A Case of Severe Cardiac Sarcoidosis with Minimal Pulmonary Involvement: A Case Report with Literature Review

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ABSTRACT

Sarcoidosis is a granulomatous disease of unknown etiology. Although sarcoidosis is a systemic disease, there appears to be a predilection for involvement of certain organs. The pulmonary system is the most commonly affected system among all racial groups. Cardiac and respiratory complications are the leading causes of death due to sarcoidosis and in certain patient populations about half of these deaths are attributed to cardiac sarcoidosis. There are few autopsy case reports of cardiac sarcoidosis with minimal respiratory involvement making this case report relevant to the importance of the recognition and awareness of this entity. *Acad Forensic Pathol.* 2018 8(2): 407-415

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INTRODUCTION

Sarcoidosis is a granulomatous disease of unknown etiology with variable clinical presentations and medical courses ranging from spontaneous resolution to chronic progression. Its dermatologic manifestation was first described by Jonathan Hutchinson in 1869 as a clinicopathologic entity causing persistent skin lesions. He described one patient with non-painful, symmetrically-purple skin plaques on the legs and hands. Another patient was described with raised, dusky-red skin lesions on the face and forearms without ulceration (1, 2). Schaumann, later in 1914, recognized sarcoidosis as a systemic, nonmalignant, and non-tuberculous granulomatous disorder (3). The etiology of sarcoidosis has been attributed to genetic, environmental, infectious, and immune dysregulation causes. Current thought is that sarcoidosis is a common endpoint granulomatous disease caused by a heterogeneous group of agents in a genetically susceptible patient (4).

In the United States, predilection of this disease towards African Americans has been reported. The age-adjusted annual incidence in the US ranges from 10.9 cases per 100 000 for Caucasians to 35.5 cases per 100 000 for African Americans (5). Incidence has been reported to be highest in individuals between the ages of 20 and 40, and in females of all ethnic and racial groups (5, 6).

Cardiac and respiratory complications are the leading causes of death, with an estimated overall mortality between 1-5% (7). In certain patient populations, about half of these deaths are attributed to cardiac sarcoidosis (8). The prevalence of cardiac sarcoidosis varies between studies. In one study, the prevalence of cardiac sarcoidosis was reported as 40% in outpatients with documented sarcoidosis, with greater than half being asymptomatic (9). In the ACCESS study of 736 patients with sarcoidosis, an expected vast majority at 95% had lung involvement; however, only 2-7% demonstrated cardiac manifestations (10).

Here, we present an autopsy case of sarcoidosis with significant involvement of the heart and spleen, and

with minimal lung involvement in a 42-year-old African American male.

CASE REPORT

The decedent was found at home by his aging mother with whom he resided. He had just been released from the county jail for a minor offense. He had no known documented medical history and an old albuterol rescue inhaler was found at the scene. His mother had severe dementia and vaguely recalled that the decedent had been diagnosed with asthma many years prior to his death but could not recall additional details. The case was taken to the medical examiner for autopsy.

External Findings

The decedent was a well-developed and nourished male at 86.6 kg and 185 cm tall. He had no outward evidence of trauma and his skin was free of any dermatologic lesions.

Gross Findings

Autopsy demonstrated a 690 g heart covered by a thickened pericardium that was markedly adherent to the tan, firm epicardium (**Image 1**). Coronal sections showed almost total replacement of the left and right ventricular myocardium by firm, tan tissue most prominent in the left lateral ventricle and nearly completely replacing the ventricular septum (**Image 2**). A thin rim of normal looking endocardium was on the posterior walls of both ventricles.

The hilar and peribronchial lymph nodes were enlarged, constituting a pattern consistent with the lambda sign seen on chest imaging. Their cut surfaces demonstrated small, irregular firm tan nodules. The lungs (603 g, right; 550 g, left) were hyperinflated and collapsed on puncturing. Their parenchyma had a few barely visible and palpable greyish nodules. Thick mucus clogged some small airways. The 300 g spleen had tan-grey capsular scarring and irregular, firm tan parenchymal nodules (**Image 3**). The rest of the autopsy was unremarkable.

Image 1: Thickened epicardium with adhesions.

Image 2: Cross sections of the heart showing replacement of myocardium with tan tissue.

Microscopic Findings

Histologic examination of the affected organs showed noncaseating granulomatous inflammation with epithelioid cells, giant cells, diffuse chronic inflammatory cells, and perilesional dense fibrosis. The inflammation was negative for infective organisms including mycobacterium and fungal organisms.

The organ most affected was the heart, where the inflammation was associated with marked scarring (**Image 4**). The sinoatrial and atrioventricular nodes were severely affected and could not be identified be-

cause of the inflammation and scarring. Sections of the spleen and lymph nodes showed a granulomatous inflammation with marked scarring.

The lungs showed granulomatous inflammation around small airways, some of which were distended with mucus and others markedly distorted accompanied by extravasation of mucus. No histologic features of bronchial asthma such as bronchial smooth muscle hyperplasia, eosinophilic infiltrates in the walls of the airways, or thickening of the basement membrane of the airways were identified. Histologic examination of remaining organs was unremarkable.

Image 3: Splenic involvement with many tan nodules.

DISCUSSION

Although sarcoidosis is a systemic disease, there appears to be a predilection for involvement of certain organs with some variability between race and geography. The pulmonary system is the most commonly and significantly affected organ system among racial groups (11). Iwai and coworkers, in their autopsy study of 503 patients (109 Caucasians, 74 African Americans, 320 Japanese), reported cardiac sarcoid prevalence of 69.1% in Japanese, 18% in Caucasians, and 14.3% in African Americans. Pulmonary sarcoidosis was the major cause of death in African American patients, but Japanese patients had the highest incidence of death caused by cardiac sarcoidosis (8). Ex-

trathoracic lymphadenopathy, eye disease, and liver disease are also not uncommon in sarcoidosis. Splenic involvement is less frequent, occurring in approximately 7% of patients in one large multicenter study (12). The splenic sarcoid granulomas may be small or coalesce to form strikingly apparent macroscopic nodules (13).

William C. Robert and colleagues, in their study of 113 autopsy cases of cardiac sarcoidosis, reported that the myocardium is the most frequently involved site of sarcoid granuloma formation (2). Additionally, the most frequent location of myocardial involvement is the free wall of the left ventricle, followed by the ventricular septum, right ventricle, and atria (2).

Image 4: Noncaseating granulomatous inflammation affecting the myocardium. Note the diffuse interstitial fibrosis with cardiac myocyte loss. Langerhans type giant cells are seen (H&E, x200).

Grossly, the granulomatous lesions can appear as yellow, white, tan, or grey nodules of varying sizes and shapes. Granulomatous inflammation elicits scarring that is randomly distributed, unlike that of a myocardial infarction where scarring is maximal in the subendocardial region extending out (14). In clinically suspected cases, an endomyocardial biopsy can provide a definitive diagnosis of cardiac sarcoidosis; however, its sensitivity is low because of the patchy distribution and the lower incidence of anterior right ventricle and septum involvement (15).

In the differential, it is of import to consider both primary cardiac tumors and metastatic tumors that may involve the heart, with the latter being significantly more common (16). The most common primary tumors of the heart are myxomas, comprising over half of primary cardiac tumors, followed by sarcomas, which comprise slightly less than a quarter (17). Primary cardiac sarcomas typically originate in the right atrium and are grossly multi-lobular, hemorrhagic, and spread along the epicardial surface (18). Though less common, primary cardiac lymphomas typically affect the right side of the heart with diffuse large B cell lymphoma being the most common type. Grossly, these tumors appear as single or multiple firm white nodular masses and may show focal necrosis (19).

Carcinomas are the most common metastatic malignancy to the heart, comprising over 50% of metastatic heart tumors with lung, esophagus, and breast cancers forming the vast majority of these (20, 21). The pericardium is the most frequent site of cardiac metastasis, comprising upwards of 69% of all cardiac metastases, followed by the epicardium and myocardium (22). Metastases to the heart typically manifest in patients with advanced disease, with cardiac tumor deposits ranging from single to diffuse (23).

Lymphoma metastatic to the heart is not uncommon among those with a history of malignant lymphoma. One autopsy study identified metastatic lymphoma to the heart in 13 of 150 patients with malignant lymphoma. The gross distribution of metastatic lymphoma on presentation ranged from an infiltrating mass to diffuse involvement of the myocardium (24).

The hallmark microscopic feature of sarcoidosis is the presence of noncaseating granulomas in the affected organs. Granulomas occur in response to a number of inciting agents and may be classified according to clinical etiologies: vascular (e.g., granulomatosis with polyangiitis, giant cell arteritis), infectious (e.g., mycobacteria, brucellosis, histoplasmosis), immunologic (e.g., Crohn's disease, primary biliary cirrhosis), leukocyte oxidase defects (e.g., chronic granulomatous disease), hypersensitivity pneumonitis (e.g., bird fanciers', Farmer's lung), neoplasia (e.g., pinealoma, dysgerminoma), and foreign substance (e.g., beryllium, zirconium, aluminum) (25). Early sarcoid granulomas may be loose and consist of macrophages and abundant lymphocytes (14, 26). Macrophages become epithelioid cells and may fuse to form multinucleated giant cells. These giant cells typically resemble those of the foreign body type, with haphazardly arranged nuclei initially and later form into Langhans type with peripherally arranged nuclei (27). The giant cells may contain cytoplasmic inclusion bodies. Schaumann bodies have been reported as being present in 70%-88% of sarcoid cases and are identified as oval concentrically laminated intracellular inclusion bodies consisting of calcified proteins (14). Asteroid inclusion bodies are not uncommon in sarcoid giant cells and are identified as stellate inclusion bodies with cytoplasmic clearing thought to be made of non-collagenous filaments and myelinoid membranes that stain with anti-ubiquitin antibodies (28).

A primary histologic differential diagnosis for cardiac sarcoidosis includes giant cell myocarditis, idiopathic granulomatous myocarditis, tuberculous myocarditis, fungal myocarditis, and Whipple disease (27). Idiopathic granulomatous myocarditis is characterized by non-necrotizing granulomas limited to the heart and may be regarded as sarcoidosis limited to the heart (29). Giant cell myocarditis is characterized by an inflammatory infiltrate of eosinophils, macrophages, and lymphocytes. The macrophages of which are not epithelioid, nor do they aggregate into granulomas. The giant cells are associated with myocyte necrosis (29). The macrophages of Whipple disease are generally foamy or granular and typically do not aggregate into granulomas.

Several cellular constituents of the reticuloendothelial cell lineage are involved in granuloma formation and maintenance. Macrophages differentiate to form epithelioid cells under the influence of cytokine production, which then fuse to form multinucleated giant cells. Macrophage chemokine secretions recruit lymphocytes from lymph nodes and monocytes from the local circulation while inciting epithelioid and fibroblast proliferation at the site of granuloma formation. Granulomas are maintained by the regulatory influence of cytokines produced by mononuclear cells, T cells, dendritic cells, and fibroblasts, which perpetuate ongoing inflammation and cytokine release (30, 31). Sarcoid granulomas typically have CD4 T cells in their center and CD8 T cells and B lymphocytes in the periphery (32, 33). The cytokines primarily involved in granuloma formation are of the TH1 lineage (interleukin IL-2, interferon γ , IL-12) with paucity of the TH2 cytokines (IL-4, IL-5) (34, 35). Conversely, sarcoidosis remission has been found in association when TH2 cytokines predominate, which are thought to be antiinflammatory, with granuloma regression (36).

Sarcoid myocardial involvement may be asymptomatic or can cause sudden death. The prognosis of symptomatic cardiac sarcoidosis is unclear, with a range of survival outcomes reported between studies (37). Involvement of the conduction system by cardiac sarcoid may cause conduction disturbances resulting in fatal arrhythmias. Alternatively, sarcoid involvement of the myocardium may cause symptomatic congestive heart failure, aneurysm, and valve dysfunction (2). Symptomatic cardiac sarcoidosis may enter remission or continue to progressive heart failure, myocardial infarction, or sudden cardiac death (38, 39). Serum markers may be useful in aiding the diagnosis and monitoring systemic sarcoidosis and include elevated serum angiotensin-converting enzyme, elevated lysozyme, and hypercalcemia. Hypercalcemia is thought to be attributed to calcitriol production by activated macrophages comprising the sarcoid granuloma (40). However, these markers lack specificity and their utility in the diagnosis and management of sarcoidosis is questionable.

The classic respiratory finding in sarcoidosis is restrictive pulmonary function due to replacement of lung parenchyma with granulomatous inflammatory nodules and scar tissue. The lungs are therefore traditionally found to be firm. However, the decedent's lungs were hyperinflated and demonstrated few barely appreciated nodules in the lung parenchyma. With the extensive replacement of the myocardium by scar tissue, it is surprising that the lungs were not congested. One might surmise that such replacement of myocardial tissue with noncontractile fibrous scar tissue would have resulted in a restrictive cardiomyopathy-type presentation resulting in pulmonary congestion and edema. Perhaps the decedent's condition, given additional time, would have presented as such.

Histologically, features of bronchial asthma, including bronchial smooth muscle hyperplasia, eosinophilic infiltrates in the walls of the airways, and thickening of the basement membrane of the airways were not identified. However, granulomatous inflammation was around the small airways, possibly impairing effective removal of mucus debris. This would be consistent with the finding that some of the small airways were distended with mucus and others markedly distorted and accompanied by extravasation of mucus. One may postulate that impaired mucus removal secondary to granulomatous inflammation would narrow the small airways causing a similar presentation to that of an asthmatic.

CONCLUSION

Sarcoidosis demonstrates a predilection for organ involvement with the pulmonary system and lymphatics involved in most cases. Though less common, cardiac sarcoidosis may occur in tandem with respiratory and lymph node involvement or in isolation. Due to the high morbidity and mortality associated with cardiac sarcoidosis, there must be an increased awareness of this disease entity and the extent to which it can affect the heart. Otherwise, this important disease entity may remain underdiagnosed or mistaken for another disease etiology if not adequately investigated. There are few autopsy case presentations of patients with isolated cardiac sarcoidosis with minimal respiratory

involvement making this case report relevant to the importance of the recognition and awareness of this entity.

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