Cardiac Involvement in Sarcoidosis Deaths in Wayne County, Michigan: A 20-Year Retrospective Study

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ABSTRACT

Background: Sarcoidosis is a disease of unknown etiology characterized by the formation of noncaseating, nonnecrotizing granulomas in various organ systems.

Methods: Reviews of 84 cases of natural death with sarcoidosis between the years 1996 and 2017 autopsied at Wayne County.

Results: The median age of decedents was 44 years (29 – 59 years of age). Blacks comprised 95% of the cohort, and 52% were female. Sarcoidosis or direct sequelae were the cause of death in 79% of cases. Twenty-nine percent of patients had a documented history of sarcoidosis and 70% of patients had evidence of systemic sarcoidosis. The most common sites of involvement were lungs or hilar lymph nodes (92%), heart (45%), liver (39%), and spleen (30%). Decedents with cardiac involvement were more likely to have no documented history of sarcoidosis (87% vs. 59%, $p=0.004$), more likely to have died of a sarcoidosis-related cause (97% vs. 65%, $p<0.001$), and died at a younger mean age (41 years vs. 46 years, $p=0.001$). In addition, individuals with cardiac involvement commonly had concurrent multiorgan involvement including lungs (90%), lymph nodes (38%), liver (40%), spleen (32%), and kidneys (7%).

Conclusions: Cardiac sarcoidosis is a uniquely poor prognostic factor and carries an increased risk of sudden death as shown by a disproportionate representation among medical examiner cases of sarcoidosis. Our findings suggest that approximately 40% may have asymptomatic cardiac involvement. The distribution of sarcoidosis within our cohort suggests that there is potentially a large undiagnosed and/or underdiagnosed demographic within large urban centers, such as Detroit, Michigan. *Acad Forensic Pathol.* 2018 8(3): 718-728

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INFORMATION

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INTRODUCTION

Sarcoidosis is a disease of uncertain etiology characterized by the systemic formation of nonnecrotizing granulomas. Jonathan Hutchinson originally described sarcoidosis in 1869 as a cutaneous disease, which he called “livid papillary psoriasis.” In 1899, Caesar Boeck coined the term “sarcoidosis,” due to its resemblance to lesions seen in sarcomas (1, 2). In 1950, the International Sarcoidosis Association set out diagnostic criteria which required granulomas in two or more separate organs in the absence of other granulomatous conditions. These criteria were further revised in 1975 to define sarcoidosis as “*a multisystem granulomatous disorder of unknown etiology*” (2, 3). Despite extensive research, the etiology of sarcoidosis remains unknown; however, it is associated with a variety of immunologic responses which result in persistent antigenic stimulation and cytokine accumulation, resulting in chronically activated macrophages forming granulomas, and ultimately, organ failure (4, 5).

Sarcoidosis has a worldwide epidemiologic distribution. In the US, it most commonly presents in black individuals between 20 and 40 years of age. It is more than twice as common in women, with a lifetime incidence of 2.4% vs 0.85% in men (2, 6), and between four to eight times more common in blacks than whites. In black patients, sarcoidosis is more likely to be chronic and fatal (7). In the US, the age-adjusted incidence ranges from 10.9 per 100 000 in the white population to 35.5 in the black population, with a lifetime risk of 2.4% in black populations (7). The incidence is higher in certain occupations, including health care workers, mechanics, firefighters, post office workers, and wood millers.

Sarcoidosis most commonly affects the lungs and hilar lymph nodes but has a variable clinical presentation and natural history. Approximately 20-40% of cases are asymptomatic and discovered on routine chest radiographs. About 90% of sarcoidosis patients will have an abnormal chest radiograph at some point in their disease course. Of symptomatic patients, 25% present with cough and 25% present with skin, eye, or nasal complaints. Mild constitutional symptoms

are common and 10-15% of patients will experience a progressive disease with multisystem involvement; 20-25% of patients will have permanent loss of lung function (8).

On pathologic examination, the characteristic feature is the presence of discrete, noncaseating or nonnecrotizing granulomas which can appear in virtually any organ system (9, 10) (**Images 1-3**). Multinucleated giant cells are frequently seen in the area of the granulomas with scattered T-lymphocytes that may rim the granuloma. Schaumann bodies, which are laminated concretions of calcium and proteinaceous material, are sometimes present and surrounded by Langerhans cells or foreign-body giant cells. Asteroid bodies, which are stellate inclusions within giant cells, can be seen in 50-60% of cases (12, 13). Chronically, the affected tissue will form a scar, which replaces the functional parenchyma and disrupts organ function (7, 14).

Because the defining feature of sarcoidosis – the granuloma – is not pathognomonic for the disease, the diagnosis can be challenging at autopsy. Diagnosis of sarcoidosis requires a combination of clinical, radiologic, and pathologic findings, together with the exclusion of other causes of granulomatous disease (**Table 1**) (13, 15, 16). Clinical and radiographic evidence may not always be available at autopsy and it may be difficult to rule out other causes of granulomas, such as berylliosis, fungal infections, syphilis, or tuberculosis. Therefore, a pathologic diagnosis of sarcoidosis is one of exclusion, and it is appropriate to perform stains for fungal and acid-fast organisms to rule out these causes of the granulomas (3, 17, 18). With chronicity, sarcoidosis may simply appear as scarring or fibrosis. Therefore, when unexplained fibrosis is present in an organ such as the lungs, careful examination of other organs is warranted to look for evidence of sarcoidosis.

Cardiac involvement in sarcoidosis is the most potentially fatal manifestation of the disease. Although only 5% of patients have clinical evidence of the cardiac involvement, many are asymptomatic and not identified. Estimates, including autopsy studies, have suggested the prevalence of cardiac involvement among

Image 1: Left ventricular free wall lesion showing late-stage granulomatous inflammation with associated fibrotic and scar-like changes involving the myocardium and endocardium. These lesions may manifest as complete heart block (23-30%), bundle branch block (12-32%), ventricular tachycardia (23%), congestive heart failure (25-75%), and sudden death (25-65%) (11).

Image 2: Microscopic image of the cardiac lesion from **Image 1** showing multinucleate giant cells and lymphocytic infiltrate and complete obliteration of normal cardiac myocytes (H&E, x200).

Image 3: Concurrent mediastinal lymph node showing diffuse replacement/effacement of nodal architecture with well-formed epithelioid nonnecrotizing granulomas, which special stains confirm are negative for organisms (H&E, x200).

sarcoidosis patients may be as high as 25%; however, clinical diagnosis is challenging due to the low sensitivity of available modalities (9, 10, 15, 19, 20). Cardiac sarcoidosis accounts for approximately 13-25% of all sarcoidosis-related deaths and carries a high risk of fatal complications, including dilated cardiomyopathy, congestive heart failure, conduction abnormalities, and sudden cardiac death (21, 22).

Many prior studies of sudden death in sarcoidosis have been limited to case reports and case series. A long-term cross-sectional study from the perspective of a large urban medical examiner's office, such as Wayne county, can provide critical epidemiological characteristics sarcoid distribution, and specifically, the prevalence of cardiac sarcoidosis in natural deaths.

METHODS

We reviewed autopsy reports from the Wayne County Medical Examiner Office (WCMEO) from 1996 through 2016 through the InQuest data management

system. Searches for "sarcoidosis," "noncaseating granulomas," "nonnecrotizing granulomas," and other similar search terms identified 84 natural deaths in which sarcoidosis was a cause of death, present in the gross or microscopic autopsy findings, or a component of the decedent's medical history.

Causes of death were classified as sarcoidosis-related if and only if the cause of death was determined to be sarcoidosis or a direct sequela (e.g., dilated cardiomyopathy, pulmonary hypertension). Some cases classified as nonsarcoidosis-related included: intracranial hemorrhage, hypertensive cardiovascular disease and coronary artery disease, septicemia, and sickle cell anemia. Other incidences of granulomatous disease occurring in nonnatural death (i.e., homicide, suicide, accidental) were omitted.

We reviewed the autopsy reports for relevant demographic data, cause and manner of death, and autopsy findings. Statistical analyses were performed in Microsoft Excel.

Table 1: Nonnecrotizing Granulomatous Diseases: Differentials

Autoimmune
Sarcoidosis
Churg-Strauss
Giant cell arteritis
Systemic lupus
Crohn disease
Primary biliary cirrhosis
Granuloma annulare
Infectious
<i>Candida spp.</i>
<i>Coccidioides immitis/Coccidioides posadasii</i>
<i>Coxiella burnetii</i>
<i>Cytomegalovirus</i>
<i>Mycobacteria spp.</i>
<i>Schistosoma spp.</i>
<i>Toxoplasma gondii</i>
<i>Rickettsia spp.</i>
<i>Salmonella typhi</i>
Hepatitis A/C
Toxic
Berylliosis
Zirconium
Extrinsic allergic alveolitis
Drug
Bacillus Calmette-Guerin
Nonsteroidal anti-inflammatory drugs
Antibiotics (various)
Methotrexate

RESULTS

We reviewed a total of 84 cases of decedents with confirmed sarcoidosis. The median age of decedents was 43 years (range 24 to 65 years). Ninety-five percent of decedents were black and 52% were female (see **Table 2** for cohort demographics). Eighty percent of decedents died of a sarcoidosis-related event (sar-

Table 2: Wayne County, Michigan Sarcoidosis Deaths, Cohort Demographics, 1997-2016

Natural Deaths With Sarcoidosis (1997-2016)	Quantity	Mean Age
Total deaths	84	
Men	40	42.4
Women	44	44.5
Sarcoid-Related Deaths (SRD)	Quantity	Percentage
Total	67	80%
History of Diagnosis at Death	Quantity	Percentage
Yes	24	28.6%
No/Unknown	9/51	71.4%
Age; SRD	Years	
Mean/Median	43	
Range	28	
Race Distribution; SRD	Quantity	Mean Age
Blacks	65	42.8
Whites	2	51
Men	30	41.2
Women	37	44.5
Race	Black	White
All Cases	80	4
SRD	65	2
Body Mass Index	NS*	

* Analysis of body mass index (BMI) showed no statistical significance.

coidosis or a direct sequela). Nonsarcoidosis-related deaths included conditions such as hypertensive-cardiovascular complications, intracranial hemorrhages, and sickle cell anemia. In 31% of cases, the decedent had a known history of sarcoidosis at the time of autopsy. Of the decedents with sarcoidosis-related deaths, males were significantly younger than females (41.2 vs 44.4 years, $p = 0.0245$) (**Table 3**).

Of all decedents, 68% had systemic sarcoidosis, which was defined as granulomatous inflammation involving two or more organ systems. The most common sites of involvement were lungs (78%), heart (42%), liver (31%), spleen (27%), kidneys (6%), central nervous system (CNS) (5%), and thyroid (2%) (**Figure 1**). Routine sections of skin and eyes were not assessed. Risk stratification of sarcoidosis distribution (**Table 4**) shows that decedents with systemic involvement had a 59% chance of having cardiac involvement.

Likewise, 44% of decedents with lung involvement (most common) also had cardiac involvement. Organ involvement other than isolated lung or heart was always found to be associated with systemic, multiorgan involvement. Thyroid and CNS involvement were exceedingly rare.

Thirty-eight decedents (45%) were found to have cardiac involvement and were significantly younger than those without cardiac involvement (40.4 years vs. 46.1 years, $p < 0.001$) (**Figure 2, Table 5**), less likely to have a known history of sarcoidosis (13% vs. 41%, $p < 0.01$), and more likely to die of a sarcoidosis-related death (97% vs. 65%, $p < 0.01$). Decedents that died prior to the cohort median age (43 years) were approximately two-fold more likely to have cardiac involvement. No statistically significant differences were identified in the organ distribution of disease between the two groups (**Table 3**).

Table 3: Cohort With and Without Cardiac Sarcoidosis

	With Cardiac Involvement	Without Cardiac Involvement	<i>p</i>
N	38	46	
Demographics			
Age, years, mean	40.7	45.7	< 0.01
Female	19 (50%)	25 (54%)	0.69
Black	37 (95%)	44 (96%)	0.67
Body mass index, mean +/- standard deviation	29.8	27.6	0.13
Sarcoidosis			
Known history of sarcoidosis	5 (13%)	19 (41%)	< 0.01
Sarcoid-related death	37 (97%)	30 (65%)	< 0.01
Non-hilar lymph nodes	15 (39%)	17 (37%)	0.81
Thyroid	1 (3%)	1 (2%)	0.89
Central nervous system	0 (0%)	4 (9%)	0.06
Liver	15 (39%)	18 (39%)	0.97
Spleen	12 (32%)	13 (28%)	0.74
Lung	34 (89%)	43 (93%)	0.51

DISCUSSION

Decedents with cardiac involvement by sarcoidosis were significantly younger, more likely to have no known history of sarcoidosis, and more likely to have died of a sarcoidosis-related causes when compared with decedents without cardiac involvement. These findings are consistent with previous reports that cardiac involvement is of uniquely poor prognosis. Granulomatous inflammation of cardiac tissue, which

specifically targets the epimyocardium and septum, disrupts the cardiac parenchyma, normal myocyte architecture, and electrical conduction causing death via dysrhythmias, heart block, and/or dilated cardiomyopathy.

Previous studies have placed the prevalence of cardiac sarcoidosis at ~25% of all sarcoid-affected patients; however, in this cohort, patients with cardiac sarcoidosis appear to be overrepresented (45%), sug-

Figure 1: Distribution and risk of organ involvement in cases examined. In the cases examined (natural deaths), pulmonary and hilar lymph node involvement was the most commonly identified (77%), followed by cardiac (38%), liver (33%), and non-hilar lymph nodes (32%). Organs such as skin and eyes were not routinely examined for granulomatous inflammation in the cohort examined. Lymph nodes include only non-hilar nodes.

CNS - central nervous system

gesting two possible explanations, 1) the prevalence of sarcoidosis in a medical examiner setting is low and is largely limited to cases of unexpected death and because individuals with cardiac involvement are largely asymptomatic or minimally symptomatic (15) until their terminal insult, this creates selection bias within this cohort, especially considering that we only examined those dying of natural disease; and 2) our data indicate that a significant proportion of cases were undiagnosed during lifetime (71.4%), and prevalence numbers for metropolitan regions may be incorrect because initial studies were performed in largely white suburban communities. Recent studies have indicated that the prevalence of sarcoidosis within urban settings may far exceed previous reports, nearing 330 per 100 000 individuals, eight-fold greater than expected (23). Furthermore, those that are affected are often of a lower socioeconomic class, where healthcare surveillance and healthcare access have been historically of limited.

Sarcoidosis can be challenging to diagnose at autopsy due to the fact that the comprehensive clinical and radiological evaluations are rarely available to the pathologist at the time of postmortem evaluation. In addition, although the presence of granulomatous inflammation consistent with sarcoidosis can be identified with great confidence, a diagnosis of sarcoidosis remains one of clinical and pathological correlation. In that respect, a postmortem evaluation is not the proper setting for diagnosis of the clinical condition, but rather only cause and manner of death. Because our cohort only includes cases falling within the medical examiner's jurisdiction, our data is limited in scope and estimation of symptomology outside the probable cause of death.

CONCLUSION

Our data show that cardiac involvement with sarcoidosis is associated with a younger age of death, great-

Table 4: Risk of Organ Involvement in Cases Examined

		Risk of Involvement								
		Systemic	Lung	Heart	LN	Liver	Spleen	Kidney	CNS	Thyroid
Organ Involvement	Systemic		0.932	0.593	0.441	0.508	0.424	0.085	0.051	0.034
	Lung	0.714		0.442	0.377	0.416	0.299	0.065	0.026	0.026
	Heart	0.921	0.895		0.395	0.395	0.316	0.079	0.000	0.026
	LN	0.813	0.906	0.469		0.438	0.438	0.500	0.063	0.000
	Liver	0.909	0.970	0.455	0.424		0.576	0.152	0.000	0.030
	Spleen	1.000	0.920	0.480	0.560	0.760		0.160	0.000	0.040
	Kidney	1.000	1.000	0.600	0.600	1.000	0.800		0.000	0.200
	CNS	0.750	0.500	0.000	0.500	0.000	0.000	0.000		0.000
	Thyroid	1.000	1.000	0.500	0.000	0.500	0.500	0.500	0.000	

The distribution of granulomatous inflammation was analyzed in each case to establish risk ratio for additional organ involvement. Cases of cardiac involvement are highly correlated to lung involvement (90% of cases); however, only 44% of cases with lung involvement had concurrent cardiac disease.

LN - Lymph nodes

CNS - Central nervous system

Figure 2: Distribution by age at demise, stratified by cardiac versus noncardiac cases. Cardiac involvement was correlated with a significant shift in mean age at the time of demise. In the absence of cardiac involvement, no other organ system involvement was observed to have significant effect on mortality. Splenic and hepatic involvement were strongly associated the late stage, multisystemic disease.

Table 5: Distribution by Race and Age at Demise Stratified by Organ System Involvement

Organ Involvement	Count; %	Black:White	Mean Age
Lung	77; 91.67%	75:2	42.98
Systemic	59; 70.24%	55:4	42.88
Heart	38; 45.24%	36:2	40.41
Liver	33; 39.29%	31:2	42.38
Lymph node	32; 38.10%	31:1	43.04
Spleen	25; 29.76%	23:2	42.60
Kidney	5; 5.95%	5:0	44.60
Central nervous system	4; 4.76%	4:0	42.50
Thyroid	2; 2.38%	2:0	45.00

er likelihood of having no known history, and greater likelihood of dying of sarcoidosis-related sequelae. These data are consistent with prior studies demonstrating that cardiac involvement is a poor prognostic factor and a risk for sudden cardiac death. Forensic pathologists should consider sarcoidosis in younger patients who present with sudden cardiac death, and this scenario should prompt a careful microscopic examination for the characteristic features of sarcoidosis.

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