Review

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Sarcoidosis and the heart: A review of the literature

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Summary **Sarcoidosis is a chronic multisystem disorder without any defined etiology. Cardiac sarcoidosis (CS) is detected in 2-7% of patients with sarcoidosis and more than 20% of the cases of sarcoidosis are clinically silent. Cardiac involvement in systemic sarcoidosis (SS) and isolated cardiac sarcoidosis (iCS) are associated with arrhythmia and severe heart failure (HF) and have a poor prognosis. Early diagnosis of CS and prompt initiation of corticosteroid therapy with or without other immunosuppressants is crucial. Electrocardiography, Holter monitoring, and Doppler echocardiography with speckle tracking imaging can serve as the initial steps to diagnosis of CS. Cardiac magnetic resonance (CMR) imaging and positron emission tomography (PET) are promising techniques for both diagnosis and follow-up of CS. This review discusses the main aspects of cardiac involvement in sarcoidosis.**

Keywords: Sarcoidosis, cardiac involvement, diagnosis, treatment

1. Introduction

Sarcoidosis, formerly called Mortimer's Malady, is a chronic multisystem disorder without any defined etiology. It is characterized by noncaseating granulomas in the affected organs or tissues (*1*). Its incidence varies from 3-4 to 35-80 per 100,000 according to ethnicity, region, and gender (*2*). Lymph nodes and lungs are the most frequently affected tissues, but sarcoidosis can also affect other organs and tissues like the skin, the central nervous system, the eyes, muscle, bone, and the heart (*1,2*). Cardiac sarcoidosis (CS) is detected in 2-7% of the patients with sarcoidosis, but more than 20% of the cases of CS are clinically silent (*3*). Interestingly, cardiac involvement can be as high as 58% in Japanese patients with sarcoidosis and CS is responsible for 85% of the deaths due to sarcoidosis in this population (*1*). Complete heart block, bundle branch block, ventricular tachycardia (VT), congestive heart failure (HF), and sudden death are common presentations in CS (*1*). Endomyocardial biopsy (EMB), electrocardiogram (ECG), Holter monitoring, two-dimensional and Doppler echocardiography including strain imaging, radionuclide studies, cardiac magnetic resonance (CMR) imaging, and positron emission tomography (PET) are among the main techniques used to diagnosis CS. Corticosteroids with or without immunosuppressants are the mainstay of therapy for CS. This review will summarize the epidemiologic, pathophysiologic, diagnostic, clinical, and therapeutic aspects of CS.

2. Epidemiology

Sarcoidosis is a chronic multisystem disorder, characterized by noncaseating granulomas in multiple tissues and organs. According to previous data, sarcoidosis has a prevalence of 10-40/100,000 persons in the United States and Europe. Interestingly, African-Americans have a higher prevalence of the disease compared to Caucasians, with a ratio between 10 and 17 to 1 (*4*). Similarly, the Scandinavians have a higher prevalence of sarcoidosis than other whites (*5*). A study in Turkey found the incidence of sarcoidosis to be 4 per 100,000 (*6*). Sarcoidosis is said to have a slight sex preference since females between the ages of 20 and 40 have the highest incidence of systemic sarcoidosis (SS), but myocardial involvement does not show any gender preference according to the current data (*7,8*). CS can

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be part of SS or it can be detected in an isolated form. According to a pathology series, cardiac involvement occurs in 20-30% of patients with sarcoidosis (*6*). Cardiac involvement is associated with a poor prognosis (*9*). Myocardial granulomas were detected in 27% of 84 autopsies of patients with pulmonary sarcoidosis (PS) (*10*). In Japanese patients with sarcoidosis, cardiac involvement was reported to be high as 58% (*11,12*). Cardiac involvement in sarcoidosis can be responsible for up to 85% of the deaths among Japanese patients with sarcoidosis (*12,13*). In clinical practice, however, only 5% of patients with sarcoidosis have clinical manifestations of heart disease, and about 50-60% of patients with CS diagnosed at autopsy were not diagnosed with the disease while they were living (*1*). According to a study by the American Thoracic Society in 1999, respiratory failure is the most common cause of mortality among patients with sarcoidosis, accounting for an overall mortality of 1 to 5% (*8*). In contrast to previous studies, isolated cardiac sarcoidosis (iCS) is much more common than suspected (*3*). In a previous autopsy study, 40% of patients with CS had no signs of extracardiac involvement (*3,14*); in a retrospective study, 66% of patients with CS had disease isolated to the heart (*3*).

3. Pathogenesis and Etiologic Factors

The etiology and pathophysiology of sarcoidosis has not been fully understood, but the literature features some promising data that can help to understand the mechanism at the core of the disease process. Discrete, compact, noncaseating epithelioid cell granuloma is the principal lesion found in organs affected by sarcoidosis (*8*). These epithelioid cell granulomas consist of highly differentiated mononuclear phagocytes (epithelioid cells and giant cells) and lymphocytes (*15,16*). Granuloma formation occurs as a result of a cell-mediated delayed hypersensitivity immune reaction in individuals with immune dysfunction. After macrophages phagocytize the antigen, they present the antigen and effector CD4+helper T cells secrete IL-2 and IFN-γ that trigger a Th1 immune response. Non-necrotizing granuloma is formed as a result of the collection of highly differentiated mononuclear phagocytes (epithelioid cells and multinucleated giant cells), Schaumann bodies or asteroid bodies, patchy fibrosis, and lymphocytes (*3,15,16*). Three categories of potential etiologic factors have previously been defined: infective, noninfective, and genetic (*17*). Viruses (herpes, Epstein–Barr, retrovirus, coxsackie B virus, and cytomegalovirus), Borrelia burgdorferi, Propionibacterium acnes, Mycobacterium tuberculosis and other mycobacteria, Mycoplasma orale, beryllium, aluminum, zirconium, clay, talc, hairspray, pine tree pollen, peanut dust, mineral oil, and drugs (*e.g.* sulfonamide or methotrexate) can induce granuloma formation in genetically-predisposed individuals with abnormal immune responses (*8,18-22*). The variability of disease presentation (pattern of disease, severity, and prognosis) among different races and in individuals with specific HLA sub-types and the presence of some familial clusters indicate a genetic susceptibility for sarcoidosis (*5,23,24*). First-degree relatives of patients with sarcoidosis were found to have a relative risk of sarcoidosis five times that of control subjects (*1,25*). In a case-control etiologic study of sarcoidosis (ACCESS) a significantly elevated risk of sarcoidosis was observed among first- and second-degree relatives of patients with sarcoidosis compared to that in relatives of matching control subjects (*26*). HLA analyses of affected families showed that the mode of inheritance of the risk for sarcoidosis can be polygenic, most commonly including the class I HLA-A1 and -B8 and class II HLADR3 genotypes (*27-29*). Genetically predisposed individuals are likely to develop granulomas after exposure to antigens that trigger an exaggerated cellular immune response (*8*). The presence of HLA-DQB1*0601 and the allele TNFA2 in Japanese female patients with CS also indicates a genetic etiology (*23,24*).

4. Clinical Manifestations

Although the incidence of cardiac involvement is higher in autopsies, the clinical manifestations of cardiac involvement are seen in about 5% of patients with sarcoidosis (*1,8,30*). The extent and location of granulomas are the determinants of the clinical manifestations of sarcoidosis. There are three consecutive histological stages including edema, granulomatous infiltration, and fibrosis leading to postinflammatory scarring (*1*). Granulomatous inflammation can involve either the myocardium, endocardium, or pericardium (*10,16,31,32*). The myocardium is the portion of the heart most commonly affected by CS, but the pericardium and endocardium are usually involved as a result of the spread of myocardial inflammation (*3,10,32,33*). The free wall of the left ventricle, interventricular septum (IVS), papillary muscles, right ventricle (RV), and atria can be involved, though with less frequency (*3,14,32*). A physician should be alert for CS if there is fibrosis and scar formation in unusual myocardial regions atypical of coronary ischemia in the absence of coronary artery disease (CAD) in a young individual (*3*).

There is significant variability in clinical presentation ranging from benign arrhythmia to severe heart block and sudden death (*7,8*). The clinical manifestations also vary from patient to patient (*7*). The presence of mere cardiac symptoms such as palpitations should be carefully evaluated. In previous studies, the most common cardiac presentations were allocated into three major groups: arrhythmia, cardiomyopathy, and pericardial involvement (*1,7,12*). The prevalence

of arrhythmia ranges from 0 to 65%. The prevalence of specific arrhythmias is as follows: 26-62% in AV block, 12-61% in bundle branch block, 0-15% in supraventricular tachycardia, 2-42% in VT, and 12-65% in sudden cardiac death (*7*). In patients with CS, complete heart block is among the most common arrhythmias and occurs in younger patients in contrast to older patients presenting with complete heart block due to other causes (*34*). Scarring or granuloma formation in the basal septum or involvement of the nodal artery leading to ischemia in the conduction system can result in complete heart block and bundle branch block (*12*). Complete heart block can directly cause sudden cardiac death. Interestingly, Japanese women over 50 years of age are frequently admitted with complete heart block, leading to diagnosis of CS in 11% of cases (*35*). VT is another common tachyarrhythmia in CS (*7*). In a previous study by Sekiguchi *et al*., sudden cardiac death due to ventricular tachyarrhythmia and complete heart block was reported to cause 25-65% of the deaths due to CS, and the study also indicated that sudden death can be the initial presentation in 40% of patients with CS (*36*). Abnormal automaticity, reentrant circuits due to sarcoid granulomas, or scar tissue can lead VT (*1*). In an emergency setting, CS should be considered in cases of sudden cardiac death with no definite etiology. Atrial arrhythmia is less common than ventricular arrhythmia and often results from atrial dilatation or pulmonary involvement rather than atrial granulomas (*32*).

Cardiomyopathy was reported to have a prevalence of 10-30% (*1,7,12*). Left ventricular (LV) systolic failure, HF with preserved ejection fraction, or right ventricular failure secondary to pulmonary disease are the main manifestations of cardiomyopathy in sarcoidosis (*1,7,12*). According to one study, 25% to 75% of cardiac deaths in patients with CS are due to progressive HF (*33*). CS can be difficult to differentiate from idiopathic dilated cardiomyopathy (IDC) (*1*). A significantly higher frequency of complete heart block (67% *vs*. 0%), right bundle branch block (57% *vs*. 17%), and abnormal left ventricular wall thickness (73% *vs*. 17%) in sarcoidosis can help to exclude IDC (*33*).

Pulmonary hypertension (PH), a predictor of poor prognosis, was found to have a prevalence of 73.8% in advanced sarcoidosis (*37*). In a previous study at a Japanese outpatient clinic, PH was found to be present in 5.7% of cases of CS (*38*). PH can be due to impaired forward flow because of poor left ventricular function and can result from PS in patients with hypoxic vasoconstriction leading to cor pulmonale (*1*). PH can be caused by encroachment of the pulmonary vasculature due to intimal and medial infiltration by noncaseating granuloma and extrinsic compression of pulmonary arteries by enlarged mediastinal lymph nodes (*39*). PH is diagnosed based on an estimation of right ventricular systolic pressure (RVSP) using Doppler echocardiography and a modified Bernoulli equation. RVSP is considered to be equal to the systolic pulmonary artery pressure (sPAP) in the absence of right ventricular outflow obstruction. It is calculated as follows: sPAP = right ventricular systolic pressure = transtricuspid gradient + right atrial pressure, where the transtricuspid gradient is $4v^2$ (v = peak velocity of tricuspid regurgitation in meters per second) (*40*). According to the WHO criteria for classification of PH, sarcoidosis is included in group 5, which includes PH with unclear multifactorial mechanisms (*41*).

Pericardial involvement is detected in 20% of patients with CS. Pericardial involvement is most commonly evident as pericardial effusion detected in echocardiography. Pericarditis is a rare clinical presentation (*1,7,12*). Direct granulomatous involvement of cardiac valves (less than 3%), coronary artery granulomatous disease leading to myocardial ischemia, constrictive pericarditis, and intracardiac masses are other rare clinical presentations of CS (*1,7,42-44*). Although direct valvular involvement is rare, valvular insufficiency secondary to papillary muscle dysfunction is seen in 68% of patients with CS (*42*).

Another issue in CS is ventricular aneurysms. These occur in 10% of patients with sarcoidosis (*1*). The most commonly affected areas are the anterior and septal walls, and apical involvement alone is very rare (*1*). Fibrotic tissue formation due to long-term corticosteroid use to treat cardiac granulomas and extension of myocardial sarcoid lesions can lead aneurysm formation (*45,46*). However, patients with untreated CS can develop myocardial aneurysms, so corticosteroids should be used if indicated (*1*). Frequent and complex ventricular arrhythmias can be seen in patients with myocardial aneurysms (*1*). Since impaired arterial perfusion in the proximity of cardiac granulomas can impair the local delivery of antiarrhythmic drugs and certain acidic acute phase molecules can react with antiarrhythmic drugs with a high pK to reduce their serum levels, resection of the aneurysm can be an option for treatment of intractable ventricular tachyarrhythmia (*1*).

5. Diagnosis

The diagnosis of cardiac involvement in sarcoidosis is somewhat challenging (*2*). There were no clinical signs or symptoms of the disease in 37% of patients with cardiac involvement (*1*). Early diagnosis and prompt initiation of antiinflammatory therapy is crucial to preventing poor outcomes (*1,47*). Nevertheless, there is no gold standard to test for CS (*2*). Over the past ten years, some important diagnostic and management strategies have been proposed like the revised Japanese Ministry of Health and Welfare Guidelines (JMHWG) from the Japan Society of Sarcoidosis and Other Granulomatous Disorders and the Delphi study (*48,49*). However, there is lack of consensus regarding

the management of CS (*2*). Medical history, physical examination, ECG, 24-hour Holter monitoring, and echocardiography should be the components of initial clinical evaluation (*2*). Patients may have some nonspecific symptoms like chest pain, palpitations, syncope, bradycardia, peripheral edema, dyspnea, and orthopnea (*50,51*). In a previous study examining a cohort with CS, patients presented with atrioventricular block (50%), left-sided HF (40%), syncope (31%), palpitations (17%), chest pain (14%), and bradycardia (10%) (Table 1) (*50*). Clinical findings can be helpful in drawing conclusions about the extent of disease and inflammatory activity (*2*). A previous prospective study reported that at least one abnormal screening result, including cardiac symptoms, a cardiac examination, 12-lead ECG, echocardiogram, and Holter monitor, had a 100% sensitivity and 87% specificity at detecting CS, with history/examination, an echocardiogram, and Holter monitor being the most useful (*47*).

5.1. *Electrocardiography*

A resting ECG is commonly accepted as an appropriate test to screen for patients with sarcoidosis (*3,8,47,52*). ECG was reported to have a sensitivity of 33% to 58% and a specificity of 22% to 71% at detecting CS (*53,54*). ECG abnormalities like conduction disturbances, arrhythmia, or nonspecific ST and T-wave changes have been detected in 20 to 31% of patients with sarcoidosis (*10,55-57*). An autopsy study of sarcoidosis with mild (microscopically evident granulomas) and severe (gross evidence of cardiac granulomas or infiltration at autopsy) cardiac involvement reported finding arrhythmia in 42% of patients and conduction disturbances in 75% of patients (*10*). ECG can be useful in estimating the extent of disease or inflammatory activity but only persistent ventricular tachycardia can predict an adverse outcome (*58*). Although the role of signal-averaged ECG (SAECG) in diagnosing CS is unclear, a recent study reported that it had a sensitivity of 52% and specificity of 82% as a technique to screen for CS (*59*). Holter monitoring can be a predictor of cardiac involvement in sarcoidosis with a sensitivity of 50% and a specificity of 97% when using CMR or PET as a reference (*47*). Another study concluded that Holter monitoring is a powerful screening tool with which to predict a positive CMR or PET scan (*60*). Yet another study reported that 24-Holter monitoring had a sensitivity of 67% and a specificity of 80% at detecting CS (*61*).

Table 1. Common presentations of patients with CS

Atrioventricular block	50 %
Left-sided heart failure	40 %
Syncope	31 %
Palpitations	17 %
Chest pain	14 %
Bradycardia	10 %

5.2. *Echocardiography*

Echocardiography is another important tool with which to diagnose CS. Echocardiographic abnormalities are detected in 24-77% of patients with CS (*7,62-64*). These abnormalities include abnormal septal thickening or thinning, dilatation and systolic dysfunction of the LV, regional wall motion abnormalities without involvement of the coronary arteries, a focal intracardiac mass caused by a large granuloma, diastolic dysfunction, valvular regurgitation, papillary muscle dysfunction, pericardial effusions, and macroscopic areas of bright echoes indicating granulomatous inflammation (a speckled or snowstorm pattern) (*1,3,7,31,33,42,65-67*). Further investigation is necessary if a patient has extracardiac sarcoidosis with abnormal 2-D echocardiographic findings and subtle abnormalities in diastolic flow patterns (*7*). A previous retrospective study reported that Doppler echocardiography was abnormal in 67% of patients, with abnormalities that included dilated cardiomyopathy (32%), abnormal left ventricular relaxation (29%), and diffuse or localized dyskinesia or hypokinesia (26%) (*1,53*). A previous study reported that 14% of patients with pulmonary sarcoidosis without known cardiac involvement had diastolic dysfunction as a result of CS (*68*). A prolonged isovolumic relaxation time and a reversed E/A Doppler ratio are the most common echocardiographic patterns of diastolic dysfunction seen in early CS (*68*). Although these Doppler findings have some role in diagnosing CS and determining its prognosis, they lack the sensitivity and specificity to detect early cardiac involvement (*7*). The cycle-dependent variation of myocardial integrated backscatter may involve mechanisms such as decreased regional myocardial contraction, altered myocardial acoustic properties due to myocytolysis, and cell infiltration in the myocardium; this variation may be reduced in the basal septum even in the absence of 2-D echocardiographic abnormalities, providing a new technique for detection of cardiac involvement (*1,69*). In a recent clinical prospective cohort study by Degirmenci *et al.*, the role of speckle tracking echocardiography (STE) was evaluated in patients with PS without clinical or echocardiographic evidence of cardiac involvement (*70*). The left atrial global longitudinal strain (LAGLS), total atrial conduction time (TACT), and LV function were studied in patients with PS (*70*). The results were as follows: LAGLS was significantly lower, TACT was significantly longer, LV longitudinal strain and strain rate (SR) measurements were significantly lower, and LVR-apical and LV-torsion (LVTR) values were significantly higher in patients with recently diagnosed sarcoidosis than in healthy controls (*70*). Thus, identification of left atrial and LV myocardial deformations with speckle tracking echocardiography can indicate subclinical LV dysfunction and subclinical electrophysiologic changes in patients with PS and aid

the physician in prompt initiation of therapy (*70*).

5.3. *Cardiac Magnetic Resonance Imaging/Positron Emission Tomography/Radionuclide Scintigraphy*

CMR imaging with a high spatial and soft-tissue resolution detects the active, inflammatory phase of disease and the chronic phase that includes mostly scarring and fibrosis in both SS and iCS (*2*). Focal wall thickening due to infiltration or edema and wall motion abnormalities seen on T1-weighted (cine) images, increased signal intensity on T2-weighted images, and early gadolinium enhancement are characteristics of the inflammatory phase (*11*). Wall thinning and delayed gadolinium enhancement, indicating myocardial damage, scarring, and fibrosis are findings in the chronic phase (*71*). Delayed gadolinium enhancement was recently reported to be the strongest hallmark of CS (*49*) and was reported to be associated with adverse events and cardiac death (2). Gadolinium enhancement can be useful in evaluating the response to steroid therapy (*72,73*). CMR imaging is probably more sensitive than radionuclide imaging (*11,51*) and has a similar sensitivity and a highly improved specificity in detecting CS compared to PET (*74,75*).

PET with 18F- fluorodeoxyglucose (FDG) is a form of functional imaging that indicates inflammation and that is useful in early diagnosis, monitoring of therapy, and image-guided biopsy (*76*). A patchy, focal uptake pattern specifically indicates CS (*2,3*). There are several ways in which 18F-FDG uptake is characterized (*77*), including no uptake, diffuse uptake, focal uptake, and focal on diffuse uptake (*78*). Other researchers have characterized patterns while incorporating data from perfusion and 18F-FDG PET images: normal perfusion and normal 18F-FDG, either abnormal perfusion or abnormal 18F-FDG, or both abnormal perfusion and abnormal 18F-FDG (*79*).

The degree of abnormal perfusion and 18F-FDG uptake can also be characterized as: normal (normal perfusion/normal 18F-FDG), early stage (mild perfusion defect/increased 18F-FDG), progressive stage (moderate perfusion defect/increased 18F-FDG), progressive myocardial impairment stage (severe perfusion defect/increased 18F-FDG), and fibrosis stage (severe perfusion defect/minimal or no 18F-FDG uptake) (*80*). These stages can be helpful in initial diagnosis and follow-up of patients and assessment of the response to therapy (*77*).

Combining 18F-FDG PET with a perfusion scan and ECG gating can rule out CAD and show resting perfusion defects due to inflammation-induced tissue damage (*76*). Cardiac imaging can be combined with whole-body imaging to evaluate extracardiac sarcoidosis lesions (*2*). In a previous meta-analysis, 18F-FDG PET imaging was reported to have a sensitivity of 89% and a specificity of 78% at detecting CS compared to the JMHWG (*81*). CMR is more specific at detecting scar formation in later stages of the disease process, but PET is more sensitive at detecting early stages of inflammation (*74*). As a result, combining PET and CMR can provide complementary data for the diagnosis of CS (*74*). In a previous study, 18FDG uptake on PET and focal perfusion detection were reported to have some impact on prognosis, including death and VT, in comparison to the Japanese criteria (*79*). Nevertheless, 18F-FDG-PET has some limitations, including physiological uptake of 18FDG in the myocardium in healthy subjects, physiologic uptake in normal myocardium on the basal and lateral LV walls, increased uptake in RV and IVS in PH because of the mechanical overload, and nonspecific uptake in non-sarcoid dilated cardiomyopathies (*82*).

Before the introduction of PET, 201 Tl, 99mTc-sestamibi, and 67 Ga scintigraphy were commonly used to diagnose and monitor cardiac involvement in sarcoidosis (*83*). Thallium-201 (201Th) or technetium-99 m (99mTc) resting perfusion scintigraphy can show areas of decreased uptake in CS due to fibrogranulomatous replacement, regional metabolic abnormalities, or microvascular vasoconstriction (*51,83-85*). In CS, perfusion defects commonly decrease with exercise and vasodilator infusion (reverse perfusion) (*54*). Accumulation of gallium-67 (67Ga) in areas of active inflammation allows the detection of CS (*7*). Unfortunately, 67Ga does not accumulate in areas of fibrogranulomatous scarring, so 67Ga scintigraphy has a lower level of sensitivity than other radionuclides (18-50%) (*11,51*). Recently, CMR and PET have replaced radionuclide studies in the detection of CS because of their superior attributes (*2,3,7*).

5.4. *Serum Markers*

There are no disease-specific markers for diagnosis of CS (*22*). Although serum angiotensin-converting enzyme (ACE) is elevated in 60% of patients with SS (*86,87*), it is not a sensitive marker and is detected in only 21.8% of patients with CS (*3,54,88*). Serum IgG (*89*), lysozyme (*90*), high-sensitivity troponin T (*90*), atrial and brain natriuretic peptides (*91*), and soluble IL-2 receptor (*89,92,93*) have been proposed as biomarkers, but they lack the sensitivity and specificity to detect CS or there are insufficient data regarding their role in CS (*22*).

5.5. *Endomyocardial Biopsy*

CS can be definitively diagnosed via an endomyocardial biopsy (EMB) indicating noncaseating epitheloid granulomas (*1*). However, the pitfalls of EMB are a low level of sensitivity (19-32%) and sampling and technical errors (*36,65,94,95*). Biopsies are commonly performed in the right ventricle, but they can be performed in the

left ventricle (*22*). EMB can reveal some nonspecific findings like myocardial interstitial fibrosis, myofibril disarrangement and fragmentation, and inflammatory mononuclear cell infiltrates (*16,36,96*). The free wall of the right ventricle and apical interventricular septum are the most common locations where biopsy specimens are obtained, but sarcoid granulomas are mostly located in free wall of the left ventricle or the basal septum (*3*). Because of the pathology and nonuniformity of sarcoid granulomas, those granulomas are seldom revealed by EMB (*94-96*). However, repeated and imaging-guided biopsies of the myocardium or mediastinal lymph nodes via CMR imaging or 18FDG-PET can be helpful and may improve the rate at which CS is detected (*94*). Since a biopsy is potentially fatal and imaging studies such as CMR imaging and PET are preferable options, EMB cannot be recommended as a routine tool for diagnosis of CS (*3,83,97,98*). Even if an EMB is unhelpful, cardiac involvement should be assumed in cases of sarcoidosis along with cardiac dysfunction and ECG abnormalities without any alternative etiology (*3*).

5.6. *Coronary Angiography*

Coronary angiography is commonly performed in patients with suspected CS in order to exclude CAD (*3*). Any wall motion abnormality can be detected during ventriculography and coronary arteries are typically normal (*3,99*). Vascular filling defects due to granulomatous vasculitis are rarely seen (*100*).

5.7. *Differential Diagnosis*

Dilated cardiomyopathy of any cause, arrhythmogenic right ventricular cardiomyopathy, idiopathic giant cell myocarditis, lymphocytic myocarditis, connective tissue diseases, vasculitis (Takayasu arteritis and Wegener granulomatosis), amyloidosis, dengue fever, Chagas disease, and other infectious causes like rheumatic fever, syphilis, fungal infections, and tuberculosis should be considered in the differential diagnosis of CS (*33,50,82,101-111*).

6. Prognosis, Therapy, and Follow-up

6.1. *Prognosis*

Cardiac involvement in SS and iCS is associated with arrhythmia and severe HF and has a poor prognosis (*22*). However, sarcoidosis without cardiac involvement is a relatively benign condition, and 28-70% of patients recover and most of their lesions disappear spontaneously within two years (*112,113*). The increased risk of sudden death in CS necessitates prompt initiation of antiinflammatory therapy (*1*). Recognizing lethal ventricular arrhythmia, including sustained VT and ventricular fibrillation, and ICD implantation for secondary prophylaxis are crucial to improving prognosis (*114*). If patients have or are likely to have CS according to different imaging modalities, a positive EMB is not necessary and medical treatment should be started immediately (*1*).

6.2. *Drug Therapy*

Corticosteroids are the mainstay of the initial therapy for CS (*1,22*). Long-term corticosteroid use was shown to be beneficial to patients with an LV ejection fraction (LVEF)> 55% and <54% by preventing LV remodelling and reducing the LV volume and increasing the LVEF (*115*). The same study also found that there was no beneficial effect of therapy in patients with an LVEF < 30%, highlighting the importance of the prompt initiation of therapy in the early or middle stages of the disease. Although there are scant data indicating that corticosteroid treatment improves prognosis, a previous study found that steroid therapy may improve survival, especially in patients with an LVEF > 50 % (*58,115,116*). Steroid therapy can alleviate an atrioventricular conduction disturbance (*35,117*) and reduce the frequency of premature ventricular beats and non-sustained VT (*118*). The evidence for use of other immunosuppressive drugs in CS, including methotrexate, azathioprine, leflunomide, mycophenolate mofetil, anti-TNFα antibodies, and hydroxychloroquine, is poor, but the use of these drugs may be reasonable in order to avoid long-term side-effects of corticosteroids, or these drugs can be given preference in cases where corticosteroids are contraindicated or the patient is resistant to corticosteroids (*114,119-124*). The optimal agents for the treatment of CS and the optimal duration of therapy remain to be elucidated (*3,22*). However, a treatment regimen including 3-day pulse intravenous methylprednisolone and prednisone 40 mg/day for a minimum of 4 weeks with a maintenance dose of 10 mg by 6 months may be reasonable (*3*). Dual or triple therapy with addition of azathioprine (or methotrexate or cyclophosphamide) and hydroxychloroquine, respectively, has been reported by Lynch *et al*. (*3*). During clinical relapses of CS, high-dose corticosteroids (IV pulse methylprednisolone) and/or immunosuppressive or cytotoxic agents may be required (*3*).

6.3. *Other Therapies*

ICD implantation is indicated for secondary prophylaxis in patients with lethal ventricular arrhythmia, including sustained VT and ventricular fibrillation (*114*). Antiarrhythmic drug therapy is controversial due to the high rate of recurrence and sudden death (*1*). Electrical ablation therapy may be efficacious in patients with sustained monomorphic VT despite medical therapy (*125-127*). Ventricular arrhythmia and heart block are among the key causes of morbidity and mortality in CS,

and appropriate risk stratification and implantable device considerations are required in all patients with CS (*7*). Although corticosteroid therapy can be efficacious at restoring AV conduction, implantation of a permanent pacemaker should be performed immediately in patients with a severe AV block (*1,7,118*).

Cardiac transplantation is reserved for end-stage disease unresponsive to medical therapy with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, and diuretics (*8,128*). Resistant ventricular tachyarrhythmia and severe intractable HF, especially in younger patients, are the major indications for cardiac transplantation (*1*). Starting corticosteroid treatment before the occurrence of severe systolic dysfunction can avoid cardiac transplantation (*1*). Sarcoidosis can develop in the transplanted heart 24 weeks to 19 months after transplantation (*1*).

6.4. *Follow-up*

Doppler echocardiography and STE at 3 months and PET and/or CMR imaging (at 3–6 months) can be used to follow up patients with CS (*3*). Serial PET/CT scans and an echocardiographic examination at 6-month intervals are reasonable for patients with complete remission (*3*). Using an ambulatory Holter ECG to observe for fatal arrhythmia should be considered for patients at 3 and 6 months (*129*).

7. Conclusion

Cardiac involvement in sarcoidosis is associated with a poor prognosis. The increased risk of sudden death in CS necessitates prompt initiation of antiinflammatory therapy. Medical history, physical examination, ECG, 24-hour Holter monitoring, and echocardiography should be the components of an initial clinical evaluation. This review has discussed 2D and Doppler echocardiography as well as a relatively new technique, STE. Using STE to identify left atrial and LV myocardial deformation can indicate subclinical LV dysfunction and subclinical electrophysiologic changes and aid the physician in the prompt initiation of therapy. The risk of sudden cardiac death in patients with CS necessitates regular monitoring by means of symptoms, ECG, ambulatory ECG, and echocardiography. The impact of CMR and PET imaging on diagnosis and follow up of CS and the smaller role played by EMB were also examined.

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