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Cardiac manifestations of sarcoidosis

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ABSTRACT

Introduction and purpose: Sarcoidosis is a chronic, multi-system inflammatory disorder of unknown etiology. Due to the varied clinical picture of patients, the diagnosis of the disease is complicated, especially when the heart is affected. The aim of this article is to review the available diagnostic tools used for the diagnosis, evaluation and monitoring of patients with suspected cardiac sarcoidosis.

Description of the state of knowledge: Sarcoidosis may affect any organ, but in particular lungs, skin, lymph nodes, eyes, liver and spleen. The most common manifestations are persistent cough, skin changes, visual disturbances, peripheral lymphadenopathy, fatigue and incidental abnormal chest radiograph. Cardiac sarcoidosis, occurring in about 5% of patients, is clinically significant with a wide range of symptoms including conduction abnormalities, ventricular arrhythmias, heart failure and sudden death. The diagnosis of cardiac sarcoidosis is challenging and often requires a combined approach using clinical data and advanced imaging. Invasive and non-invasive diagnostic tests are helpful in assessing the severity of heart involvement, with non-invasive tests becoming increasingly important, due to low sensitivity (30%) and high complication rate of endomyocardial biopsy for the diagnosis of cardiac sarcoidosis.

Summary: Sarcoidosis significantly increases the mortality of patients and furthermore causes impaired quality of life and disability. Attempts to accurately assess the development of disease provide a more comprehensive and personalized care for patients. Especially cardiac sarcoidosis, as a potentially life-threatening localization, requires early diagnosis and appropriate treatment.

Keywords: sarcoidosis; cardiac sarcoidosis; cardiac magnetic resonance; cardiac positron emission tomography; heart failure.

Introduction

Sarcoidosis is a chronic, multisystem inflammatory disease characterized histologically by formation of non-caseating granulomas. The cause of the disease remains unknown. Many studies suggest that genetic susceptibility and environmental factors contribute to development of the disease. Immunologically, sarcoidosis is an exaggerated granulomatous reaction after exposure to unidentified antigens. The incidence of sarcoidosis is 4.7-64 in 100 000. Sarcoidosis most commonly affects women, especially Scandinavian and African Americans, aged 25 to 60 years. Differences in prevalence, incidence and clinical expression depend on age, sex, genetic predisposition, ethnicity and geographic location. Research suggests that sarcoidosis appears to be becoming more prevalent, which is probably associated with better diagnostic methods. This heterogeneous disease may affect any organ, but most commonly: lungs (90%), skin (20-35%), lymph nodes (15%), eyes (12%), liver (12%), spleen (7%). Cardiac involvement is relatively rare in patients with sarcoidosis and is associated with significant morbidity and mortality. [1,2,3,4,5,6,7,8].

Symptoms and course of the disease

The spectrum of symptoms in patients can be very diverse and depends on the organs affected and the dynamics of the disease. Sarcoidosis may have an acute, subacute or chronic course. Patients with subacute and chronic disease have more heterogeneous course of the disease and may present nonspecific general symptoms including cough, shortness of breath, arthralgia, fatigue (50-70%), chest pain, muscle pain, night sweats, and weight loss. In patients with acute disease, the onset of symptoms occurs suddenly and is often a reason to seek medical attention. A special form of the disease is Lofgren's syndrome, which consists of an acute-onset symptoms including fever, erythema nodosum, arthritis and bilateral hilar lymphadenopathy [1,4,5,6].

However, the greatest impact on the spectrum of symptoms in a given patient is exerted by the inclusion of individual organs in the disease process.

Dyspnea, persistent dry cough and chest discomfort are usual symptoms associated with the most common form of the disease - pulmonary sarcoidosis. Wheezing, haemoptysis and crackles are infrequent. In the presence of such symptoms, a chest X-ray should be performed routinely. Abnormalities in chest radiographs in patients with sarcoidosis most commonly include diffuse pulmonary infiltration, lymphadenopathy and pulmonary fibrosis. Lung function tests may reveal obstructive, restrictive or mixed changes. Further diagnosis of lung lesions may show impaired diffusion capacity of carbon monoxide (TLCO) and reduced forced expiratory volume in the 1st second (FEV1). Sometimes patients have only asymptomatic chest involvement. The incidence of pulmonary sarcoidosis varies with race, sex, and age. Patients have an increased risk of progressive fibrosis (pulmonary and extrapulmonary), pulmonary arterial hypertension (PAH) and permanent loss of lung function [1,2,4,5].

Cutaneous sarcoidosis occurs in about 20-35% of patients and is usually an early manifestation of the disease. Sarcoidosis lesions are usually multiple, red to brownish and commonly remain asymptomatic, although pruritus occur in 10-15% of patients. Wide range of dermatological lesions include maculopapular eruptions, papules, plaques, nodules, alopecia, ulcerative lesions, hypopigmentation, erythema nodosum, lupus pernio, granuloma annulare, scar infiltration and among others. Histologic evaluation of sarcoidal changes reveals the presence of noncaseating granulomas at different skin depths. Specific skin lesions are correlated with presence of noncaseating granulomas on histologic examination, while nonspecific lesions represent only a reactive process of the disease. An infrequent manifestation of sarcoidosis is mucosal involvement, which affects the oral, nasal and anogenital mucosae. Also nail changes are rare and are usually a marker of chronic disease, while the triad of erythema nodosum, arthritis and hilar lymphadenopathy (Lofgren’s syndrome) characterize the acute onset of the disease. The diagnosis of cutaneous sarcoidosis includes clinical evaluation, diascopy and histological examination of skin lesions. [1,4,5,6]

Peripheral lymphadenopathy includes preferentially nodes of the cervical or supraclavicular group, but also inguinal, axillary, epitrochlear, or submandibular lymph nodes may be affected. Usually, the nodes are painless and mobile [1,2]. Symptoms of eye sarcoidosis include anterior uveitis with an acute pain and blurred vision, photophobia. The onset of symptoms may be nonspecific and may precede diagnosis by many years [1,2]. Involvement of the liver and spleen often remains asymptomatic, although hepato- or/and splenomegaly may occur in some patients [2].

Less commonly, sarcoidosis includes the nervous system, kidney, parotid glands, nose, larynx, bones, skeletal muscles, gastrointestinal tract and genitourinary system. Symptoms of these organs are non-specific, so it is often difficult to diagnose sarcoidosis on their basis [2].
In order to diagnose a patient with suspected sarcoidosis, the following criteria should be taken into account: clinical and radiological manifestation of the disease, presence of noncaseating granulomas in histopathological examination and the exclusion of other diseases as the cause of abnormalities.

Cardiac sarcoidosis

Cardiac sarcoidosis is diagnosed clinically in about 5% of patients with sarcoidosis, but it may be underestimated. Autopsy studies reported that it may be present in up to 20-30% of autopsy specimens. About 20-25% patients with systemic sarcoidosis have asymptomatic cardiac sarcoidosis (clinically silent disease) - in these patients, non-cardiac symptoms may be predominant (such as chest pain, dyspnea, and fatigue). However, cardiac sarcoidosis may also be the first clinical manifestation of a disease that already affects other organs. Cardiac disturbances may be clinically more severe than extracardiac symptoms and approximately 30% of patients have isolated cardiac sarcoidosis. Sometimes, despite its clinical manifestation, cardiac sarcoidosis as the underlying disease remains undiagnosed [3,5,6].
The pathophysiological processes underlying the disease in patients with cardiac sarcoidosis include the formation of non-caseating granulomas. Most frequently sarcoid granulomas affect left ventricular free wall, posterior interventricular septum, papillary muscles, right ventricle and the atria, but it may involve any site of the heart. In the initial stages, edema and granulomatous inflammation develops, and in subsequent stages, fibrosis progresses leading to post-inflammatory scarring [3,5,6,8].
Clinical features of cardiac sarcoidosis depend on the location, extent, and activity of the disease. Cardiac abnormalities are caused by myocardial inflammation and fibrosis. The three most common groups of manifestations of cardiac sarcoidosis are: conduction abnormalities, ventricular arrhythmias and progressive heart failure. Heart involvement may occur as: cardiomyopathy (arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy), congestive cardiac failure, unexplained LVEF <40%, unexplained sustained (spontaneous or induced) ventricular tachycardia in apparently healthy subjects, atrio-ventricular (A-V) block of various degrees (Mobitz type II second- or third-degree heart block), pericarditis, aneurysm. Clinically, heart involvement may appear as palpitations, syncope or even sudden cardiac death. Symptoms associated with decreased cardiac out-put also include oliguria, neurological signs, malaise or confusion. Some patients remain asymptomatic despite heart involvement [3,5,6,8].

The diagnosis of cardiac sarcoidosis is challenging and often requires a combined approach. Diagnostic tools that help diagnose heart involvement include: clinical symptoms of the patient, chest imaging (chest radiography, high-resolution CT), electrocardiogram (ECG), echocardiography (ECHO), biomarkers (troponin, angiotensin-converting enzyme levels, soluble interleukin-2 receptor levels, etc.), CMR imagining (with LGE - late gadolinium enhancement), fluorodeoxyglucose PET imaging (^{18}F-FDG PET) and endomyocardial biopsy (EMB). Each of these tests may show abnormalities, which after excluding other potential causes of cardiac disorders and in combination with the patient's clinical symptoms supported by histological evidence of non-necrotizing granulomas can contribute to an accurate diagnosis. [2,3,5,6,8]
The classic test for the diagnosis of cardiac sarcoidosis is an endomyocardial biopsy (EMB). The presence of non-necrotic granulomas in histopathology confirms the diagnosis.

Nevertheless, the biopsy is a low-sensitivity test (30%) and its negative result does not exclude the disease when the clinical picture of patient suggests sarcoidosis. In a patient with negative endomyocardial biopsy but with cardiac symptoms and histologic diagnosis of extracardiac sarcoidosis, while reasonable alternative cardiac causes other than sarcoidosis have been excluded, a diagnosis of cardiac sarcoidosis can be made [3,6,8].

Endomyocardial biopsy, although helpful in making an accurate diagnosis, is the most invasive test that may lead to undesirable consequences such as damage to the tricuspid valve, the right ventricular myocardium, or veins through which access is obtained. Therefore, non-invasive cardiovascular imaging plays an increasingly important role in the diagnosis and management of cardiac sarcoidosis and is indicated in all patients with suspected cardiac sarcoidosis [3,6,8].

Electrocardiogram (ECG) testing should be routinely performed in any patient with suspected sarcoidosis for the initial assessment of the extent of the disease, and for the monitoring of already diagnosed disease, even in asymptomatic patients. Typical signs of cardiac involvement in ECG include: PR prolongation, fragmented QRS, A-V nodal block, atrial or ventricular premature beats. However, a normal EKG does not preclude heart involvement. If an abnormal ECG is present, further diagnosis is required. In the next diagnostic stage, a 24-hour Holter ECG and echocardiography should be performed [2,6].

In the diagnosis of patients with sarcoidosis, serum biomarker measurements are also used, including serum angiotensin converting enzyme (sACE – elevated in 30-80%), neopterin, interleukin, interferon, lysozyme, CD163, CRP, B-type natriuretic peptide or highly sensitive levels of troponin. The levels of these biomarkers are often elevated in patients. However, these measurements should only be regarded as diagnostic aid due to their low sensitivity and specificity. Most of the overproduced biomarkers result from increased activity of cells involved in the inflammatory process, including macrophages, monocytes, T and B lymphocytes [9,10].

Echocardiography (ECHO) is a non-invasive diagnostic method that shows changes in both morphology and heart function. ECHO is useful for initial diagnosis, but also for quick and easy comparisons of heart function at follow-up. Abnormalities in the ECHO are described in 14–77% of patients with sarcoidosis, including patients with a normal ECG recording. Potential echocardiographic findings include hypokinesis or dyskinesia, chamber enlargement, aneurysms, wall thinning and regional wall motion abnormalities, ventricular dilatation, impaired right or left ventricular systolic or diastolic function, depressed ejection fraction, valvular dysfunction, papillary muscle involvement, pericardial effusion. However, the results of echocardiography in the early stages of the disease may not show abnormalities, therefore in patients with sarcoidosis, they should be periodically repeated, especially in the event of an escalation of cardiac symptoms. The advantage of echocardiography is its widespread availability and ease of interpretation [3,6,7].

Due to the limited accuracy of echocardiography, patients with a clinical suspicion of cardiac sarcoidosis generally should be referred to advanced non-invasive cardiovascular imaging methods including cardiac magnetic resonance (CMR) and nuclear imagining [3,6]. The advantage of CMR is the lack of ionizing effect, although side effects related to the use of contrast markers may occur. However, for the most commonly used gadolinium based contrast, the risk is relatively small [3].

Cardiac magnetic resonance (CMR) is a non-invasive, highly accurate imaging method, which is used to diagnose and monitor the degree of cardiac involvement in the course of the sarcoidosis and as a prognostic indicator for disease severity. Late gadolinium enhancement (LGE) on CMR is typically seen in patients with cardiac involvement due to sarcoidosis. In CMR imagining the absence of late gadolinium enhancement is associated with a high negative predictive value for excluding disease.

CMR imaging allows detection of scar, edema, thinning of the ventricular wall, assessment of global or regional biventricular function and myocardial perfusion defects. Gadolinium enhanced CMR images show the typical pattern of patchy focal enhancement in regions with granulomatous myocardial infiltration. Most typically, late gadolinium enhancement covers sub-epicardial and mid-wall along the basal septum and/or inferolateral wall. For more accurate imaging, T1/T2 mapping is used to distinguish fibrosis (T1 mapping) from extracellular water/edema (T2-weighted sequences). In some cases, significant edema causes enlargement of the interstitial space and additional formation of areas of late gadolinium enhancement. CMR may also exhibit right ventricular dysfunction, as a consequence of elevated right heart pressures from pulmonary sarcoidosis or right ventricular granulomatous infiltration. In CMR, the reduction in the size and intensity of late gadolinium enhancement areas reflects the effectiveness of the anti-inflammatory treatment applied [3,6,8,12].

Nuclear imaging allows for the evaluation of myocardial involvement in sarcoidosis patients by assessing myocardial perfusion and inflammation. The SPECT and PET methods are used to evaluate defects in resting perfusion, while the 18F-FDG PET imaging allows revealing active inflammation and scar. PET was estimated to have a sensitivity of 89% and specificity of 78% in the assessment of myocardial involvement [2,3,6,11,12].

18F-FDG PET is considered to be the most effective imaging method for early diagnosis and monitoring of treatment in patients with cardiac sarcoidosis. The process of granuloma formation involves immune cells (activated macrophages and CD4+ cells), which are characterized by increased cellular metabolism, which leads to excessive accumulation of the glucose analog 18F-FDG. Thus, 18F-FDG PET imaging can reveal the involvement of the heart by sarcoidosis. Typical for sarcoidosis is patchy and focal increased myocardial uptake, however other patterns of 18F-FDG PET abnormalities have also been shown in patients, including no uptake, diffuse uptake and focal on diffuse uptake. However, for an accurate diagnosis, a combined visual and quantitative analysis of myocardial perfusion and 18F-FDG PET imaging is necessary due to the heterogeneous cardiac manifestation of the disease. 18F-FDG PET abnormalities may occur with impaired but also normal myocardial perfusion and vice versa. These abnormalities change over time, depending on the activity of the disease and the effectiveness of the treatment applied. In progressive disease, perfusion defect and increased 18F-FDG uptake are usually observed. In the late stages of heart involvement, when fibrous disease predominates, there is severe perfusion defect and minimal 18F-FDG uptake. On the other hand, the normalization or improvement of myocardial perfusion and 18F-FDG uptake proves the favorable response to treatment and limitation of the disease process in the heart [2,3,6,11,15].

Both CMR and 18F-FDG PET can be used as an imaging tool for diagnosis and monitoring the progression of heart involvement in the course of sarcoidosis. CMR and 18F-FDG PET can also be treated as complementary tests as they detect different pathologies. It is postulated that CMR may be more accurate in the initial diagnosis and furthermore may be preferred as a first line test to minimize ionizing radiation, while 18F-FDG PET is believed to be more accurate and clinically useful in the follow-up of patients, although it does expose patients to ionizing radiation. 18F-FDG PET with resting myocardial perfusion imaging is also the preferred method in patients with CMR contraindications. In addition, serially repeated 18F-FDG PET allows to assess the severity of inflammation, and thus helps to establish the validity of pharmacotherapy, monitor its effectiveness and regulate the duration and type of treatment. The use of anti-inflammatory therapy should be considered in patients with active inflammation in 18F-FDG PET imagining. Test should be repeated within 3-6 months to assess response to treatment [3,6,10].

Sarcoidosis can manifest itself in various ways and with varying degrees of severity in patients.

Therefore, the diagnostic course, staging and management should be individually selected for a given patient suffering from sarcoidosis. It is beneficial to combine several diagnostic methods that may reveal various abnormalities, which will allow to plan the most effective treatment to reduce the disease and its negative effects.

Treatment of cardiac sarcoidosis

Sarcoidosis cannot be cured. The treatment used in patients is expected to reduce the granulomatous process and limit possible complications. Not every patient has indications for pharmacotherapy, as in some patients the disease is self-limiting. Different treatment regimens are recommended depending on the severity of the disease. Systemic corticosteroids remain the gold standard treatment. Other immunosuppressive drugs may be valid alternatives when first-line drugs are ineffective or there are contraindications to their use.

Cardiac sarcoidosis is one of the indications for the introduction of pharmacological treatment - most experts recommend treatment with corticosteroid therapy. The treatment algorithm depends on the clinical manifestation and severity of cardiac sarcoidosis. The exact indications, dosages of drugs, and the length of treatment are debated. Treatment can be started with an oral prednisone dose of 0.3–0.5 mg/kg of ideal body weight (usually 20-40 mg) for 6-12 weeks. In more severe cases, the initial dose is 1 mg/kg/per day. After approximately 6 weeks, the patient should be re-evaluated. When the patient's condition improves, the dose should be gradually reduced to maintenance treatment (5-10 mg) over 6-9 months. Sometimes the patient requires long-term treatment for more than 2 years or even for the rest of his life [1,3,5,6,13].

Alternative treatment includes other immunosuppressants (methotrexate, azathioprine, cyclophosphamide, hydroxychloroquine, mycophenolate mofetil) or biologic treatment (infliximab, adalimumab, rituximab). Combining treatment of glucocorticosteroids with other immunosuppressive drugs in order to reduce the dose of steroids, allows to reduce the exposure to potential side effects, which is important especially in the case of the need for long-term continuation of treatment [1,5,6].

Some patients require antiarrhythmics (the most effective are beta-blockers, sotalol and amiodarone), ablation, device therapies [implantable cardioverter-defibrillator (ICD)], surgical therapies (resection of ventricular aneurysms, pericardiectomy) and in patients with end-stage heart failure even heart transplantation. Less frequently performed procedures include surgical resection of ventricular aneurysms or pericardiectomy [1,5,6].

Prognosis in cardiac sarcoidosis

Mortality rates in sarcoidosis patients are higher than in the general population. Cardiac involvement is additionally associated with worse prognosis. Patients with sarcoidosis are at risk of cardiac death due to either heart failure or sudden death (particularly in patients aged over 40 years). In patients with clinically manifested cardiac sarcoidosis, the extent of left ventricular dysfunction is the most important predictor of prognosis. According to studies, survival in patients with normal ejection fraction (EF) is >10 years, while in patients with acute dysfunction (EF <30%) only 19% survive 10 years. Patients with clinically silent cardiac sarcoidosis have potentially better prognosis. [1,2,5,6]

Sarcoidosis activity has also been shown to be related to the risk of potentially fatal ventricular arrythmias. Study by Betensky et al. showed that patients with implantable cardioverter-defibrillators (ICDs) with active inflammation imaged by PET in the course of sarcoidosis had a higher risk for ventricular arrhythmias (ventricular tachycardia/ventricular fibrillation). The estimated prevalence of ventricular tachyarrhythmias requiring ICD therapy was 15% per year [14].

Summary
Sarcoidosis is a heterogeneous disease with unknown etiology. Due to the diverse clinical picture of patients with sarcoidosis, doctors through diagnostic work-up should strive to diagnose all manifestations of the disease (including asymptomatic ones), assess the patient's general condition, health status, and quality of life. The cooperation of internists, dermatologists, cardiologists, neurologists, and other specialists in complex patient's care is often necessary. Only such a comprehensive approach will allow to correctly assess the severity of the disease and appoint an appropriate therapeutic treatment.

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