

CLINICAL VIGNETTE

A Case of Infiltrative Cardiomyopathy

Elmar Malek, Danica Lomeli M.D., Ramin Tabibiazar M.D., and Ravi H. Dave M.D

A 75-year-old woman with chronic atrial fibrillation, osteoporosis complicated by vertebral fractures, presented to cardiology with three weeks of progressive exertional chest pressure and dyspnea. The patient was limited in her daily activities by her cardiopulmonary symptoms. She was on Warfarin, and was rate-controlled on beta blockers and Digoxin. Her physical examination was notable for mild fluid overload and a 2/6 systolic murmur.

She underwent non-invasive cardiac evaluation. Transthoracic echocardiogram showed a dilated left ventricle with left ventricular systolic dysfunction with EF of 30% and segmental wall motion abnormalities with aneurysmal formation, left-atrial enlargement, and thickening of mitral valve apparatus associated with mild moderate mitral regurgitation. Stress testing showed poor functional capacity with EKG tracings showing stress-induced ST depressions in the inferior leads and frequent PVCs. Nuclear imaging showed large fixed perfusion defects, suggesting stress-induced ischemia.

She underwent invasive cardiac catheterization. Coronary angiogram showed no evidence for obstructive disease. Left ventriculogram showed LV systolic dysfunction, regional wall motion abnormalities and aneurysmal formation in the inferolateral wall. Cardiac MRI showed areas of chronic fibrotic changes compatible with cardiac sarcoid. There were wall motion abnormalities and paradoxical bulging during systole, severe left ventricular systolic dysfunction, and fibrosis of the papillary muscles causing immobility of the leaflets and resulting in mitral regurgitation.

Cardiac involvement in sarcoidosis was first described in 1929 by Bernstein and has since become increasingly recognized.¹ At least 25% of patients with sarcoidosis in the U.S. have myocardial involvement, which accounts for 13-25% of deaths from sarcoidosis.¹ Cardiac sarcoidosis (CS) presents with a wide range of clinical manifestations that mimic more common conditions.²

Pathophysiology

The etiology of CS remains poorly understood. There are potential environmental, occupational, and infectious factors associated with an immunologic response which may play a role in the pathophysiology of sarcoidosis. It is most likely initiated by an unidentified antigen or antigens, triggering an immune response leading to the formation of non-caseating,

granulomatous lesions.^{1,3} Implicated factors include infectious (*Mycobacterium tuberculosis*, *Mycoplasma* species, *Corynebacteria* species, spirochetes), environmental (aluminum, pollen, clay, talc), and occupational etiologies.^{1,2} Genetic factors are also thought to contribute, considering that sarcoidosis is more likely to occur in monozygotic twins. Associations between sarcoidosis and HLA-typing, tumor necrosis factors, and immunoglobulin receptor genes have been reported varying by race and ethnic background.^{1,2} Thus, the etiology of sarcoidosis is complex and likely a heterogeneous group of disorders resulting in granulomatous inflammation.²

The pathologic mechanisms of cardiac sarcoid are also unknown but appears to be secondary to architectural disruption from the sarcoid granulomas and localized destruction of normal tissues. There is no evidence to suggest the release of secondary mediators causing surrounding tissue damage.^{2,3} Post-mortem histologic findings reveal that CS may involve any part of the heart, including the pericardium, endocardium, and, most commonly, the myocardium.⁴ The most commonly affected myocardial locations are the left ventricular free wall and ventricular septum followed by the right ventricle and atrial walls.^{1,2,4}

Presentation

Clinical manifestations of CS range from asymptomatic conduction abnormalities to congestive heart failure and, most notably, sudden cardiac death.³ Conduction abnormalities are common in CS and can disturb affect any location in the conduction system.² Complete heart block is a common finding in patients with overt evidence of CS, frequently presenting with syncope. Ventricular tachycardia (VT) is reported in 23% of patients.^{1,2} CS may affect the atrioventricular node or bundle of His, resulting in P-R interval prolongation or other intraventricular conduction delays. Both heart block and VT can lead to sudden death, which may be the initial presenting sign of CS.² Supraventricular arrhythmias have also been reported, including ectopic atrial rhythm, atrial fibrillation/flutter, and sinus arrest.

Congestive heart failure is the second most frequent cause of death in CS patients and can manifest as either systolic or diastolic heart failure.^{1,3} When compared to patients with idiopathic dilated cardiomyopathy and similar degree of LV dysfunction, CS patients with heart failure have poorer 3- and 5-year survival³.

Valvular dysfunction may occur due to CS. Mitral regurgitation may occur secondary to LV systolic dysfunction and LV dilation or due to involvement of papillary muscle with

granulomas. Tricuspid regurgitation and aortic valve incompetence have also been reported. Although rare, aneurysms of the aorta (thoracic and abdominal) have been documented.

Less frequent clinical manifestations of CS include chest pain, ECG findings that may mimic transmural myocardial infarction, pericardial effusions, constrictive pericarditis, and tamponade.¹ CS may affect coronary arteries, resulting in coronary spasm or vasculitis. Regional wall motion abnormalities and aneurysms may be present on cardiac imaging and may not be in a coronary distribution. Pericardial effusions have been reported in 19% of patients with CS.²

Diagnosis

The diagnosis of CS can be difficult, particularly in patients without evidence of systemic sarcoidosis.¹ Currently, there is no single diagnostic test.³ However, due to potential life-threatening complications and potential benefits of treatments, patients should be evaluated carefully for CS.² The U.S. lacks a standardized diagnostic approach for CS and thus guidelines written by the Japanese Ministry of Health and Welfare in 1993 are commonly followed.²

In patients with known extra-cardiac sarcoidosis, an initial assessment includes a detailed history, physical exam, surface ECG, and transthoracic echocardiogram (TTE), followed with Holter monitoring and additional cardiac imaging (MRI, PET, SPECT) in case of positive results.² Endomyocardial biopsy revealing non-caseating granulomas remains the 'gold standard'; however, it is not required for the diagnosis. Endomyocardial biopsy has low sensitivity (less than 20%) for the diagnosis of CS due to the patchy distribution of non-caseating granulomas.⁵ In addition, routine endocardial biopsy is not desirable due to its invasiveness.^{3,6} Echocardiographic findings include abnormal wall motion, ventricular aneurysms, pericardial effusions, left ventricular systolic or diastolic dysfunction, valvular abnormalities, and abnormal septal wall thickness.²

Perfusion defects by thallium-201 radionuclide testing or abnormal accumulation by gallium-67 have been shown in CS³, although they have been supplanted by PET and MRI scanning.⁶

Positron emission tomography (PET) scanning has become a key diagnostic technique for active CS, where uptake of 18F-fluorodeoxyglucose (¹⁸FDG) into inflammatory cells can be utilized to assess active inflammation and response to steroid treatment in CS.^{3,6}

Cardiac MRI (CMR) may detect subclinical myocardial involvement even in patients lacking cardiac symptoms.⁷ Cardiac MRI may detect areas of acute inflammation, and it may assess fibrosis and scar formation using gadolinium,

Management

Therapy is targeted to reduce inflammation, minimize fibrosis, and prevent cardiac dysfunction. Corticosteroids are the mainstay of CS treatment and may halt the progression of granulomata and improve survival. Steroids have not been shown to consistently reduce the incidence of ventricular arrhythmias.^{1,2} Optimal dosing and duration of corticosteroid treatment is still undetermined, despite their extensive use³.

Treatment of associated heart failure follows standard heart failure guidelines with a more measured approach in beta-blocker use, as they may precipitate heart block, and amiodarone use, which may exacerbate restrictive lung disease in sarcoidosis.^{1,3}

Placement of internal cardioverter-defibrillators (ICD) is highly recommended in patients with sarcoidosis and history of non-sustained VT.¹

Additionally, surgical resection of ventricular aneurysms in refractory VT may become necessary.⁵ Cardiac transplantation is an option for younger patients with class IV heart failure or refractory arrhythmias.³ Recurrent sarcoid after transplant has been reported.³

Prognosis

Data on CS prognosis is quite variable with 5-year survival ranging from 60-90% in patients with treatment and preserved systolic function.² Important independent predictors of mortality include New York Heart Association (NYHA) functional class, left ventricular end-diastolic diameter, and sustained VT.^{1,3}

Conclusion

Given the increased risk of sudden death, early recognition of cardiac involvement in sarcoidosis is important. The diagnosis of CS, despite advances in imaging remains a challenge, and is underdiagnosed. Therapy for CS remains unstandardized, although corticosteroids are utilized as first-line treatment along with additional therapies including antiarrhythmic agents, implantable devices, and heart transplantation.

REFERENCES

1. **Doughan AR, Williams BR.** Cardiac sarcoidosis. *Heart*. 2006 Feb;92(2):282-8. Review. PubMed PMID: 16415205; PubMed Central PMCID: PMC1860791.
2. **Kim JS, Judson MA, Donnino R, Gold M, Cooper LT Jr, Prystowsky EN, Prystowsky S.** Cardiac sarcoidosis. *Am Heart J*. 2009 Jan;157(1):9-21. doi:10.1016/j.ahj.2008.09.009. Epub 2008 Nov 12. Review. PubMed PMID: 19081391.
3. **Habersberger J, Manins V, Taylor AJ.** Cardiac sarcoidosis. *Intern Med J*. 2008 Apr;38(4):270-7. doi: 10.1111/j.1445-5994.2007.01590.x. Review. PubMed PMID: 18380701.

4. **Roberts WC, McAllister HA Jr, Ferrans VJ.** Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). *Am J Med.* 1977 Jul;63(1):86-108. Review. PubMed PMID: 327806.
5. **Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H.** Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. *Am Heart J.* 1999 Aug;138(2 Pt 1):299-302. PubMed PMID: 10426842.
6. **Lynch JP 3rd, Hwang J, Bradfield J, Fishbein M, Shivkumar K, Tung R.** Cardiac involvement in sarcoidosis: evolving concepts in diagnosis and treatment. *Semin Respir Crit Care Med.* 2014 Jun;35(3):372-90. doi: 10.1055/s-0034-1376889. Epub 2014 Jul 9. Review. PubMed PMID: 25007089; PubMed Central PMCID: PMC4253029.
7. **Vignaux O, Dhote R, Duboc D, Blanche P, Dusser D, Weber S, Legmann P.** Clinical significance of myocardial magnetic resonance abnormalities in patients with sarcoidosis: a 1-year follow-up study. *Chest.* 2002 Dec;122(6):1895-901. PubMed PMID: 12475823.

Submitted June 19, 2017