CME CREDIT

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Cardiac sarcoidosis: A cause of infiltrative cardiomyopathy

A 52-YEAR-OLD MAN presents to a hospital emergency department after 6 months of intermittent episodes of palpitations and shortness of breath. He is admitted to a telemetry unit, where he has frequent episodes of self-terminating ventricular tachycardia at 180 beats per minute (FIGURE 1).

Medical history

The patient has a history of hypertension. Holter monitoring 1 month ago documented frequent multiform premature ventricular complexes.

Physical examination

Vital signs: temperature 36.9°C (98.4°F), blood pressure 142/86 mm Hg, pulse 90, respiratory rate 20.

Cardiac examination: regular rate and rhythm, no murmurs, gallops, rubs, or jugular venous distention.

Chest: clear to auscultation without rhonchi or rales.

Diagnostic tests

Chest radiograph: mild bilateral hilar prominence and mild apical infiltrates (FIGURE 2).

Right and left cardiac catheterization: mild diffuse disease, 50% focal stenosis of the distal left anterior descending artery, ejection fraction 30%.

Cine magnetic resonance imaging (to evaluate right ventricular dysplasia): normal.

Electrophysiologic study: easily inducible rapid ventricular tachycardia without focal lesion that can be ablated.

Computed tomography of the chest with contrast: bilateral hilar adenopathy with carinal and mediastinal adenopathy, diffuse interstitial infiltrates throughout both lungs (FIGURE 3).

Pulmonary function tests: mild restrictive pattern.

Purified protein derivative (tuberculin) and **anergy panels:** normal.

Bronchoscopy with biopsy and bacterial cultures: non-necrotizing granulomas, no infectious etiology identified.

The diagnosis of sarcoidosis is considered.

The patient has a history of hypertension and premature ventricular complexes

The patient's electrocardiogram on admission

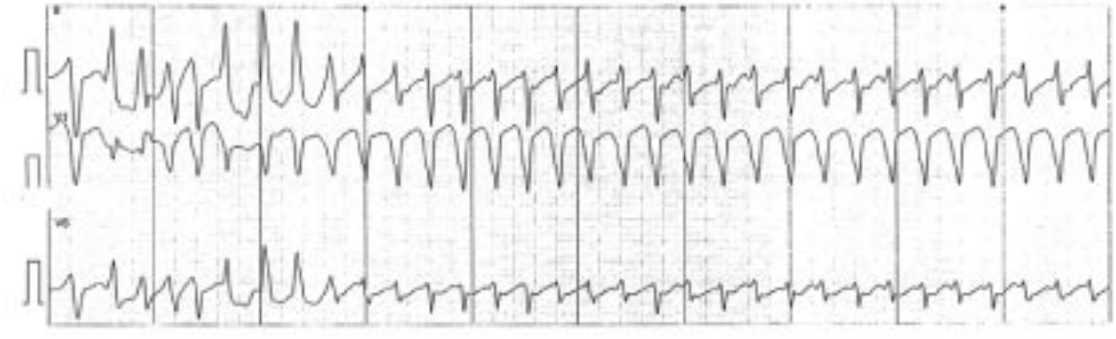

FIGURE 1. Self-terminating ventricular tachycardia.

The patient's chest radiograph on admission

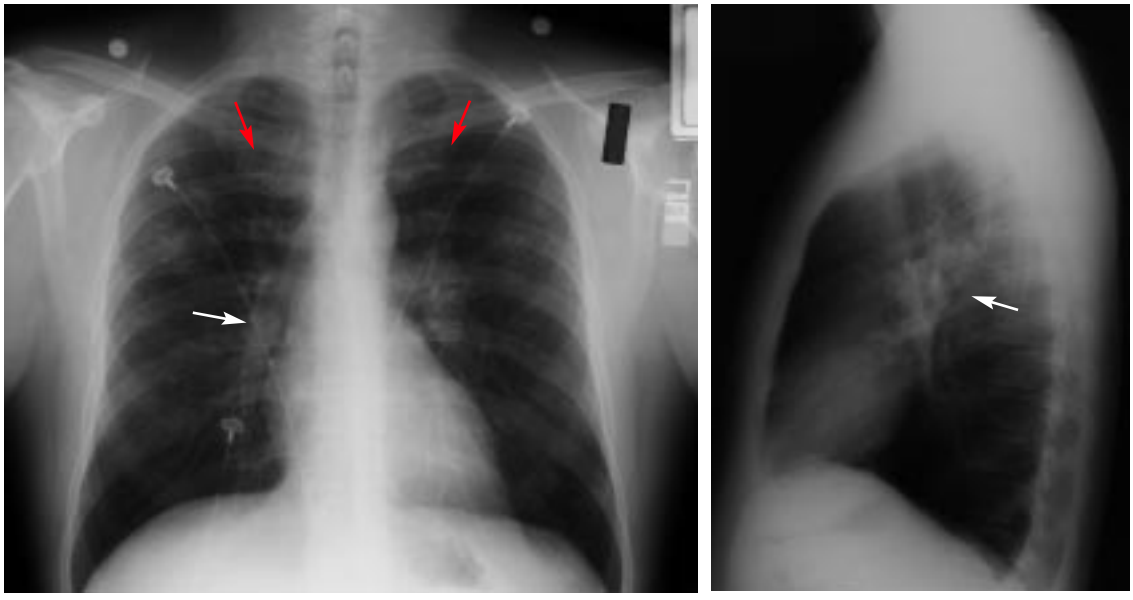

FIGURE 2. Anterior-posterior and lateral chest radiograph demonstrates hilar prominence (white arrows) and apical infiltrates (red arrows).

Cardiac sarcoidosis can mimic myocardial infarction

CARDIAC MANIFESTATIONS

1 What is the most common cardiac manifestation of sarcoidosis?

- ❑ Complete heart block
- ❑ Ventricular arrhythmias
- ❑ Congestive heart failure
- ❑ Supraventricular tachycardia

Complete heart block is the most common finding in patients with clinically evident cardiac sarcoidosis.[1] Clinical manifestations depend on the location and extent of granulomatous inflammation within the myocardium.

First-degree heart block also often occurs, due to inflammation around the atrioventricular node or bundle of His. Although these lesions may be clinically silent initially, they may progress directly to extensive atrioventricular node infiltration and cause complete heart block.

Any patient with sarcoidosis who presents with syncope or presyncope should be evaluated for complete heart block with electrocardiography (ECG) and Holter monitoring.[1]

Ventricular arrhythmias such as premature ventricular complexes and nonsustained ventricular tachycardia are also common, seen by ECG in as many as 22% of patients with sarcoidosis.[2] Sudden death from ventricular tachyarrhythmias and complete heart block accounts for up to 65% of deaths from cardiac sarcoidosis.[3]

Congestive heart failure is the second most common cause of mortality in patients with cardiac sarcoidosis and can be categorized as either systolic or diastolic dysfunction. Granulomatous inflammation within the myocardium may cause loss of functioning myocardium, scarring with fibrotic changes, or both.[4]

Because cardiac manifestations of sarcoidosis may precede, follow, or occur at the same time as other systemic symptoms of the disease, diagnosing cardiac sarcoidosis as the cause of cardiomegaly and congestive heart failure can be challenging. Cardiac sarcoidosis should be suspected in a young patient who has congestive heart failure with advanced atrioventricular block, abnormal cardiac wall thickness, regional wall motion abnormalities, or perfusion defects that predominantly affect anteroseptal and apical regions and that improve with stress (a "reverse redistribution" pattern).[5]

Supraventricular arrhythmias (eg, atrial flutter, fibrillation, and paroxysmal atrial tachycardia) and valvular dysfunction may occur in cardiac sarcoidosis but are less common.[6]

The patient's CT scan on admission

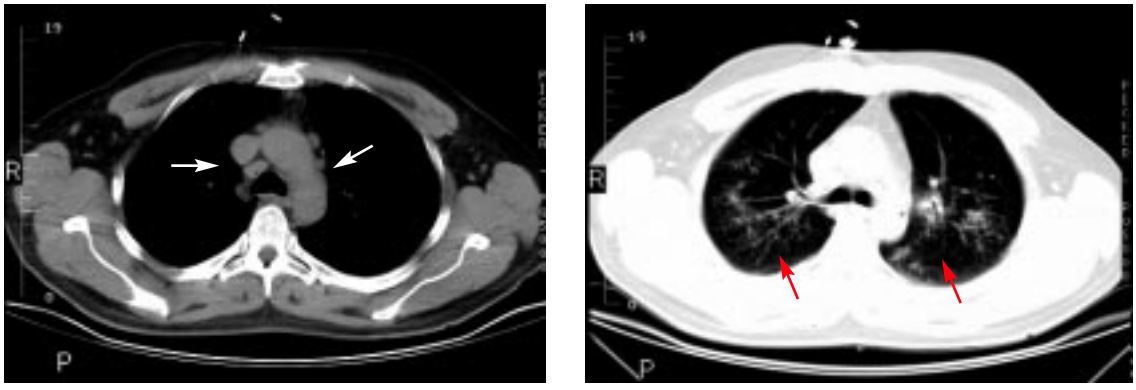

FIGURE 3. Computed tomographic scan of the chest demonstrates the bilateral hilar adenopathy (white arrows) as well as diffuse interstitial infiltrates (red arrows) throughout both lungs.

PSEUDOINFARCTION

Cardiac sarcoidosis may mimic myocardial infarction in its symptoms and electrocardiographic findings, a presentation called a *pseudoinfarction*. Localized granulomatous inflammation may mimic a transmural infarction on ECG and correlate with gross pathology. Although granulomatous vasculitis may cause partial or complete narrowing of coronary arteries, thrombosis and aneurysm formation are rare.[3]

Coronary angiography is needed to rule out coronary artery disease; however, in patients with traditional risk factors for coronary artery disease (such as our patient), it is difficult to determine the exact cause of any coronary narrowing seen on the angiogram. Thallium or technetium-99m-based perfusion scanning may help distinguish coronary artery disease from cardiac sarcoidosis: sarcoidosis may mimic coronary artery disease during imaging at rest, but the perfusion defects of cardiac sarcoidosis lessen during stress.[7]

MANAGING VENTRICULAR ARRHYTHMIAS

2 How should a patient with ventricular arrhythmias and a new diagnosis of sarcoidosis be managed?

- ❑ Placement of an implantable cardioverter-defibrillator (ICD)
- ❑ Amiodarone (Cordarone) to control the arrhythmia
- ❑ Heart transplantation
- ❑ Rate control with a beta-blocker

ICD placement may be a good option. Guidelines for deciding which patients should receive an ICD were published in 1998 by a joint task force of the American College of Cardiology and the American Heart Association and in 2001 by the working groups on arrhythmias and cardiac pacing and a task force on sudden cardiac death of the European Society of Cardiology.

ICD placement for patients with cardiac sarcoidosis has not been thoroughly evaluated on the basis of the presence of disease alone. However, congestive heart failure with nonsustained multiform premature ventricular contractions is a class 1 indication for ICD placement.[8] (Class 1 refers to level of evidence on a scale of 1 [strongest] to 5 [weakest]).

Given that sudden death due to ventricular tachyarrhythmias or conduction blocks accounts for 30% to 65% of deaths due to cardiac sarcoidosis, some experts recommend ICD placement in any patient with sarcoidosis and ventricular tachycardia.[9] Evidence supporting this recommendation is that ventricular arrhythmias tend to recur even with maximal antiarrhythmic drug therapy.[9]

Amiodarone is indicated to control hemodynamically stable ventricular tachycardia, polymorphic ventricular tachycardia, or wide-complex tachycardia of uncertain origin.[8]

However, amiodarone has several drawbacks that would make it a less attractive option

On thallium scanning, the perfusion defects of cardiac sarcoidosis lessen during stress

for a patient with newly diagnosed sarcoidosis. It is a class D drug (shown to be harmful to human fetuses) and is therefore contraindicated for pregnant women. Women are at slightly higher risk for sarcoidosis, and peak rates are at 20 to 29 years.[10] Used long-term, amiodarone can also cause irreversible pulmonary fibrosis, further exacerbating a condition already inclined to cause restrictive lung disease. Furthermore, it can cause hypo- or hyperthyroidism as well as corneal deposits. Therefore, when considering using amiodarone, the physician should obtain baseline pulmonary function tests, thyroid function tests, and an eye examination.

Cardiac transplantation is indicated in patients with severe, irreversible sarcoid-induced heart failure, but probably not in someone with newly diagnosed disease. Whether the disease recurs in the donor organ has not been sufficiently studied.[10]

Beta-blockers have not been prospectively tested in patients with cardiac sarcoidosis. The managing physician should balance the benefits of beta-blockers (rate control and antiarrhythmic benefits) against the risks of exacerbation of heart block and restrictive lung disease.

Sarcoidosis usually presents with hilar adenopathy, lung infiltrates, or skin or eye lesions

EXTRACARDIAC MANIFESTATIONS

3 Sarcoidosis affects many systems. Sites involved other than the lungs and heart include all the following except which one?

- ❑ Skin: erythema nodosum
- ❑ Renal: nephrocalcinosis and chronic renal insufficiency
- ❑ Eyes: uveitis
- ❑ Gastrointestinal: hypocalcemia from decreased absorption
- ❑ Parotid glands: swelling

Sarcoidosis usually presents with bilateral hilar adenopathy, pulmonary infiltrates, skin or eye lesions, or a combination of these abnormalities. The patient's immunologic and genetic background play a role, and symptoms vary by sex, race, and age at presentation:

- African Americans are more likely to have acute and severe disease
- Women are more likely to have neurologic and ocular involvement
- Men more frequently have abnormalities of calcium homeostasis.[11]

The lungs are involved in 95% of patients. The most common initial complaints are cough, shortness of breath, and chest pain, often accompanied by fatigue, weakness, and malaise. In approximately one half of patients, the disease is detected incidentally on chest radiographs before symptoms develop.[11]

The skin is involved in more than 20% of patients. Two types of lesions are common: lupus pernio (large bluish-red lesions on the nose, cheeks, ears, fingers, and toes) and erythema nodosum (raised, red, tender nodules on the front of the legs with occasional adjacent joint pain and swelling). Erythema nodosum is the hallmark of acute sarcoidosis.[12]

Eyes are involved in about 12% of patients. Any part of the eye may be affected, but uveitis is the most common. Acute anterior uveitis usually clears spontaneously or after treatment with local steroid eye drops. Chronic uveitis forms adhesions between the lens and iris, causing glaucoma and blindness.[13]

Parotid and salivary glands are swollen in 5% of patients.[11] Peripheral lymph nodes are enlarged in about one third of patients.

Abnormalities of calcium metabolism occur in 4% to 10% of patients[14] and are the most common electrolyte abnormality of sarcoidosis. Activated macrophages within the granulomas produce calcitriol, causing *increased* intestinal absorption of calcium (not decreased, as in question 3 above), hypercalciuria, and eventually hypercalcemia and nephrocalcinosis.

Untreated, calcium deposition within the kidneys can lead to chronic renal insufficiency and end-stage renal disease.[14]

ESTABLISHING THE DIAGNOSIS

4 Which of the following is diagnostic of cardiac sarcoidosis in this patient?

- ❑ An electrocardiogram showing ventricular arrhythmias
- ❑ A positive thallium scan of the heart
- ❑ An echocardiogram showing segmental or global hypokinesia of the left ventricle
- ❑ An endomyocardial biopsy demonstrating non-necrotizing granulomas

An electrocardiogram showing ventricular arrhythmias or cardiomyopathy suggests cardiac sarcoidosis, but does not diagnose it.[11]

A positive thallium perfusion scan of the heart is also nonspecific because many diseases that replace the normal myocardium with inflammatory tissue or scar tissue cause perfusion defects.

Echocardiographic findings such as wall motion abnormalities and valvular regurgitations can help monitor cardiac sarcoidosis but are not specific for it.[15]

A positive endomyocardial biopsy proves the presence of sarcoidosis. Transvenous endomyocardial biopsy, introduced in 1962, is recommended whenever cardiac sarcoidosis is considered,[6] even though its sensitivity has been reported to be as low as 20%.[16] The high false-negative rate arises because myocardial involvement is uneven, resulting in frequent sampling error.

According to ACCESS (A Case Control Etiologic Study of Sarcoidosis),[11] in a patient with biopsy-proven sarcoidosis, any one of the following can also confirm cardiac involvement:

- Treatment-responsive cardiomyopathy
- Electrocardiogram demonstrating a nonspecific atrioventricular nodal or intraventricular conduction defect
- Positive gallium scan of the heart.

The use of gallium-67 and thallium-201 scans has been suggested to improve detection of cardiac sarcoidosis. However, both have their limitations. Gallium-67 accumulates only in areas of active inflammation, so the test is positive only when the disease is active.

Although perfusion defects seen on a thallium scan strongly suggest cardiac involvement in someone with known systemic sarcoidosis, coronary artery disease must be ruled out with coronary angiography.[7]

THERAPY

5 How should this patient be treated?

- ❑ Oral steroids
- ❑ Angiotensin-converting enzyme (ACE) inhibitors
- ❑ Antituberculosis therapy
- ❑ Methotrexate or azathioprine
- ❑ Antimalarial medications

Symptomatic systemic sarcoidosis is treated with oral steroids. While the optimal dosage and duration of therapy have not been studied in randomized, prospective trials, the consensus is that pulmonary sarcoidosis requires an initial low dose of prednisone, whereas cardiac or neurosarcoidosis requires higher doses.[17] Patients should be re-evaluated after 3 months, and if the disease is responding, the dose is tapered to 5 to 10 mg/day for 12 months.

Patients who do not respond to steroids may need additional medications, such as methotrexate, azathioprine, or even antimalarials.[17]

ACE inhibitors and antituberculosis therapy are not used in patients with sarcoidosis unless specifically indicated.

Because medications do not cure sarcoidosis, all patients should be monitored with serial chest radiography, pulmonary function testing, 24-hour ECG, and thallium plus gallium scanning for disease progression and relapse.[18]

Case continued

The patient received an ICD and was treated with sotalol (Betapace) and prednisone. However, during the next 3 to 4 months he experienced seven episodes of ventricular tachycardia, which his ICD successfully terminated. Sotalol was discontinued and amiodarone was started. His ICD continued to discharge but not as often.

In view of these problems, and because he was experiencing vague chest pain that radiated to his left axilla, the patient was admitted to the hospital. His electrocardiogram on admission demonstrated nonsustained ventricular tachycardia (FIGURE 4).

A pharmacologic thallium stress test, performed to exclude coronary artery disease as the cause of his ventricular tachycardia, demonstrated stress-induced ischemia with acute right ventricular dilatation. The patient underwent cardiac angiography, which showed a moderately severe lesion in his left anterior descending coronary artery. Because the patient had risk factors for coronary artery disease, the lesion was thought to be secondary to atherosclerosis, and a stent was placed.

Thereafter, he maintained a stable rhythm with episodes of nonsustained ventricular tachycardia. He was discharged on long-acting

Patients with sarcoidosis need serial chest radiographs, pulmonary function tests, 24-hour ECGs, and thallium plus gallium scanning

Follow-up electrocardiogram

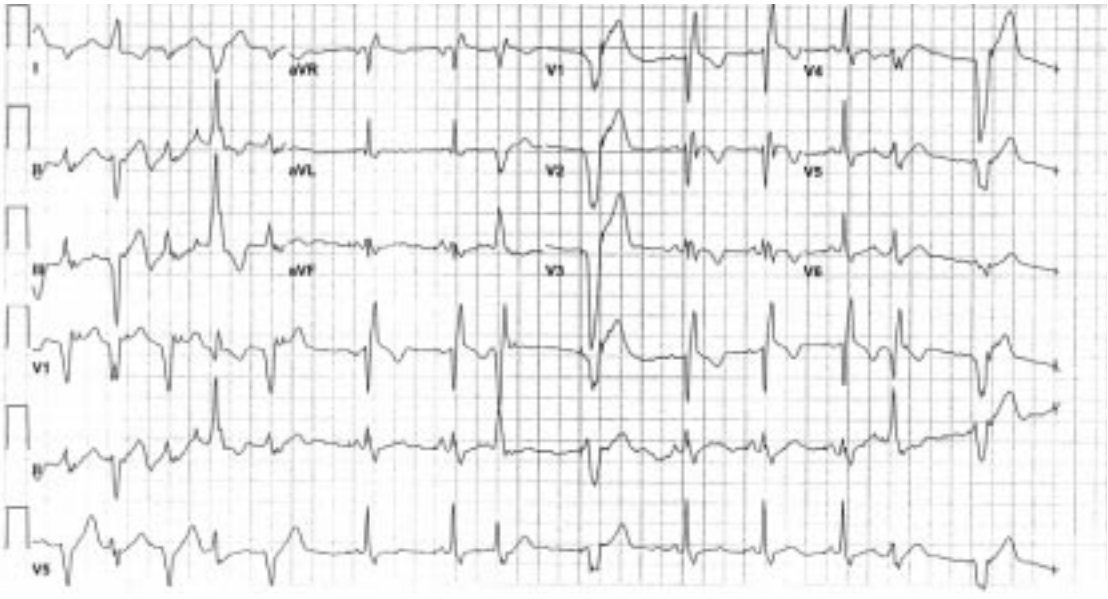

FIGURE 4. Nonsustained ventricular tachycardia.

metoprolol (Toprol XL) 100 mg/day, atorvastatin (Lipitor) 20 mg/day, aspirin 325 mg/day, and clopidogrel (Plavix) 75 mg/day (which were stopped after 6 months), plus amiodarone 400 mg/day and prednisone 40 mg/day (which were continued).

On follow-up with his primary care physician, he reported no symptoms since discharge. ECG demonstrated that his ejection fraction had normalized, and a chest radiograph showed that his hilar adenopathy had resolved. A nuclear stress test was planned in 6 months to monitor coronary disease progression.

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