PATHOLOGY IMAGE OF THE MONTH

Sudden Cardiac Death Caused by an Uncommon Disease

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CASE REPORT

A 57-year-old female, found dead lying supine in bed, was transferred to the autopsy service for an unrestricted autopsy to be performed under the authorization by the coroner. Medical history was unknown. At the time of autopsy, an implantable cardioverter-defibrillator (ICD) was identified in the subcutaneous tissues of the left subclavicular chest, with distal leads terminating in a small amount of fibrous tissue within the right auricular appendage and along the medial wall of the right ventricle. The heart was enlarged at 430gm (312 ±78) and cross sections were notable for left ventricular hypertrophy at 1.9cm (1.0-1.5cm) and for dilatation of the right ventricular chamber on initial apical cross section. All cross sections, from cardiac apex to subvalvular base, showed broad patches of white-yellow myocardial discoloration, without obvious hemorrhage, along the free wall of the left ventricle, the free wall of the right ventricle, and within the anterior interventricular septum (Figure 1). Additional notable findings at autopsy included a vena caval filter devoid of thromboembolic material, a patent foramen ovale (0.7cm) and microscopic plexogenic arteriopathy, low grade, consistent with pulmonary hypertension within the intrapulmonary vasculature. Histology from the discolored patches of myocardium is seen in Figure 2. Special stains for microorganisms (periodic acid-Schiff, Gomori methanamine silver, and Fite) were all negative.

What is the most likely underlying disease process in this case and what was the most likely immediate cause of death?

Answer is on p. 107
Figure 1: Gross image of the heart at autopsy demonstrating the broad patches of white-yellow myocardial pallor in the free wall of the left ventricle, the free wall of the right ventricle, and within the interventricular septum.

Figure 2: Microscopic image of the heart at autopsy demonstrating the noncaseating granulomatous inflammation with giant cell formation (hematoxylin and eosin, 40x). Similar findings were seen in the epicardium, the left ventricle, the right ventricle, and within the interventricular septum.
PATHOLOGY DIAGNOSIS:
Cardiac sarcoidosis (CS); fatal arrhythmia

DISCUSSION

Sarcoidosis is a chronic inflammatory disease characterized by the presence of noncaseating epithelioid granulomas in tissue. Infectious, other environmental, and genetic factors have all been implicated in the pathogenesis of sarcoid, but the precise etiology remains obscure other than to suggest an aberrant immunological reaction to an unidentified antigenic trigger. Although sarcoidosis has been described for more than 150 years, its propensity to involve cardiac muscle was not recognized until 1929. Cardiac involvement in sarcoid is being reported more frequently and is thought to carry a frequency of between 20-30 percent of all cases if microscopic analysis is performed on myocardium.

Patients with sarcoidosis are often young to middle aged adults. Women are more often affected than men; and American Blacks carry a 3-4 fold greater risk when compared to American whites. The annual incidence in American Blacks is estimated at approximately 35 cases per 100,000. The pathologic hallmark of sarcoidosis is the presence of granulomatous inflammation without central caseous necrosis. Granulomas are frequently found in high number and are loosely formed with abundant multi nucleated giant cells. A variety of inclusions can be found within the cytoplasm of the giant cells including the stellate asteroid bodies and concentric calcifications known as schaumann bodies. Though neither inclusion is pathognomonic for sarcoidosis, their presence can be helpful in suggesting the condition.

Cardiac Sarcoid (CS) is a rare but potentially fatal condition that presents in a variety of ways including sudden death. CS can affect any part of the heart including the conduction system and thus presents with a wide array of clinical manifestations. Within the myocardium of the heart, the predominant sites are, in decreasing order of frequency, the left ventricular free wall and papillary muscles, the basal aspect of the interventricular septum, the right ventricular free wall and the atrial walls. Complete heart block is the most common finding in patients with clinically evident CS and is reported in up to 30 percent of patients. Other clinical manifestations include re-entrant tachyarrhythmias including ventricular tachycardia in nearly one-quarter of cases and supraventricular arrhythmias in 15-17 percent. CS is thought to impart a poor clinical prognosis on patients, and is believed to carry a frequency of between 20-30 percent of all cases if microscopic analysis is performed on myocardium.

In fatal CS, the most common reported terminal event is sudden cardiac death due to arrhythmia; with the second most common fatal event being progressive congestive heart failure in one-quarter of cases. In one retrospective study of 41 autopsy cases of CS, the cause of death in over 60 percent was ultimately classified as sudden cardiac death due to the precipitating mechanism of presumed arrhythmia. In these cases of sudden death, the authors determined the pattern of the CS distribution within the heart was more likely to involve the epicardium and the interventricular septum.

Because of the potential life-threatening nature of CS, early diagnosis is critical. The antemortem diagnosis remains challenging with only 40 percent of those proven to have CS at autopsy ever showing clinical signs before death. Just recently, the first expert committee was convened to write a consensus statement on the diagnosis and management of CS, from which two diagnostic pathways were developed (Table 1). The authors also suggested a screening protocol for those with known extracardiac sarcoidosis that included not only a detailed clinical history for cardiac symptoms, but also a 12-lead electrocardiogram and an echocardiogram.

Therapy for CS is not standardized but corticosteroid therapy is the current mainstay. Additional therapies may be considered in select patients including antiarrhythmics, additional immunosuppressive drugs, implantable cardioverter-defibrillator devices, cardiac surgery and heart transplantation. The prognosis in CS is not precisely known but sudden cardiac death despite a functioning implantable cardioverter-defibrillator (ICD) is well described and has been previously documented in 28 percent of 320 deaths occurring in a series of ventricular tachycardia/ventricular fibrillation (VT/VF) patients who were treated with ICD.

The case presented here of sudden death in the context of multiple myocardial noncaseating granuloma along with features of pulmonary hypertension and antemortem cardiac compromise evidenced by the presence of an ICD are all classic features of CS. Of note, the autopsy did not reveal any significant lymphadenopathy. However, histologic evidence of sarcoidosis was also found along the pulmonary subpleural lymphatic channels. Though the most likely underlying disease and immediate cause of death in this case are CS and a fatal arrhythmia, respectively, the absolute certainty of the diagnosis is limited by both the paucity of antemortem clinical information, as well as the fact that sarcoidosis is frequently a diagnosis of exclusion. Granulomatous inflammation is a nonspecific histopathologic finding that is not pathognomonic for sarcoidosis. Myocardial granulomas are relatively rare and generate a rather limited differential diagnosis that includes myocarditis, metabolic disorders, foreign body reactions, tuberculosis or fungal infection and CS. But, the absence of any microorganisms on special staining, the noncaseating nature of the granuloma, the lack of polarizable material, the lack of eosinophils and the absence of myocyte cell necrosis, as well as the distribution of the granulomas along the epicardium, within both ventricular free walls and within the interventricular septum, all strongly support the diagnosis of CS.

In conclusion, CS is a rare but potentially fatal condition that may present with a wide range of clinical manifestations including congestive heart failure, conduction abnormalities, and sudden cardiac death. Because of the
Table 1: Two Diagnostic Pathways for Establishing Cardiac Sarcoidosis (CS)\textsuperscript{a,b}\textsuperscript{9}

| 1. | Noncaseating granulomas in myocardial tissue with no alternative cause identified (including organismal stains if applicable) |
| 2. | Noncaseating granulomas in other, extracardiac organ systems, and the presence of one or more of the following cardiac findings so long as other causes for the cardiac manifestations have been reasonably excluded: |
| a. | Corticosteroid and/or immunosuppressant responsive cardiomyopathy or heart block |
| b. | Unexplained reduced LVEF (<40\%) |
| c. | Unexplained sustained VT |
| d. | Mobitz type II second-degree heart block or third-degree heart block |
| e. | Patchy uptake on dedicated cardiac PET |
| f. | Late gadolinium enhancement on cardiovascular MR |
| g. | Positive gallium uptake |

LVEF: left ventricular ejection fraction
VT: ventricular tachycardia
PET: positron emission tomography
MR: magnetic resonance

potential life-threatening complications, a deliberate and algorithmic approach to screening all sarcoidosis patients for cardiac involvement has been recently proposed. The autopsy case presented here, though limited by the incompletely available antemortem clinical information, also serves to support the current call for additional emphasis on interdisciplinary, multicenter collaborations to further advance knowledge about CS including the creation of a prospective patient database.\textsuperscript{a,b}\textsuperscript{9}

REFERENCES


Dr. Li is a first year pathology resident and Dr. McGoey is an Associate Professor of Pathology and Residency Program Director in the Department of Pathology at Louisiana State University School of Medicine in New Orleans, LA.

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