J Forensic Sci, March 2008, Vol. 53, No. 2
doi: 10.1111/j.1556-4029.2008.00662.x
Available online at: www.blackwell-synergy.com

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Sarcoidosis and Mechanisms of Unexpected Death

ABSTRACT: Sarcoidosis is a multisystem disease of uncertain etiology characterized by multifocal areas of discrete and confluent granulomatous inflammation that may rarely be responsible for sudden and unexpected death. Two cases are reported to demonstrate disparate pathological features in fatal cases, one involving cardiac sarcoidosis, and the other neurosarcoidosis with hypothalamic infiltration. Sarcoidosis in individuals dying suddenly may be completely unrelated to the death, contributory or causal. Cardiovascular causes of sudden death in sarcoidosis include arrhythmias associated with cardiomyopathy and ischemia, ventricular rupture, and cor pulmonale due to pulmonary hypertension; respiratory causes include hemorrhage and upper airway obstruction; central nervous system causes include arrhythmias from infiltration of autonomic centers, epilepsy, and obstructive hydrocephalus from brainstem involvement; and gastrointestinal deaths may be due to hemorrhage from esophageal varices associated with portal hypertension. The diagnosis relies on the demonstration of typical noncaseating granulomas and the exclusion of other infective and environmental diseases with similar histopathological findings.

KEYWORDS: forensic science, sarcoidosis, noncaseating granulomas, sudden death

Sarcoidosis is a chronic inflammatory disease of uncertain etiology involving a variety of organ systems that was first described in 1869 by Hutchinson in a patient with characteristic skin lesions. The name sarcoid was coined by Boeck in 1899 due to the resemblance of the lesions to sarcomas, and derives from the Greek *sarcos* for flesh and *eidos* meaning form (1). The condition has quite protean manifestations characterized by the presence of noncaseating granulomas that are typically found within the lungs and lymph nodes (2). Incidental lesions are not uncommonly found at autopsy, although on occasion there may be manifestations resulting in significant disease. Sarcoidosis may also very rarely be a cause of sudden and unexpected death. Two cases are reported to demonstrate significant features in the forensic evaluation of sarcoidosis with an analysis of the findings at autopsy and possible mechanisms of death.

Case Reports

Case 1

A 65-year-old woman with a past history of hypertension and ischemic heart disease collapsed after an episode of vertigo. At autopsy the body was that of an obese white female (length: 167 cm; weight: 88 kg; BMI: 31.6) with significant findings limited to the cardiovascular system. The heart weighed 790 g with a left ventricular free wall thickness of 25 mm. There was marked fibrous scarring and mottling of the anterior left ventricular free wall and the intraventricular septum that on histology was shown to be composed of noncaseating loosely aggregated epithelioid granulomas typical of sarcoidosis. No fungal, bacterial, or mycobacterial organisms were identified on special staining. No foreign body material was present. There were no acute ischemic changes. Granulomas were also present within the lungs. The only other finding of significance was marked atherosclerosis with >80% narrowing of all three major epicardial coronary arteries and the left renal artery ostium with scarring of the left kidney. Previous coronary artery bypass grafting to the circumflex and left anterior descending coronary arteries was in good order. Death was attributed to cardiac sarcoidosis complicating ischemic and hypertensive cardiac disease.

Case 2

A 56-year-old woman with a history of polydipsia, polyphagia with marked weight gain, somnolence, and hypothermia presented to hospital with an altered conscious state and leg weakness. She was found to be confused and hypothermic (32°C) with no localizing neurological signs. An MRI scan of the brain showed subtle symmetrical enhancement of the hypothalamus in keeping with an inflammatory condition. She was managed expectantly and died suddenly while eating a meal. At autopsy the body was that of a morbidly obese white female (length: 163 cm; weight: 150 kg; BMI: 56.5) with significant findings limited to the upper airway and brain. A bolus of vegetable matter occluded the laryngeal inlet. The brain was macroscopically normal with extensive granulomatous inflammation on microscopy involving the interventricular septum, septal nuclei, diagonal band of Broca, preoptic region, substantia innominata, nucleus accumbens extending into the adjacent caudate nucleus and internal capsule, rostrum of the corpus callosum, inferior internal capsule, mamillothalamic tract, posterior hypothalamus, and periventricular hypothalamic nuclei. The inflammatory infiltrates consisted of multiple, well-defined noncaseating granulomas surrounded by reactive gliosis and intense perivascular lymphocytic cuffing. No fungal, bacterial, or mycobacterial organisms were identified on special staining. There were no granulomas

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Received 19 May 2007; and in revised form 9 Aug. 2007; accepted 26 Aug. 2007.

elsewhere and the remainder of the autopsy was unremarkable. Death was attributed to aspiration of food complicating polyphagia due to neurosarcoidosis.

Discussion

These cases demonstrate the contribution that sarcoidosis may have to unexpected death. Sarcoidosis varies in incidence among countries and ethnic groups with high rates in Sweden of 64 per 100,000 of the population and in Finland with 11.4 per 100,000, compared to Japan with 1 per 100,000 (3). In the United States, the incidence varies from 1 to 40 per 100,000, with an age-adjusted annual incidence rate in the United States of 10.9 per 100,000 in the white population and 35.5 per 100,000 in the black population (2). There is a predilection for females, with a peak incidence between 20 and 40 years of age and a lifetime incidence rate of 0.85–2.4% (2,4). Occasional cases occur in childhood, and certain occupations have a higher rate including health care workers, mechanics, fire fighters, post office workers, and wood millers (3,5).

Although infectious causes have been extensively investigated, no specific viral, bacterial, or other agents have been definitively linked to sarcoidosis. Possible inciting agents have included fungi, molds, mycobacteria, viruses, spirochetes, *Nocardia sp*., *Corynebacterium*, *Propionibacterium*, *Rickettsia sp*., and *Tropheryma whippelii*. While *Rhodococcus equi* has been associated with macrophage aggregation in malacoplakia, it has not been confirmed as an etiological agent in sarcoidosis (3,6–8). Isolation of micro-organism DNA from tissue and fluid samples from patients with sarcoid may, therefore, represent a coincidental finding.

Granulomatous inflammation may be incited not only by infectious organisms, but also by foreign material (9,10) and so represents a relatively nonspecific cellular response. Organic and inorganic dusts and certain heavy metals including talc, clay, pine pollen, aluminum, zirconium, and beryllium have all been investigated with no confirmation of an association with sarcoidosis. Photocopier toner dust and insecticides have also been proposed as possible inciting antigens (3,11).

A variety of immunological disturbances occurs in affected individuals, with activation of T cells and increase in $CD45RO^+$ (memory) T-lymphocytes and macrophages. These cells result in an increased release of TH 1-predominant cytokines such as interleukin-2, interleukin-12, and interleukin-15. The CD4/CD8 ratio may have been inverted on previous clinical testing and cytokines such as interferon-γ, macrophage inflammatory protein 1α, and transforming growth factor β are also released (7). There is an increase in both tumor necrosis factor-α (TNF) and its receptors resulting in clinical improvement when treatment is initiated with anti-TNF agents (3). The reason for granuloma formation and persistence is not well understood, but it is believed to result from persistent antigenic stimulation with resultant cytokine accumulation and a human leukocyte antigen (HLA) class II mediated T-cell response causing chronic macrophage stimulation (3).

The possibility of a genetic basis has been considered, particularly following episodes of familial clustering; however, it appears unlikely that there is a single gene defect (2). Associations have been shown with class I HLA-A1 and B 8 and class II HLA-DR3 (7) but it is likely that other polymorphisms exist that may enhance susceptibility to the disease following exposure to certain antigens that then incite an exaggerated cellular immune response (12). The phenotypic heterogeneity of sarcoidosis may partly be explained by genotypic heterogeneity with, for example, patients with severe pulmonary involvement having an association with the HLA-DQB1*0602-DRB1*150101 haplotype (13) and those with self-limiting disease associated with interleukin-1B, interleukin-8 growth-related gene product β and γ, and chemokine receptor 2, 5, and 6 (14). There is an association with HLA-DQB1*060 and the allele TNFA2 in Japanese women with cardiac sarcoidosis (15). It appears, therefore, that sarcoidosis involves a chronic immunological response to specific environmental antigens in a genetically susceptible individual.

The three requirements for sarcoidosis to develop are exposure to an antigen, development of acquired cellular immunity to the antigen involving antigen-presenting cells and antigen specific T lymphocytes, and action of immune effector cells causing a less specific inflammatory response (2). The significant effects of sarcoidosis depend on localization at vulnerable points such as the brainstem, extensive tissue infiltration with fibrosis as in the lungs, and metabolic derangements with hypercalcemia (4). Fibroblast proliferation is believed to be induced by both macrophages and mast cells mediated by early growth response 1 and interleukin-6, with resultant laying down of collagen and fibronectin in the lungs with scarring (2,16).

The characteristic feature of sarcoidosis is the presence of scattered noncaseating granulomas in a variety of organs. Given that the clinical diagnosis of sarcoidosis requires integration of the presentation and the radiographic findings with the typical histological features (17), it is obvious that the diagnosis based purely on autopsy findings may be difficult, particularly as similar noncaseating granulomas may be found in berylliosis, fungal infections, syphilis, and tuberculosis. The diagnosis is, therefore, one of exclusion and special staining for micro-organisms should be undertaken. Typical granulomas consist of collections of epithelioid macrophages and multinucleated Langhans or foreign body-type giant cells (7). CD4 (helper-inducer) T-lymphocytes are dispersed throughout the granulomas and over time CD4 and CD8 lymphocytes with scattered B-lymphocytes aggregate around the edges. At the same time, fibroblast proliferation occurs with collagen and proteoglycan deposition around the granulomas with the presence of scattered mast cells (2). This eventually leads to hyalinized scars and may result in significant parenchymal disruption and loss of organ function. Examination of the granulomas reveals Schaumann bodies (laminated proteinaceous intracytoplasmic concretions that stain positively for calcium), and asteroid bodies (stellate shaped inclusions within giant cells) (7). Within the lungs, an alveolitis precedes the formation of granulomas (4).

Determining the preceding clinical manifestations of the cohort of patients who present to medicolegal autopsy is difficult, as histories are often incomplete and manifestations may have been subtle. At autopsy there may be lesions found in almost any organ with lymph node involvement in most cases, usually of the pulmonary hilar and mediastinal nodes. Lymph nodes in the neck are also often involved and there may be granulomas in the tonsils in 25–33% of cases. Lesions are also commonly found within the lungs that may not be visible macroscopically, or that may consist of palpable small nodules located along lymphatics, blood vessels, and bronchi. Clinically these lesions may regress or progress to scarring with significant pulmonary fibrosis. Lesions may also be found in the oropharynx and sinuses in 2–18% of patients (2). The spleen is involved in *c*. 75% of cases, but there is macroscopic enlargement in only 20%. Lesions may be found within the liver, often around portal areas, and within the bone marrow, heart, skeletal muscle, brain, and endocrine glands including the pituitary, all of which should be sampled at autopsy.

Cardiac lesions may occur in any part of the heart, including the pericardium and endocardium, but have a predilection for the left ventricular free wall (94%), followed by the base of the interventricular septum (68%), the right ventricular free wall (45%), and finally within the atrial walls (17%) (18,19). This distribution may merely be a result of the amount of myocardial mass at those sites (20). Less commonly there may be involvement of small coronary vessels and valves (15). The differential diagnosis of giant cell lesions within the heart includes Wegener granulomatosis, Takayasu arteritis, rheumatoid arthritis, infective endocarditis, and occasionally ischemic heart disease, with or without hypertension (20). Roberts et al. consider that histologic examination of the heart alone will not enable differentiation between sarcoidosis and idiopathic giant cell myocarditis, and that a diagnosis of giant cell myocarditis can only be made once extracardiac sarcoidosis has been thoroughly excluded. In their opinion, failure to adequately sample other tissues has resulted in the misdiagnosis of cardiac sarcoidosis in the past as giant cell myocarditis (20).

Liver involvement may cause hepatic vein obstruction resulting in Budd-Chiari syndrome (21). Other areas that may be involved include the skin, mucous membranes, the eye (in 25–80% of cases), lacrimal, and salivary glands (7,22). Skin involvement may take the form of erythema nodosum or macules, papules and nodules, sometimes within tattoos and scars (2). There may also be effects from drug therapy noted at autopsy such as immunosuppression with opportunistic infections.

Death in cases of sarcoidosis may be due to respiratory, renal, or hepatic failure. Renal failure has been associated with granulomatous interstitial nephritis, with and without nephrocalcinosis, and hepatic failure may be due to granulomatous inflammation with in-trahepatic cholestasis. Interstitial fibrosis may complicate pulmonary sarcoidosis causing progressive pulmonary deterioration (21). All of these conditions tend to run chronic courses with *c.* 25% of patients with sarcoidosis dying of respiratory failure (2). However, on occasion, death may be more rapid and unexpected, as in the two reported cases, and although mostly due to cardiac involvement a variety of other quite diverse mechanisms may occur (Table 1).

Determining the incidence of sudden death is not easy, as sarcoidosis lacks a precise definition, and the overlap of clinical features with other conditions, with insensitive and nonspecific diagnostic tests (2) may result in cases being misdiagnosed and not being assessed at autopsy. Sudden and unexpected death may occur in individuals who have an established diagnosis of sarcoidosis, or in those who have either remained undiagnosed, or who have had minimal clinical manifestations.

TABLE 1—*Complications of sarcoidosis that may result in unexpected death.*

Cardiovascular
Arrhythmias from
Ischemia
Cardiomyopathy
Cardiac rupture
Pulmonary hypertension
Respiratory
Fibrosis with cor pulmonale
Pulmonary hypertension
Upper airway obstruction
Hemorrhage
Central nervous system
Hypothalamic/periventricular infiltration with arrhythmias
Polyphagia/café coronary
Brainstem infiltration
Obstructive hydrocephalus
Epilepsy
Gastrointestinal
Cirrhosis
Portal hypertension with esophageal varices

Affected individuals may also die with sarcoidosis, and not from it (23), and if lesions are identified at autopsy that are not associated with fibrosis and/or organ parenchymal disruption, it is most likely that they are incidental to the fatal episode, particularly if no plausible link can be established to a lethal mechanism. On the other hand, disruption of critical organ areas may well explain the cause of death.

In a study of nonischemic causes of sudden cardiac death in 483 patients aged between 15 and 81 years, 2.2% of deaths were associated with cardiac sarcoidosis (24). Despite cardiac involvement in 20–50% of cases, only 5% of individuals with sarcoidosis will have clinically detectable signs (19,25). However, there remains a significant risk of a lethal outcome, with cardiac sarcoidosis being responsible for 33–66% of all sarcoid deaths, and sudden death being the initial presentation in 17–35% of cases (20,25,26).

Sudden death may be related to an arrhythmia, or may be associated with papillary muscle dysfunction or infiltrative cardiomyopathy (2). Other presentations include rapidly progressive congestive cardiac failure, dilated cardiomyopathy, recurrent pericardial effusion, constrictive pericarditis and ventricular aneurysm (27). Ventricular tachycardia is the most common arrhythmia and complete heart block is the most common conduction disturbance, occurring in 30–65% of patients with lethal cardiac sarcoidosis (18,20,28,29). The effect of sarcoidosis on the heart depends on the amount of infiltrated myocardium, the volume of ventricular wall scarring, and the position of the granulomas within the heart (20). Sarcoidosis may also exacerbate preexisting disease as in case 1.

Sudden death due to cardiac sarcoid has occurred at all ages, including early adulthood and childhood (30,31). Myocardial ischemia may occur and rarely there may be spontaneous cardiac rupture. This was first reported by James as a cause of sudden death in a 56-year-old woman who collapsed and was found to have a hemopericardium with cardiac tamponade due to rupture of the right ventricle associated with underlying cardiac sarcoidosis (32). Outflow obstruction does not appear to be a problem. Despite extensive infiltration of the heart there may be no evidence of other organ dysfunction (33).

Pulmonary hypertension may result from venous or arterial compression by granulomas or hilar lymph nodes, resulting in cor pulmonale (34), and has been associated with sudden death (35). It may also derive from small vessel disease (27). Portal hypertension due to liver parenchymal infiltration may result in esophageal varices that increase the risk of catastrophic hemorrhage. Death may result from massive hemoptysis due to diffuse pulmonary sarcoidosis (36). Although rare in the pediatric age group, cases have been reported of laryngeal disease associated with dyspnea, sleep apnea, and in one case with airway obstruction during anesthetic induction (1,37).

Hypothalamic involvement in sarcoidosis with extensive granulomatous inflammation involving the paraventricular nucleus may result in unexpected death due to disturbance of autonomic cardiorespiratory control. This was the mechanism considered responsible for the death of a 23-year-old woman reported by Gleckman et al. (38). In this case, there had also been evidence of significant recent weight gain as was found in case 2 of our series. Polyphagia in case 2 was associated with hypothalamic infiltration and had led to

TABLE 2—*Classification of lesions of possible sarcoidosis detected at autopsy.*

Category I
Lesions not related to death
No infectious agent demonstrated
No heavy metal exposure
With no previous clinical diagnosis, finding = *''incidental sarcoid-like granulomas''
With previous clinical diagnosis, finding = *''incidental sarcoidosis''
Category II
Lesions related to death with plausible lethal mechanism
Characteristic pathological features
+/− Clinical diagnosis
No infectious agent demonstrated
No heavy metal exposure
Cause of death = *''sarcoidosis''

*Suggested diagnostic terms.

upper airway obstruction by food, or so-called ''café coronary'' syndrome (39). Although seizures in cases of neurosarcoidosis do not necessarily indicate a poor prognosis (40), epilepsy does have an associated risk of sudden death. Brainstem infiltration may result in lethal obstructive hydrocephalus (42).

In conclusion, sarcoidosis is an ill understood entity with no pathognomonic pathological features. Given the difficulties that may occur in attempting to establish the diagnosis at autopsy, it may be most appropriate to determine firstly whether the lesions identified played a role in the terminal episode or not. If the lesions were not related to the cause of death, and if no infectious agents were identified on special staining, in the absence of a history or established clinical diagnosis, then the term ''incidental sarcoid-like granulomas'' may be most appropriate. If a clinical diagnosis had been established, then the term ''incidental sarcoidosis'' could be used. If a lethal mechanism linking the typical pathological lesions to death could be demonstrated, and other causes of granulomatous inflammation have been excluded, then death can be attributed to sarcoidosis of a particular organ (Table 2), as in the two reported cases.

Acknowledgments

We would like to thank Judge Wayne Chivell, previously South Australian State Coroner, for permission to publish selected details of case 2 and Drs Andrew Ruszkiewicz and Grace Scott for pathological opinions in case 2.

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