Case Reports

Primary Cardiac Sarcoidosis with Syncope and Refractory Atrial Arrhythmia:

A Case Report and Review of the Literature

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We discuss the case of a 38-year-old black man who presented at our hospital with his first episode of syncope, recently developed atrial arrhythmias refractory to pharmacologic therapy, and a left atrial thrombus. He was diagnosed with primary cardiac sarcoidosis characterized by predominant involvement of the epicardium that caused atrial fibrillation and atrial flutter. Histologic analysis of his epicardial lesions yielded a diagnosis of sarcoidosis. This patient's atrial arrhythmia was successfully treated with a hybrid operation that involved resection of his atrial appendage, an Epicor maze procedure, and radiofrequency ablation during a catheter-based electrophysiologic study. The cardiac sarcoidosis was successfully managed with corticosteroid therapy.

Our case report shows that sarcoidosis can initially manifest itself as syncope with new-onset atrial arrhythmia. Sarcoidosis is important in the differential diagnosis because of its progressive nature and its potential for treatment with pharmacologic, surgical, and catheter-based interventions. ***(Tex Heart Inst J 2016;43(3):236-40)***

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Sarcoidosis, first described by Jonathan Hutchinson in 1877,[1,2] is a multisystem disease characterized by noncaseous granulomas.[3] Sarcoidosis is most often associated with the lungs, but the disease can manifest itself in any tissue. Cardiac involvement was not described until 1929.[4,5] In recent times, cardiac manifestations have been understood to play a greater role in sarcoidosis morbidity than previously thought. In this report, we present a case of primary cardiac sarcoidosis that was successfully treated with a hybrid pharmacologic, surgical, and catheter-based intervention.

Case Report

A 38-year-old black man presented at our clinic for evaluation of his first syncopal episode and atrial fibrillation (AF), this last accompanied by a rapid ventricular rate that was refractory to diltiazem, metoprolol, and digoxin therapy. The patient reported shortness of breath, intermittent palpitations, and chest pain. His medical history was significant for hypertension, obstructive sleep apnea, and diabetes mellitus type 2. Further, he had an implantable cardioverter-defibrillator to prevent sudden cardiac death due to his congestive heart failure (left ventricular ejection fraction [LVEF], 0.20–0.25, at the time of implantation). No electrocardiogram before the onset of AF was available at the time of his presentation to our clinic.

The patient's initial evaluation included a transesophageal echocardiogram (TEE) that suggested left atrial thrombus with a preserved LVEF of 0.50 to 0.55. Rigorous anticoagulation therapy with a target international normalized ratio (INR) of 3.0 maintained for 6 months was apparently unsuccessful in dissolving the atrial thrombus. The patient had a high risk for thrombus embolization and for further clot formation from his newly documented atrial flutter. We determined that he would benefit from a hybrid procedure incorporating surgical excision of the atrial appendage and atrial mass, with subsequent catheter-based ablation targeting the atypical flutter. The atrial flutter and AF were the only arrhythmias identified by means of rhythm monitoring.

After extensive discussion of the risks and benefits of a hybrid operation versus continued anticoagulation with higher INR goals, the patient chose the operative approach. He obtained surgical clearance and was sedated with general anesthesia. Preoperative TEE revealed left ventricular dilation, global hypokinesis, and an LVEF of 0.20 to 0.25, which was lower than that seen on a transthoracic echocardiogram (TTE) one month earlier. Subsequent TTEs confirmed this new globally depressed left ventricular function without regional wall-motion abnormalities, which most likely arose from tachycardia-induced cardiomyopathy. No coronary angiography was performed before the procedure, because there was no suggestion of coronary ischemia. Upon opening the pericardium, we saw 5- to 7-mm epicardial masses throughout the exposed heart. The masses were biopsied at multiple sites and sent for gram staining, cultures, cytology, and evaluation by our pathology department. After cannulating the aorta and right atrium, we resected the left atrial appendage, which revealed no thrombus within the left atrial cavity. The maze procedure was successfully performed with the Epicor™ Cardiac Ablation System (St. Jude Medical, Inc.; St. Paul, Minn). Then the chest was partially closed, and the groin was examined in preparation for catheter-based evaluation and ablation of the atrial flutter. We completed an electrophysiologic study, intracardiac echocardiography, and 3-dimensional mapping of the atrium before we began radiofrequency ablation of 3 pulmonary veins, the mitral isthmus, the cavotricuspid isthmus, and the posterior left atrial wall—all with the goal of eliminating atrial flutter. Upon completion of these procedures, we closed the chest wall in the usual fashion. The patient had an uncomplicated hospital course and was discharged from the hospital 6 days after his operation.

Histologic results revealed epicardial lesions consisting of fibroadipose tissue with nonnecrotic centers and granulomatous inflammation characterized by multinucleated giant cells surrounded by lymphocytes (Fig. 1). These findings were most consistent with sarcoidosis, because the patient showed no signs of mycobacterial or fungal growth. The superior vena cava lesions biopsied at the time of surgery showed similar granulomas with multinucleate giant cells peripherally bordered by lymphocytes, but those lesions also showed focal central necrosis. Despite this necrosis, the vena cava lesions were negative for mycobacterial and fungal stains, which rendered them most consistent with sarcoidosis. No endocardial or myocardial granulomas were noted on gross or histologic examination of the left atrial appendage or the right atrial tissue. Diagnostic confirmation of the sarcoidosis prompted high-resolution computed tomography of the chest. No hilar adenopathy or pulmonary abnormalities were identified.

The patient was diagnosed with primary cardiac sarcoidosis with predominant involvement of the epicardium and consequent AF and atrial flutter. He was treated successfully with initial doses of prednisone at 1 mg/kg/d for 3 months, before reduction to 40 mg/d. He experienced improvement of heart-failure symptoms, as evidenced by increased activity, duration, and distance achieved during exercise, which was accompanied by the resolution of his AF with sustained sinus rhythm and the resolution of his clinical symptoms, including syncope. After his discharge from our hospital, the patient was monitored at an outpatient clinic for 2 years. He had sinus rhythm at every visit.

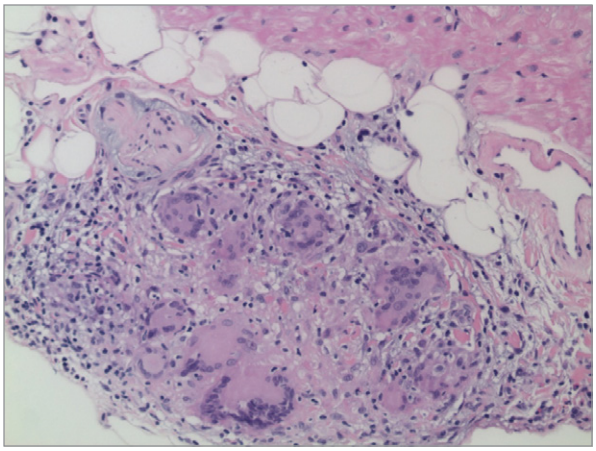

Fig. 1 *Photomicrograph shows a noncaseating granuloma with numerous multinucleated giant cells in the epicardium adjacent to epicardial adipose tissue and the myocardium (H & E, orig. ×20).*

Discussion

In the United States, sarcoidosis occurs most often in black women, who have an incidence of 39.1 per 100,000, followed by black men, who have an incidence of 29.8 per 100,000.[6,7] Compared to the 12.1 and 9.6 cases per 100,000 seen in white women and men, respectively, there is a clear racial disposition within the black population of the U.S. It is worth noting that in other parts of the world sarcoidosis is most prevalent in Scandinavia, Ireland, and Japan.[6,8,9] Cardiac sarcoidosis is an unusual manifestation of the disease characterized by granuloma formation within heart tissue. Although some studies suggest that cardiac involvement occurs in only 2% to 5% of cases of sarcoidosis, most data suggest that cardiac manifestations of the disease are largely unrecognized and underdiagnosed—partly because of the wide degree of manifestations.[3,6] Perhaps necropsy studies yield the most alarming data regarding the impact of cardiac sarcoidosis: 40% to 50% of those who die of sarcoidosis complications have evidence of concurrent (although not primary) cardiac sarcoidosis.[8-10]

Most of the literature pertaining to this topic originates in Japan, most likely because of the predominance

of cardiac sarcoidosis in that country and its contribution to death among elderly Japanese women. Cardiac involvement is estimated to be responsible for 58% to 85% of all sarcoidosis deaths in Japanese women.[8,9] It is crucial for us to consider cardiac sarcoidosis in patients who have other manifestations of the disease, especially if they are members of high-risk populations, which include Japanese, Scandinavian, and black patients.

Cardiac sarcoidosis can manifest itself in numerous forms, ranging from no symptoms to severe heart failure, and even to sudden cardiac death. The effects are directly related to the degree and location of granuloma formation and subsequent scarring. Sarcoidosis can produce granulomatous inflammation in any area of the heart, including the endocardium, myocardium, pericardium, conduction system, coronary arteries, and vena cava.[11-14] Frequently, patients present with various degrees of heart block and arrhythmia, with generalized symptoms of weakness, dizziness, dyspnea, palpitation, or chest pain.[8] Arrhythmias are especially important because of their potential contribution to morbidity and death. The pathophysiology of arrhythmias secondary to sarcoidosis could be a result of reentry circuits generated by granuloma and scar formation. One case report,[15] arising from the histopathologic examination of conduction pathways, described scar tissue that comprised nontransmural lesions and surviving myocardium, which acted as a reentrant substrate for the propagation of arrhythmias. Notably, this scar matrix with viable myocardium was amenable to radiofrequency ablation. Persistent atrial arrhythmia increases the risk for left atrial thrombus formation.

The left atrial thrombus that we had identified in our patient—in several echocardiograms before his surgery, and even after 6 months of anticoagulation—was absent when his heart was opened. There are several possible explanations for this. Spontaneous echo contrast could have been misinterpreted as a thrombus. Thrombus dislodged from the atrium could have entered the systemic circulation, although no thromboembolic event was registered in our patient. Finally, sarcoidosis in the form of a focal mass could have been mistaken for thrombus.

Ventricular arrhythmias are more common than supraventricular arrhythmias. One study revealed that only 1 out of 17 confirmed cases of cardiac sarcoidosis in North America included atrial flutter.[16] Retrospective analysis evaluating more than 100 biopsy-confirmed cases of cardiac sarcoidosis found that supraventricular arrhythmia occurred in 32% of cardiac sarcoidosis patients. Atrial fibrillation was the prevalent arrhythmia (18% of the total burden), followed by atrial tachycardia (7%), atrial flutter (5%), and other supraventricular tachycardias (2%).[17] Other rare presentations include extensive coronary artery involvement that presents with dyspnea, and thrombus formation in the atria and ventricles that presents with syncope.[11,12,14]

The diagnosis of cardiac sarcoidosis can be based on histologic or clinical observations. Although the discovery of granulomatous inflammation with nonnecrotic centers is the gold standard, it is often difficult to obtain such conclusive biopsies. Sarcoid tissue growth occurs in patchy distributions, and extensive progressive fibrosis is seen concurrently in new areas of inflammation. The patchy distribution, in combination with the variable stages of inflammation, makes conclusive biopsies difficult to obtain.[6,18] One study involved more than 1,200 patients who, over 15 years, underwent endomyocardial biopsies to identify causes of the cardiomyopathy. Histologic identification of the disease could be confirmed in only 7 of the 28 patients who met the clinical criteria for cardiac sarcoidosis.[19] The results of a recent study among patients with severe heart failure who needed a left ventricular assist device (LVAD) suggest that left ventricle core examination at the time of LVAD implantation can clarify the diagnosis of granulomatous myocarditis in patients with nonspecific clinical manifestations and perhaps assist in their management.[20] The current guidelines for diagnosing cardiac sarcoidosis, published in 2006, are from the Japanese Society of Sarcoidosis and Other Granulomatous Disorders.[6,21]

When biopsy is impossible or unproductive, imaging is the next diagnostic method of choice. Radionuclide scintigraphy using thallium 201, gallium 67, or technetium 99m has shown a wide range of sensitivity, from 18% to 64%, with data suggesting that technetium is the most accurate agent.[6,8,22] Positron emission tomography (PET) scanning is more reliable, with sensitivities between 82% and 100%. However, the reported specificity for PET varies widely, between 39% and 91%. Because PET incorporates the analysis of F-fluorodeoxyglucose uptake measurements and perfusion imagery, it is able to accurately detect cardiac sarcoidosis.[6,8,22] The disadvantages of PET are its higher cost, lesser availability, and extraneous exposure of the patient to ionizing radiation—this last is complicated by the potential need for serial scans to monitor disease progression. Therefore, the most frequently used diagnostic method is magnetic resonance imaging (MRI). Sensitivities have been reported between 75% and 100%, with specificity at up to 78%. Lower cost, greater availability, and lack of radiation exposure are advantages of MRI. However, the prevalence of implanted devices, such as pacemakers or defibrillators, is a substantial limitation to its use.[6,8,10] This was a limitation in our case as well, because our patient had an implantable cardioverter-defibrillator.

Symptomatic treatment by means of diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers serve as the fundamentals of cardiac sarcoidosis therapy. The next course of action, the addition of high doses of steroids, is supported by prospective and retrospective trials that have shown

evidence of preserved LVEF, maintained left ventricular function, 75% survival rates at 5 years, and 61% survival rates at 10 years.[8] Higher survival rates were noted in patients whose LVEFs were greater than 0.50.[8] Early in the disease process, cardiac sarcoidosis is apparently amenable to high-dose corticosteroid therapy, which is recommended at a starting dose of 60 mg every other day, tapered over the following several months to 10 mg every other day. Several studies have concluded that individuals with an LVEF of less than 0.30 or with extensive scar formation were unlikely to receive much benefit from steroid therapy, whether at low or high doses.[8] This was most likely the consequence of irreversible fibrosis in advanced stages of sarcoidosis.[8] Cardiac function should be evaluated with imaging techniques such as cardiac MRI, at 3 months after initial treatment and again at 9 months, and yearly after that. Discontinuation of steroid therapy is controversial because approximately 25% of cases relapse after cessation.[6] It might be beneficial to maintain the lowest steroid dose that curtails the disease process while attempting to avoid the potential sequelae of steroid therapy—such as hyperglycemia, weight gain, fluid retention, immune suppression, and osteoporosis.[6,8]

Other immunosuppressive therapies used to treat sarcoidosis with limited success include infliximab, methotrexate, azathioprine, antimalarial agents, cyclophosphamide, pentoxifylline, and thalidomide.[6] For the treatment of cardiac sarcoidosis patients who have heart failure with reduced LVEF, sustained ventricular tachycardia, or a history of ventricular fibrillation, cardiac defibrillators carry class IIa recommendations on the basis of the 2008 American College of Cardiology and American Heart Association guidelines.[8] The prognosis of cardiac sarcoidosis is quite variable: the 5-year survival rate ranges from 60% to 90%.[4,6] New York Heart Association functional class, left ventricular function, and LVEF all seem to be prognostic indicators.[6,8] Early identification and treatment of cardiac sarcoidosis is associated with resolution of symptoms, higher functional status, and increased survival rates.[6,8]

Conclusion

Cardiac sarcoidosis is an important differential diagnosis to consider because of its progressive nature and its potential for treatment with pharmacologic, surgical, and catheter-based interventions. We present an illustrative case of this disease that began with an episode of syncope, new-onset atrial arrhythmias refractory to pharmacologic therapy, and atrial thrombus formation. This patient's atrial arrhythmia was successfully treated with a hybrid operation involving resection of the atrial appendage, an Epicor maze procedure, and radiofrequency ablation. The cardiac sarcoidosis was successfully managed with corticosteroid therapy. The patient enjoyed significantly improved cardiac function, as evidenced by his increased level of activity and the resolution of his clinical symptoms.

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