

Cardiac sarcoidosis, a cause of sudden cardiac death

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Abstract

A 35-year-old white male with no medical history was found unresponsive. A postmortem examination revealed an enlarged heart showing left ventricular thickening and diffuse pale areas. Hilar lymphadenopathy was noted, and numerous white-tan nodules were present throughout the lungs and spleen, and, focally, in the liver. Postmortem toxicology testing revealed no significant findings. Histology demonstrated extensive non-caseating granulomas with multinucleated giant cells, asteroid bodies, Schaumann bodies and lymphocytic inflammation within the heart, lungs, spleen, lymph nodes and the liver. Sections of the heart also showed widespread fibrosis. A diagnosis of systemic sarcoidosis with cardiac involvement was offered, which likely lead to a fatal cardiac arrhythmia. This case highlights the importance of meticulous postmortem evaluation in suspected sudden cardiac deaths, as this will inform whether genetic testing for inherited cardiac conditions should be offered to the family of the deceased. A comprehensive work-up of a case with suspected sudden cardiac death should include histology, toxicology and consideration of the need to retain spleen for future genetic testing.

Keywords Autopsy; cardiac arrhythmias; cardiovascular pathology; conduction system; granuloma; sarcoidosis; sudden cardiac death

Case report

A 35-year-old white male was found unresponsive with no history of recent illness and no significant past medical history. Cardiopulmonary resuscitation attempts were unsuccessful, and the death was referred to the Coroner due to there being no available cause of death.

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Postmortem examination revealed numerous pale nodules within and on the surface of both lungs. The heart was enlarged (590 g) with a thickened left ventricle (18 mm; normal = 10–15 mm) showing ill-defined, pale areas throughout the free wall and septum. Similar pale lesions were seen on the surface of and within the right lobe of the liver. Hilar lymphadenopathy was noted, alongside splenomegaly and diffuse splenic parenchymal replacement by innumerable pale nodules. All other viscera were unremarkable. Given the patient's age and circumstances surrounding the death, sudden cardiac death (SCD) was suspected, prompting a thorough review of postmortem histology and toxicological analysis.

Toxicology testing revealed no significant abnormality. Histology demonstrated widespread systemic sarcoidosis, with extensive involvement of the heart (Figure 1), lungs, spleen, lymph nodes and focal involvement of the liver. Affected organs showed characteristic appearances with multinucleate giant cells, variably well-formed non-caseating granulomas, asteroid bodies, Schaumann bodies, lymphoid inflammation and fibrosis. Large areas of replacement-type fibrosis were observed in the heart (Figure 1a) with all sampled regions of the myocardium affected, including the anterior, lateral and posterior left ventricle, the right ventricle, the apex and the interventricular septum. There was no evidence of acute infarction or myocyte disarray to suggest a primary cardiomyopathy. All sampled regions of the lungs, representing the upper, middle and lower zones bilaterally, showed widespread giant cell infiltration and granuloma formation.

The appearances were felt to be characteristic of sarcoid, and the following cause of death was offered:

1a Systemic sarcoidosis (cardiac, pulmonary, hepatic, splenic and lymph-node involvement)

1b

1c

2

The clinicopathological correlation emphasized the extensive cardiac involvement, likely leading to a sudden fatal cardiac arrhythmia.

Discussion

This case highlights the autopsy findings of cardiac sarcoidosis (CS), which can manifest as SCD. In individuals under 40, potential causes of SCD include structural cardiac abnormalities,

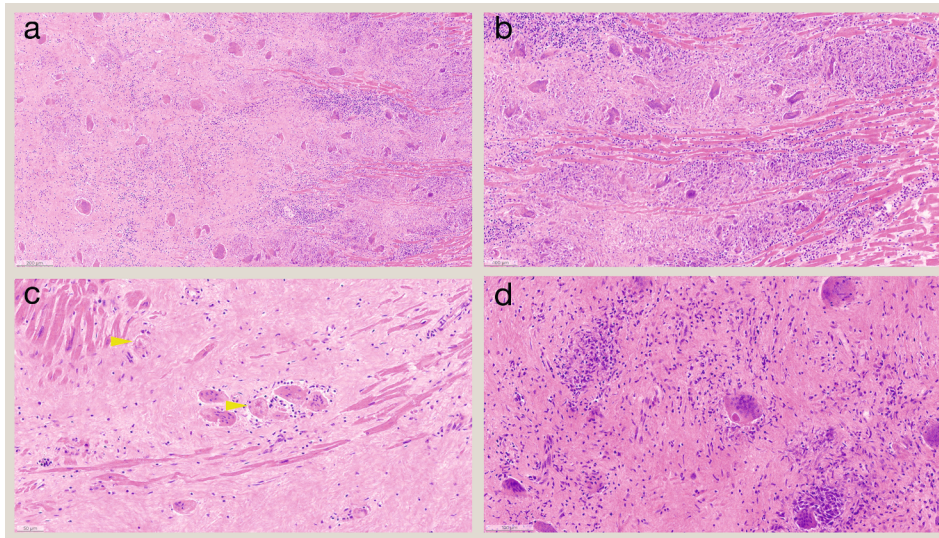


Figure 1 Cardiac sarcoidosis on post-mortem sections of the heart. (a) The interventricular septum showing extensive myocardial replacement by fibrosis associated with granulomatous inflammation and giant cell formation. (b) Non-necrotising, compact granulomas with epithelioid histiocytes, a thin rim of lymphocytes and giant cell formation. (c) Asteroid bodies – intra-cytoplasmic, star-shaped structures in giant cells. (d) Schumann body - a lamellated, basophilic, round inclusion in a giant cell.

inherited arrhythmia syndromes, myocarditis and infiltrative disorders, which include amyloid and sarcoid. In many cases this condition is clinically silent with no family history. As such, the diagnosis depends on the postmortem cardiac histology and exclusion of other causes. It is, therefore, crucial that autopsy pathologists approaching a case with a suspected SCD should (1) consider whether this could be attributable to cardiac disease and perform a thorough examination of the heart, (2) obtain post-mortem histology and toxicology for further testing and (3) consider possible inheritance, necessitating genetic material retention and clinical screening, if appropriate. Colleagues are directed to the Royal College of Pathology cardiovascular tissue pathway¹ and autopsy guidelines related to suspected cardiac deaths for more information.²

Sarcoidosis is a multi-system inflammatory disorder characterized by granulomatous inflammation. Its aetiology remains poorly understood, although familial clustering and genetic susceptibility have been suggested. Sarcoidosis is more common among middle-aged adults (35–50 years) with a slight female predominance, and is more frequent in people of African American descent. The disease most commonly affects the lungs, with pulmonary involvement in up to 90% of cases, leading to symptoms of fatigue, breathlessness and a cough.³ Cardiac involvement is less common, with clinically apparent cardiac disease identified in only 5–7% of systemic sarcoidosis patients. This contrasts with some autopsy studies, which estimate at least 25% prevalence of cardiac infiltration among patients with sarcoidosis.⁴ Involvement of the heart in sarcoidosis is, therefore, an important differential in cases of SCD, particularly among otherwise healthy adults.

The findings of CS can be subtle and non-specific. Gross examination of the heart during autopsy may be normal in these cases or show only patchy myocardial fibrosis that does not correspond to a particular coronary artery distribution. Sarcoid is characterized by non-caseating, “naked” (i.e., without an abundant surrounding cuff of lymphocytes) granulomas. In the heart,

these can macroscopically appear as small, well-defined, tan nodules which histologically comprise epithelioid histiocytes with, at most, a thin rim of lymphocytes and multinucleated giant cells (Figure 1b). Asteroid bodies or Schaumann bodies can be seen but are not essential for the diagnosis of sarcoidosis (Figures 1c and d). Granulomas caused by CS can be differentiated from other causes of granulomatous inflammation by their epithelioid and compact appearance and associated cardiac fibrosis. Granuloma formation and fibrosis, particularly within the interventricular septum (Figure 1a), can interrupt the cardiac conduction system and predispose the patient to arrhythmias and pump failure.⁵ In this case, the enlarged heart, left ventricular thickening and diffuse myocardial fibrosis in the absence of coronary artery disease or infarction strongly supported CS as the primary arrhythmic substrate.

The main differential diagnosis to consider when giant cells are seen within the myocardium is giant cell myocarditis (GCM). There is an ongoing debate amongst some pathologists and cardiologists regarding whether GCM and CS are distinct entities, fuelled by lack of consensus criteria for histologic diagnosis, overlapping histological and clinical features, and the controversy regarding existence of isolated CS. However, GCM and CS are generally regarded as separate conditions, with lymph nodes showing reactive changes in the former and granulomas in the latter, supporting the presence of systemic sarcoidosis.⁶ Additionally, GCM typically shows widespread myocyte necrosis, an absence of granulomas and fibrosis and follows a more fulminant clinical course. Distinguishing between the two is particularly important in life due to the differing treatment strategies and prognostic implications.⁷ However, for the autopsy pathologist, it is crucial to differentiate CS and GCM from potential inherited cardiac conditions, such as a cardiomyopathies or sudden arrhythmic death syndrome (SADS), which would necessitate referral of family members to local Inherited Cardiac Condition services for screening.² The specific diagnostic features of each

cardiomyopathy are beyond the scope of this article but the finding of a morphologically normal heart alongside a “negative” postmortem examination and normal toxicology should prompt suspicion of SADS. Expert cardiac review, such as by the UK Cardiac Pathology Network,⁸ of either tissue, slides or photos, may be warranted, and fresh spleen should be retained at the time of postmortem as per the NHS and Coronial Sudden Unexpected Death programme.⁹

This case underscores the need for a thorough histological examination of the heart in sudden deaths, which, by demonstrating the unexpected finding of sarcoidosis, has both provided the cause of death and prevented over-investigation of surviving relatives.

Conclusion

Systemic sarcoidosis with cardiac involvement is a rare but important cause of SCD. Meticulous autopsy examination, including histological sampling of the heart, is essential to establish the diagnosis, provide clarity for families and differentiate these cases from SADS, where Inherited Cardiac Condition testing should be offered to families of the deceased. ◆

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Practice points

- Systemic sarcoidosis is a multisystem granulomatous disorder that may be asymptomatic
- Cardiac involvement in systemic sarcoidosis can cause sudden cardiac death through generation of fatal cardiac arrhythmias
- Gross cardiac findings in cardiac sarcoidosis can be subtle and histological sampling of multiple myocardial regions is essential for a definitive diagnosis
- Histology of cardiac sarcoidosis is characterized by compact, ‘naked’, epithelioid non-caseating granulomas, with peripheral giant cells and associated fibrosis
- Recognition of cardiac abnormalities, such as cardiac sarcoidosis, are essential to rule out sudden arrhythmic death syndrome, defined as a sudden death with a morphologically normal heart and a normal toxicology panel, which implies inherited cardiac conditions and should prompt familial screening

Self-assessment multiple-choice questions

1. Which histological description is the most characteristic of cardiac sarcoidosis?

- A. Caseating granulomas surrounded by a rim of chronic inflammatory cells
- B. Replacement of myocardium by fibrous and adipose tissue
- C. Cardiomyocyte hypertrophy, fibrosis and disarray
- D. Non-necrotising granulomas with giant cell formation and fibrosis
- E. Coagulative necrosis and acute inflammation

Answer: D

2. Which myocardial region should be sampled during a post-mortem examination on a patient with suspected cardiac sarcoidosis?

- A. Anterior left ventricle
- B. Lateral left ventricle
- C. Posterior left ventricle
- D. Interventricular septum and right ventricle
- E. All of the above

Answer: E

3. Why is it important to retain a sample of spleen during post-mortem examinations in patients suspected of sudden cardiac death?

- A. It is the best tissue for potential future research applications into sudden cardiac death
- B. To evaluate it for infiltrative or granulomatous processes such as systemic sarcoidosis
- C. To rule out haematological malignancy with secondary cardiac involvement
- D. To preserve tissue for potential genetic analysis in case of an inherited cardiac condition
- E. To detect occult splenic infections that mimic cardiac death

Answer: D