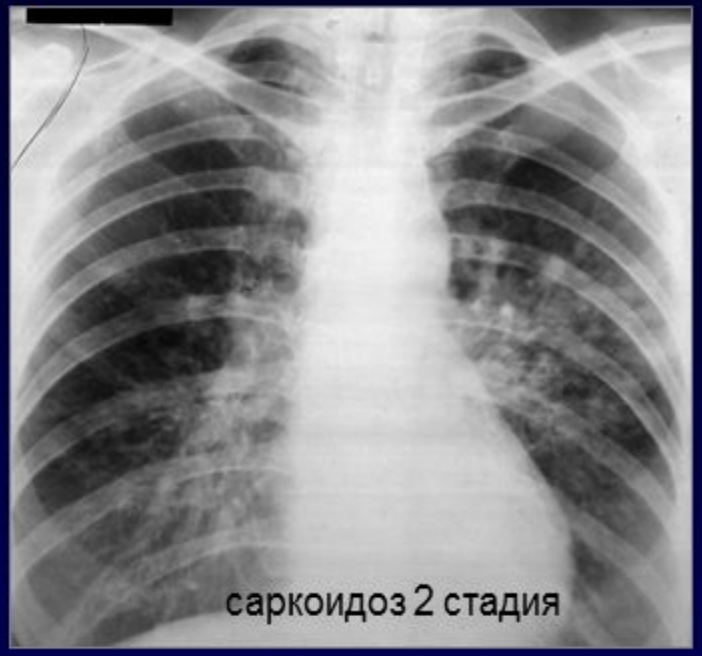
Instrumental investigations:

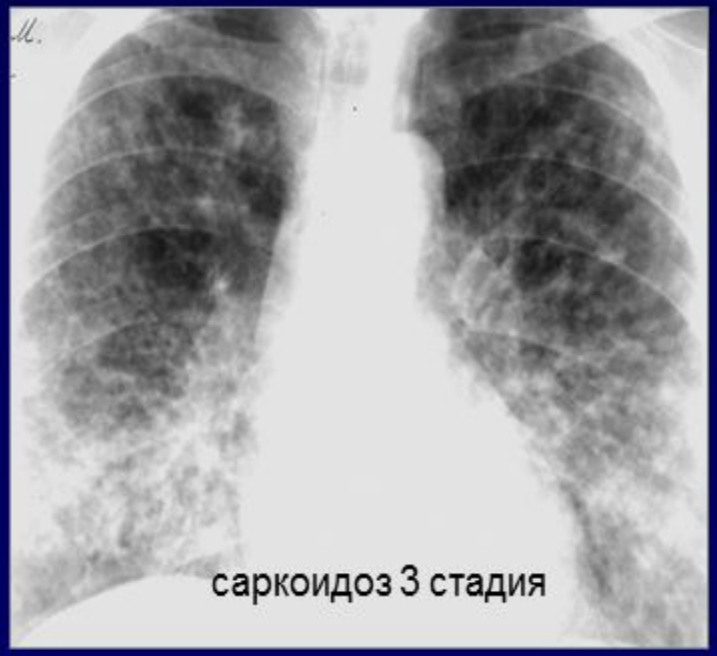
- **Chest x-ray**
- **CT**
- **Biopsy**
- **Endoscopic examination: bronchoscopy and thoracoscopy**
- Pulmonary function tests (to assess the severity of the disease)

Chest X-ray:

- **Sarcoidosis—Stage I:** Bilateral hilar adenopathy in stage I sarcoidosis
- **Sarcoidosis—Stage II:** Bilateral hilar adenopathy with interstitial opacities in stage II sarcoidosis.
- **Sarcoidosis—Stage III:** Diffuse interstitial opacities without hilar adenopathy in stage III sarcoidosis.
- **Sarcoidosis—Stage IV:** Severe, diffuse fibrosis with hilar adenopathy and cystic changes of the upper lobes in stage IV sarcoidosis.


саркоидоз 1 стадия


саркоидоз 2 стадия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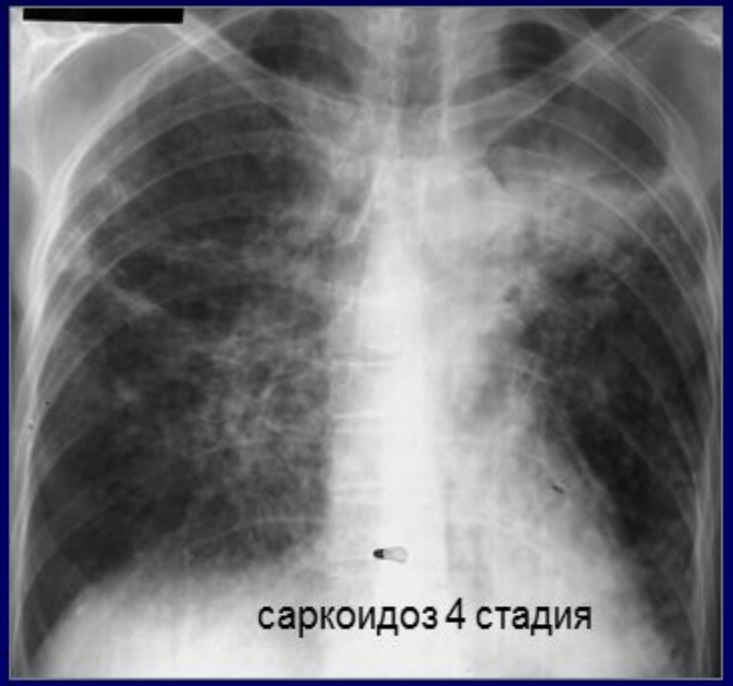
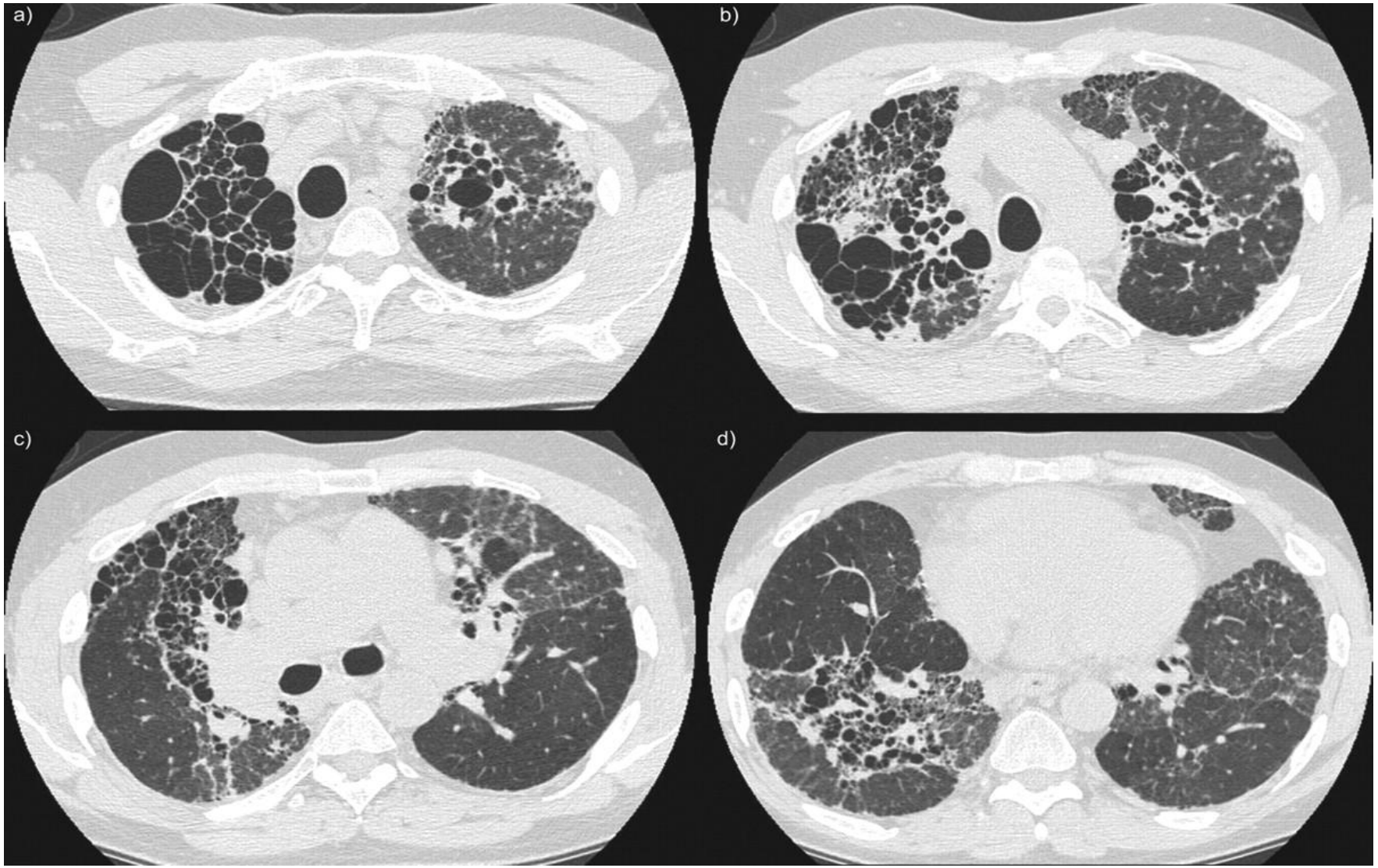

саркоидоз 4 стадия

CT findings in more advanced stages (II to IV) include:

- Thickening of the bronchovascular bundles and bronchial walls
- Beading of the interlobular septa
- Ground-glass opacification
- Parenchymal nodules, cysts, or cavities
- Traction bronchiectasis

CT imaging of sarcoidosis:



When imaging suggests sarcoidosis, the diagnosis is confirmed by demonstration of noncaseating granulomas on **biopsy** and exclusion of alternative causes of granulomatous disease .

Biopsy sites:

- peripheral lymph nodes;
- skin lesions;
- conjunctiva;

Biopsy methods:

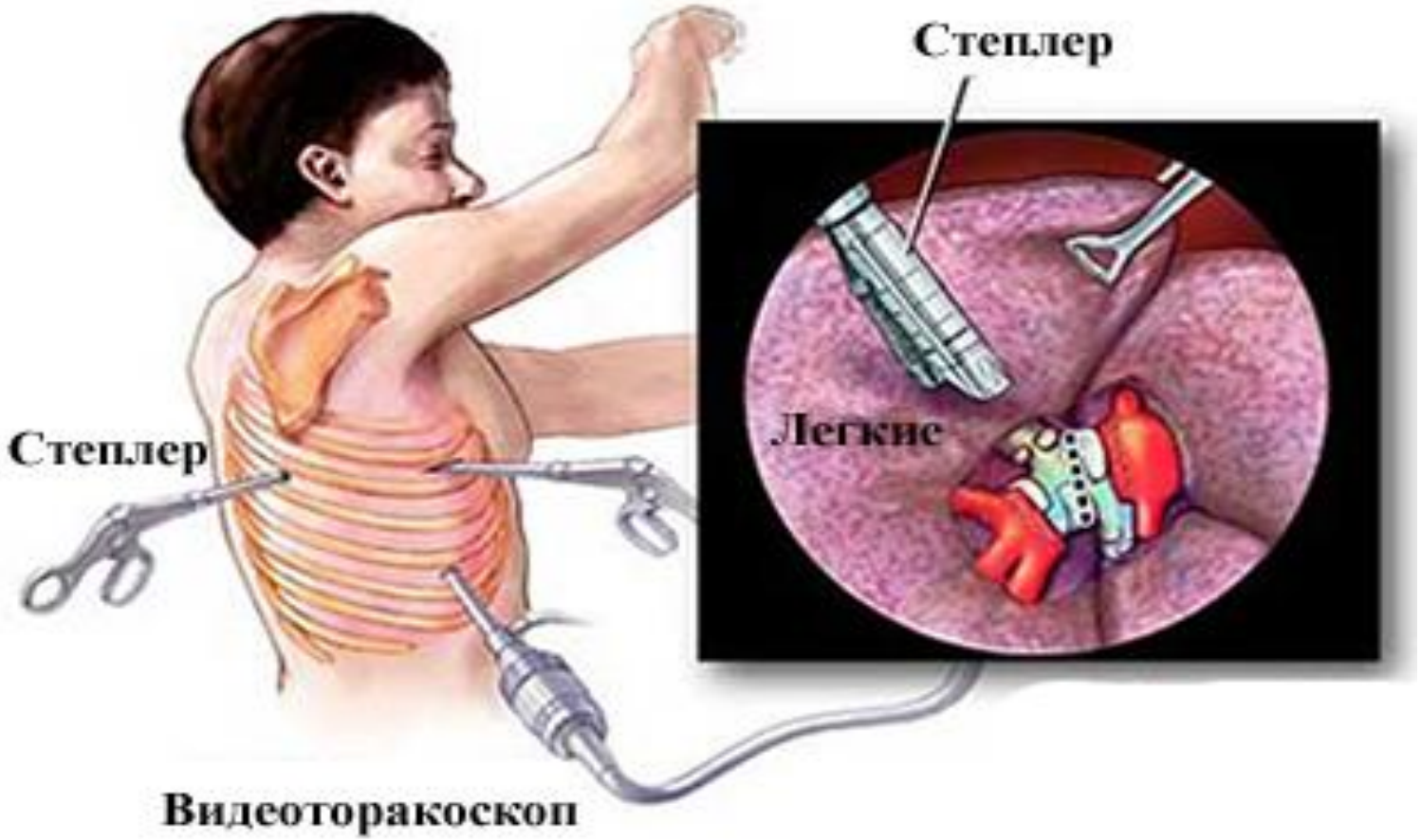
Bronchoscopic:

- Transbronchial lung biopsy (PLL).
- Classical transbronchial needle biopsy of intrathoracic lymph nodes
- **Endoscopic fine-needle puncture of mediastinal lymph nodes under the control of endosonography.**
- Direct biopsy of the bronchial mucosa (direct biopsy).
- Brush biopsy of the bronchial mucosa (brush biopsy).
- Bronchoalveolar lavage (BAL).

Surgical biopsy techniques:

- Thoracotomy with biopsy of the lung and intrathoracic lymph nodes.
- Video-assisted thoracoscopy
- Mediastinoscopy.

Video-assisted thoracoscopy:



Bronchoscopy:

- changes in the vessels of the bronchial mucosa (expansion)
- lumpy eruptions (sarcoid granulomas) in the form of plaques of various sizes (from millet grains to a pea);
- on the mucous membrane of the bronchi, ischemic spots are visible - pale areas devoid of blood vessels.

Thoracoscopy:

- Whitish-yellowish sarcoid granulomas are visible on the pleural surface.

Pulmonary function test:

- Pulmonary function test results are often normal in early stages but demonstrate restriction and reduced diffusing capacity for carbon monoxide (DL_{CO}) in advanced disease.

Differential diagnosis

sarcoidosis

Disease	Clinical manifestations	X-ray picture
Sarcoidosis	More often asymptomatic onset, with progression of subfebrile fever, weakness, aching chest pain	An increase in hilar lymph nodes, less often parabronchial, tracheobronchial. The apperance of a large-spotted pattern in the basal and small-spotted in the meddle zones, as well as small focal shadows
Silicosis	Shortness of breath, cough, chest pain, lymph nodes are not enlarged. Slowly progressive course.	Diffuse interstitial fibrosis, nodular process. Monomorphic shadows.
Disseminated tuberculosis	Intoxication syndrome. There may be a cough, excretion of micobacterium tuberculosis in the macrobacterium, hemoptysis, chest pain.	Shadows are polymorphic. There may be interstitial changes and enlargement of the LN.
Exogenous allergic alveolits	Chills, fever, shortness of breath, cough, pain in the chest, muscles, joints.	Strengthening the pulmonary pattern due to the intertial component, the summation of these shadows creates a picture of miliary foci.
Idiopathic fibrosing alveolits	Dyspnoe with acute progressive course, fever, weight loss, chest pain, muscles, joints	Strengthening and deformation of the pulmonary pattern, interstitial fibrosis.
Lymphogranulomatosis	General malaise, fever	An increase in the mediastinal lumen, more often with the formation of conglomerates. In the lung tissue, interstitial and infiltrative changes

Disease	External respiration function	Changes in peripheral blood	Morphological signs
Sarcoidosis	Mixed type of disorders depending on the severity of the process	absolute lymphopenia	epithelioid cell granuloma (all cells of the tuberculous tubercle without caseosis)
Silicosis	increase in restrictive type of disorders	absent	nodules with dust particles (SiO_2) inside and fibrous rings around
Disseminated tuberculosis	restrictive and obstructive disorders of varying degrees	leukocytosis and lympho- and monocytosis, increased ESR	tuberculous tubercles, consisting of cells: epithelioid, lymphoid, Pirogov-Langhansa, with caseosis
Exogenous allergic alveolits	In the acute stage - obstructive changes, with chronicity - restrictive	Leukocytosis, a shift in the leukocyte formula, an increase in ESR	Epithelial - cell granulomas
Idiopathic fibrosing alveolits	Progression of restrictive type of emphysema disorder	Fluctuations from normal values to severe violations	Consolidation and thickening of interalveolar septa, obliteration of alveoli and capillaries with fibrous tissue
Lymphogranulomatosis	Obstructive type of disorder	Increased ESR, lymphopenia, eosinophilia	Granulomas, Berezovsky-Sternberg cells

Differential diagnosis of granulomatous disease

	Risk factors	Clinical presentation	Biopsy	Other laboratory findings
Sarcoidosis	•African American females in the US	•Dry cough •Erythema nodosum •Lupus pernio •Anterior (and possibly posterior) uveitis	•Non-caseating granulomas •Giant cells	•↑ $CD4^{\pm}$/$CD8^{\pm}$ ratio in bronchoalveolar lavage
Tuberculosis (TB)	•Immunocompromised individuals •Previous TB and/or recent TB exposure	•Fever, weight loss, and night sweats •Productive cough that does not respond to conventional antibiotic therapy •Hemoptysis	•Caseating granulomas •Langhans giant cells, epithelioid macrophages, and lymphocytes •Acid-fast *M. tuberculosis*	•*M. tuberculosis* or its DNA
Hodgkin lymphoma	•History of infectious mononucleosis	•Pel-Ebstein fever •Alcohol-induced pain •Pruritus	•Non-caseating granulomas •Reed-Sternberg cells •Inflammatory cell infiltrate (e.g., eosinophils, fibroblasts, plasma cells)	•Single or combined cytopenias (i.e., anemia, leukopenia, and/or thrombocytopenia)
Non-Hodgkin lymphoma	•Infections (e.g., EBV infection or Helicobacte	•Indolent lymph node enlargement	•Non-caseating granulomas without Reed-Stern	•Single or combined cytopenias

		examination is unremarkable. •In symptomatic patients • Progressive exertional dyspnea • Chronic cough (possibly with sputum) • Auscultatory findings (e.g., rales, crackles) • Signs of respiratory failure (e.g., digital clubbing)		
Granulomatosis with polyangiitis	•Caucasian individuals aged 65–74 years	•Chronic rhinitis/sinusitis with thick purulent/bloody discharge •Treatment-resistant pneumonia •Glomerulonephritis	•Non-caseating granulomas	•Positive cytoplasmic ANCA
Histoplasmosis	•AIDS •Exposure to bird or bat excrement	•Pulmonary (e.g., dry cough, oral ulcers) or extrapulmonary (e.g., splenomegaly) manifestations	•Caseating granulomas •Identification of *H. capsulatum* yeast with silver stain	•Positive polysaccharide urine and serum antigen test

Treatment

- NSAIDs
- Corticosteroids
- Sometimes used immunosuppressants

- **Patients who need treatment regardless of stage include the following:**
- Worsening symptoms
- Activity limitation
- Significant impairment or deterioration in lung function
- Significant changes on x-rays (cavities, fibrosis, conglomerates, pulmonary hypertension)
- Damage to the heart, nervous system, or eyes
- Renal or hepatic impairment
- Moderate to severe hypercalcemia
- Disfiguring lesions of the skin or joints
- For the treatment of discomfort from the musculoskeletal system, NSAIDs are used.

Corticosteroids

- Symptom management begins with corticosteroids.
- *! The presence of abnormalities on chest scans without significant symptoms or evidence of decreased organ function is not an indication for treatment.*
- The standard protocol is **prednisone 20–40 mg orally once a day**, depending on symptoms and severity of the disease. Alternatively, you can use an every other day regimen: for example, prednisone 40 mg orally once every other day.
- Although patients rarely need a **dose> 40 mg / day**, higher doses may be required to reduce complications of **neurological disease**. Response usually occurs within 6-12 weeks, so symptoms and pulmonary function tests can be re-evaluated between 6 and 12 weeks. In chronic and latent cases, the reaction may be delayed. If there is an effect, the dose of corticosteroids is gradually reduced to maintenance (for example, prednisone 10-15 mg / day); with improvement, therapy is continued for at least 6-12 months.

- The optimal duration of treatment is unknown. A premature dose reduction may lead to relapse. In case of a doubtful reaction or ineffectiveness of treatment, the use of the drug is gradually discontinued. Ultimately, corticosteroids can be discontinued in most patients, but since relapse occurs in 50% of cases, follow-up examinations should be performed, usually every 3–6 months.
- **Treatment with corticosteroids should be resumed** if complaints and symptoms recur, including dyspnea, arthralgia, fever, liver failure, cardiac arrhythmias, CNS symptoms, hypercalcemia, eye damage, lack of topical drug control, and disfiguring skin lesions. Because low doses of corticosteroids suppress ACE production, it may be useful to monitor serum ACE levels over time when assessing adherence to corticosteroid treatment in the presence of elevated ACE levels.

- **Inhaled corticosteroids** can relieve cough in patients with *endobronchial involvement or airway hyperresponsiveness*. Inhalation of large doses of **budesonide** or **fluticasone** has sometimes been shown to be effective in pulmonary stages I-III, while combinations of systemic and inhaled steroids have a positive effect on both clinical symptoms and changes on radiographs in stages II-IV.
- **Local corticosteroids** may be helpful in treating dermatitis, sinusitis, and eye diseases.
- When treating with corticosteroids or immunosuppressants, prophylaxis for Pneumocystis jirovecii pneumonia should be considered.

Immunosuppressants

- ***!*** *Treatment with immunosuppressants is carried out in case of intolerance to moderate doses of corticosteroids, refractoriness of sarcoidosis to corticosteroids, or if treatment with corticosteroids is required for a long time.*
- In about 10% of cases when therapy is necessary, tolerated doses of corticosteroids are ineffective, and a 6-month trial of **methotrexate therapy at a dose of 10-15 mg / week** should be carried out. Methotrexate and corticosteroids are given initially; after 6-8 weeks, the dose of corticosteroids can be gradually reduced, and in many cases their use can be discontinued. However, the maximum effect of methotrexate can be observed after 6-12 months. In such cases, the dose of prednisolone should be decreased more slowly. Determination of blood corpuscles and liver enzymes should be performed first every 1–2 weeks, then every 4–6 weeks, as soon as a stable dose is reached. In patients receiving methotrexate, folate (1 mg orally per day) is recommended.

- Other drugs that have been effective in a small number of patients who do not respond to corticosteroid treatment or who experience complicating side effects include **azathioprine, mycophenolate mofetil, cyclophosphamide, chloroquine or hydroxychloroquine, and infliximab**. Immunosuppressants are often more effective in refractory cases, and relapse is common after stopping treatment. The **TNF inhibitor infliximab** may be effective in treating chronic steroid-dependent pulmonary sarcoidosis, refractory lupus fever, and neurosarcoidosis. It is administered intravenously at a dose of 3-5 mg / kg once, repeated in 2 weeks, and then administered 1 time / month.
- **Hydroxychloroquine** 400 mg orally once a day or 200 mg orally twice a day may be as effective for treating hypercalcemia, sarcoid skin lesions, or enlarged patient-discomfortable or disfiguring peripheral lymph nodes.

Oxygen therapy

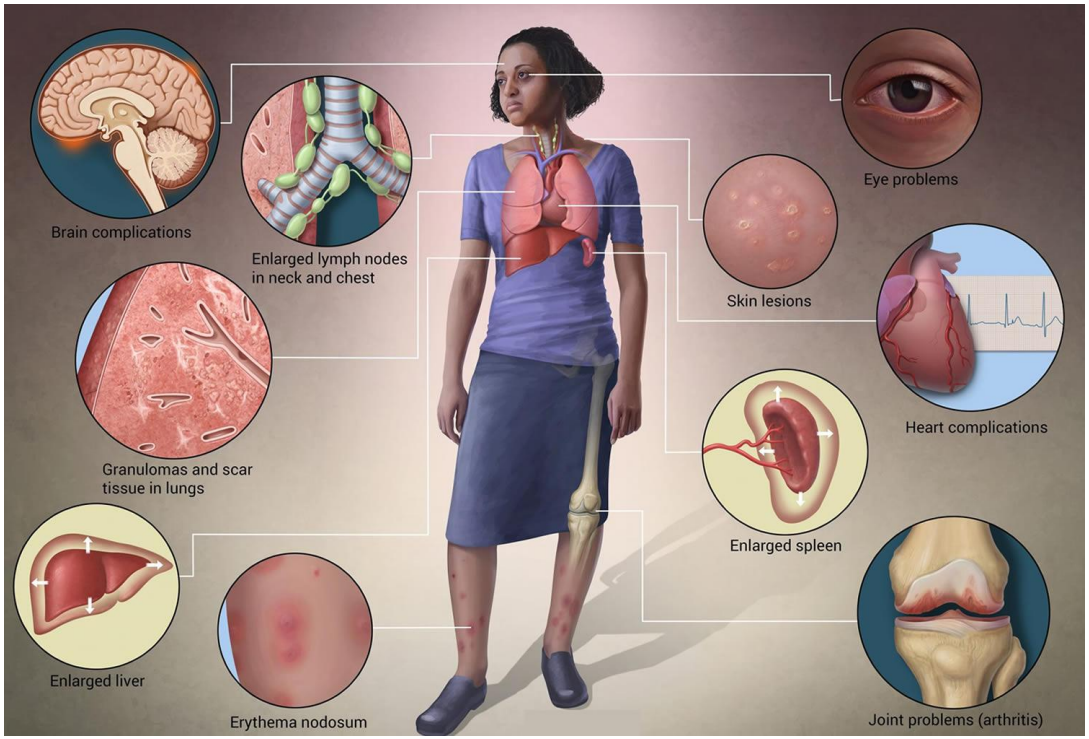
The administration of oxygen to patients with LH on the background of sarcoidosis is indicated for chronic hypoxemia (Rao2 < 55 mm Hg), while the dose is titrated to reach SpO2 >90% when breathing through an oxygen concentrator

Specific LH therapy for sarcoidosis

Currently, there are effective drugs for the treatment of pulmonary arterial hypertension (PAH), such forms as idiopathic (primary) PAH, PAH in systemic scleroderma, etc. It is possible that these same drugs are also the most effective therapy for LH associated with sarcoidosis.

Surgery

- Organ transplant may be considered if sarcoidosis has severely damaged your lungs, heart or liver.

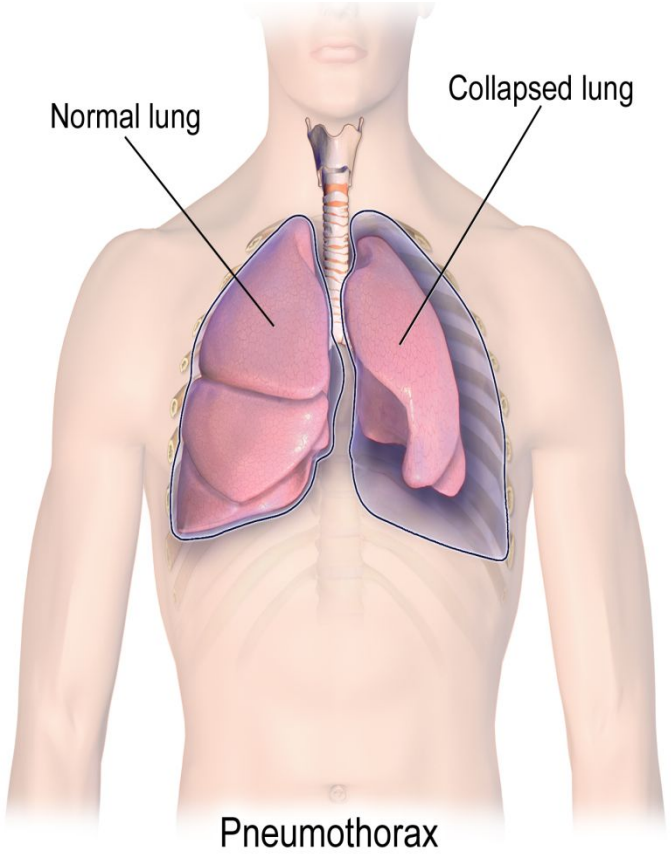


Complication of sarcoidosis:

Complications list for Sarcoidosis:

- Lung damage - about 90% of cases
- Collapsed lung
- Lung granulomas
- Lung fibrosis
- Frequent pneumonia
- Bleedings
- Eye complications:
  - Cataracts
  - Glaucoma
  - Blindness
- Heart damage
- Nervous system - only about 1-5% of cases.
- Liver damage
- Death
- Kidney damage
- Arthritis
- Psychological problem

Collapsed lung



inflammation or the growth of granulomas

↓

rupture of pleura

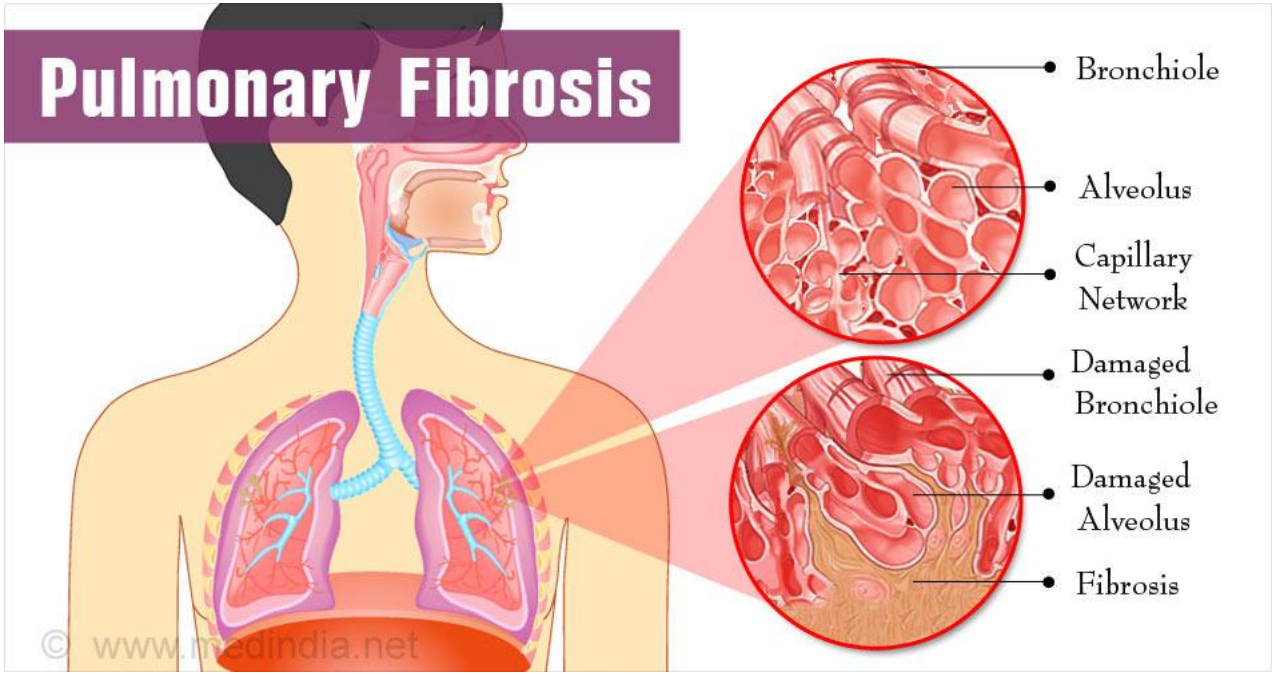
↓

the pressure is equalized with atmospheric pressure

↓

the lungs begin to shrink

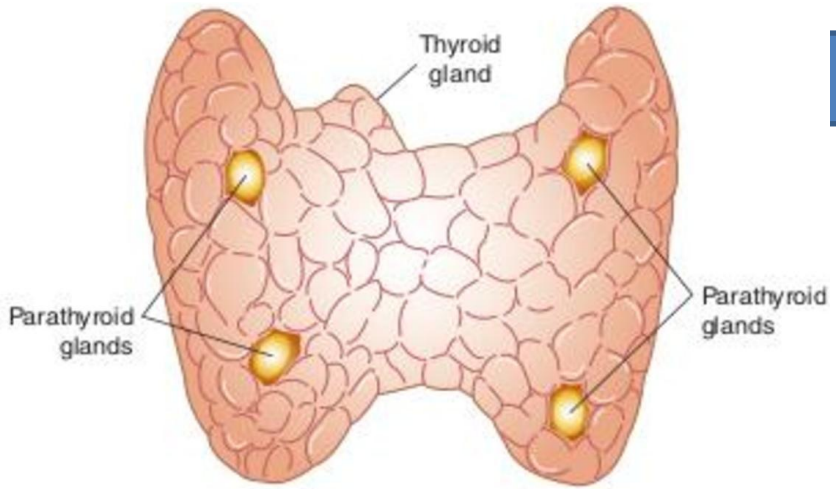
Pulmonary fibrosis



Pulmonary fibrosis is the end stage of pulmonary sarcoidosis. This process begins at stages 2 - 3 of the disease, when symptoms are just beginning to appear

Due to the formation of granulomas in sarcoidosis, pathology is observed on the part of the organs on which they appear (if the granuloma affects the parathyroid glands, calcium metabolism is disturbed in the body, hyperparathyroidism is formed, from which patients die). Against the background of a weakened immune system, other infectious diseases (tuberculosis) may join.

parathyroid glands



hyperparathyroidism