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Cardiac sarcoidosis

Because many patients are asymptomatic or have nonspecific symptoms, cardiac sarcoidosis can be difficult to diagnose.

ABSTRACT: One of the main challenges for clinicians evaluating patients with systemic sarcoidosis is determining when and how to investigate for cardiac involvement. Owing to a low index of suspicion, and in some cases lack of pulmonary involvement, it may take many years before cardiac sarcoidosis is finally diagnosed. This is regrettable as cardiac sarcoidosis is readily treatable with corticosteroids, and because prompt diagnosis and treatment may prevent severe complications such as left ventricular dysfunction, heart failure, malignant arrhythmias, and even death. The literature supports screening for cardiac sarcoidosis with a clinical approach that includes history taking, physical examination, an electrocardiogram, an echocardiogram, and Holter monitoring. When the results of these investigations indicate abnormalities, cardiac MRI should be considered. While endomyocardial biopsy can confirm cardiac sarcoidosis, in most cases it is not required. Once cardiac sarcoidosis is confirmed, the patient should be monitored closely for the development of lethal arrhythmias and referred to an electrophysiologist if these are detected.

A 49-year-old Caucasian female with a medical history of bronchial asthma presented in 2005 with third-degree heart block. A transthoracic echocardiogram showed mild left ventricular (LV) dysfunction with a left ventricular ejection fraction (LVEF) of 55%. She subsequently underwent cardiac pacemaker insertion.

In 2007, the patient presented to her family physician with increasing breathlessness (NYHA class II), orthopnea, and lower extremity edema. Her chest X-ray was unremarkable but high-resolution thoracic computed tomography (HRCT) imaging revealed a mild peribronchial and perifissural nodularity without significant axial interstitial thickening or nodules. There was no evidence of hilar or mediastinal lymphadenopathy. A pulmonary function test at that time was normal, with an FEV_1 of 106% of predicted and FVC of 105% of predicted, diffusing capacity of 90% of predicted, and total lung capacity of 104% of predicted. A repeat echocardiogram revealed marked deterioration in LV function with an LVEF of 20%. A subsequent coronary angiogram revealed normal coronary arteries. She received an implantable cardioverter-defibrillator device (ICD) for primary prevention of sudden cardiac death.

In 2008, the patient experienced ventricular tachycardia (VT) and underwent ablation therapy. During the procedure, she suffered a cardiac arrest and received cardiopulmonary resuscitation for 3 minutes, which successfully revived her.

In 2010, the patient underwent a repeat HRCT for breathlessness, which demonstrated progression of the interstitial nodularity in addition to the development of mild peribronchovascular and axial interstitial thickening

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in keeping with pulmonary sarcoidosis (Figure 1). She also demonstrated slight enlargement of right paratracheal (station 4R) and small subcarinal (station 7) nodes. In addition, the HRCT scan revealed features of significant cardiac chamber enlargement. The patient did not undergo any invasive procedures to investigate for pulmonary sarcoidosis owing to her deteriorating cardiac status and risks associated with ventricular arrhythmias. Later that year, she underwent a cardiac biopsy. When analyzed, an endomyocardial biopsy specimen was found to contain a granuloma (Figure 2) consistent with a diagnosis of cardiac sarcoidosis (CS). A cardiac MRI was not performed because of the ICD implanted previously. Following pathological confirmation of CS, the patient was treated with 60 mg of prednisone daily for 5 weeks, which was then tapered gradually over several months to a maintenance dose of 5 mg every other day. Despite the immunosuppressive therapy, the patient continued to experience recurrent ventricular arrhythmias, and as a consequence underwent successful cardiac transplantation in 2011.

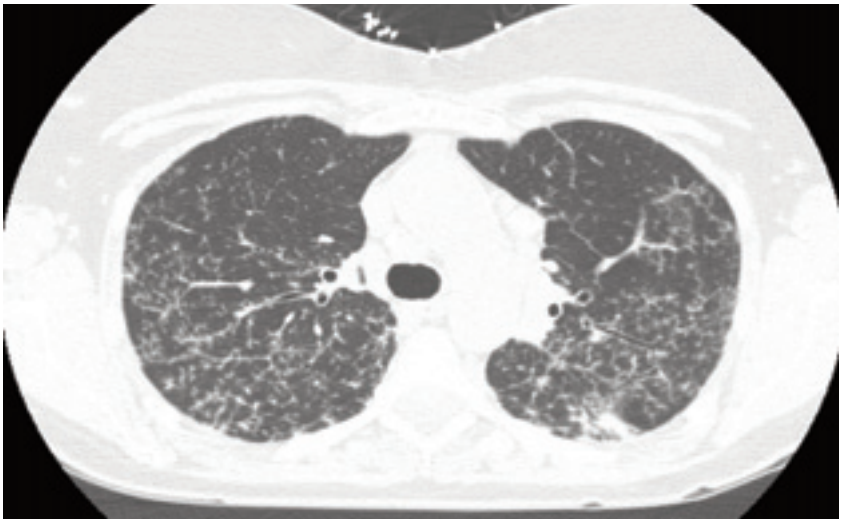

Figure 1. A CT image of the chest shows peribronchovascular thickening and nodularity in a patient with pulmonary sarcoidosis.

Evaluation

One of the main challenges for respirologists and other clinicians evaluating patients with systemic sarcoidosis is determining when and how to investigate for possible cardiac involvement. Only about 5% of patients with systemic sarcoidosis have overt clinical evidence of cardiac involvement,[1] such as heart failure, conduction defects, or arrhythmias, but one study showed that nearly one-third of patients were found to have cardiac involvement on autopsy.[2] The risk of cardiac sarcoidosis differs across races: the prevalence in African Americans is three times greater than in Caucasians. CS is also more prevalent and more aggressive in Japanese patients than in North American patients, with higher case fatality rates.[3]

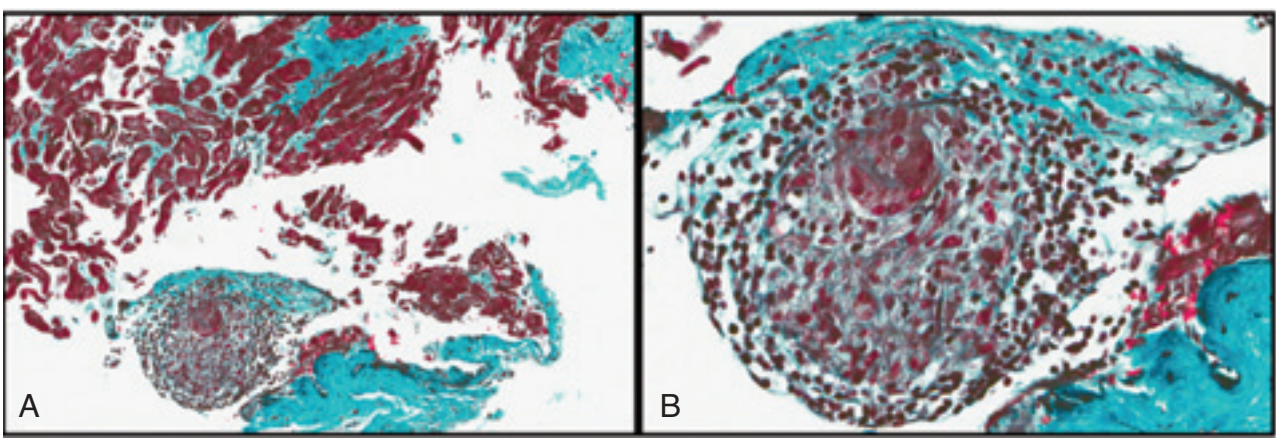

Figure 2. Photomicrographs of an endomyocardial biopsy specimen show a well-formed granuloma characteristic of sarcoidosis.

In photomicrograph A (magnification by 125) focal areas of fibrosis are colored sea-green with Masson trichrome stain. In photomicrograph B (magnification by 330) higher magnification of the granuloma reveals a central multi-nucleated giant cell with surrounding epithelioid phagocytic cells and an outer collar of lymphocytes.

CS is associated with extremely poor prognosis, especially once overt cardiac symptoms and signs develop (e.g., ventricular arrhythmias or LV dysfunction). CS presents most commonly as atrioventricular block, which occurs in 26% to 62% of CS cases, and is seen most frequently as syncope, followed by bundle branch block, which occurs in 12% to 61% of CS cases. Ventricular tachycardia is less common, with a prevalence rate of between 2% and 42%. Congestive heart failure occurs in 10% to 30% of cases, while sudden death has been reported in 12% to 65% of CS cases, usually arising from ventricular arrhythmia or complete heart block.[4] As well as being more common among Japanese people and African Americans, CS is more common in young adults.[5] There appears to be no relationship between the risk of CS and whether the disease presents as pulmonary or extrapulmonary sarcoidosis. Also, CS can occur at any point during the course of disease.

The diagnosis of CS can be difficult because many patients with CS are asymptomatic or present with nonspecific symptoms such as dyspnea or malaise. Owing to a low index of suspicion, and in some cases lack of pulmonary involvement, it may take many years before the diagnosis is finally made. This is regrettable as CS is treatable with corticosteroids such as prednisone, and because prompt diagnosis and treatment may prevent severe complications such as LV dysfunction, heart failure, malignant arrhythmias, and even death.

Treatment options

There have been no randomized controlled trials of prednisone for the treatment of CS. However, in one of the largest retrospective studies to date, Yazaki and colleagues showed that while the 5-year case fatality rate of untreated CS was 90%, with prednisone treatment the 5-year mortality rate was less than 25%.[6] Further, Kato and colleagues[7] examined the role of prednisone in 20 patients with CS who demonstrated atrioventricular block on ECG over 79 months of follow-up: 7 patients were treated with prednisone and 13 did not receive treatment. In the prednisone treatment group, there were no deaths, the LVEF did not change, and only one patient had VT. However, in the control group, two patients died, LVEF decreased from 60% to 38%, and VT was observed in eight patients. Similar data have been reported by other investigators[6,8]

An optimal dose of prednisone and duration of therapy to control CS has not been determined. Retrospective studies suggest that an initial dose as low as 30 mg per day may be effective in controlling CS.[6] Once symptoms are controlled on this dose, many clinicians then taper to a small maintenance dose (10 mg per day or less) over 6 to 12 months.[9] Consistent with this data, the joint statement on CS from the American Thoracic Society suggests starting at a higher dose of prednisone and evaluating the patient's response after 1 to 3 months. Among responders, prednisone should be slowly tapered to a maintenance dose of 5 to 10 mg per day for 12 months.[10] However, there are also many observers who believe that treatment should be much longer, perhaps even lifelong.[11] The data suggest that treatment with prednisone is effective in preventing progressive pump failure, scar formation, and death,[6-8] while treatment in early stages (before the development of overt clinical symptoms) appears to be highly effective in preventing severe cardiac complications.[9]

In addition to prednisone, ICD should be considered for CS patients with an LVEF of less than 35% and who are categorized as NYHA class II or III, or in those who have had a spontaneous sustained VT, as well as for patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or ventricular fibrillation (VF) induced at electrophysiological study. Finally, other immunosuppressive drugs may be considered as alternatives to prednisone. Methotrexate (10 to 20 mg per week) and azathioprine (2 mg per kg per day) have been used to treat CS.[10] Cyclophosphamide and infliximab have also been used in refractory cases.[12] However, it should be noted that there have been no randomized controlled trials of these or other agents for CS.

Investigation options

The current gold standard for the diagnosis of CS is endomyocardial biopsy (EMB), even though false-negatives are quite common. While CS involves mostly the free wall of the left ventricle and the interventricular septum, most EMB specimens are taken from the right ventricle apex because it is more easily accessed by way of the internal jugular vein. Left ventricle EMB is possible but is technically more challenging because the arterial system has to be accessed and cannulated. Owing to the patchy distribution of tissue affected by the disease, EMB specimens are positive in fewer than 25% of cases.[13]

More attractive options for investigating CS are three noninvasive or minimally invasive methods: electrocardiography, echocardiography, and Holter monitoring. The least expensive modality is electrocardiography. ECG reveals abnormalities in 60% to 75% of CS patients, but specificity is low.[14] The most common abnormality is a conduction defect such as bundle branch block (12% to 61%), atrioventricular block (26% to 62%), or com-

plete heart block (23% to 30%). Ventricular arrhythmias are another common abnormality (2% to 42%).

An abnormal Holter record is defined as one showing significant premature ventricular contractions (more than 10 per hour), nonsustained ventricular tachycardia (more than 3 beats), supraventricular tachycardia (more than 3 beats), VT, or VF. Holter monitoring has a sensitivity of 67% reported in the literature.[15]

The results of echocardiography are dependent on the body habitus of patients studied and the experience of the operator. Echocardiographic abnormalities can be seen in 14% to 56% of patients with CS.[4] These include regional wall motion abnormalities, valvular regurgitation, systolic dysfunction, or diastolic dysfunction (i.e., impaired ventricular relaxation). These screening methods are good, but none of the abnormalities they identify are highly specific for CS.

The most clinically useful imaging modality is cardiac magnetic resonance imaging. Smedema and colleagues found that among 58 patients with biopsy-confirmed pulmonary sarcoidosis, the positive predictive value of cardiac MRI was 55%, while the negative predictive value was 100%.[16] The most characteristic finding on cardiac MRI is a transmural myocardial delayed enhancement in the ventricular septum or free wall in a nonischemic pattern (**Figure 3**). In a recent study by Patel and colleagues,[17] patients with this pattern of abnormality on cardiac MRI were 9.0 times more likely to experience an adverse event (death, ICD shock, or pacemaker requirement) and 11.5 times more likely to experience cardiac death than patients without this pattern. If possible, cardiac MRI should be considered before implantation of pacemakers or other metallic devices, as they are strong relative contraindications to MRI, with only highly experienced centres having the capacity to perform examinations in patients with such devices.

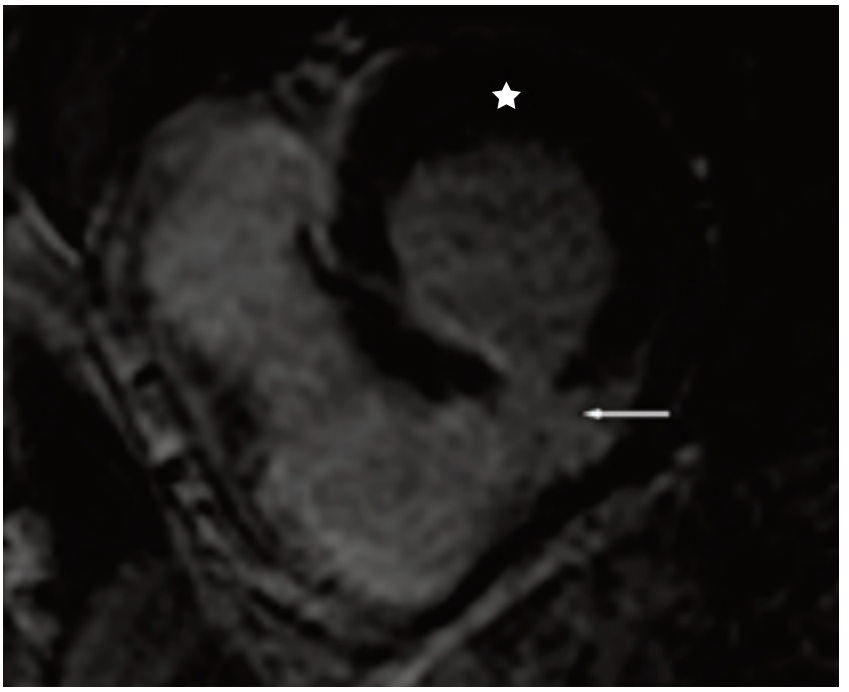

Figure 3. A short-axis delayed contrast-enhanced inversion-recovery MR image acquired 12 to 15 minutes after gadolinium injection. Normal myocardium (star) contrasts with transmural myocardial delayed enhancement in the mid-inferoseptum region in a nonischemic pattern and supports a diagnosis of cardiac sarcoidosis (arrow).

Imaging with positron emission tomography (PET) is a reasonable alternative to cardiac MRI when cardiac involvement is suspected. Small studies suggest that PET has a sensitivity of 82% to 100% in detecting CS and a specificity of 39% to 91%.[4] The use of cardiac biomarkers such as brain natriuretic peptide or troponin has been found to add very little to the diagnostic workup for CS.

Screening proposal

Based on the medical literature summarized here, we propose a clinical approach to screening for CS in patients with known pulmonary or systemic sarcoidosis.

We believe that the most important first step is to take a detailed cardiac history on the initial clinical visit to identify salient cardiac symptoms such as palpitations, dyspnea, presyncope, or syncope. The presence of significant palpitations (defined as a prominent patient complaint lasting more than 2 weeks) is one of the strongest predictors of cardiac involvement.[18] However, because palpitations are extremely common and nonspecific they should be used as a guide to further investigations. In addition, a thorough physical examination should be conducted. Attention should be paid to central nervous system, ocular, and cutanaeous symptoms of systemic sarcoidosis. History taking and physical examination should be complemented by a select number of baseline investigations, including a 12-lead ECG, transthoracic echocardiography, and 24-hour Holter recording.

Based on the Netherlands study by Smedema and colleagues that showed asymptomatic patients did not experience any cardiac complications over a 1.7-year period,[19] asymptomatic patients with no abnormalities on baseline testing (ECG, echocardiography, Holter record) require no further cardiac investigations. These asymptomatic patients should be seen annually or earlier should cardiac symptoms develop.

The most clinically useful imaging modality is cardiac magnetic resonance imaging.

Patients with cardiac symptoms (especially palpitations) or significant abnormalities on either baseline ECG (e.g., heart block), echocardiography (e.g., wall motion abnormalities), or Holter monitoring (ventricular arrhythmias), should be considered candidates for cardiac MRI. If cardiac MRI is not available or cannot be performed owing to previous pacemaker or ICD insertion, PET imaging can be considered as an alternative. In most cases EMB is not required. However, if histological confirmation is needed, MRI can be used to determine the site for EMB and thus increase the likelihood of a positive yield from the biopsy.

If CS is suspected or confirmed with screening, then the patient should be monitored closely for the development of lethal arrhythmias such as VT or VF. If these are detected, the patient should be referred promptly to an electrophysiologist so that antiarrhythmic therapy and insertion of an ICD can be considered.

Competing interests

None declared.

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