

CASE REPORT



Challenges in diagnosing cardiac sarcoidosis: should we increase our index of suspicion?

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ABSTRACT

Sarcoidosis is a multisystem disease involving the lungs in up to 90% of cases; however, 30% of patients will have systemic sarcoidosis, including involvement of the heart. Cardiac sarcoidosis can affect any part of the heart and manifest in various ways, with the most common presentations being AV block, arrhythmias, heart failure and sudden cardiac death. Due to the overlap of symptoms and other cardiac diseases, including silent disease, cardiac sarcoidosis is difficult to diagnose. Many cases are underreported. However, due to the nature of the disease, cardiac sarcoidosis can have serious consequences that can be prevented with early intervention. This paper will focus on the challenges in diagnosing cardiac sarcoidosis, how to differentiate cardiac sarcoidosis from other common conditions by detecting subtle clinical differences, and how various investigations and imaging modalities should be used in aiding diagnosis and determining prognostic severity, such that early intervention can be initiated.

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1. Introduction

Sarcoidosis is characterized by a non-caseating granuloma, which is formed via an inflammatory reaction resulting in an accumulation of epithelial cells, monocytes, lymphocytes, macrophages and fibroblasts [1]. There are various histological subtypes [1]. Pulmonary sarcoidosis (PS) affects the upper lobes of the lung and is associated with hilar and mediastinal adenopathy [2]. PS is staged via radiographic findings [2]. The onset occurs between 20 and 60 years old, although is 10 years earlier in African Americans than in whites [2]. The lifetime risk of sarcoidosis in US African Americans is 2.4% compared to 0.85% lifetime risk in whites. The etiology of sarcoidosis is unknown, but there have been reports linking MHC alleles on the short arm of chromosome 6 to the disease [2].

Thirty percent of patients with systemic sarcoidosis have cardiac sarcoidosis (CS) [3]. CS presents at an average age of 50, affecting all racial backgrounds [4]. CS can involve any part of the heart, although the ventricular myocardium is most commonly affected [3]. Chronic inflammation leads to granuloma formation and scarring, but the extent of heart damage varies between individuals. Cardiac dysfunction is characterized by the number and anatomical location of the granulomas, as well as the degree of ventricular scarring [5]. The disease does not progress linearly, and thus staging is not utilized. Instead, patients are categorized by patterns of involvement [6]. CS is difficult to diagnose because patients can be

asymptomatic or present with nonspecific symptoms. The most common manifestations of CS are AV block, arrhythmias, HF and sudden cardiac death. CS may occur alone in 25% of cases, and thus, the absence of sarcoidosis elsewhere should not rule out CS [7]. In fact, autopsy studies indicate the CS is largely underreported, even with 70% of systemic cases having undiagnosed cardiac involvement [7].

Although one would think treatment is targeted at controlling arrhythmias, it also focuses on preventing disease progression, development or worsening LV dysfunction and minimizing the risk of sudden cardiac death [8]. Prognosis is variable, as the clinical manifestations and severity differ among patients [5–7,9]. Those with symptomatic CS tend to have worse outcomes than those with subclinical disease [10]. Patients with CS and coexisting PS have the worst survival rates. One of the greatest clinical predictors of mortality is the severity of systolic HF [8]. Although a high initial dose of prednisone has not proven to be superior to low doses, the use of prednisone at the earliest detection of systolic dysfunction has shown to be effective in improving clinical outcomes for patients [8]. The use of glucocorticoids can improve survival by more than 5 years following the diagnosis of CS [8,10]. Patients refractory to steroids can be treated with other immunosuppressive therapies and anti-arrhythmic medications [5,9]. Additionally, implantable cardioverter-defibrillator (ICD) placement is also effective as the presence of myocardial granulomas causes electric

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instability in the ventricles [10]. Although ICD placement is not without risk, this procedure can be considered in either symptomatic patients refractory to other medical management or in asymptomatic patients and/or in those awaiting heart transplantation [5]. Thus, the treatment for CS is not simple and therefore early detection can lead to a prevention in the proliferation of granulomas, which lead to cardiac dysfunction and subsequent death.

2. Case

A 71-year-old male presented with exertional dyspnea, palpitations, dizziness, and episodes of central chest pain radiating to the left arm and neck, lasting less than 20 minutes. He has a history of chronic PS, for which he takes prednisone. He also has a longstanding history of Paroxysmal Atrial fibrillation, for which he takes Apixaban, and has good rate control with Metoprolol. The patient has chronic pre-ventricular complexes and was recently started on flecainide after years of amiodarone treatment that lead to the development of hypothyroidism. Past medical history is also significant for anxiety.

On admission, the patient's troponin was negative, and electrocardiogram demonstrated sinus rhythm, left axis deviation and bigeminal pre-ventricular complexes. All other laboratory values were unremarkable, including brain natriuretic protein. Chest X-ray showed hilar adenopathy and granulomas with bilateral scar tissue, unchanged from previous imaging. On further workup, a nuclear stress test did not show signs of edema or ischemia. Transthoracic-echocardiogram showed mitral annular calcifications and Ejection Fraction of 55%, but otherwise normal anatomy. A right and left cardiac catheterization was performed to evaluate for Coronary Artery Disease and pulmonary pressures but was unremarkable. Holter monitoring calculated numerous ventricular ectopic events and isolated pre-ventricular complexes. Paroxysmal Atrial fibrillation and atrial flutter accounted for 22% of the rhythms associated with symptoms.

These findings were concerning for CS. Other initial differentials of concern included acute coronary syndrome, anxiety and drug-induced arrhythmias secondary to flecainide use. Once stable, he was referred to a cardiac specialist to undergo FDG-PET scan. His FDG-PET scan revealed evidence of active myocardial inflammation involving the basal to apical anterolateral wall, with a resting small non-transmural perfusion defect involving the mid to apical anterolateral wall. This 'mismatch-perfusion' pattern was suggestive of underlying active CS.

3. Discussion

The manifestations of CS mimic other common cardiac conditions, therefore decreasing overall clinical

suspicion. As AV block is the most common manifestation of CS, differentials will include other etiologies of AV block, such as myocarditis, Lyme disease or idiopathic progressive cardiac conduction disease [4]. Myocarditis is distinguished from CS by clinical history and cardiac biomarkers, although an endomyocardial biopsy is required to definitively diagnose. Additionally, CS patients will present at a younger age with AV block than those with other etiologies [11].

PVC's and VT are the second most common clinical presentation of CS, occurring in approximately 30% of cases [11]. As granulomas form in the myocardium, re-entrant arrhythmias arise from disrupted ventricular activation. Granulomas around the sinus node cause SVT, atrial flutter and Afib [11]. Fatigue, dyspnea and orthopnea can be seen in HF, PS and CS. CS rarely causes angina, and if present should suggest atherosclerotic CAD [4].

Many non-invasive tests lead to results that are not sensitive nor specific to CS. An ECG may show prolongation of PR interval, 2nd/3rd degree AV block, atrial arrhythmias and nonspecific ST changes. A CXR may show PS, HF or pleural effusions; however, the absence of these findings does not exclude CS. Often, ACE levels and urinary calcium are elevated in CS patients, but they do not have a role in assigning diagnostic probability [4]. Patients are at high risk for developing diastolic HF, although it is also non-specific. Echocardiograms have low sensitivity but may show focal areas of edema, increased wall thickness, focal akinesis or aneurysm. Holter monitoring is useful to trend arrhythmias with clinical symptoms [9]. Biopsy is the definitive diagnosis, although sensitivity is 20–30% compared to the high sensitivities of biopsies from extracardiac sites [9].

The first step is to determine the probability of CS using the following criteria:

- (1) Patients with systemic sarcoidosis ± cardiac symptoms
- (2) Young adults <60 y.o. with unexplained syncope or unexplained new-onset conduction abnormalities
- (3) Patients with unexplained SVT
- (4) Patients with unexplained cardiomyopathy

Patients with probability should undergo advanced imaging with CMR (cardiac magnetic resonance) or FDG-PET (F-fluorodeoxyglucose-positron-emission-tomography) [12]. Both imaging techniques can detect disease severity. CMR detects small areas of myocardial tissue damage with high sensitivity, and assesses ventricular function, predicting outcomes for patients with HF. Scar tissue is always detected on CMR, despite reductions in myocardial inflammation. Those with diffuse scar tissue and ventricular dysfunction have the highest risk

of developing sustained VT and often require ICDs. Therefore, CMR is helpful in targeting those at risk for sudden death [13]. The FDG-PET scan evaluates metabolic perfusion data, detects active myocardial/extracardiac inflammation and serves as a baseline to determine treatment responsiveness in those undergoing immunosuppressive therapy [3]. It has been shown that a mismatch in perfusion metabolism denotes myocardial tissue likely to regain full functional recovery after revascularization compared to myocardial tissue with a matched absence or reduction in perfusion. Compared to those on medical therapy, studies show better clinical outcomes in those revascularized using FDG-PET [12]. A meta-analysis of histologically diagnosed CS concluded that there were certain patterns of myocardial involvement in >90% of cases. These findings can improve the diagnosis and prognostication of patients with suspected CS, using CMR and FDG-PET [1].

Since our patient's FDG-PET scan revealed a perfusion mismatch, it is likely that he will recover the full function of his heart. This case was particularly interesting because although he had a history of longstanding pulmonary sarcoidosis, his main problem was his arrhythmias. This was initially attributed to his longstanding paroxysmal atrial fibrillation and a new concern for heart failure given his TTE findings. However, his catheterization was non-contributory and so the mixed picture for arrhythmias and cardiomyopathy raised concern for cardiac sarcoidosis. It is likely that if it were not for his past history of pulmonary sarcoidosis, this patient would not have undergone workup for cardiac sarcoidosis. Thus, this finding was potentially life-saving for him.

4. Conclusion

Diagnosing CS is challenging due to the various presentations, lack of specific findings and/or isolated CS. However, the complications can lead to fatality at a young age and early diagnosis is crucial. It is imperative that we increase our clinical suspicion and make use of advanced imaging modalities, such as late gadolinium enhancement, to aid in diagnosis, prognostication and direction of treatment. Initiating treatment at an earlier stage might be life saving for many. The use of prophylactic ICDs and pacemakers, in conjunction with steroids, immunosuppressants and anti-arrhythmic medications, will delay the need for heart transplantation and improve overall longevity in these patients.

CMR and FDR-PET scans can be further studied to identify patterns of involvement in low-risk vs. high-risk patients, as well as early vs. late disease states. By identifying these sub-populations, we can further modify and cater treatments to individuals.

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Disclosure statement

The authors report no conflict of interest. Ethical review is not necessary, because this is a case report.

Consent

As this is a case report, no consent was needed for the purpose of this paper.

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