Cardiac sarcoidosis

Sarkoidoza serca

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ABSTRACT

Cardiac sarcoidosis (CS) is a rare and difficult-to-diagnose condition that leads to conduction disorders, arrhythmias, and sudden cardiac death. Diagnosing CS is extremely difficult because it can be asymptomatic in its early stages and often mimics other conditions. The diagnostic tools used in the diagnosis of CS are: echocardiography, magnetic resonance imaging, positron emission tomography and biopsy of the affected tissue. Treatment involves the use of drugs that suppress the immune system. Some of the arrhythmias and conduction disturbances associated with CS may be reversible, but more often they require protection with devices such as pacemakers or defibrillators. More research is needed to develop more effective diagnostic strategies to improve the detection and treatment of this condition.

KEYWORDS

cardiac sarcoidosis, sarcoidosis, arrhythmia, heart failure

STRESZCZENIE

Sarkoidoza serca (cardiac sarcoidosis – CS) jest rzadkim i trudnym do zdiagnozowania schorzeniem prowadzącym do zaburzeń przewodzenia, rytmu i naglej śmierci sercowej. Rozpoznanie CS jest niezwykle trudne, ponieważ we wczesnych stadiach może nie dawać objawów i często imituje inne stany. Narzędzi diagnostycznych wykorzystywanych w diagnostyce CS są: ekoekardiografia, rezonans magnetyczny, pozytonowa tomografia emisyjna oraz biopsja zmienionej tkanki. Leczenie polega na zastosowaniu leków hamujących układ odpornościowy. Niektóre zaburzenia rytmu serca i przewodzenia związane z CS mogą mieć charakter odwracalny, jednak częściej wymagają one zabezpieczenia urządzeniami takimi jak rozruszniki serca czy defibrylatory. Konieczne są dalsze badania w celu opracowania skuteczniejszych strategii diagnostycznych dla poprawy wykrywania i leczenia tego stanu.

SŁOWA KLUCZOWE

sarkoidoza serca, sarkoidoza, arytmie, niewydolność serca

Received: 10.05.2023
Revised: 09.06.2023
Accepted: 09.06.2023
Published online: 04.12.2023

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Publisher: Medical University of Silesia, Katowice, Poland
Introduction

Sarcoidosis is a rare multi-system disease in which the inflammatory process leads to the formation of granulomas. It is most often manifested by mild or asymptomatic lung disease [1,2]. It can also involve the heart and blood vessels. This condition can lead to serious complications, including arrhythmias, heart failure and sudden cardiac death [3,4]. Cardiac sarcoidosis (CS) was first described in 1929 in a 52-year-old shoemaker dying of heart failure [5]. The exact cause of CS is not fully understood, but is believed to be related to an abnormal immune response to an unknown trigger, such as infection or exposure to a specific substance that causes granulomatous pericarditis, myocarditis, and endocarditis [6].

The symptoms of CS may include shortness of breath, chest pain, fatigue, leg swelling, and ventricular arrhythmias, high-grade blocks, and sudden death [7]. Diagnosing CS can be difficult because it often mimics other conditions and may not cause any symptoms in the early stages. The diagnostic tools that can be used to confirm the diagnosis include imaging studies such as echocardiography, magnetic resonance imaging (MRI) and positron emission tomography (PET), as well as biopsy of the affected tissue [8,9].

The treatment of CS can be based on the use of medications that suppress the immune system and reduce inflammation, such as corticosteroids, immunosuppressants and biologics. In severe cases, surgery may be required to remove the affected tissue or the implantation of devices such as pacemakers or defibrillators to control the arrhythmia [10,11].

However, more research is needed to better understand the causes and risk factors for CS, and to develop more effective treatment options for the condition.

Epidemiology

Myocardial sarcoidosis is more common in Scandinavian countries and among African Americans, and is estimated to affect 1–30 per 1,000,000 people [12,13,14]. Among patients diagnosed with sarcoidosis, CS concerns less than 10% of patients [15]. The condition is also more common in women than men [16,17,18,19,20,21,22,23,24,25] and usually develops in people between the ages of 20 and 50 [14,26,27].

Myocardial sarcoidosis can occur as a standalone condition or in association with other types of sarcoidosis, such as pulmonary sarcoidosis or cutaneous sarcoidosis. It is also more likely in people with a family history of sarcoidosis. In addition, it has been proven that a low socioeconomic status is associated with a more severe course [28,29]. Recent studies suggest that as a result of the development of imaging technology and increased interest in this disease, the incidence of CS and the number of hospitalizations are increasing [15,30,31]. Interestingly, however, there is a decrease in in-hospital mortality [32].

Pathogenesis and etiology

The exact cause of CS, despite many studies, is not fully understood, but it is believed to be associated with an abnormal immune response in individuals genetically exposed to an unknown trigger, such as infection or exposure to a specific substance [33,34,35,36,37,38,39,40,41,42,43,44,45]. As a result, noncaseating granulomas are formed, characterized by the presence of, among others, macrophages, giant cells, epithelioid histiocytes and lymphocytes [46]. It has been shown that myocardial involvement may be associated with DQB1*0601 and DRB1*0803 alleles [47,48,49,50]. Other non-HLA genes have also been associated with the disease: CCR2, CCR5, IL1A, IL23R, TNF-α, NOD2 and FCGR [51]. In the immune response, the key role is attributed to Th1 and Th17 lymphocytes, regulatory T cells and an increased number of cytokines such as IL-2, IL-12, IFN-γ and TNF-α [46,52,53,54,55]. Several pathogens have also been suggested that may play an important role in the pathogenesis of CS, including Propionibacterium acnes, which was isolated from sarcoid lesions, and Chlamydia pneumoniae. In addition, some sources suggest that sarcoidosis is more common in people exposed to insecticides and mold [45,56,57,58,59,60,61]. An increased frequency in identical twins was also observed, which confirms the genetic background [62]. Interestingly, according to some sources, smoking may protect against sarcoidosis by disrupting the interaction between macrophages and lymphocytes [63,64,65].

Location within the muscle

Sarcoid granulomas most commonly involve the interventricular septum, the basal segments of the left ventricle, and the lateral wall (Figure 1). Full-thickness myocardial involvement is usually sporadic and results in dilated cardiomyopathy, leading to left ventricular dysfunction. Right ventricular involvement may result from granulomatous infiltration (very rarely), but is usually a consequence of left ventricular failure and pulmonary hypertension [66,67].
Fig. 1. Myocardial involvement in cardiac sarcoidosis (based on: Bravo P.E., Singh A., Di Carli M.F., Blankstein R. Advanced cardiovascular imaging for the evaluation of cardiac sarcoidosis. J. Nucl. Cardiol. 2019; 26(1): 188–199); LV – left ventricular; RV – right ventricular.

**Symptoms**

The symptoms of myocardial sarcoidosis can vary greatly. In some cases, the condition may not cause any symptoms. They also depend on the age, sex, ethnicity, primary clinical condition of the patient and the number of organs involved [68,69,70,71,72,73,74,75]. According to research conducted in the years 2003–2011, it was proved that Japanese patients have a much higher risk of eye and heart diseases in the course of sarcoidosis. It has also been suggested that ocular and skin lesions are much more common in women [76,77,78,79,80]. Nevertheless, the lungs are by far the most frequently affected organ in the course of sarcoidosis [81,82,83].

In 2018, a study was conducted on the basis of which 5 sarcoidosis phenotypes were distinguished. Myocardial involvement was of the ocular-cardiac-cutaneous-central nervous system phenotype [84]. Additionally, it has been proven that patients with CS may also have asymptomatic chest involvement or minimal extra cardiac disease [85]. The possible symptoms of myocardial sarcoidosis vary depending on the location, extent and degree of involvement of the organ (Figure 2). Generally, the symptoms may include:

- shortness of breath, especially during physical activity or when lying down
- chest pain, which may feel like pressure or squeezing
- tiredness
- swelling of the legs, ankles or feet
- palpitations or abnormal heart rhythms
- dizziness or fainting.

Nonetheless, the most common are arrhythmias caused by ventricular arrhythmias and atrioventricular blocks, and congestive heart failure caused by myocardiopathy [86]. Untreated myocardial sarcoidosis can lead to serious complications, including heart failure and sudden cardiac death [87,88].

**Diagnostic tests**

CS can be extremely difficult to recognize because it often mimics other conditions and may not cause any symptoms in its early stages. There is no single test that can confirm a diagnosis, so several diagnostic tools must be used to assess a person’s symptoms and rule out other potential causes (mainly ischemic heart disease). The classic triad of diagnosis includes: 1) concordant clinical/radiological findings, 2) the presence of noncaseating granulomas on histopathology, and 3) the exclusion of other possible diseases [1,89,90].

| Diagnostic tests used to diagnose myocardial sarcoidosis (based on: Kouranos V., Sharma R. Cardiac sarcoidosis: state-of-the-art review. Heart 2021; 107(19): 1591–1599) |
|---|---|---|
| **screening tests** | **imaging tests** | **others** |
| history | chest X-ray | biopsy |
| physical examination | ECHO | |
| ECG/2-hour Holter | MRI | |
| blood tests for inflammation and myocardial damage markers | FDG-PET | |

The diagnostic tests that can be used to diagnose myocardial sarcoidosis are presented below (Table I).
Screening test

The screening for myocardial sarcoidosis should begin with a thorough history, a physical examination, electrocardiogram (ECG), and blood tests for markers of inflammation and markers of myocardial damage [91,92]. A chest X-ray and 24-hour Holter monitoring may also prove necessary [93]. Patients with any disturbing symptoms, ECG abnormalities or cardiomegaly on a chest X-ray should be referred for further, more specialized examinations [94]. Patients with isolated CS without previously diagnosed sarcoidosis are a minority and require special suspicion and exclusion of other possible causes.

Electrocardiogram and 24-hour Holter monitoring

An ECG can record any abnormalities associated with myocardial sarcoidosis, which mainly include:

− various degrees of conduction blocks, e.g. a bundle branch block and bundle blocks
− fragmentation of the QRS complex
− pathological Q waves
− ST segment changes
− epsilon waves [95].

The ECG is also an indispensable diagnostic tool in the long-term monitoring of extracardiac sarcoidosis because it is not uncommon for pathological ECG recordings to appear many years after the diagnosis of sarcoidosis [96].

Many studies also indicate that the Holter test shows a significant predictor of myocardial involvement with a sensitivity of 89% and a specificity of 21% [97]. It also has an important role in monitoring the response to immunosuppressive therapy [98].

Echocardiography

An echocardiogram can help identify any abnormalities in the heart muscle. The results can be divided into primary and secondary diagnostic criteria [8,15,87,99,100]. One of the most characteristic pathologies is thinning of the interventricular base. In addition, there may also be:

− isolated abnormalities concerning the mobility of the walls of the heart muscle
− aneurysms
− left/right ventricular systolic and diastolic dysfunction [101,102,103,104].

The function determining the rate of myocardial strain is also very useful [105,106]. However, the results are not pathognomonic and cannot be used as part of the screening test owing to the low sensitivity of 25% [107].

Biomarkers

Significantly specific and sensitive markers for myocardial sarcoidosis have not been demonstrated. In addition, many of them may also be affected by pharmacotherapy [108,109,110]. Nevertheless, several parameters have been identified that may support the diagnosis of CS:

− increased level of angiotensin-converting enzyme (increased level in 60% of patients, low sensitivity and specificity)
− elevated troponin levels
− increased level of brain natriuretic peptide (BNP)
− hypercalciuria
− increased IL-2 receptor
− increased level of neopterin
− increased activity of chitotriosidase
− bronchoalveolar lavage (BAL) biomarkers (elevated CD4+/CD8+ ratio and KL-6, decreased Natural Killer and CD103+ CD4+cells) [108,111].

Magnetic resonance imaging

MRI of the myocardium can identify areas of inflammation or damage to the myocardium and is considered the test of choice for the diagnosis of CS. Characteristic changes that can be visualized in MRI are:

− late gadolinium enhancements (LGEs) [112]
− wall thinning
− aneurysms
− disturbances in the functional parameters of the ventricles.

Gadolinium reinforcement corresponds to scarring tissue, but also to inflamed tissue. The enhancement is often multifocal but not pathognomonic [113]. It most often involves the basal segments of the left ventricle, the septum and the lateral wall. Occasionally, full-thickness involvement of the myocardium and the free wall of the right ventricle is also observed. Simultaneous involvement of the basal anteroseptal segment, the lower septum and the right ventricle is highly specific for CS. In contrast to sub-endocardial scarring, which is characteristic of myocardial infarction [114,115], LGEs occur in both the chronic and acute phases of CS.

Based on studies conducted in 2008–2015, it was confirmed that LGE is also a predictor of CS complications such as ventricular tachycardia (VT), atrioventricular blocks, heart failure and sudden cardiac death [116,117,118]. In addition, the presence of LGE in the presence of normal or near-normal left ventricular ejection fraction (LVEF) has been shown to
increase the risk of adverse events [111,119,120,121,122,123,124]. Involvement of the right ventricle instead of the left one occurred to be an unfavorable predictive factor [125].

In the case of active inflammation, LGE seems to be a less sensitive parameter; however, the latest MR techniques using T1 and T2 mapping significantly increase the sensitivity towards active inflammation in CS and may be helpful in monitoring the response to treatment [126,127].

Due to the ability to identify small areas of myocardial damage, MR is increasingly used to assess the clinically silent forms of CS.

The main advantage of MR in CS is the high negative predictive value, which exceeds 90% [128].

**Positron emission tomography scan**

If the MR result is negative or access to it is limited, it is reasonable to perform a PET scan, which will allow differentiation of inflamed tissue from healthy tissue. Glucose analogue fluorodeoxyglucose (FDG) is used for this [129]. Nonetheless, the use of PET in the assessment of myocardial involvement in sarcoidosis should be preceded by extensive preparation. In order to inhibit the physiological uptake of glucose by normal myocardial cells, it is necessary to refrain from all meals and drinks for about 4 hours before the examination (the only exception being water). Then there is a decrease in the level of insulin in the body and, consequently, glucose uptake in the skeletal muscles, heart muscle and adipose tissue. About 24 hours before the examination, one should also refrain from any physical activity [130].

Although there are no specific imaging findings for myocardial sarcoidosis that would enable a reliable diagnosis, focal or diffuse FDG uptake is considered to support active CS [131,132]. The probability of CS occurrence may be determined on the basis of FDG uptake and perfusion abnormalities. Multifocal cardiac and extracardiac FDG uptake or multifocal cardiac FDG uptake and multifocal perfusion abnormalities allow CS detection in 90%. In addition, the presence of FDG uptake and perfusion defects in the right ventricle were associated with a worse prognosis, which was also observed in MRI [133].

Studies conducted in 2005 showed that the sensitivity of PET in diagnosing CS is 89%, while the specificity is 78% [131].

In recent years, PET has become the gold standard for detecting active myocarditis and monitoring response to immunosuppressive therapy in CS.

### Table II. Description of PET examination (based on: Bravo P.E., Singh A., Di Carli M.F., Blankstein R. Advanced cardiovascular imaging for the evaluation of cardiac sarcoidosis. J. Nucl. Cardiol. 2019; 26(1): 188–199)

<table>
<thead>
<tr>
<th>CS probability</th>
<th>Description of PET examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td>- FDG uptake (-)</td>
</tr>
<tr>
<td></td>
<td>- perfusion abnormalities (-)</td>
</tr>
<tr>
<td>10–50%</td>
<td>- FDG uptake (-)</td>
</tr>
<tr>
<td></td>
<td>- minor perfusion abnormalities (+) or - non-specific FDG uptake (+)</td>
</tr>
<tr>
<td></td>
<td>- perfusion abnormalities (-)</td>
</tr>
<tr>
<td>50–90%</td>
<td>- focal FDG uptake (+)</td>
</tr>
<tr>
<td></td>
<td>- resting perfusion abnormalities (+) or - multifocal FDG uptake (+)</td>
</tr>
<tr>
<td></td>
<td>- perfusion abnormalities (-)</td>
</tr>
<tr>
<td>&gt; 90%</td>
<td>- multifocal cardiac FDG uptake (+) or - multifocal extracardiac FDG uptake (+)</td>
</tr>
<tr>
<td></td>
<td>- multifocal FDG uptake (+)</td>
</tr>
<tr>
<td></td>
<td>- multifocal perfusion abnormalities (+)</td>
</tr>
</tbody>
</table>

CS – cardiac sarcoidosis; FDG – fluorodeoxyglucose; PET – positron emission tomography.

**Biopsy**

The histological confirmation of CS is difficult as a consequence of its low sensitivity (36%) [96,134]. This is due to the focal nature of the disease. However, based on a study conducted in 2019, it was shown that finding an increased number of lymphatic vessels in a biopsy, with the simultaneous absence of granulomas, can increase the sensitivity of the biopsy to 75% [135]. In addition, it has been proven that high specificity towards the diagnosis of CS is demonstrated by a high number of dendritic cells, a reduced percentage of M2 cells among all macrophages, and the absence of granulomas [136].

**Diagnosis**

The diagnostic criteria for CS are not universally agreed upon and may vary depending on the source. A multidisciplinary approach involving many specialists (such as cardiologists, pulmonologists and radiologists) is needed to make an accurate diagnosis. There are three recommended sets of diagnostic criteria for the diagnosis of CS.
One of the first diagnostic criteria according to the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) was published in 2014 and then modified by the American Thoracic Society [103,137] (Table III). The second is the Heart Rhythm Society (HRS) consensus, also from 2014, which suggests two diagnostic paths [8] (Table IV).

A third set of diagnostic criteria was proposed in 1993 and modified in 2017 by the Japanese HRS. It includes primary/major and secondary/minor criteria (Table V). To be diagnosed with CS, at least two major criteria or one major and two minor criteria must be met.

### Table III. Diagnostic criteria according to World Association of Sarcoidosis and Other Granulomatous disease (WASOG) (based on [100,137])

<table>
<thead>
<tr>
<th>Diagnostic criteria according to WASOG 2014</th>
<th>Modified diagnostic criteria by the American Thoracic Society 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treatable cardiomyopathy or atrioventricular block</td>
<td>1. Sensitive cardiomyopathy or atrioventricular block</td>
</tr>
<tr>
<td>2. Decreased left ventricular ejection fraction in the absence of other clinical risk factors</td>
<td>2. Decreased left ventricular ejection fraction in the absence of other clinical risk factors</td>
</tr>
<tr>
<td>3. Spontaneous or inducible sustained ventricular tachycardia without other risk factors</td>
<td>3. Spontaneous or inducible sustained ventricular tachycardia without other risk factors</td>
</tr>
<tr>
<td>4. Second or third degree Mobitz-type atrioventricular block</td>
<td>4. New onset third-degree atrioventricular block in young or middle-aged adults</td>
</tr>
<tr>
<td>5. Non-uniform uptake on dedicated cardiac PET</td>
<td>5. Increased inflammatory activity in the heart (MRI, PET and gallium)</td>
</tr>
<tr>
<td>6. Delayed amplification in CMR</td>
<td></td>
</tr>
<tr>
<td>7. Positive gallium uptake</td>
<td></td>
</tr>
<tr>
<td>8. Defect in perfusion scintigraphy or SPECT</td>
<td></td>
</tr>
<tr>
<td>9. T2 extension on CMR</td>
<td></td>
</tr>
</tbody>
</table>

PET – positron emission tomography; CMR – cardiac magnetic resonance; SPECT – single photon emission computed tomography; MRI – magnetic resonance imaging.

### Table IV. Heart Rhythm Society diagnostic criteria (based on [8])

<table>
<thead>
<tr>
<th>Diagnostic paths for diagnosis of myocardial sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Histological diagnosis from myocardial tissue</td>
</tr>
<tr>
<td>The presence of a noncaseating granuloma on myocardial tissue histology without identifying an alternative cause</td>
</tr>
<tr>
<td>2. Clinical diagnosis based on invasive and non-invasive tests</td>
</tr>
<tr>
<td>Possible occurrence of CS if:</td>
</tr>
<tr>
<td>a) Histological diagnosis was extracardiac sarcoidosis</td>
</tr>
<tr>
<td>And</td>
</tr>
<tr>
<td>b) 1 or more of the following are present:</td>
</tr>
<tr>
<td>− Cardiomyopathy responsive to steroid immunosuppression or heart block</td>
</tr>
<tr>
<td>− Unexplained LVEF &lt; 40%</td>
</tr>
<tr>
<td>− Unexplained sustained (spontaneous or induced) ventricular tachycardia</td>
</tr>
<tr>
<td>− Second degree or third degree Mobitz type II atrioventricular block</td>
</tr>
<tr>
<td>− Non-uniform uptake in dedicated cardiac FDG-PET</td>
</tr>
<tr>
<td>− LGE CMR</td>
</tr>
<tr>
<td>− Positive gallium uptake</td>
</tr>
<tr>
<td>And</td>
</tr>
<tr>
<td>Other causes of cardiac symptoms were excluded</td>
</tr>
</tbody>
</table>

CS – cardiac sarcoidosis; LVEF – left ventricular ejection fraction; FDG-PET – 18F-fluorodeoxyglucose positron emission tomography; LGE – late gadolinium enhancement; CMR – cardiac magnetic resonance.


<table>
<thead>
<tr>
<th>Main criteria</th>
<th>Secondary criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Noncaseating granuloma confirmed by biopsy in myocardium or extracardiac tissue</td>
<td>1. Electrocardiogram abnormalities (such as atrioventricular block or ventricular arrhythmias)</td>
</tr>
<tr>
<td>2. Positive positron emission tomography scan of gallium-67 or fluorodeoxyglucose (FDG-PET)</td>
<td>2. Decreased left ventricular ejection fraction or wall motion abnormalities on echocardiography</td>
</tr>
<tr>
<td>3. Magnetic resonance imaging (MRI) or computed tomography (CT) showing delayed enhancement or nodular or band-like changes in the myocardium</td>
<td>3. Elevated level of angiotensin converting enzyme in serum</td>
</tr>
<tr>
<td></td>
<td>4. Incorrect Holter monitoring</td>
</tr>
<tr>
<td></td>
<td>5. Abnormal cardiac conduction test</td>
</tr>
<tr>
<td></td>
<td>6. Histological evidence of granulomatous inflammation in other organs</td>
</tr>
<tr>
<td></td>
<td>7. Response to steroid therapy</td>
</tr>
</tbody>
</table>

To be diagnosed with cardiac sarcoidosis, at least two major criteria or one major and two minor criteria must be met.
Differential diagnosis

CS is a condition that causes significant diagnostic difficulties because its symptoms can mimic those of other heart diseases. One of the diseases that should be differentiated from CS is myocarditis. Both conditions can cause symptoms of heart failure, chest pain, arrhythmias, the presence of LGE on MRI, and impaired FDG-PET uptake. Nevertheless, myocarditis is often caused by a viral infection, which is likely to cause prodromal symptoms. The course of giant cell myocarditis is usually more fulminant [138]. Endomyocardial biopsy may be necessary to distinguish myocarditis from sarcoidosis. Another condition that can be confused with CS is arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is a genetic disease of the heart, leading to arrhythmias and heart failure. However, in the case of ARVC, the right ventricle is predominantly affected and LGE in the interventricular septum is virtually absent [139,140,141]. LGE in MRI may also be present in ischemic heart disease, Fabry disease, amyloidosis, hypertrophic cardiomyopathy and hemochromatosis. In the case of ischemic heart disease, the distribution of the LGE area, which correlates with the coronary artery system, may be helpful. Dark skin pigmentation and diabetes will also be present in the course of inherited haemochromatosis [142]. Granulomas can also be seen in tuberculosis, systemic vasculitis and mycosis [143]. Nonetheless, taking a detailed history will help to exclude these conditions owing to the different clinical course.

Treatment

The treatment for myocardial sarcoidosis involves a combination of medications and lifestyle changes. The goals of treatment are to reduce inflammation, prevent complications, and improve the patient’s quality of life. Lifestyle changes that may be recommended to treat myocardial sarcoidosis include regular exercise, a healthy diet, and reducing stress.

The European Society of Cardiology (ESC) has developed guidelines for the treatment of CS (Figure 3). According to these guidelines, in the case of a mild form of CS with mild symptoms, treatment may include only observation and control of the patient’s condition, adherence to the principles of a healthy lifestyle, as well as anti-inflammatory medications and medications that reduce the risk of cardiovascular complications, such as angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers. For moderate to severe cardiac sarcoidosis accompanied by arrhythmias, heart failure or atrioventricular block, treatment with corticosteroids is recommended. In the absence of improvement or side effects associated with corticosteroids, immunosuppressants such as azathioprine or methotrexate may be used. For serious arrhythmias such as atrial fibrillation, ablation (removal) of the heart cells responsible for the arrhythmia is recommended. In heart failure, an implantable cardioverter defibrillator (ICD) may be required. Medications that can be used to treat myocardial sarcoidosis include the ones described below.

Corticosteroids

The use of corticosteroids in the treatment of CS has been the subject of much discussion and research. While some studies have shown that corticosteroids may be effective in reducing inflammation and improving cardiac function in patients with CS, other studies have shown that corticosteroids may actually worsen the condition [117,144,145,146]. One of the potential benefits of corticosteroids in the treatment of CS is their ability to suppress the immune system, which can help reduce inflammation and prevent further damage to the heart muscle. Retrospective studies have shown that the use of corticosteroids in CS results in the interruption of atrioventricular (AV) block, a reduction in VT events, improvement in the ejection fraction, and improvement in survival [147,148,149,150,151]. However, the long-term use of corticosteroids can have a number of side effects, including weight gain, high blood pressure, diabetes, and osteoporosis [117,144,145,146]. Because of these potential risks, many doctors only prescribe corticosteroids for short periods of time, usually a few weeks to a few months, to control the symptoms and reduce inflammation. After this initial treatment period, the patient may be switched to another medication or therapy, depending on their individual needs. The initial dose of corticosteroid used in patients with CS in monotherapy is 40 mg/day. In the case of people using an additional immunosuppressive medication – ≤ 20 mg/d. It has been shown that higher doses are not more effective and may be more toxic. Depending on the response to treatment, these doses should be reduced to 5/15 mg/d after 1–3 months and maintained for an additional 9–12 months. The follow-up period should be 3 years [152]. In silent CS, there is no clear evidence of benefit from corticosteroids. Therefore, the decision to include them, additionally considering the fact that the use of corticosteroids is associated with many side effects, can be extremely difficult [153,154,155,156]. Ultimately, the use of corticosteroids to treat CS should be carefully considered on a case-by-case basis, taking into account the patient’s general health, medical history, and individual needs.
Immunosuppressants

Although the use of methotrexate in the treatment of CS is still being studied, it is one of the most commonly used second-line medications in CS. Nevertheless, there are potential side effects to consider. They include nausea, vomiting, hair loss and weakened immune function. The dose of methotrexate used is 10–25 mg and is used once a week with an addition of 5 mg of folic acid [122].

Other immunosuppressants used in CS also include azathioprine, mycophenolate mofetil, cyclophosphamide, and infliximab [157,158].

In order to prevent a recurrence of the disease, immunosuppression is used for a long time. After the end of treatment, close observation of the patient and PET examination are recommended [159,160].

Angiotensin-converting enzyme inhibitors

In the mild form of CS, ACEIs may also be included in the treatment due to their ability to improve myocardial function, reduce the risk of arrhythmias and cardiovascular complications, and their anti-inflammatory properties. In moderate to severe CS accompanied by arrhythmias, heart failure or atrioventricular block, ACEIs may be used as adjunctive therapy.

Beta blockers

In the mild form of sarcoidosis, in addition to ACEI, beta-blockers are also used in the treatment. Beta-blockers can help treat CS in several ways. First, they improve heart function and reduce the risk of arrhythmias. Secondly, they have anti-inflammatory effects and reduce inflammation in the heart. Third, they can reduce blood pressure and workload on the heart, which can improve heart function and reduce the risk of heart complications. In moderate to severe CS accompanied by arrhythmias, heart failure or atrioventricular block, beta blockers may be used as supportive medications.

The treatment of arrhythmia in CS depends on the severity of the disease, the symptoms experienced by the patient, and the degree of involvement of the heart. The classic choice of antiarrhythmic medications for VT includes amiodarone and sotalol. Nonetheless, amiodarone can cause severe side effects such as pneumonia and fibrosis. Therefore, the long-term use of amiodarone is contraindicated, especially in young patients.

Atrial arrhythmias may also require anticoagulation [8]. In severe, medication-resistant cases, ablation or an ICD may be required [161,162]. The goal of ablation is to eliminate the abnormal electrical signals that trigger the arrhythmia. This procedure is indicated when medication-resistant VT develops. In case of difficulties in making the decision to qualify a patient for ablation, the results of MR and PET examinations may be helpful [163]. Unfortunately, some studies suggest that despite a properly performed procedure, the recurrence rate of VT after ablation is still high. There are also more optimistic results, which have shown that the overall burden of arrhythmia can be reduced by up to 88% in patients after a properly performed course of ablation [164,165,166].

ICDs are mainly used to prevent sudden cardiac death and are usually recommended for patients with severe arrhythmias or those who have already had a cardiac arrest. According to the HRS, atrioventricular block is an indication for the implantation of an ICD or a defibrillator for cardiac resynchronization therapy (CRT-D) [8].

Heart transplantation is a rare therapeutic option, mainly recommended in young patients with refractory VT or in the presence of severe heart failure [142]. In conclusion, the treatment of arrhythmia in CS is a complex process that requires a multidisciplinary approach. The goal of treatment is to control arrhythmias, prevent further events and improve the patient’s quality of life.
Prognosis

The prognosis of CS may be affected by the degree of cardiac involvement, the presence of other organ involvement, and the severity of cardiac dysfunction. Clinically manifested heart failure and reduced left ventricular ejection fraction carry a worse prognosis, with a 10-year survival rate of 19–53% [155]. Patients with abnormalities in MR (LGE) and PET (abnormal FDG uptake) are also associated with an increased risk of death [151]. It is not fully clear whether silent CS has a better prognosis [155]. The early detection and treatment of CS is critical. The use of immunosuppressive medications has been shown to be effective in reducing inflammation and preventing disease progression.

Clinical case

We would like to present an unusual clinical case of a 39-year-old patient with a history of pulmonary sarcoidosis admitted to the cardiology department due to chest pain, arthralgia, palpitations and an episode of pre-syncope. The level of troponin was elevated, and the ECG showed dynamic changes in the T wave in leads V3-V6. Further examinations revealed abnormalities in left ventricular contractility and the suspicion of non-ST-segment elevation myocardial infarction (NSTEMI) was raised. However, coronary angiography showed no abnormalities. Neither hypercalcemia nor hypercalcuiuria were found during hospitalization. Owing to the suspicion of myocarditis or active CS, additional tests were ordered. Nevertheless, despite extensive diagnostic tests, including PET (Figure 4 A–C), the presence of active sarcoidosis in the heart could not be confirmed. This created a dilemma as to whether steroids should be used for treatment. Finally, a month after hospitalization, the laboratory tests showed hypercalcemia and hypercalcuiuria in the patient, which led to the introduction of steroids. After some time, temporary regression of the symptoms and improvement of left ventricular systolic function was observed. This case highlights the diagnostic challenges and uncertainties associated with the treatment of sarcoidosis, especially in cases where active sarcoidosis cannot be confirmed despite extensive testing.
Corticosteroids are the primary treatment for CS, and identifying patients at risk for arrhythmias is critical as further electrophysiological testing and additional treatment may be required. CS is a complex condition that requires constant monitoring. More research is needed to develop new diagnostic strategies to improve the detection and treatment of this condition. One of the key issues to be addressed in the future is the diagnosis of the probable cases of CS, especially in isolated forms, the monitoring of patients with already diagnosed CS, and the management of clinically silent cases.

**References**

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