Sarcoidosis — Symptoms, Diagnosis and Treatment

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Sarcoidosis, also referred to as Morbus Boeck or Morbus Besnier-Boeck-Schaumann disease, usually attacks the lungs and is therefore frequently taught within the scope of pulmonary diseases. The bottom line is, however, that this disease can also affect any other organ meaning that medical students may not only encounter its clinical picture in many exams dealing with various specialties but also in their clinical routines in different specialty disciplines. You will learn in this article how to accurately classify the progression and symptoms of sarcoidosis and to take the right steps to diagnose and treat it.

Definition of Sarcoidosis

Sarcoidosis – A Multisystem Disease
Sarcoidosis is a multisystem disease whose genesis is not yet completely known and which is characterized by non-caseating granulomas in the affected organs. The main locations for this disease to manifest itself in are the lungs and the hilar lymph nodes. One has to differentiate between acute sarcoidosis (also includes Löfgren’s syndrome, a special form of the disease) and chronic sarcoidosis. It is important to understand that acute and chronic sarcoidosis progress differently, usually independent of one another. The chronic form of this disease does not follow the acute form of the disease, as is typical in many other illnesses.

Epidemiology of Sarcoidosis

Sarcoidosis as Interstitial Lung Disease

Sarcoidosis is among the most frequent interstitial lung diseases, with an incidence of 10 in 100,000 per year in Western Europe. While considering this number, one has to assume that there are a high number of individuals who have the disease but are not diagnosed. Sarcoidosis usually peaks between the ages of 20 and 40 and affects women slightly more frequently than men, especially the acute form of the disease.

Note: In typical case studies involving Löfgren’s syndrome, it is usually a young woman who is affected by the disease!

Etiology of Sarcoidosis

Causes of Sarcoidosis
The cause of sarcoidosis is not yet known. Various theories, however, describe a multifactor genesis in which, both genetic predispositions as well as certain environmental factors, seem to be relevant. In many cases, family members of an affected patient acquire the disease as well. Furthermore, studies have shown that a mutation of the gene \texttt{BTNL2}, as well as the \texttt{HLA-DQB1} variant of the gene \texttt{HLA}, are associated with an increased risk for the disease.

The increased occurrence of the disease among hospital nursing staff members, the role of bacterial nucleic acids, or inhalation of talc or aluminum gathered from the patient's medical history, all point to the influence of many environmental factors.

**Pathology and Pathophysiology of Sarcoidosis**

**Sarcoidosis on a Cellular Level**

\begin{center}
\textbf{Image:} Sarcoidosis. By Leslie KO, Licence: CC BY 2.0
\end{center}

**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'. 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!

## Symptoms of Sarcoidosis

### General Symptoms of Sarcoidosis

While it would be best to further differentiate between acute and chronic sarcoidosis, there are some general symptoms that many patients with sarcoidosis display:

- Fatigue and exhaustion
- Fever
- Weight loss
- Night sweats

### Acute Sarcoidosis

In cases of **acute sarcoidosis** (10% of cases), the fever is frequently high. Usually, the skin, lymph nodes, and joints (in cases of polyarthritis) are affected. An acute attack on the lungs manifests itself as dyspnea and cough and even thoracic pain. A special form of the disease is **Löfgren’s syndrome**. The following **triad of symptoms** of Löfgren’s syndrome is a popular topic for exams:

- Polyarthritis (it usually affects the ankle joints)
- Bilateral hilar lymphadenopathy
- Erythema nodosum (it especially affects the extensor sides of the lower legs)

### Chronic Sarcoidosis and Study Table

**Chronic sarcoidosis** usually progresses slowly with few symptoms, which is why it is usually diagnosed by accident or so late in the progression that there is already structural damage to organs.

The following is an overview of the key locations where the disease manifests itself as well as the symptoms associated with it:

<table>
<thead>
<tr>
<th>Location of the manifestation and frequency</th>
<th>Symptoms</th>
<th>Image</th>
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</table>

[Table content to be filled in]
<table>
<thead>
<tr>
<th><strong>Lungs:</strong> very frequently, ~ 95%</th>
<th>In the beginning, there are no symptoms in many cases! It frequently happens that there is an astonishing discrepancy between the patient being in good clinical condition and objective findings. (In many cases, the disease is found by accident when chest X-rays are taken!) <strong>Dry cough</strong> and <strong>exertional dyspnea</strong> may occur during the progression of the disease. The most feared complications are <strong>pulmonary hypertension</strong> or even <strong>pulmonary heart disease (cor pulmonale)</strong> as a consequence of <strong>pulmonary fibrosis</strong>.</th>
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<tbody>
<tr>
<td><img src="https://example.com/scan" alt="CT Scan of Sarcoidosis" /></td>
<td><img src="https://example.com/histopathological" alt="Histopathological image of sarcoidosis" /></td>
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<tr>
<td><strong>Lymphoid organs:</strong> ~ 90%</td>
<td>There are lymph node enlargements, especially in the intrathoracic area (bilateral hilar). There are also peripheral lymph node enlargements. However, they may occur in the cervical or axillary region, and this should definitely be considered during the clinical examination!</td>
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<tr>
<td><img src="https://example.com/histopathological" alt="Histopathological image of sarcoidosis" /></td>
<td></td>
</tr>
<tr>
<td><strong>Liver:</strong> ~ 80%</td>
<td><strong>Elevated liver enzymes</strong> and, in some cases, <strong>hepatomegaly</strong> may be found. Clinically, there are usually no symptoms.</td>
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<td><img src="https://example.com/histopathological" alt="Histopathological image of sarcoidosis" /></td>
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<tr>
<td><strong>Joints:</strong> ~ 40 %</td>
<td><strong>Joint pain</strong> and swollen joints occur frequently. In rare cases, the corresponding muscles are affected as well.</td>
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<td><strong>Skin:</strong> ~ 30 %</td>
<td>The typical clinical picture in these cases is <strong>erythema nodosum</strong> (an inflammation of the subcutaneous fat tissue in the form of red nodules that turn blue, especially on the extensor sides of the lower legs that are very painful) as well as <strong>lupus pernio</strong> (fibroid skin sarcoidosis which frequently affects extensive areas of the nose and cheeks and is accompanied by significant scar formation).</td>
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<tr>
<td><strong>Eyes:</strong> Depending on the location, the frequency fluctuates between 25–80%</td>
<td>In most cases where sarcoidosis attacks the eyes, <strong>iridocyclitis</strong> or <strong>uveitis</strong> can be found. Calcium deposits in connective tissue or the cornea, tear duct enlargements, or retinal vasculitis may also occur.</td>
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<td><strong>Heart:</strong> ~ 25 %</td>
<td>As the left ventricle, as well as the septum, are affected in many cases, <strong>cardiac arrhythmia</strong> with an increased risk of sudden cardiac death may occur during the progression. Atrioventricular block formation, left ventricular insufficiency, and pericardial effusion has been reported.</td>
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<tr>
<td><strong>Bones</strong></td>
<td>Sarcoidosis may attack the bones as well, causing, among others, <strong>cystic changes</strong> in the phalanges of fingers. This condition is referred to as <strong>Jüngling disease</strong>, which is very rare. (Nevertheless, or possibly because of that very fact, it has been included in questions posed in medical exams).</td>
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</tbody>
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### Diagnosis of Sarcoidosis

#### Diagnosing Sarcoidosis in the Lab

After clinical findings have been established, the **laboratory diagnosis** may deliver further indications that may support the suspected diagnosis.

In **acute cases of the disease**, the **inflammatory parameters** are usually significantly elevated (especially the **erythrocyte sedimentation rate, ESR**).

In **chronic cases of the disease**, approx. half of the patients have **elevated IgG levels**. Furthermore, **calcium levels** in blood or urine may be elevated as the epithelial cells produce vitamin D. In some cases, **leukocytopenia (leukopenia)** or **lymphocytopenia (lymphopenia)** may occur. As the **activity parameter** and to control the progression, either an **angiotensin-converting enzyme (ACE)** or the **soluble interleukin-2 receptor** are frequently used. In cases of high disease activity, both of them are elevated; during remission or with successful therapy, they normalize.

#### Diagnosing Sarcoidosis via Radiology

The next step should be **chest X-rays**. According to the results, one can classify **chronic sarcoidosis into 5 different stages, according to Scadding**:

<table>
<thead>
<tr>
<th>Stages of sarcoidosis</th>
<th>Radiographic correlate</th>
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<tr>
<td><strong>Stage 0</strong></td>
<td>Normal radiographic findings (positive bronchoalveolar lavage or a rare case of pure extrapulmonary sarcoidosis)</td>
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<tr>
<td><strong>Stage I</strong></td>
<td>Enlarged bilateral hilar lymph nodes only (these findings are usually present in acute cases of sarcoidosis as well)</td>
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<tr>
<td>Stage  II</td>
<td>Enlarged bilateral hilar lymph nodes with pulmonary involvement (increased reticulonodular, pulmonary infiltrates)</td>
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<td>---------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Stage III</td>
<td>Pulmonary involvement without enlarged lymph nodes</td>
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<tr>
<td>Stage IV</td>
<td>Advanced, irreversible pulmonary fibrosis</td>
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In cases of unclear or not quite specific radiological findings, but with typical clinical signs present, it may be necessary to follow up with a **high-resolution CT (HRCT)**. The HRCT will show changes in pulmonary structure sooner than chest X-rays: Interlobular septal thickening or fine nodular densification are signs of fibrotic changes in pulmonary tissue.

**Transbronchial Biopsy and Histology in Cases of Sarcoidosis**

The histological examination of affected tissue is another important step in diagnosing sarcoidosis. The results of the biopsy can prove the presence of non-caseating granulomas or histologically rule out other differential diagnoses. In cases of pulmonary tissue involvement, performing a **bronchoscopy** with **transbronchial biopsy** and **bronchoalveolar lavage (BAL)** are appropriate. The latter may reaffirm typical findings: In cases of active sarcoidosis, the **CD4/CD8 ratio** is > 5 (the higher the ratio, the more probable the diagnosis) and a shift of the T-helper/T-suppressor ratio in favor of the T-helper cells can be seen (**caused by the lymphocyte alveolitis**).
**Hint:** The CD4/CD8 ratio also plays a role in diagnosing other diseases! In cases of HIV infections, for instance, the **CD4/CD8 ratio is lower as well!**

### Sarcoidosis and the Pulmonary Function Test

**Pulmonary function** may reveal signs of **restrictive ventilation disturbance**, especially if pulmonary fibrosis has already begun. **Reduced oxygen diffusion capacity** is a very early and sensitive parameter for sarcoidosis activity.

### Cardiological Diagnosis of Sarcoidosis

As mentioned above, sarcoidosis may attack many organs, and it would, therefore, be prudent to also follow up with **cardiac diagnostic tests (ECG, echocardiography)** and an **ophthalmological examination**, possibly even other specialist consultations, should such a suspicion exist.

![Fragmented QRS](image)

**Image:** Fragmented QRS in a 52-year-old patient with cardiac sarcoidosis. By Take Y, Morita H, Licence: [CC BY 2.5](https://creativecommons.org/licenses/by/2.5/)

### Assessing Chronic Sarcoidosis Activity

First and foremost, to assess the disease activity, especially in cases of chronic sarcoidosis, observing the progression of the clinical signs as well as the laboratory findings is appropriate (**ACE, soluble IL-2 receptor, inflammatory parameters, calcium**). The parameters of the pulmonary function test (diffusion capacity, in particular) are suitable to monitor the progression. Depending on symptoms, the corresponding organ-specific changes must be monitored regularly (i.e. **chest X-rays** in cases of pulmonary involvement and bilateral hilar lymphadenopathy, an ECG in cases of cardiac arrhythmia, etc.).

### Differential Diagnoses of Sarcoidosis

**Clinical pictures similar to sarcoidosis**

Sarcoidosis can mimic many diseases. Differential diagnoses include, among others:
- **Tuberculosis** (However, the disease presents with caseating granulomas!)
- **Hodgkin’s disease** (This is the reason why a lymph node biopsy followed by histology is so important.)
- **Pneumoconiosis** (Occupational history: branches of the industry that work with beryllium, for instance.)
- **Exogenous allergic alveolitis**
- In cases of acute sarcoidosis: **arthritis** of another genesis

### Therapy of Sarcoidosis

As acute sarcoidosis as well as chronic sarcoidosis stage I showed high **spontaneous cure rates**, it is routine to wait and watch while monitoring the patient and forego the side effects of long-term steroid therapy.

### Indications for Corticosteroid Therapy in Cases of Sarcoidosis

- Starting with stage II, with simultaneous restricted pulmonary function
- Hypercalcemia and hyperuricemia (threat of chronic renal insufficiency)
- Involvement of the eyes, liver, CNS, myocardium or skin
- Severe general symptoms, severe arthritis (i.e. Löfgren’s syndrome)

Should the patient not respond to therapy with glucocorticoids after 3 months, it does not seem promising to continue with it. In this case, a **combination of immunosuppressive drugs** (i.e. azathioprine, methotrexate, anti-TNF-alpha) can be tried.

![Structural Formula of Azathioprine](image)

In cases of local symptoms such as uveitis or skin lesions, **steroids** can be administered locally as well.

Should the patient complain about severe pains (with arthritis, for instance), the additional supportive administration of **non-steroidal antirheumatic drugs (NSAR)** is appropriate.

In cases of pronounced pulmonary fibrosis, a **lung transplant** is the last resort.

### Progression and Prognosis of Sarcoidosis
Remission and Spontaneous Cure Rates with Sarcoidosis

**Acute sarcoidosis** has a **remission rate of > 95%** within 2 years. Stage I chronic sarcoidosis has a spontaneous cure rate of up to 70% within 1 to 3 years. With regard to stage II, the cure rate is only approx. 50%, and with regard to stage III, the rate drops to 20%.

The risk factors for a more progressive and chronic progression are patients over the age of 40 when first diagnosed, hypercalcemia, lupus pernio, uveitis, neurosarcoidosis, cardiac involvement, pulmonary sarcoidosis stage III.

The **mortality rate** for sarcoidosis is at **less than 5%**.

**References**


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