Clinical Case of the Month

A 52-Year-Old Woman With Headache and Bradycardia

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CLINICAL VIGNETTE

A 52-year-old woman presented to the emergency department with a chief complaint of headache for one day. She reported a "left frontal headache," which she described as "pressure-like," non-radiating, and 9 out of 10 in intensity, beginning on the evening prior to presentation. The patient denied any aggravating or relieving factors. Associated symptoms included blurred vision and a left facial paresthesia. The patient also endorsed nasal congestion and several episodes of palpitations over the few months prior to presentation but denied photophobia, meningismus, facial asymmetry, weakness, and dysarthria. She did admit to previous episodes of headache, which were similar in nature, though not as severe or progressive, and never associated with visual changes or paresthesia.

The patient reported a history of diabetes mellitus, hyperlipidemia, and hypertension - all of which were poorly controlled due to medication non-adherence. Her home medications included fexofenadine, ibuprofen, and acetaminophen. The patient quit smoking one year ago and reported occasional alcohol use but denied illicit drug use. Vital signs in the emergency department demonstrated a temperature of 98.9°F, heart rate of 47 beats per minute, respiratory rate of 20 per minute, blood pressure of 158/71 mmHg, oxygen saturation of 98% on room air, and a BMI of 26 kg/m.^{2} Physical examination revealed a well-nourished female who was fully oriented. No cervical, axillary, or inguinal lymphadenopathy was appreciated. She was bradycardic without murmurs or gallops. Her lungs were clear to auscultation without wheezes or crackles. Neurologically, she demonstrated no motor or sensory deficits in her extremities. There was normal coordination and no ataxia. Her face was symmetric, and cranial nerve examination demonstrated a right homonymous hemianopsia.

Initial laboratories demonstrated normal blood cell lines and chemistries, with the exception of hyperglycemia (250 mg/dL). An EKG demonstrated sinus rhythm with complete heart block, right bundle branch block, and left anterior fascicular block, as well as T wave abnormalities suggestive of possible ischemia (Figure 1). Chest X-ray demonstrated hilar fullness but was otherwise within normal limits. Non-contrast computed tomography scan (CT) of the head demonstrated a hypodensity in the calcarine region of the left occipital cortex; magnetic resonance imaging (MRI) study of the brain demonstrated a hyperintensity on diffusion-weighted imaging suggestive of an acute ischemic event. A CT of the thorax with contrast confirmed bilateral hilar lymphadenopathy. Endobronchial ultrasound with fine needle aspiration biopsy identified multiple small non-caseating epithelioid granulomas in several mediastinal lymph nodes (Figure 2), and competing etiologies of granulomatous inflammation were ruled out with special stains and cultures. A transthoracic echocardiogram demonstrated grossly normal chamber size and proximal aorta left ventricular ejection fraction of >55%, mild apical hypokinesis, elevated pulmonary arterial systolic pressures of 42 mmHg, mild tricuspid and mitral regurgitation, and a moderately sized intracavitary mass attached to the apicoposterior wall of the left ventricle (Figure 3), consistent with a left ventricular thrombus. Cardiac technetium (^{99m}Tc) sestamibi perfusion scan demonstrated a paucity of photon uptake in the anterior wall of the left ventricle, consistent with a perfusion defect of scar or stunned myocardium. Cardiac MRI demonstrated normal atrial and ventricular volumes; normal left and right ventricular ejection fraction; and no evidence of delayed hyperenhancement, thereby, suggesting a lack of active myocardial granulomatous inflammation. The patient was initiated on oral steroids and referred for sarcoidosis management. In addition, a dual chamber implantable cardioverter defibrillator was placed and was functioning well following discharge.

INTRODUCTION

Sarcoidosis is an idiopathic disease of chronic granulomatous inflammation. There is a bimodal distribution (peaks between the ages of 20-29 and 50 years of age), and

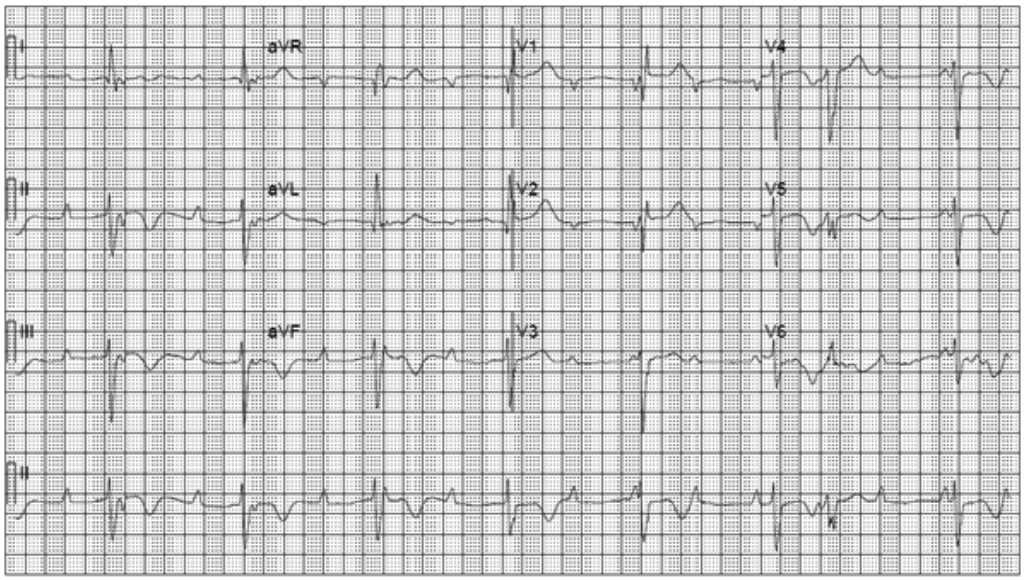


Figure 1: EKG on admission demonstrating normal sinus rhythm with complete heart block. Ventricular escape rhythm has right bundle branch and left anterior fascicular morphology. A premature ventricular complex is noted toward the end of the EKG (second beat from the end).

prevalence approaches 10-40 per 100,000.[1] There is also a propensity towards African Americans (10-17:1) and women.[1] Sarcoidosis predominantly affects the lung parenchyma and mediastinal lymph nodes; patients often present with chronic respiratory complaints, including dyspnea on exertion, cough, and chest pain.[2] Although pulmonary complaints are most common, sarcoidosis may affect virtually any organ system.

Extrapulmonary manifestations of sarcoidosis include neurologic complaints, ocular pain and pruritus, cutaneous manifestations (such as lupus pernio and erythema nodosum), hepatosplenomegaly, polyarthralgia (Lofgren's syndrome), constitutional symptoms (fatigue, anorexia, weight loss, fever), and cardiac abnormalities.[2] Cardiac sarcoidosis is a subset of sarcoidosis that may precede, follow, or be concurrent with involvement of other organs. Upon autopsy, about 25% of patients with sarcoidosis are found to have cardiac involvement, while only about 5% of patients have clinically apparent cardiac disease.[3] When present, cardiac sarcoidosis portends a poorer prognosis.[4-5]

PATHOPHYSIOLOGY

The etiology of sarcoidosis is unknown, and by definition, is considered an idiopathic inflammatory condition. There are multiple hypotheses involving the confluence of genetic susceptibility with antigenic triggers from particular exposures (including environmental, occupational, and infectious).[6] Agricultural occupations with exposure to insecticides and bioaerosols have been implicated, as have microbes such as *Mycobacteria*, *Borrelia*, *Rickettsia*, and herpes virus.[6-7]

The classic lesion of sarcoidosis is the non-caseating epithelioid granuloma. Its genesis is thought to be the result of a process of immune dysregulation, which requires an antigenic exposure, cell-mediated immune response against that antigen, and effector cells, which facilitate a granulomatous inflammatory response. Mononuclear phagocytes and Type 1 helper CD4 T cells predominate in the early granulomatous infiltrates, with cytokine expression predominated by interleukin-2 and interferon-*v*, in addition to interleukin-6.[8] Late granulomas demonstrate a predominance of Type 2 helper CD4 T cells and fibroblasts with production of interleukin-10 and transforming growth factor-*B*, which inhibits the Th1 response while promoting fibrosis and scar formation.[8]

In cardiac sarcoidosis, the characteristic non-caseating granuloma may be found in the left ventricular free wall, ventricular septum, right ventricular wall, papillary muscle, and either the right or left atrium.[9] When left unchecked, the natural history of the disease follows a progression

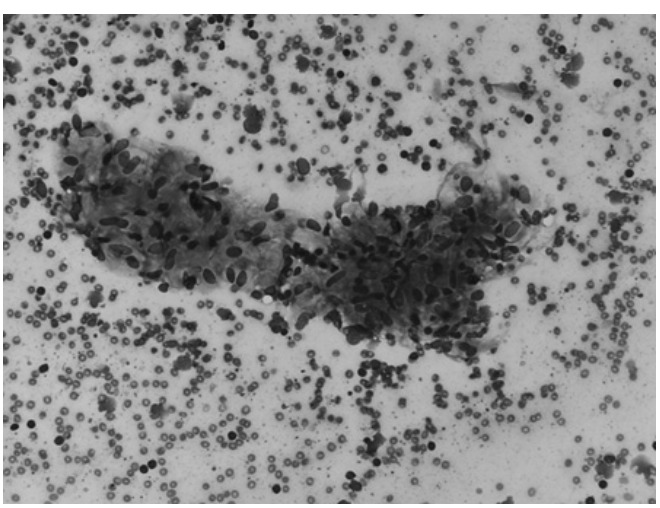


Figure 2: Mediastinal lymph node fine needle aspiration biopsy reveals a small epithelioid granuloma, consisting of a loose syncytial aggregate of epithelioid histiocytes with elongated nuclei.

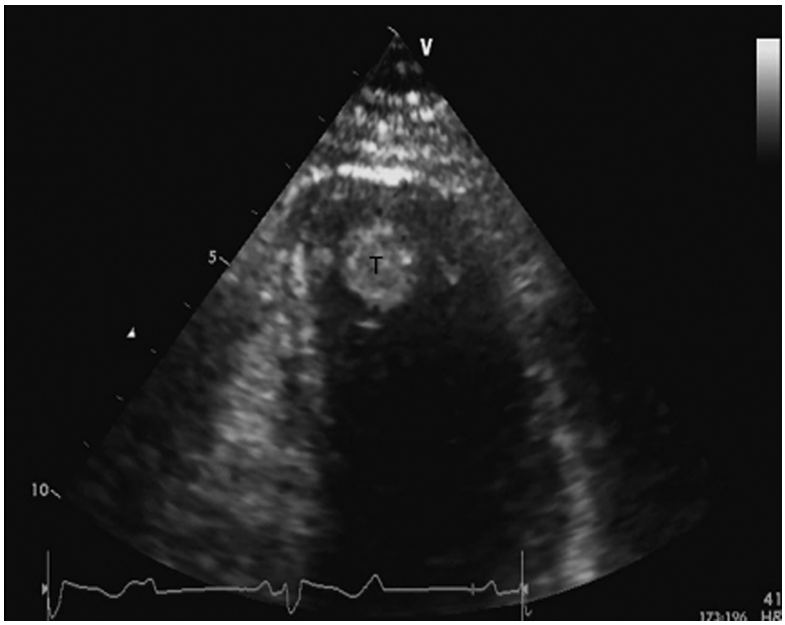


Figure 3: Echocardiogram demonstrating well-circumscribed mass at the left ventricular apex consistent with thrombus (T).

from edema to granulomatous inflammation to fibrosis, and finally, scar formation.[9]

Genetic factors appear to play a role in the pathophysiology of sarcoidosis. It appears that some individuals may be more likely to respond to an antigenic trigger with a more robust cellular immune response leading to granuloma formation. The familial relative risk is five times that of the average individual; in African-American women there is a 19% percent risk of familial occurrence.[2-10] Class I HLA-A1 & B8, as well as class II HLA-DR3, demonstrate an association in Caucasians.[2]

CLINICAL MANIFESTATIONS

In patients with clinically apparent cardiac sarcoidosis, the severity ranges from a benign incidental finding to life-threatening conduction abnormalities, arrhythmias, and structural heart disease. Only about half of those with autopsy-confirmed cardiac sarcoidosis ever experience clinical manifestations during their lifetime, and more than a third never experience any systemic symptoms related to sarcoidosis.[11] In as many as 40% of patients with cardiac sarcoidosis, the initial presentation is sudden death.[12]

Cardiac conduction abnormalities are the most common clinical manifestation of cardiac sarcoidosis.[12] They are often initially silent but frequently progress to severe conduction delays. Any conduction defect is possible, but when symptomatic, complete heart block is most commonly reported in 23-30% of patients, followed by bundle branch block at 12-32%.[12] Conduction blocks are generally found when there is infiltration of the basal aspect of the interventricular septum. Clinical presentation varies from pre-syncope to syncope to sudden death. Cardiac sarcoidosis should be considered when a patient with a confirmed conduction defect is far younger than the age range which is classically associated with that defect, especially in the setting of extracardiac sarcoidosis.[12]

Ventricular arrhythmias are the second most common manifestations in cardiac sarcoidosis. The granulomas act as foci for abnormal automaticity and reentry (via dispersion of activation and recovery) thereby leading to arrhythmia. This process occurs both in the setting of active disease, as well as inactive disease (e.g. fibrosis and scar).[13] When the patient is symptomatic, ventricular tachycardia and premature ventricular contraction are second only to complete heart block in terms of incidence at about 23%.[14] Ventricular arrhythmias and complete heart block combined account for 25-65% of sudden deaths in patients with cardiac sarcoidosis.[13]

Atrial arrhythmias are rarer than ventricular arrhythmias at about 15-17%. They are more likely to be the result of atrial enlargement and the effects of pulmonary sarcoidosis than the direct result of granulomatous infiltration or scar.[9] When present, paroxysmal atrial tachycardia, atrial fibrillation, and atrial flutter are most common.

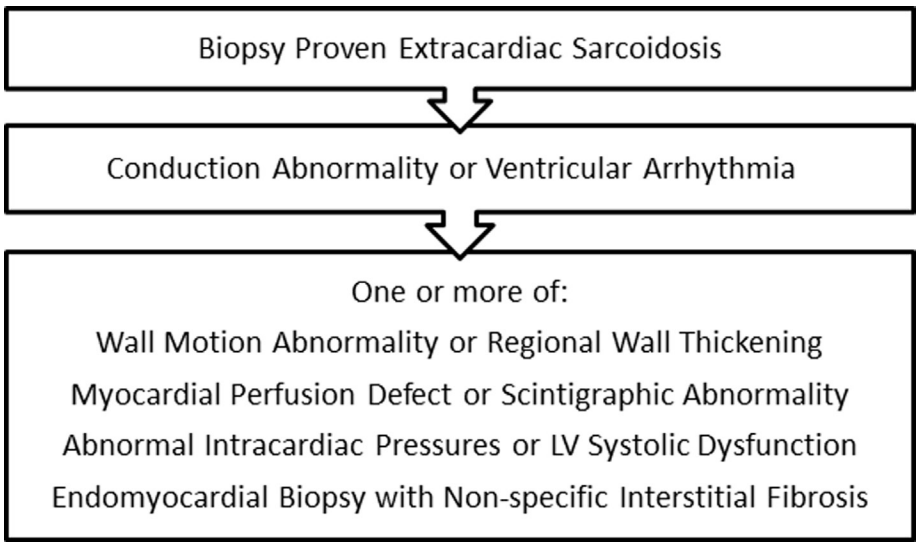
Heart failure may present as either left ventricular systolic or diastolic dysfunction and may take the form of restrictive or dilated cardiomyopathy from granulomatous infiltration of the myocardium. Heart failure accounts for 25-75% of cardiac-related deaths in cardiac sarcoidosis patients.[15] In comparison to other forms of dilated cardiomyopathy, cardiac sarcoidosis patients have a higher rate of complete heart block (67% vs. 0%), right bundle branch block (57% vs. 17%), and abnormally thickened left ventricular wall (73% vs. 17%).[16]

Extensive granulomatous infiltration may also lead to ventricular aneurysms, occurring in about 10% of patients.[17] They are most commonly found in the anterior and septal walls and are often with associated apical hypokinesis. These aneurysms may also serve as a nidus for complex ventricular tachycardias.[18]

Valvular dysfunction may also occur, with mitral insufficiency being the most common presentation. Direct involvement of the valve occurs in less than 3% of patients; instead, insufficiency is more likely to be due to papillary muscle dysfunction (68%).[19] Mechanistically, valvular dysfunction may occur indirectly due to left ventricular dilatation from systolic dysfunction or directly via granulomatous infiltration or scarring of the papillary muscle.[19]

Pulmonary hypertension may be present in an as many of 5.7% of all patients with sarcoidosis and up to 74% of those who require lung transplant.[20-21] Elevated pulmonary arterial pressures occur due to a variety of etiologies, including left ventricular systolic dysfunction, hypoxic pulmonary vasoconstriction (i.e. cor pulmonale), extrinsic compression

Table 1: Guidelines for diagnosis of cardiac sarcoidosis (adapted from Japanese Ministry of Health Clinical Diagnostic Guidelines)



(e.g. lymph nodes, granulomas), or possibly a sarcoidosis-associated vasculopathy.[22]

Finally, rare manifestations of cardiac sarcoidosis include pericardial effusion and pericarditis; they are usually asymptomatic and are found in 19% and 10% of patients, respectively.[23-24] In some cases, cardiac sarcoidosis may even mimic myocardial ischemia or infarction on EKG, echocardiogram, and non-invasive stress testing or perfusion studies.

Overall, cardiac sarcoidosis presents with a varied set of non-specific symptoms and requires a high degree to suspicion. Otherwise healthy, young patients, presenting with unexplained heart block or arrhythmia should raise one's suspicion for cardiac sarcoidosis, especially if the patient has a personal or family history of sarcoidosis.

DIAGNOSIS

Classically, the diagnostic strategy for cardiac sarcoidosis follows one of two main algorithms, using either histological diagnosis or the clinical diagnostic guidelines established by the Japanese Ministry of Health in 1993. Histological diagnosis is made via endomyocardial biopsy; meanwhile, the guidelines set forth by the Japanese Ministry of Health require the use of various common clinical tools and the satisfaction of at least three of the six criteria.[25] To date, the optimal diagnostic strategy is uncertain as most modalities have less than ideal sensitivity and specificity.

The endomyocardial biopsy is achieved via right heart catheterization and is the gold standard for the diagnosis of cardiac sarcoidosis. The aim is to demonstrate non-caseating granulomas within the myocardium. When present, this finding confirms the diagnosis of cardiac sarcoidosis without the requirement of satisfying the clinical criteria. Although the specificity of endomyocardial biopsy approaches 100%, the random distribution of myocardial granulomas, predominantly in the interventricular septum and left ventricle, results in a sensitivity of only about 20%.[26] The use of adjunct modalities, such as echocardiography and cardiac MRI, to guide the selection of biopsy sites aims to improve sensitivity; however, even with this directed approach the endomyocardial biopsy continues to have a high false negative rate and often misses cases diagnosed by the clinical criteria and/or confirmed during autopsy. The differential diagnosis includes Lyme disease, amyloidosis, alcoholic cardiomyopathy, dermatomyositis, giant cell myocarditis, and rheumatoid arthritis. With the exception of giant cell myocarditis, which may present with heart block and ventricular tachycardias, these diagnoses are able to be distinguished clinically.[27]

The Japanese Ministry of Health clinical diagnostic guidelines for cardiac sarcoidosis aim to identify a constellation of otherwise non-specific symptoms, which when assimilated, raise the suspicion of cardiac involvement of sarcoidosis (Table 1).[25] When three of the six criteria are met, the sensitivity and specificity are both within an acceptable range.[25] The paramount clinical diagnostic criterion is the presence of biopsy-confirmed extracardiac sarcoidosis. Second, there must be the presence of either a conduction abnormality or ventricular arrhythmia. In addition to first and second criteria listed above, one or more of the following three criteria must also be present: wall motion abnormality or regional wall thickening on echocardiography, myocardial perfusion defect or scintigraphic abnormality on myocardial perfusion imaging, and abnormal intracardiac pressures or left ventricular systolic dysfunction on echocardiography or ventriculography. In addition, if endomyocardial biopsy demonstrates non-specific interstitial fibrosis, it may be used as substitute for any of the latter three criteria.

The clinical diagnostic guidelines listed above require the utilization of several commonly clinical modalities in order to detect the aforementioned findings. In one study, electrocardiography was evaluated for its ability to detect cardiac sarcoidosis using a cut-off of greater than 100 PVCs per day; in this case, it was found to be 67% sensitive and 62% specific.[28] Echocardiographic features include abnormal septal thickening or thinning, segmental hypokinesis, valvular dysfunction, chamber enlargement (especially the left ventricle), and impaired systolic and/or diastolic function.[19,29] More specific, but rarer, echocardiographic findings, including septal and mural hyperechogenicity, are sometimes present and may even be useful in elucidat-

ing higher yield sites for endomyocardial biopsy. Thallium 201 and Technetium (^{99m}Tc) sestamibi radionuclide scans are the most efficacious studies when attempting to detect myocardial perfusion defects.[30] These perfusion defects may mimic myocardial ischemia or infarct; however, the distribution may be atypical for ischemic disease and there is demonstration of "reverse distribution." This "reverse distribution" phenomenon is characterized by the resolution of perfusion defects following pharmacological coronary dilation with dipyridamole.[31] This is contradictory to the worsening of perfusion defects expected following exercise or dipyridamole in the setting of coronary artery disease. When used alone, SPECT imaging is rather sensitive but poorly specific for cardiac sarcoidosis; however, when combined with thallium and gallium scanning the specificity of SPECT imaging is improved.[32] When perfusion defects are equivocal or if the patient demonstrates anginal or heart failure symptoms, the use of coronary artery catheterization in conjunction with radionuclide scanning may aid in ruling out ischemic disease in favor of infiltrative etiologies.

Cardiac MRI is not distinctly included in the clinical diagnostic guidelines set forth in 1993; however, it has been shown to correlate well with other clinical modalities included within the criteria.[33] On MRI, evidence of cardiac sarcoidosis may be noted in the ventricular and/or septal walls as increased mural signal intensity on T2 imaging; there may also be areas of wall thickening attributable to granuloma-associated edema.[35-36] Additional MRI findings include areas of delayed gadolinium hyperenhancement on T1 signal. These locations often correspond with regional wall motion abnormalities and perfusion defects found on echocardiogram and radionuclide imaging, respectively.[34] The elevated T2 signal intensity and any associated wall thickening or edema correlates with the degree of active granulomatous inflammation.[35-36] Although not used alone as a diagnostic criteria, MRI abnormalities are a poor prognostic indicator and are strongly predictive of adverse events and risk of cardiac death.[33] Serial MRI is also useful in following therapeutic efficacy of steroids and other interventions as the degree of response correlates with the relative decline in gadolinium hyperenhancement.[37]

PET scanning may also prove beneficial in the diagnosis and follow-up of patients with cardiac sarcoidosis. It is an efficacious alternative for those unable to undergo MRI due to implanted devices or other contraindications. One study demonstrated 82% sensitivity in detection of cardiac sarcoidosis.[38] During therapy, a relative decline in uptake seems to correlate with steroid-associated therapeutic response.[38]

MANAGEMENT

Glucocorticoids are a first-line therapeutic option in most forms of sarcoidosis, including cardiac sarcoidosis. Glucocorticoids can limit the degree of granulomatous inflammation, thereby limiting the extent of myocardial infiltration. When steroids are initiated early, a higher proportion of cardiac function is preserved.[39] Initiation of steroid therapy when the left ventricular ejection fraction is >55% may prevent left ventricular remodeling and limit decline in cardiac function.[39] When the left ventricular ejection fraction is <30%, there is no benefit to steroid therapy.[39] The greatest impact of steroid therapy is demonstrated in those with a left ventricular ejection fraction ranging from 30-54%. In these patients, significant improvements in left ventricular volume and ejection fraction may be garnered from optimal steroid therapy. Not only do glucocorticoids provide a functional benefit, but there is also a survival benefit with a mean five-year survival of 75% in those taking steroids versus 10% for those not taking steroids.[40-41] In two additional studies, the five year survival rate was as high as 90% in those who initiated steroid therapy early enough to maintain their systolic function.[15-16]

Although steroids successfully limit the progression of granulomatous inflammation, steroid therapy alone is not indicated in those with significant conduction defects and arrhythmias due to cardiac sarcoidosis. In these patients, antiarrhythmic agents are indicated as an adjunctive therapy. While steroid therapy may halt progressive infiltration of the myocardium and conduction pathways, premorbid damage is not reversed. Instead, subsequent fibrosis in infiltrated areas of the myocardium and conduction pathway continues to provide a nidus for arrhythmias and conduction abnormalities.[17-18] There is also evidence that steroid-induced remission of granulomatous infiltration leads to intramural fibrosis and scar, thereby weakening the ventricular wall and increasing the risk of ventricular aneurysm formation.[17-19]

Although the optimal glucocorticoid dose is not certain, an initial course of prednisone 60-80mg per day, followed by a six-month taper down to 10-15mg daily is often used.[42] During the course of the taper, serial evaluations should be performed to detect possible recurrence. In the case of suspected recurrence, restarting the taper at 60mg or more per day is recommended.[42] Additional tapering of the maintenance dose may be appropriate if the disease is considered dormant by lack of recurrence.

In most cases, long-term steroid therapy is required. Steroids, however, carry a well known plethora of adverse effects. Consequently, steroid sparing agents such as chloroquine, cyclosporine, and methotrexate may be preferred in some cases.[43-44] These alternative agents are also preferred for refractory disease and when steroids are contraindicated. Although the data is limited to case reports, infliximab has also demonstrated efficacy in the treatment of cardiac sarcoidosis-related conduction defects.[45]

Conduction blocks and arrhythmias are common end points, which are treated similarly regardless of the etiology. Cardiac sarcoidosis-associated abnormalities are managed in a fashion similar to those associated with ischemic or other non-ischemic cardiomyopathies. Pacemakers are indicated for high-degree AV blocks, including Mobitz II and third-degree AV block, as well as symptomatic bradycardia, sick sinus or tachy-brady syndrome, and other abnormalities.[46] Indications for implantable cardioverter defibrillator are similar to those for other non-ischemic cardiomyopathies.

Primary prevention dictates implantation of an ICD for NYHA Class II to III with an ejection fraction of less than 35%; meanwhile, secondary prevention is useful for survivors of sudden cardiac death or those with refractory ventricular arrhythmias.[46-49] Electrophysiological ablation is also effective for elimination or reduction of ventricular tachycardias, which are not well controlled with oral antiarrhythmic agents.[50-51] Glucocorticoid therapy should be continued in order to limit progression of granulomatous infiltration.

In end-stage cases of cardiac sarcoidosis, valvular repair and even transplant may be indicated. Transplant is generally reserved for those with end-stage disease that is refractory to medical therapy.[52] End-stage disease may be defined as refractory arrhythmia or stage D systolic heart failure refractory to optimization with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, and diuretics.[53] Recurrence of cardiac sarcoidosis in a transplanted heart or heart valve is possible and may occur months to years post-operatively. As a result, protracted post-operative monitoring is required. Ideally, early institution of steroid therapy should limit progression to end-stage disease and obviate the need for transplant.

SUMMARY

Cardiac sarcoidosis should be suspected in young patients with cardiac symptoms, especially when there is concurrent personal or family history of sarcoidosis. While sarcoidosis is self-limiting in about 40% of cases, cardiac involvement portends a more ominous prognosis with higher mortality rates. The definitive diagnostic test for cardiac sarcoidosis is the endomyocardial biopsy, an invasive test with low sensitivity. The multiple clinical modalities, which comprise the Japanese Ministry of Health clinical diagnostic guidelines, and newer modalities, including MRI, are more sensitive and demonstrate reliable diagnostic efficacy when compared to endomyocardial biopsy. Management of cardiac sarcoidosis involves early initiation of corticosteroid therapy to limit progression and maintain the structural and electrical integrity of the heart. When necessary, more invasive modalities (e.g. ICD, pacemaker, and transplant) may improve outcomes in advanced disease.

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