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 differentiates between acute sarcoidosis (this 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 it is typical in many other illnesses.

Epidemiology of Sarcoidosis

Sarcoidosis as Interstitial Lung Disease

With incidents of 10/100,000 per year in Western Europe, sarcoidosis is among the most frequent interstitial lung diseases, whereby one has to assume that there is also 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 that are introduced in your studies, 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 predisposition 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 BTNL2 as well as the HLA-DQB1 variant of the gene HLA are associated with an increased risk for the disease.

The increased occurrence of the disease among hospital nursing staff members, among others, proof 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

Caused by a disturbance of T cell function and increased B cell activity, immunological hyperactivity occurs. 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. Surrounded by lymphocytes (= lymphocyte accumulation), 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 may not be as relevant for the exam, one of your patients 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)
- **Bihilary 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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<tr>
<th>Lungs: very frequently, ~ 95 %</th>
<th>In the beginning, there are no symptoms in many cases! It frequently happens that there is an amazing 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 done!) It is possible that dry cough and effort dyspnea may occur during the progression of the disease. The most feared complications are pulmonary hypertension or even pulmonary heart disease (cor pulmonale) as consequences of pulmonary fibrosis.</th>
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<tbody>
<tr>
<td>Lymphatoid organs: ~ 90 %</td>
<td>There are lymph node enlargements especially in the intrathoracic area (biliary). There are also peripheral lymph nodes enlargements, however, that occur frequently, may they be cervical or axillary in particular. This should definitely be considered during the clinical examination!</td>
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<tr>
<td>Liver: ~ 80 %</td>
<td>Elevated liver enzymes and in some cases hepatomegaly may be found. Clinically, there are usually no symptoms.</td>
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<tr>
<td>Joints: ~ 40 %</td>
<td>Joint pain and swollen joints occur frequently. In rare cases, the corresponding muscles are affected as well.</td>
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<tr>
<td>Skin: ~ 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>
<th>Eyes: Depending on the source, the frequency fluctuates between 25 and 80 %</th>
<th>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.</th>
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<tr>
<th>Heart: ~ 25 %</th>
<th>As the <strong>left ventricle</strong> as well as the <strong>septum</strong> are affected in many cases, <strong>cardiac arrhythmia</strong> with an increased risk of sudden cardiac death may occur during the progression. AV block formation, left ventricular insufficiency, and pericardial effusion have been reported.</th>
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<tr>
<th>Bones</th>
<th>Sarcoidosis may attack the bones as well causing, among others, <strong>cystic changes</strong> in the phalanges of fingers. This is referred to as <strong>Jüngling syndrome</strong>, which is very rare, though. (Nevertheless, or possibly because of that very fact, it has been included in questions posed in medical exams.)</th>
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</table>
### Nervous system

In these cases, **facial paralysis**, diabetes insipidus, hypopituitarism or granulomatous meningitis may occur, for instance. In 10% of cases, the peripheral nervous system is affected. In very rare cases, psychiatric symptoms were observed as well. The combination of facial paralysis, uveitis, and parotitis are referred to as **Heerfordt’s syndrome**.

### Other organs: < 6%

Spleen, kidney, parotid gland or the gastrointestinal tract for instance, are not affected as much.

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### Diagnosis of Sarcoidosis

#### Diagnosing Sarcoidosis in the Lab

After the 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**, approximately half of them 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 activity parameter and to control the progression, either **ACE (angiotensin converting enzyme)** 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 five different stages according to Scadding**:

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<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 BAL or a very rare case of pure extrapulmonary sarcoidosis)</td>
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<tr>
<td><strong>Stage I</strong></td>
<td>Enlarged biliary lymph nodes only (these findings are usually present in acute cases of sarcoidosis as well)</td>
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<tr>
<td><strong>Stage II</strong></td>
<td>Enlarged biliary lymph nodes with pulmonary involvement (increased reticulonodular, pulmonary infiltrates)</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>Pulmonary involvement without enlarged lymph nodes</td>
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</table>
In cases of unclear or not quite specific radiological findings but with typical clinical signs present, it may be necessary to follow up with an **HRCT** (high-resolution CT). 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, respectively. In cases of pulmonary tissue involvement, performing a **bronchoscopy** along with a **transbronchial biopsy** and **bronchoalveolar lavage (BAL)** are appropriate. The latter may reaffirm typical findings: In cases of active sarcoidosis, the **CD4/CD8 quotient** is $>5$ (the higher the quotient, 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 quotient 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 O2 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.

Assessing Chronic Sarcoidosis Activity

First and foremost, in order 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 IL2-receptor, inflammatory parameters, calcium**). The parameters of the pulmonary function test (the **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 bilharic 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** (presents with caseating granulomas, however!)
- **Hodgkin’s disease (morbus hodkin)** (This is the reason why a lymph node biopsy followed by histology is so important.)
- **Pneumoconioses** (Occupational history: branches of the industry that work with beryllium, for instance.)
- **Exogenous allergic alveolitis**
  - In cases of acute sarcoidosis: **arthritis** of other genesis

### Therapy of Sarcoidosis

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

### Indications for Corticosteroid Therapy in Cases of Sarcoidosis

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

![Structural Formula of Azathioprine](image)

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

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 two years. Chronic sarcoidosis stage I also has a spontaneous cure rate of up to 70 % within one to three years. With regard to stage II, the cure rate is only at approximately 50 % and with
regard to stage III, the rate drops all the way 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%.

Review Questions

The answers are below the references.

1. In which of the following syndromes do cystic changes in the phalanges take place within the scope of a chronic form of extrapulmonary sarcoidosis?

   A. Löfgren’s syndrome
   B. Heerfordt’s syndrome
   C. Jüngling syndrome
   D. Raynaud’s syndrome

2. What findings match the clinical picture of sarcoidosis the least?

   A. Increased erythrocyte sedimentation rate (ESR).
   B. A lower CD4/CD8 quotient in the cytological examination after bronchoalveolar lavage.
   C. Hypercalzuria
   D. Lymphopenia

3. Which diagnostic tool is most likely to be used to monitor the progression of chronic sarcoidosis?

   A. Pulmonary function test and determining diffusion capacity.
   B. Thoracic high-resolution CT.
   C. Regular bronchoscopies and transbronchial biopsy.
   D. Assessment of peripheral oxygen saturation.

References


Correct answers: 1C, 2B, 3A

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