SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2016; 33; 275-280

Causes of death in patients with sarcoidosis

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Abstract. *Introduction:* Sarcoidosis is a multi-system, granulomatous disorder of unknown etiology that is associated with a variable prognosis and sometimes results in death. There are conflicting reports regarding the causes of death in patients with sarcoidosis. *Methods:* Forty-four consecutive patients with sarcoidosis who underwent an autopsy (35 patients) or died at Mayo Clinic (Rochester, MN, USA) over a 20-yr period, from January 1, 1994 to December 31, 2013 were analyzed. *Results:* The median age at death was 63 years (range, 33-94 years) and there were 22 (50%) women. Sarcoidosis had not been clinically diagnosed in 16 (36%) patients before death. Fifteen deaths (34%) were related to sarcoidosis and included seven deaths (16%) from cardiac sarcoidosis and four deaths (9%) from progressive pulmonary sarcoidosis. Other sarcoidosis-related causes of death included advanced hepatic sarcoidosis (5%) and opportunistic infections (5%) related to immunosuppressive therapy for treating sarcoidosis. Among seven patients dying from cardiac sarcoidosis, three had been diagnosed with sarcoidosis during life and cardiac involvement was known in two of them. Six of seven deaths from cardiac sarcoidosis occurred in the autopsied cohort while all four deaths from pulmonary sarcoidosis occurred in those not autopsied. *Conclusions:* In the majority of patients dying with sarcoidosis the cause of death is unrelated to sarcoidosis. Cardiac involvement is the most common cause of sarcoidosis-related deaths in patients subjected to postmortem examination and was usually undiagnosed during life. The cause distribution of death in patients with sarcoidosis differed depending on whether autopsy was performed. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 275-280)*

Key words: autopsy; cardiac disease, mortality, sarcoidosis

List of Abbreviations:

MRI = magnetic resonance imaging
PET = positron emission tomography

Introduction

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology that generally has a favorable prognosis with the majority of patients experiencing spontaneous remission (1-3). However, disease progression causing pulmonary or extrapulmonary morbidity can be seen in about one-third of patients with sarcoidosis. It is estimated that between 1% and 5% of patients with sarcoidosis will die from sarcoidosis-related causes (1, 4). Respiratory failure secondary to pulmonary complications has generally been identified to be the most common cause of death from sarcoidosis in the USA and Europe (4-6). However, Perry and Vuitch (7) reported cardiac involvement to be the most common cause of death among 38 autopsy cases of sarcoidosis encountered in Dallas, Texas, USA between 1958 and 1992. Cardiac sarcoidosis was not known before autopsy in the majority of their cases. Similarly, cardiac involvement has been reported to be the major cause of mortality

Received: 26 July 2015
Accepted after revision: 11 January 2016
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in Japanese patients with sarcoidosis (8, 9). In order to reassess the cause and clinical characteristics of sarcoidosis deaths in the current era, we analyzed 44 consecutive patients with sarcoidosis who underwent an autopsy or died at our medical center.

Methods

Study subjects

Using a computer-assisted text search of medical records including autopsy reports we identified 44 consecutive patients with sarcoidosis (diagnosed during life or at autopsy) that underwent an autopsy or died at the Mayo Clinic (Rochester, MN, USA) over a 20-year period from January 1, 1994 to December 31, 2013. Diagnostic criteria for sarcoidosis included the following: (1) compatible clinical and radiologic findings; (2) histopathologic finding of noncaseating epithelioid granulomas; and (3) the absence of an identifiable cause for the granulomatous process (*e.g.*, infection, occupational exposures, granulomatosis with polyangiitis, etc.) based on exposure history, serologic and microbiologic testing, and histopathologic analysis (1). We excluded subjects whose diagnosis could not be substantiated or analyzed due to insufficient clinical or pathologic data. We also excluded subjects who had a prior history of sarcoidosis with subsequent remission of disease, *i.e.*, no evidence of sarcoidosis-related organ dysfunction at the time of death. Forty-four subjects with sarcoidosis were identified, 35 (80%) of whom had undergone an autopsy. This study was approved (study ID# 13-001511) by the Mayo Foundation Institutional Review Board.

Clinical data

Medical records were examined in detail and the following data were retrieved: age, sex, race, clinical features and course, and organ involvement. We also reviewed clinicians' diagnoses as to the cause of death. We identified the immediate causes of deaths based on analysis of clinical data and autopsy findings. The diagnosis and causes of deaths were determined by consensus of the two of the authors (XH and JHR) based on review of all available data.

Statistical analyses

Continuous data are presented as median and range, when appropriate, and number and percentages for categorical variables.

Results

Of 44 patients with sarcoidosis, 22 (50%) were female. The median age at death was 63 years (range, 33 to 94 years). All patients were Caucasian with the exception of four (9%) African Americans. Sarcoidosis was clinically known in 28 (64%) of the 44 patients including all 9 patients who did not undergo an autopsy, and was diagnosed only at autopsy in 16 (36%) patients.

Organ involvement noted for the 35 autopsied patients is summarized in Table 1. The most common organ involved was the lung as seen in 22 (63% of autopsied cases) of these cases followed by lymph nodes in 21 (60%) cases. Nineteen (54%) patients had been diagnosed to have sarcoidosis during life and 11 (31%) had been treated with prednisone. None of the autopsied patients manifested evidence of advanced pulmonary fibrosis or honeycombing. Less commonly involved organs included liver, heart, spleen, and kidney. Incidental cancers were found at autopsy in five patients (14%) and included papillary thyroid cancer (<1 cm) in three patients while pulmonary carcinoid tumor (2.5 cm) and renal cell carcinoma (1.9 cm) were found in one patient each.

Among these 35 autopsied cases, sarcoidosis-related causes accounted for seven deaths (20% of autopsied cases) and included six deaths resulting from cardiac sarcoidosis (Table 2). Four of these deaths from cardiac sarcoidosis were sudden due to dysrhythmias and occurred in those aged 35, 47, 60, and

Table 1. Organ Involvement in Autopsied Patients with Sarcoidosis

Involved organs N (%)	Longcope, 1952[13]	Huang, 1981[5]	Iwai, 1993[12]	Current study
Lung	79 (86)	25 (100)	261 (82)	22 (63)
Lymph node	79 (86)	20 (80)	279 (88)	21 (60)
Liver	60 (65)	16 (64)	137 (45)	10 (29)
Heart	18 (20)	4 (16)	217 (69)	9 (26)
Spleen	58 (63)	18 (72)	127 (41)	9 (26)
Kidney	17 (19)	10 (40)	40 (13)	4 (11)

Table 2. Causes of deaths in 44 patients with chronic sarcoidosis

Cause of death, N (%)		Autopsied (n=35)	Not autopsied (n=9)	All (n=44)
Sarcoidosis-related		7 (20)	8 (89)	15 (34)
	Cardiac sarcoidosis	6 (17)	1 (11)	7 (16)
	Pulmonary sarcoidosis	0	4 (44)	4 (9)
	Hepatic sarcoidosis	0	2 (22)	2 (5)
	Opportunistic infections	1 (3)	1 (11)	2 (5)
Not sarcoidosis-related		28 (80)	1 (11)	29 (66)
	Cardiac disorders[a]	9 (26)	0	9 (20)
	Pneumonia	4 (11)	1 (11)	5 (11)
	Pulmonary embolism	3 (9)	0	3 (7)
	Stroke	3 (9)	0	3 (7)
	Accidental trauma	2 (6)	0	2 (5)
	Alcohol intoxication	2 (6)	0	2 (5)
	Aortic dissection	2 (6)	0	2 (5)
	Gastrointestinal hemorrhage	1 (3)	0	1 (2)
	Cancer	1 (3)	0	1 (2)
	Diabetic ketoacidosis	1 (3)	0	1 (2)

[a] Included cardiac dysrhythmia (without cardiac sarcoidosis) in five cases, acute myocardial infarction in three cases, and ischemic cardiomyopathy in one.

69 years, respectively; two older patients manifested grade 1 to 2 (of 4) coronary atherosclerosis at autopsy while the younger two patients did not. Two other deaths (ages 52, 78 years) from cardiac sarcoidosis resulted from chronic heart failure related to sarcoid cardiomyopathy. Among six autopsied patients dying from cardiac sarcoidosis, two had been clinically diagnosed to have sarcoidosis and cardiac involvement known in one (35-year-old African American male on chronic prednisone treatment for sarcoid cardiomyopathy) of these two patients. Thus, five (83%) of the six deaths from cardiac sarcoidosis among autopsied cases occurred in those not clinically detected to have cardiac involvement with sarcoidosis. One remaining sarcoidosis-related death resulted from invasive aspergillosis complicating chronic prednisone therapy. Three additional patients had cardiac sarcoidosis but died from acute myocardial infarction, septic shock related to pneumonia, and invasive pulmonary aspergillosis, respectively. In two of these three patients, sarcoidosis had not been clinically diagnosed. Thus, among these nine patients with evidence of cardiac sarcoidosis at autopsy, six (67%) had not been clinically diagnosed to have sarcoidosis.

Among nine patients who did not undergo an autopsy, the cause of death was sarcoidosis-related in all but one patient who died from a community-acquired pneumonia. All nine patients had been known to have sarcoidosis and treated with prednisone. Four patients (44%) ranging in age from 69 to 80 years died from progressive respiratory failure with advanced pulmonary sarcoidosis; all were Caucasian and had been known to have sarcoidosis for a median duration of 27 years (range, 17 to 42 years). Pulmonary function measurements obtained within one year of their death demonstrated forced vital capacity ranging from 39% to 56% predicted and diffusing capacity for carbon monoxide ranging from 26% to 37% predicted. All four patients were on chronic supplemental oxygen therapy before death. Two patients (22%) died from advanced hepatic sarcoidosis with cirrhosis complicated by variceal bleeding, hepatorenal syndrome, hepatic encephalopathy, and multiorgan failure. Both of these patients had multi-system involvement with sarcoidosis including the lung and hepatic involvement had been known for three and 13 years before death, respectively. One patient (11%) died from progressive heart failure related to sarcoid cardiomyopathy which had been diagnosed nine years prior to death. The remaining patient died from *pneumocystis jiroveci* pneumonia that complicated immunosuppressive therapy (prednisone and azathioprine) for her sarcoidosis diagnosed 3 months before. She had been started on immunosuppressive therapy at an outside medical center after a surgical lung biopsy demonstrated evidence of advanced pulmonary sarcoidosis with noncaseating granulomas and parenchymal fibrosis.

Discussion

In this autopsy study of 44 consecutive patients with sarcoidosis, the lung was the most common organ involved but only one-third of patients died from sarcoidosis-related causes. Among 15 patients dying from sarcoidosis-related causes, cardiac sarcoidosis was the cause of death in nearly one-half of patients in whom the majority (five of seven patients) were not clinically known to have cardiac sarcoidosis. To our knowledge, this is the first autopsy analysis of sarcoidosis patients in the Western population since the study of Perry and Vuitch nearly 20 years ago (Table 3) (7). However, it should be noted that our study cohort was comprised mostly of Caucasians seen at a tertiary referral center and relatively few African Americans who are known have more severe and chronic course with sarcoidosis.

We found the lung to be the most commonly involved organ in this study which is consistent with current concepts regarding sarcoidosis (10, 11). In two prior autopsy studies from Japan and USA, pulmonary involvement was described in 81% and 86%, respectively (12, 13). However, the percentage of patients that died from progressive pulmonary sarcoidosis as the immediate cause was not specified in these prior studies. Although pulmonary sarcoidosis was the most common cause of death among our patients not autopsied, none of our autopsied patients died from pulmonary sarcoidosis. This difference between the two groups is likely explained on the basis of progressive pulmonary involvement in patients with sarcoidosis being readily recognized clinically; thus, these patients are less likely to undergo an autopsy compared to those with less clinically apparent causes of death such as cardiac sarcoidosis. This difference in the causes of deaths as ascertained from autopsied and non-autopsied cohorts has implications on the interpretation of previously published data with respect to cause distribution of death in patients with sarcoidosis. Data derived from unverified death certificates are likely to underestimate deaths related to cardiac sarcoidosis while deaths related to progressive pulmonary sarcoidosis will be underrepresented in autopsy series.

Aside from cardiac and pulmonary involvement, hepatic sarcoidosis and opportunistic infections comprised other sarcoidosis-related causes of death in our cohort. Liver involvement in sarcoidosis is thought to be relatively common but is usually not associated with symptoms (2, 14, 15). Rarely, hepatic sarcoidosis can result in cirrhosis, portal hypertension, cholestasis, and Budd-Chiari syndrome (15, 16).

Five patients in our study had cancers newly diagnosed at autopsy and included three papillary thyroid cancers, one pulmonary carcinoid tumor and one renal cell cancer. The possibility of a relationship between these cancers discovered at autopsy and sarcoidosis cannot completely be excluded but seems unlikely. The frequency of incidental cancers found at autopsy in our study is similar to that reported for autopsies in the general population (17, 18). In particular, incidental papillary thyroid carcinomas have been found in up to 36% of autopsies (17). Pulmonary carcinoid and renal cell carcinoma were both small and interpreted to be incidental at postmortem examination in those two patients who exhibited widespread presence of noncaseating granulomas.

Corticosteroid therapy is generally the preferred initial treatment for patients with progressive sarcoidosis. When corticosteroids are contraindicated, inadequately effective, or associated with adverse effects, other immunosuppressive agents are employed.

Table 3. Causes of death in patients with sarcoidosis

Cause, n (%)	Hagerstrand, 1964[22]	Huang, 1981[5]	Iwai, 1993[a8]	Perry and Vuitch, 1995[7]	Current study
Pulmonary sarcoidosis	2 (5)	13 (32)	18 (6)	12 (32)	4 (9)
Cardiac sarcoidosis	1 (2)	2 (5)	150 (47)	14 (37)	7 (16)
Hepatic sarcoidosis	0	0	0	1 (3)	2 (5)
Neurologic sarcoidosis	0	4 (10)	12 (4)	1 (3)	0
Opportunistic infection	0	9 (22)	14 (4)	0	2 (5)
Not sarcoidosis-related	40 (93)	13 (32)	123 (38)	10 (26)	29 (66)
Comments	Autopsy study	Autopsy in 25 (61%)	Autopsy study	Autopsy study	Autopsy in 35 (80%)

[a]3 patients died of unknown cause

These "corticosteroid-sparing" agents include methotrexate, azathioprine, leflunomide, tumor necrosis factor inhibitors, and many others (19, 20). Use of immunosuppressive therapy in chronic inflammatory disorders such as sarcoidosis is associated with opportunistic infections as seen in two patients in the current study. Our patient who died from invasive pulmonary aspergillosis had been on chronic prednisone treatment of 11 years' duration for chronic pulmonary sarcoidosis and also had diabetes mellitus. The patient who died from *pneumocystis jiroveci* pneumonia had been treated with prednisone and azathioprine for advanced pulmonary sarcoidosis but was not on *pneumocystis* prophylaxis.

Swigris and colleagues analyzed 23,678 sarcoidosis cases in USA using death certificate data and showed 58.8% of sarcoidosis patients to have died of sarcoidosis itself. Similar findings have been reported from other studies of death certificate data in USA and Europe (4, 5, 21, 22). In a recent French retrospective cohort study of 142 stage IV (advanced lung fibrosis) sarcoidosis patients seen at a tertiary referral center for sarcoidosis the survival rate was 84% at 10 years, which was worse than for the general population (4). Among the sixteen fatal cases (11%), 75% were felt to be directly attributable (no autopsy data) to respiratory causes including refractory pulmonary hypertension, chronic respiratory insufficiency, complications related to pulmonary aspergilloma. It is possible that respiratory causes may have been overdiagnosed as the cause of death in these patients with known pulmonary sarcoidosis. Although death certificates are an important source of epidemiologic data they are less reliable in assessing the actual causes of death. Discrepancy between clinical and autopsy diagnoses regarding the cause of death has been estimated to be around 50% (23).

Sarcoidosis had been clinically diagnosed in 28 patients (64%) in our study including all nine patients who did not undergo an autopsy. In comparison, a Swedish autopsy study from fifty years ago reported only three among 43 sarcoidosis cases to have been diagnosed during life (24). Perry and Vuitch reported 55% of their 38 sarcoidosis cases to be incidentally diagnosed at autopsy (7). Although the intervening decades have brought increased awareness of sarcoidosis and improved diagnosis of sarcoidosis our results suggest that a substantial portion of patients with sarcoidosis may still go undiagnosed during life particularly when involving heart, liver and spleen.

We acknowledge that the limitations of our study including the retrospective design which limited the analysis to clinical data available in medical records and autopsy. In addition, this study includes a modest number of patients, partly related to sarcoidosis being an uncommon cause of death. We also acknowledge studies involving autopsy data tend to enrich for atypical and diagnostically challenging cases in defining the causes of death.

Our data regarding cardiac sarcoidosis are in agreement with prior observations that cardiac sarcoidosis frequently caused fatal outcome but was commonly diagnosed only at autopsy (7). In a retrospective study of 320 autopsies of patients with sarcoidosis in the Japanese population, Iwai and colleagues found 60% to have died from sarcoidosis-related causes, mainly cardiac sarcoidosis (47% of all deaths) (8). The optimal mode of detecting cardiac involvement in sarcoidosis has been debated (25-28). The Heart and Rhythm Society recently published an international expert consensus statement on screening, diagnosis and management of cardiac sarcoidosis (27). In their statement, screening for cardiac involvement in patients with biopsy-proven extracardiac sarcoidosis is recommended by asking for symptoms of presyncope, syncope and significant (lasting >2 weeks) palpitations and obtaining an electrocardiogram. Furthermore, it is stated that screening with an echocardiogram "can be useful" for patients with biopsy-proven extracardiac sarcoidosis. An integrated imaging approach including the use of cardiac magnetic resonance imaging (MRI) or positron emission tomography (PET) has been proposed for patients with sarcoidosis who have cardiac symptoms or abnormal results on screening tests (27, 29, 30).

Conclusions

The majority of patients with sarcoidosis die from causes unrelated to sarcoidosis. Cardiac involvement is the most common cause sarcoidosis-related deaths in patients subjected to postmortem examination but cardiac sarcoidosis is usually diagnosed only at autopsy. The cause distribution of death in patients with sarcoidosis will vary depending on whether autopsy was performed.

Authors' contributions

Dr. Hu contributed to conception of the study design, performed the data analysis, produced the initial draft of the manuscript, approved the final manuscript, and served as principal author.

Dr. Carmona contributed to conception of the study design, data interpretation and preparation and approval of the final manuscript.

Dr. Yi contributed to data interpretation and preparation and approval of the final manuscript.

Dr. Pellikka contributed to data interpretation and preparation and approval of the final manuscript.

Dr. Ryu contributed to conception of the study design, data interpretation and preparation and approval of the final manuscript.

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