Short Communication

Coronary Sarcoidosis Presenting as Acute Coronary Syndrome

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ABSTRACT

Sarcoidosis is a systemic disorder of uncertain etiology characterized by noncaseating granulomatous inflammation. The disease often involves the heart on autopsy, but the antemortem diagnosis of cardiac sarcoidosis is frequently missed. Cardiac involvement usually includes granulomatous inflammation or fibrosis of the myocardium, conduction system, or pericardium. We now describe a case of epicardial coronary involvement by sarcoidosis, where the diagnosis was made by surgical biopsy of the coronary artery in an African American man presenting with acute coronary syndrome and recurrent symptomatic restenosis following coronary intervention. The case extends the spectrum of common cardiac syndromes that cardiac sarcoidosis can masquerade as and highlights the importance of maintaining a high index of suspicion for early recognition and instituting specific treatment that might improve prognosis. A review of the literature also suggests the need for improvement in diagnostic approaches and prospective clinical trials to establish the best management strategy for this disease.

Introduction

Sarcoidosis is a systemic disorder of uncertain etiology characterized by noncaseating granulomas and increased cellular immune response at sites of disease activity. Almost any organ may be involved. The first report of cardiac sarcoidosis was in 1929,[2] with subsequent autopsy studies reporting cardiac involvement in up to 76% of patients with sarcoidosis.[3] However, a antemortem diagnosis of cardiac sarcoidosis is frequently overlooked because the disease masquerades as many commonly encountered clinical syndromes.[4–7] Nonetheless, a high index of suspicion is vital for early recognition and institution of aggressive specific treatments that might improve prognosis

Chest pain is a frequent presenting symptom, but is often too nonspecific to initiate a search for sarcoidosis. In the only series specifically examining the significance of anginal chest pain in patients with sarcoidosis, perfusion abnormalities indicative of myocardial ischemia were demonstrated on thallium 201 scintigraphy in half the cases with angina but in none of the controls without angina.[8] However, pathologic evidence of epicardial coronary involvement was not available until recent isolated case descriptions in explanted hearts.[9,10] We now describe a case of coronary sarcoidosis diagnosed by surgical biopsy of the coronary artery in a man presenting with recurrent angina and aggressive restenosis following coronary intervention.

Case Description

A 68-year-old African American man presented in February 2005 with an acute anterior ST-elevation myocardial infarction and underwent uncomplicated percutaneous coronary intervention to the left anterior descending artery. His history was significant only for a submental swelling in 1999, which revealed noncaseating granulomas on biopsy, for which he was treated with 6 weeks of prednisolone. He had no modifiable cardiovascular risk factors, unusual occupational or pet exposures, or family history of sarcoidosis or cardiovascular disease.

He was discharged well but experienced unstable angina within a month. Repeat coronary angiography showed extensive restenosis in the body of the stent (Figure 1). Target vessel revascularization (TVR) was performed with satisfactory angiographic results. Despite compliance with maximal medical therapy, he presented 3 more times over the following year with unstable angina and aggressive culprit vessel restenosis on angiography, which led to repeat TVR. Transthoracic echocardiography showed a left ventricular (LV) ejection fraction of 52%, mild ventricular septal thickening (12 mm; LV mass index 87 g/m^2), no significant valvular disease, and normal right ventricular size and function. Regional wall motion abnormalities were noted in the anterior and septal LV segments, consistent with a previous myocardial infarction.

At his last recurrence, in December 2006, a decision was made to proceed with coronary artery bypass surgery. Intraoperatively, a significant inflammatory reaction was

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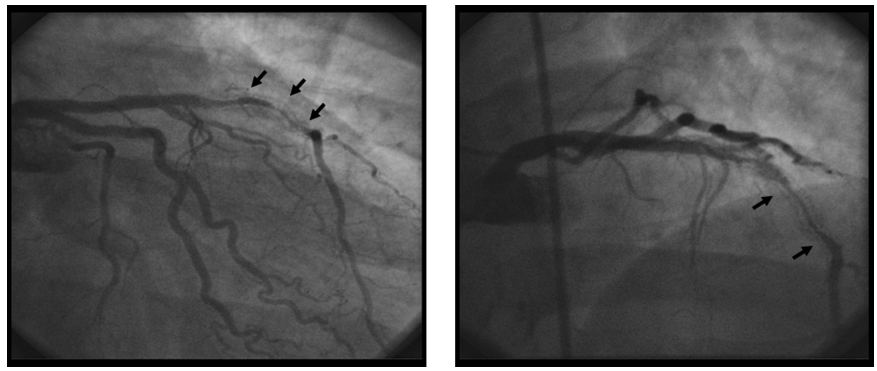

Figure 1. Coronary angiogram showing extensive restenosis within the body of the left anterior descending artery stent (arrows; A). Note the tapered narrowing at the outer edges of the stent (arrows; B).

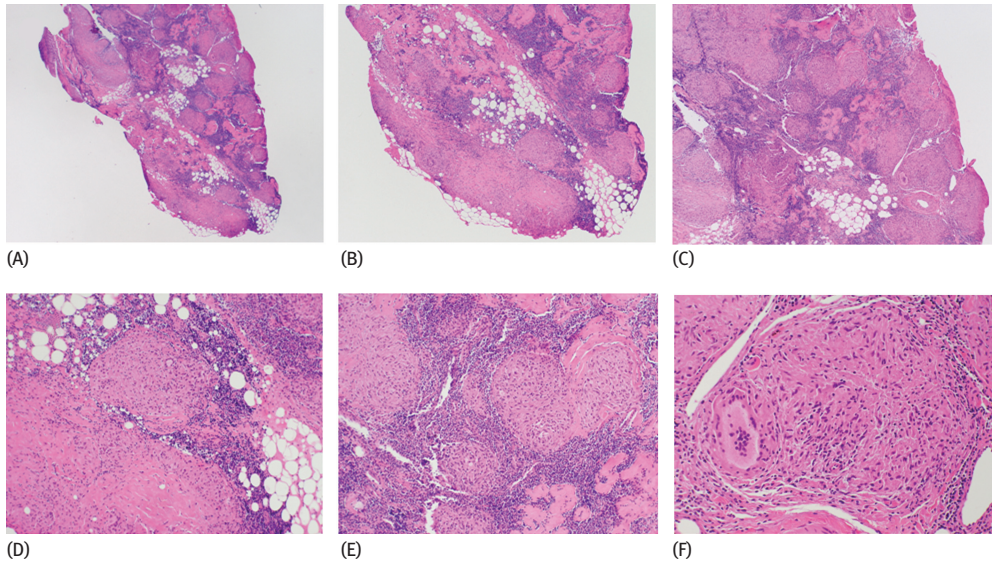

Figure 2. Histological sections from the epicardium over the right coronary artery showing extensive inflammatory infiltrates throughout the specimen on low magnification (A–C), with noncaseating granulomas confirmed on higher magnification (D–E). Close-up of a granuloma (F) showing a classic multinucleated giant cell.

noted around the stented left anterior descending artery region along with mediastinal lymphadenopathy. Biopsy of the epicardium from the right coronary artery revealed noncaseating granulomatous inflammation (Figure 2). Special stains for fungi and acid-fast bacilli were negative. A diagnosis of sarcoidosis was made, and steroid therapy (prednisolone 60 mg/d) was initiated. A systemic review did not reveal evidence of medium vessel vasculitis, aortitis, or active disease elsewhere. To evaluate whether the myocardial abnormalities were a result of granulomatous inflammation or ischemia, a cardiac MRI with gadolinium was obtained (Figure 3). In the mid-LV anteroseptum and inferoseptum, hypokinetic segments were associated with myocardial thinning and subendocardial hyperenhancement on delayed enhancement images, consistent with a prior myocardial infarction (Figure 3A). In addition, a small focus of mid myocardial hyperenhancement in the mid–LV lateral wall was seen without associated segmental thinning or hypokinesis, suggesting a focus of granulomatous sarcoid involvement. Further postgadolinium sequences of higher resolution showed thickened coronary arterial walls with epicardial hyperenhancement consistent with coronary vasculitis (Figure 3B). Continued treatment of sarcoidosis included tapering doses of prednisolone with the addition of mycophenolate mofetil (Cellcept, 500 mg twice per day) when the prednisolone dose was reduced to 5 mg/d. His

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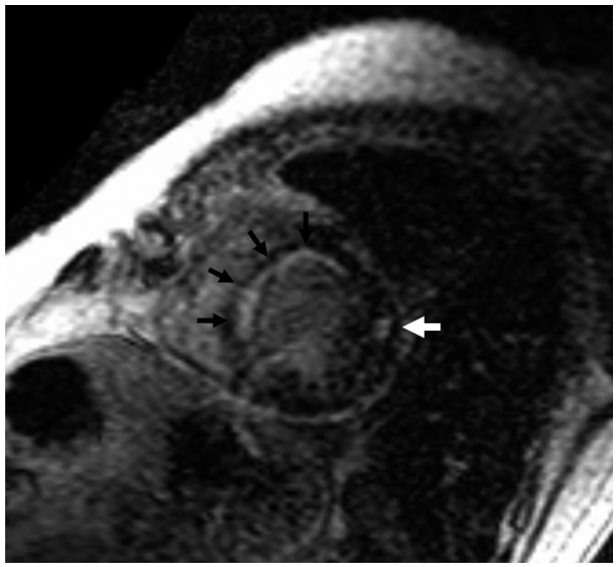
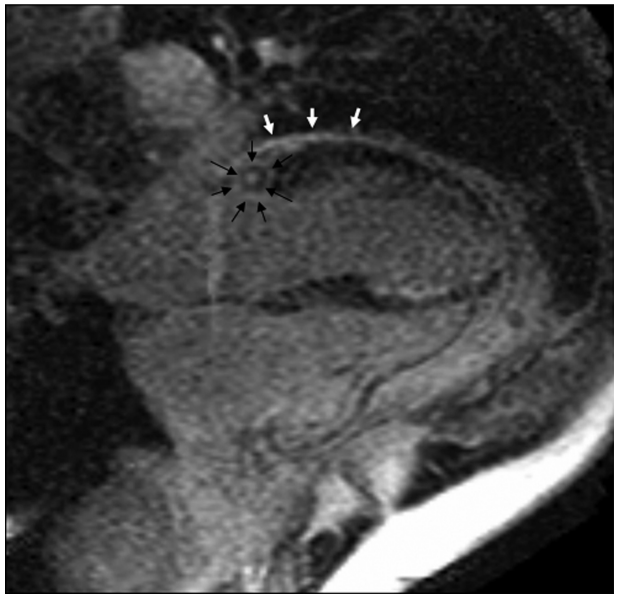


(A)



(B)

Figure 3. Cardiac magnetic resonance images with delayed gadolinium enhancement. (A) Short axis image at the midventricle shows subendocardial hyperenhancement extending through 50% of the wall thickness in the anteroseptum and inferoseptum (black arrows). This was associated with hypokinesis and myocardial thinning in these segments, consistent with prior myocardial infarction. In addition, a small focus of midmyocardial hyperenhancement is shown in the lateral wall that was not associated with segmental thinning or hypokinesis, suggesting a focus of granulomatous sarcoid involvement (white arrow). (B) Four-chamber image showing thickening of the wall of the right coronary artery (black arrows) as well as hyperenhancement of the overlying pericardium (white arrows), consistent with coronary vasculitis.

angiotensin-converting enzyme (ACE) level remained completely suppressed, and there was no further recurrence of angina or symptoms of active disease elsewhere.

Discussion

Sarcoid coronary vasculitis has only recently been recognized as a pathologic entity.[9,10] To the best of our knowledge, this is the first description of the disease presenting as an acute coronary syndrome complicated by aggressive recurrent target lesion restenosis, where antemortem diagnosis was confirmed histologically by surgical biopsy. The case expands the spectrum of clinical manifestations that cardiac sarcoidosis can mimic and highlights the role of inflammation in the pathophysiology of coronary artery disease.

The key role that inflammation plays in the pathophysiology of coronary artery disease has been increasingly recognized. Atherosclerosis is now thought to essentially represent an inflammatory disease, in which immune cells accumulate in early atherosclerotic lesions, released cytokines accelerate progression, and inflammatory activation causes destabilization of the lesion, manifesting as acute coronary syndromes.[11] This inflammatory activation is not restricted to the particular lesion but involves the entire coronary tree.[12] In our patient, widespread inflammation in the coronary tree was evident because gross abnormalities of both coronary arteries were noted on direct visual inspection, whereas histological proof of granulomatous inflammation was obtained in the right coronary artery. That the left-sided events were solely a result of a nonspecific foreign body reaction to the stent seems less likely given the right-sided changes.

Cardiac sarcoidosis is a difficult diagnosis to make. As this case illustrates, the disease is a great mimicker of many common clinical entities. A high index of suspicion and early recognition of atypical features of common cardiac syndromes may offer first clues to the diagnosis. For example, this patient's African American ethnicity and history of noncaseating granulomatous inflammation of the submental node were early clues. Further, his lack of metabolic risk factors, as well as the tapered edges of the culprit stenosis on angiography rather than abrupt edges as with a ruptured atherosclerotic plaque, may raise suspicion for a nonatherosclerotic cause of inflammation. Once there is diagnostic suspicion, efforts should be made to confirm the diagnosis of cardiac sarcoidosis. This, too, can be very challenging because the gold standard, endomyocardial biopsy, performed "blindly" at the right ventricular septal wall, has a sensitivity of only 25%.[13] The low diagnostic sensitivity is likely largely a result of focal involvement[5] with the resultant sampling error. Even when granulomatous inflammation is confirmed on histology, other causes of granulomatous lesions must be excluded by special stains (acid-fast stain for mycobacteria, fungal stains) and appropriate serological tests. No ideal noninvasive

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screening or confirmatory test exists. Although elevated serum ACE concentrations and hypercalcemia support the diagnosis, these tests are not specific for sarcoidosis. Newer imaging modalities have emerged as potentially useful diagnostic tools. Cardiac magnetic resonance imaging (MRI) with gadolinium enhancement may show increased signal intensity in affected myocardium, increasing the diagnostic sensitivity to 83%,[14] and changes may normalize during steroid treatment, reflecting clinical improvement. However, similar changes may also be seen in nonspecific myocarditis, leading some investigators to propose targeted endomyocardial biopsy guided by enhancing areas on magnetic resonance imaging as the best approach to optimize specificity and overall diagnostic yield.[15]

Specific treatment of cardiac sarcoidosis is largely based on expert opinion.[16–18] Corticosteroids are generally recommended, but there are no prospective data to guide the timing, intensity, or duration of steroid therapy in cardiac sarcoidosis. The risk of recurrence after steroids are tapered or discontinued is unknown. Observational studies have however suggested that steroids may prolong survival in patients who require permanent pacemakers.[19] In the absence of trial data, we recommend prednisolone started at 1 mg/kg per day for 2 wk in the absence of contraindications, then decreased every 2 weeks as follows: 0.75 mg/kg per day, then 0.5 mg/kg per day, then 20, 15, and 10 mg per day, followed by a decrease every 4 weeks in 1-mg decrements until the taper is complete. Additionally, in our experience we have found that mycophenolate mofetil started after the first month of steroid therapy allows steroids to be tapered to 5 mg per day within 2 months without disease recurrence. Other than specific therapy for sarcoidosis, general measures should be instituted according to the presenting cardiac syndrome, such as antifailure, anti-ischemic, or antiarrythmic (both medical and device) therapy. Finally, cardiac transplantation can be considered for end-stage disease.[20]

Conclusion

In conclusion, this initial report of sarcoid coronary vasculitis, manifesting as acute coronary syndrome complicated by aggressive restenosis, highlights the need for a high index of suspicion for the diagnosis of cardiac sarcoidosis. Although histological diagnosis remains the gold standard, promising new, noninvasive imaging modalities such as cardiac MRI may offer diagnostic utility. The importance of establishing the diagnosis lies in the potential for early specific therapy to improve prognosis. Ongoing studies such as the National Heart, Lung and Blood Institute–sponsored multicenter case–control study (ACCESS)[21] will advance our understanding of this disease and hopefully lead to much-needed prospective clinical trials of available immunosuppressive therapy.

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