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CASE REPORT

Cardiac sarcoidosis: a case report and review of current diagnosis and management

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Abstract

Cardiac sarcoidosis is a manifestation of sarcoidosis that is challenging to diagnose due to its clinical silence, but its identification is vitally important, as its consequences are potentially devastating. These consequences include conduction defects, arrhythmias, cardiomyopathy, congestive heart failure and sudden cardiac death. This case describes a 47-year-old male with a history of dilated non-ischaemic cardiomyopathy who had a delayed diagnosis of sarcoidosis with cardiac involvement after cardiac MRI proved to be inconclusive. It was later deemed to be cardiac sarcoidosis after the onset of systemic symptoms with a liver biopsy that showed sarcoid. Initial testing for cardiac sarcoidosis should include cardiac MRI. Treatment focuses on optimising heart failure therapy and placement of a biventricular implantable cardioverter defibrillator for primary prevention of sudden cardiac death. Although some studies suggest a potential benefit from glucocorticoid therapy, conclusive evidence revealing the true value of this treatment regimen has yet to be determined.

Introduction

Cardiac sarcoidosis has been described in 5% of patients with systemic disease,[1,2] commonly manifesting as conduction disease, arrhythmia or heart failure. Diagnosis remains a challenge due to the high prevalence in asymptomatic patients and the absence of proper screening criteria given the overall paucity of data in this population. Cardiac magnetic resonance imaging (CMR) has become an attractive diagnostic non-invasive modality in view of its ability to identify small regions of myocardial damage, even in individuals with preserved left ventricular systolic function.[3] Presence of late gadolinium enhancement (LGE) on CMR is the best independent predictor of lethal events and thus its presence is associated with a higher rate of major adverse cardiac events and death; however, larger studies are needed to define sensitivity and specificity of various screening processes for detection of asymptomatic cardiac involvement.[4-6] There is no specific pattern of LGE that is pathognomonic for cardiac sarcoidosis; therefore, images must be interpreted in the context of the patient's history and by a cardiologist or radiologist with specific expertise.[7]

Case Report

A 47-year-old Caucasian male with a past medical history of hypertension, hyperlipidaemia, plaque psoriasis, type 2 diabetes mellitus and dilated non-ischaemic cardiomyopathy (ejection fraction of 15-20%) presented to the emergency department complaining of acute-onset severe pain in the right hip. It was initially thought that the hip pain was likely to be of a musculoskeletal nature. While obtaining the history, the patient revealed that he had been experiencing worsening dyspnoea on exertion, paroxysmal nocturnal dyspnoea, lower extremity oedema and abdominal distension for the last three to four weeks. He also complained of drenching night sweats and fevers of several months duration. He admitted to taking furosemide at a dose two to three times higher than prescribed in order to alleviate his heart failure symptoms. Per the patient's record, four years prior to this admission he was found to have diffuse mediastinal and retroperitoneal lymphadenopathy during computed tomography (CT) of the abdomen. He was directed to repeat imaging in several months' time and referred to oncology. The patient was subsequently lost to follow-up until presenting to the emergency department during this admission. Physical examination revealed the presence of an S3 gallop, rales in both lung bases and +1 bilateral lower extremity pitting oedema. There were pink coloured nodules scattered over the trunk, back and lower extremities, which were new to the patient. A repeat echocardiogram demonstrated a slightly worsened ejection

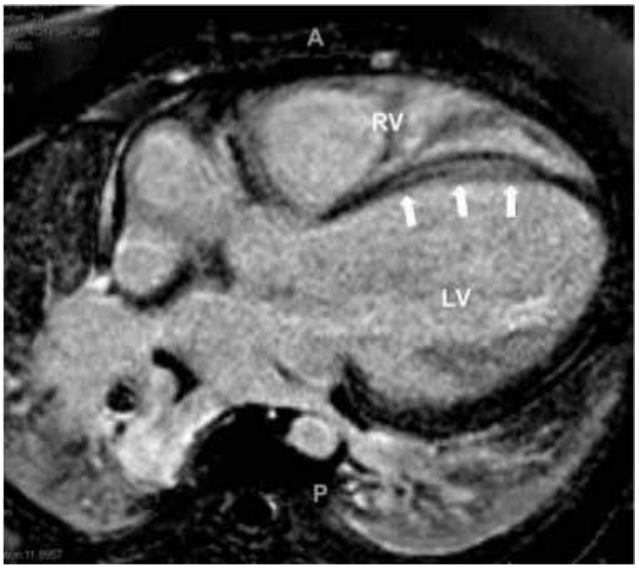

Figure 1. CT scan of the chest: multiple enlarged hilar lymph nodes can be seen in A, B, C. Liver enhancement seen in D. Measurements as noted in the image above

fraction of 10-15%. The aetiology of his cardiomyopathy was not entirely clear at this point. It was suggested that the patient's history of alcohol abuse was the culprit. A CT scan of the chest was obtained which demonstrated worsening retroperitoneal, hilar and mediastinal lymphadenopathy without parenchymal changes *(figure 1)*. Endobronchial ultrasound with biopsy was negative for malignancy and demonstrated several eosinophilic epithelioid macrophages, histiocytes and Langhans giant cells suggestive of a granulomatous process. A CMR was obtained

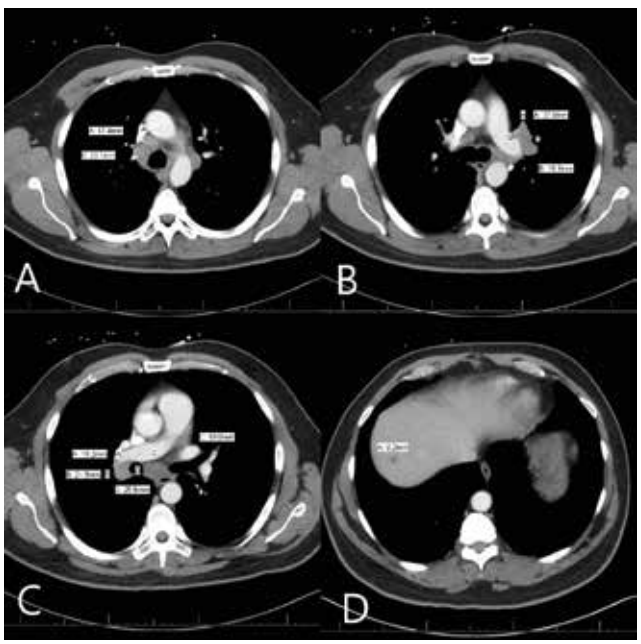

Figure 2 Cardiac MRI: An isolated intramural stripe of delayed enhancement within the interventricular septum (arrows)

to evaluate for infiltrative cardiac disease. CMR revealed an isolated intramural stripe of delayed enhancement within the interventricular septum; the findings were interpreted as nonspecific and not pathognomonic for sarcoidosis *(figure 2)*. The cardiologist recommended placement of a biventricular implantable cardiac defibrillator (BiV-ICD) for primary prevention of sudden cardiac death given his severely depressed ejection fraction. He was again lost to follow-up until he presented once more with similar complaints of dyspnoea, lower extremity oedema as well as abdominal distention, bloating and anorexia. Gastroenterology was consulted and initially evaluated the patient with abdominal ultrasound, which demonstrated a small to moderate amount of ascites. The liver appearance was abnormal and cirrhosis was suspected. The patient had not consumed alcohol for many years. The patient's serological evaluation was negative for hepatitis, iron markers and autoimmune markers were also unremarkable. A liver biopsy was performed which demonstrated non-necrotising granulomatous inflammation associated with bands of bridging fibrosis, suspicious for hepatic involvement by sarcoidosis.

Since his diagnosis of dilated non-ischaemic cardiomyopathy in 2013, the patient's management in our department first focused on heart failure stabilisation and optimisation of the medication regimen. Although he was known to have dilated non-ischaemic cardiomyopathy, the aetiology remained unclear. What made us consider alternative causes of his heart failure were the systemic nature of his symptomatic presentation. After a negative endobronchial biopsy, we began by ruling out other possible aetiologies including: beri-beri, haemochromatosis, hepatitis, human immunodeficiency virus, syphilis, Lyme disease, antinuclear antibodies, rheumatoid involvement, tuberculosis, and cryoglobulins. Despite the negative biopsies, our clinical suspicion for sarcoidosis remained high, in the setting of his constellation of symptoms. At this time, primary prevention and placement of a BiV-ICD device remained our priority. His eventual liver biopsy, which happened rather coincidentally, helped to unveil and confirm our suspected diagnosis of sarcoidosis.

Since implantation of BiV-ICD, the patient's heart failure symptoms have remained stable. His baseline New York Heart Association (NYHA) classification is Class III. The patient demonstrated incremental improvement in his symptoms during his one month of follow-up with his medical therapy consisting of furosemide, carvedilol, spironolactone and digoxin. He was unable to tolerate ACE inhibitor therapy secondary to hypotension. This patient was not treated with corticosteroid therapy considering he had symptomatic improvement after initiation of heart failure medical therapy.

Discussion

Cardiac sarcoidosis has been described in about 5% of patients with systemic involvement.[1] Diagnosis is often a challenge

given that there is no consensus for disease detection, monitoring and treatment. As mentioned previously, clinical manifestations of cardiac involvement may include conduction defects, arrhythmias, cardiomyopathy, congestive heart failure and sudden cardiac death. Asymptomatic cardiac involvement exists as well and based on several pooled studies, autopsies demonstrated cardiac involvement in approximately 70% of the cases.[2] Currently, the majority of current data on cardiac sarcoidosis comes from Japan. Recent guideline revisions by the Japan Society of Sarcoidosis and Other Granulomatous Disorders in 2006 had provided updated criteria for diagnosis of cardiac sarcoidosis which included CMR.[8] CMR is currently considered the gold standard as it is more sensitive for detection of cardiac involvement.[9] It provides high sensitivity by using T2 weighted imaging for detection of acute inflammation, T1 weighted imaging to assess wall motion abnormalities, hypertrophy, infiltrative processes, wall thinning and heart failure; and late gadolinium enhancement (LGE) for assessment of fibrosis or scar tissue. A study by Irving and colleagues compared CMR LGE to the modified Japanese Ministry of Health and Welfare (JMH) criteria in a series of 81 patients with biopsy proven extracardiac sarcoidosis who were followed for a mean of 21 months for major adverse events. [10] LGE was identified in 21 patients compared with 10 by JMH. LGE had a 9-fold greater rate of adverse events and 11.5-fold higher rate of cardiac death in comparison to patients without. Furthermore, this relationship was further solidified in a German study by Greulich et al., which included 155 patients with known cardiac sarcoidosis who were followed for a mean of 2.5 years.[11] Cardiac involvement with evidence of LGE on CMR had an over 30-fold increased risk of death, sudden cardiac death and implantable cardioverter defibrillator discharge compared to patients without LGE. Lastly, Smedema and colleagues found that among 58 patients with biopsy confirmed pulmonary sarcoidosis, the positive predictive value of CMR was 55%, while the negative predictive value was 100%.[6] The diagnosis and long-term management of patients with cardiac sarcoidosis remains challenging at best. This underscores the value of using various diagnostic techniques such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).[12] Even though questions remain about their diagnostic accuracy, research suggests that FDG-PET and CMR are clinically useful in determining the extent of cardiac involvement in systemic sarcoidosis.[12] Furthermore, using these methods in combination can provide valuable clinical insight and therefore should be considered when constructing immunosuppressive therapy regimens (i.e. glucocorticoids).[12] A brief note is necessary on the role of endomyocardial biopsies in the diagnosis and treatment of patients with cardiac sarcoidosis. Because of the unique and focal distribution of granulomas within the heart of patients with cardiac sarcoidosis, endomyocardial biopsies provide a low diagnostic yield.[12] Therefore, the treatment of cardiac sarcoidosis is often warranted even in the absence of histological proof.[13]

Glucocorticoids are a therapeutic choice when it comes to sarcoidosis; however there is a scarcity of data in regards to their implication in the treatment of cardiac sarcoidosis. Anecdotal data from an observational survey based study of 104 cases demonstrated increased survival.[14] Another retrospective observational study from Japan by Yazaki et al. demonstrated a 75% survival at five years in the glucocorticoid arm versus 10% in non-steroid treated patients. The optimal dose of prednisone and duration of therapy has not been established. Yazaki et al. suggested that an initial dose as low as 30 mg per day may be effective, followed by a slow taper over 6-12 months once symptomatic improvement has been achieved.[4] Other data suggested that treatment with prednisone is effective in preventing progressive pump failure, scar formation and sudden death.[5,14] The role of glucocorticoids in the management and treatment of patients with cardiac sarcoidosis remains unclear at present. Although no randomised controlled studies have been performed, certain retrospective and observational studies suggest a potential survival benefit.[15, 16] Further research is necessary to elucidate in full the impact this treatment regimen will have on patients with ventricular arrhythmias.[14,17] This is important to note, considering that mortality due to ventricular tachyarrhythmias or conduction block in patients with cardiac sarcoidosis is 30 to 65%.[18] Immunosuppressive therapy, including cyclophosphamide, infliximab, azathioprine and methotrexate, have also been tried, but their outcomes have not been supported by randomised controlled trials.[6,19] In regards to prevention of sudden cardiac death, ICD implantation should be strongly considered in patients with known cardiac sarcoidosis, LVEF less than 35%, NYHA class III-IV or those with history of spontaneous sustained VT/VF. The 2008 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines for device-based therapy offer clinical considerations for patients with cardiac sarcoidosis and indicate that cardiac sarcoidosis is a reasonable indication for ICD implantation, but do not offer more specific recommendations regarding ICD therapy.[18]

Conclusion

One of the main challenges in the assessment of patients with systemic sarcoidosis is determining when and how to evaluate for cardiac involvement. In patients with a high clinical suspicion for cardiac sarcoidosis, CMR is generally recommended as the initial imaging study. FDG-PET should also be considered when the diagnosis of cardiac sarcoidosis has not been firmly established. Although no randomised controlled studies have been performed regarding the role of glucocorticoids in the management of patients with cardiac sarcoidosis, certain retrospective and observational studies suggest a potential survival benefit. Further research is necessary

to fully understand the impact this treatment regimen will have on patients with cardiac sarcoidosis. Currently, treatment for cardiac sarcoid should focus on optimising heart failure therapy and the placement of BiV-ICD for primary prevention of sudden cardiac death.

Disclosures

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