

Epidemiology and clinical characteristics of sarcoidosis: an update from a population-based cohort study from Olmsted County, Minnesota

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SUMMARY

Information about the epidemiology, clinical manifestations and comorbidities of sarcoidosis among Caucasians is relatively scarce. This review focuses primarily on the data from a recently published Caucasian-predominant population-based cohort from Olmsted County, Minnesota. Overall, the incidence rate was 10.0 per 100,000 population, which suggested that sarcoidosis is less common in Caucasians than in Blacks, but is more common in Caucasians than in Asians. Intrathoracic involvement was seen in the vast majority of patients, but less than half have respiratory symptoms. The most common extra-thoracic manifestations were skin rash followed by arthralgia, ophthalmologic involvement, hepatic involvement, splenomegaly, renal involvement, neurological involvement, extra-thoracic lymphadenopathy, exocrine gland involvement, upper respiratory tract involvement and cardiac involvement. Compared to sex and age-matched subjects, patients with sarcoidosis suffer from increased rates of cardiovascular disease, venous thromboembolism and hospitalized infection.

Key words: Sarcoidosis; pulmonology; interstitial lung disease.

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INTRODUCTION

Sarcoidosis is a multi-system disorder of unclear etiology characterized by the presence of non-caseating granuloma, which are comprised of macrophages, epithelioid cells, mononuclear cells and CD4+ T cells with a few CD8+ T cells in the peripheral zone. Lung and intra-thoracic lymph node are the most commonly affected organs although any organs can be involved. The clinical course of sarcoidosis ranges from an indolent process to an acute self-limited process to a progressive disease with permanent organ damage (1, 2).

There is only limited information regarding the epidemiology and clinical characteristics and outcome of sarcoidosis, partic-

ularly among Caucasians. The purpose of this review is to summarize the data from a recently published Caucasian-predominant cohort of residents of Olmsted County, Minnesota, United States who were first diagnosed with sarcoidosis between 1976 and 2013 with an emphasis on epidemiology, clinical characteristics and comorbidity (3).

EPIDEMIOLOGY OF SARCOIDOSIS

Incidence and mortality

In this population, the annual incidence of sarcoidosis among adults in 1946-2013 was 10.0 per 100,000 population. Sarcoidosis was slightly more common among fe-

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males than males (10.5 per 100,000 population among females and 9.4 per 100,000 population among males). No significant calendar year trend in incidence was observed in either females or males. Mean age at diagnosis was 48.3-years in females and 42.8 years in males. The observed incidence rate was in line with other Caucasian studies that reported incidence rates of 5 to 19 per 100,000 population per year (4-6) and prevalence of 160 per 100,000 population (6). Compared to other ethnic groups, the incidence rate of sarcoidosis among Caucasians is lower than Blacks (with reported incidence of 40 to 70 per 100,000 population per year) (7, 8) but is higher than Asians (with reported incidence of 1 per 100,000 population per year) (9).

The overall mortality of patients with sarcoidosis in this cohort was not different from the general population. This is in contrast to previous reports that observed an approximately 2-fold increased rate of mortality (4, 10). This discrepancy may reflect differences in management of sarcoidosis in different regions or the difference of severity and outcome of sarcoidosis across ethnic groups (11, 12).

Risk factors

Despite decade-long research effort, the etiology and pathogenesis of sarcoidosis remains poorly understood. A widely accepted hypothesis is that of a complex interaction between environmental factors and genetic factors (13). Data from this U.S. population-based cohort may provide further insights into the possible etiologies of sarcoidosis.

First, there is some seasonality of sarcoidosis, as the incidence rate of sarcoidosis was persistently lower in autumn compared to the rest of the year across 4 decades of study (14). This may reflect seasonality of environmental trigger(s) associated with the granuloma-formation in sarcoidosis. Nonetheless, this observed seasonal variation is not consistent across different regions of the world. For example, a study from Turkey (15) reported the lowest incidence in summer, while a study from India (16) observed the lowest incidence in win-

ter. The different patterns of seasonality might reflect different environmental stimuli. Second, obesity was associated with a higher risk of sarcoidosis. The odds of developing sarcoidosis were about 2.4 times higher among obese subjects (*i.e.*, body mass index ≥ 30 kg/m²) compared to those who were not obese (17). While certainly speculative, this observation may suggest the role of leptin, a hormone secreted by adipocytes, in the pathogenesis of sarcoidosis. Leptin is a pro-inflammatory adipokine with a potent immuno-modulatory effect that is able to sustain autoreactive cell proliferation, which may increase the risk of autoimmune disease, including sarcoidosis (18). An increased risk of autoimmune diseases, such as psoriasis and rheumatoid arthritis, has been described among obese subjects (19).

Third, the risk of developing sarcoidosis was lower among active smokers. The odds ratio of sarcoidosis comparing current smokers with never smokers and former smokers adjusted for age and sex was 0.38 (17). This is an interesting observation, as smoking is generally associated with a higher risk of pulmonary disease, such as chronic obstructive pulmonary disease and lung cancer. The lower risk of sarcoidosis among active smokers has been demonstrated in other cohorts as well (20, 21). Furthermore, smoking has been associated with severity mitigation in another autoimmune disease, ulcerative colitis (22). It is known that smoking can suppress T-lymphocyte function and phagocytic activity of macrophages. Possibly of relevance to sarcoidosis, it is also possible that smoking might interfere with the macrophage-lymphocyte interaction that results in the formation of granuloma (23).

■ CLINICAL MANIFESTATIONS

Pulmonary sarcoidosis

Intrathoracic involvement was the characteristic finding among patients with sarcoidosis that was seen in the vast majority of the cohort (97%). In 87% of cases this consisted of intrathoracic lymphadenopathy, and 50% had evidence of pulmonary

parenchymal infiltration. The higher frequency of intrathoracic lymphadenopathy compared with pulmonary parenchymal infiltration is expected as patients with stage I pulmonary sarcoidosis have only intrathoracic lymphadenopathy without any pulmonary parenchymal abnormality. The relatively low sensitivity of conventional chest radiography in detecting infiltration in the lung parenchyma may also contribute to this discrepancy as only about 50% of patients in this cohort had computed tomography scan of the lung.

However, respiratory symptoms were relatively infrequent, and occurred in less than half of the patients (43%) (3). This observation suggests the necessity of thoracic imaging, preferably computed tomography scanning, if sarcoidosis is suspected, despite lack of pulmonary symptoms.

Extra-thoracic sarcoidosis

Extra-thoracic manifestations were observed frequently in this cohort (3). The most common extra-thoracic manifestations were skin rash (18%), followed by arthralgia (12%), ophthalmologic involvement (7%), hepatic involvement (6%), splenomegaly (4%), renal involvement (3%), neurological involvement (3%), extra-thoracic lymphadenopathy (3%), exocrine gland involvement (2%), upper respiratory tract involvement (2%) and cardiac involvement (1%). Bone involvement was

observed in only one patient. The frequency of organ involvement by sarcoidosis is summarized in Table I.

Skin

Cutaneous involvement was the most common extra-thoracic manifestation of sarcoidosis, occurring in 18% of patients with sarcoidosis. Approximately 60% of patients with cutaneous sarcoidosis had sarcoidosis-specific skin lesions (defined as the presence of non-necrotizing granuloma on skin biopsy) while the rest had erythema nodosum (24).

Among those with sarcoidosis-specific skin lesions, subcutaneous nodules (33%) were the most common type of lesions followed by papules (31%), plaques (19%), tattoo/scar sarcoidosis (11%), lupus pernio (11%) and ulcer (8%). The lesions were more frequently found on the extremities and head/neck area than on the trunk.

Response to treatment was favorable with complete response by 2-years after diagnosis in over 80% of patients with sarcoidosis-specific skin lesions and almost all patients with erythema nodosum. The median time from the first appearance of cutaneous lesions to resolution of all skin lesions was 4.4 months, and to resolution of erythema nodosum was 1.6 months. Oral glucocorticoids were the most frequently used medication to treat patients with sarcoidosis-specific skin lesions followed by topical glucocorticoids, intralesional glucocorticoids and topical calcineurin inhibitor.

Joints

Arthropathy was the second most common extra-thoracic disease manifestation of sarcoidosis in this cohort, with joint pain occurring in 12% and swollen joints occurring in 10% of patients with sarcoidosis (25). Oligoarthritis was by far the most common pattern of joint involvement (88%). The most commonly affected joints were ankles (91% total with 14% one ankle and 77% both ankles), followed by knees (29%) and wrists (14%). Involvement of small joints and tendinitis/enthesitis was uncommon. Costochondritis, axial joint involvement and sacroiliac joint involvement

Table I - Frequency of organ involvement by sarcoidosis.

Organ	Frequency
Intrathoracic	97%
Hilar and mediastinal lymph nodes	87%
Lung parenchyma	50%
Skin	18%
Joints	12%
Eyes	7%
Liver	6%
Spleen	4%
Kidneys	3%
Nervous system	3%
Extrathoracic lymph node	3%
Upper respiratory tract	2%
Heart	1%

Table II - Cumulative incidence at 10 years of selected comorbidities of patients with sarcoidosis and hazard ratio compared to sex- and age-matched subjects.

Comorbidities	Cumulative incidence at 10 years (95% CI)	HR (95% CI) for all events after index date, adjusting for age, sex and calendar year
Cardiovascular disease	17.6 (12.9-22.0)	1.57 (1.15-2.16)
Venous thromboembolism	4.0 (1.6-6.3)	3.04 (1.47-6.29)
Malignancy	3.8 (1.5-6.1)	0.72 (0.49-1.06)
Hospitalized infection	13.2 (9.1-17.0)	2.00 (1.41-2.84)

HR, hazard ratio; CI, confidence interval.

were not seen in this Olmsted County cohort. Classic sarcoidal bone lesions, such as bone cyst or lytic appearance, were not observed on radiographic investigations either. Classic Lofgren syndrome (arthritis, erythema nodosum and hilar adenopathy) was observed in about a quarter of those with joint involvement. The outcome of sarcoid arthropathy is good, as the majority of patients (88%) achieved complete remission within 6 weeks. Most patients with active joint disease were treated with a short duration of non-steroidal anti-inflammatory drugs (NSAIDs) and/or oral glucocorticoids (25).

Parotid glands

Parotid gland involvement is a well-recognized extra-thoracic feature of sarcoidosis. However, only 2% of patients with sarcoidosis in this population-based cohort had parotid gland involvement (26). Unilateral painless gland swelling was the most common presentation of parotid gland disease. This differed from what has been reported in other cohorts, which report bilateral involvement in more than 70% of cases (27, 28). More importantly, parotid gland disease was the initial manifestation in 57% of patients in the Olmsted County cohort, highlighting the vital role of the otolaryngologic assessment in the diagnosis of systemic sarcoidosis.

COMORBIDITY

Over the past few decades, morbidity and mortality from direct organ damage have been declining in patients with autoimmune diseases because of the availability

of novel effective treatments, such as disease-modifying anti-rheumatic agents and biologic agents. As a result, patients with autoimmune diseases live longer, and comorbidities have emerged as a major cause of morbidity and mortality. Several studies have described the characteristics and outcomes of comorbidities in several autoimmune diseases, particularly rheumatoid arthritis and systemic lupus erythematosus (29, 30). However, there is a dearth of studies on comorbidities of sarcoidosis. Table II summarizes the cumulative incidence at 10-years of comorbidities examined in the Olmsted County cohort of patients with sarcoidosis and sex- and age-matched comparator subjects.

Cardiovascular disease

The risk of cardiovascular disease (CVD), including coronary artery disease (CAD), congestive heart failure (CHF), atrial fibrillation (AF), cerebrovascular accident (CVA), transient ischemic attack (TIA), peripheral arterial disease (PAD) and abdominal aortic aneurysm (AAA), was investigated in this Olmsted County cohort using sex- and age-matched subjects from the same underlying population as comparators. The cumulative incidence of all CVD events among patients with sarcoidosis at 10 years was 17.6%. The risk of incident CVD, adjusted for age, sex, calendar year, was significantly higher among patients with sarcoidosis with a hazard ratio (HR) of 1.57 (95% confidence [CI], 1.15-2.16). Further adjustment for baseline CVD risk factors yielded a similar result. Significantly elevated risk was observed for several subtypes of CVD including CAD, CHF, AF and CVA (31).

Chronic inflammation is probably the key driver behind this increased risk of CVD (32). While not specifically studied in sarcoidosis, it has been demonstrated that several inflammatory cytokines, such as interleukin-1 and tumor necrosis factor, can promote premature atherosclerosis through a number of mechanisms including vascular adhesion molecule-1 and leukocyte and matrix metalloproteinase activation (33, 34). Chronic inflammation may trigger the initiation and propagation of the coagulation cascade, downregulate anti-coagulation pathways and inhibit removal of fibrin (35, 36), thereby promoting thrombosis in coronary and intra-cerebral arteries.

Glucocorticoids, the most commonly used medication for the treatment of sarcoidosis, may also be a contributing factor to the increased risk of CVD, as use of glucocorticoids is associated with several metabolic sequelae such as diabetes mellitus, hypertension and dyslipidemia, which are traditional risk factors for CVD (37).

Venous thromboembolism

Similar to CVD, an increased incidence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), has been observed in several autoimmune diseases (38-40). However, data on the risk of VTE among patients with sarcoidosis are limited. In this cohort, the cumulative incidence of VTE among patients with sarcoidosis at 10 years was 4.0%, which corresponded to an approximately 3-fold increased risk of incident VTE adjusted for age, sex and calendar year. Significantly elevated risk was observed in both DVT and PE (41).

Three main predisposing factors of VTE, known as Virchow's triad, include venous stasis, endothelial injury and hypercoagulability. Chronic inflammation is known to provoke a hypercoagulable state through several mechanisms including stimulation of the coagulation cascade by increased expression of tissue factor induced by inflammatory cytokines, mobilization of clot-promoting membrane phospholipids by complement complexes and suppression of natural anti-coagulants such as

thrombomodulin by tumor necrosis factor-alpha (35, 36). Chronic inflammation can also induce endothelial injury as a result of the detrimental effect of inflammatory cytokines and oxidative stress (32). Patients with sarcoidosis may also be less active than sex- and age-matched subjects due to respiratory symptoms. These factors could predispose patients with sarcoidosis to the development of DVT and PE. In addition, use of glucocorticoids may also increase the propensity to blood clots. A case-control study has demonstrated a dose-response relationship between glucocorticoids and incidence of VTE (42).

Malignancy

The possible relationship between malignancy and sarcoidosis is a subject of debate. The possible link has been a matter of concern for decades, with several case series reporting patients diagnosed with cancer shortly before or after the diagnosis of sarcoidosis (43). Nonetheless, subsequent epidemiologic studies have yielded conflicting results (44-46).

This cohort was utilized to investigate this controversial association. There was no difference in the prevalence of malignancy at index date among patients with sarcoidosis compared to non-sarcoidosis subjects. Similarly, there was no difference in the incidence of malignancy after index date, with the cumulative incidences at 10-years of 3.8% and 7.1% for patients with sarcoidosis and comparators, respectively. The difference corresponded to HR of 0.72 (95% CI, 0.49-1.06) (47).

Infection

Infection is one of the most common complications of autoimmune diseases. An increased risk of both pyogenic and opportunistic infection has been observed in them. Use of immunosuppressive agents and immune dysregulation related to the pathogenesis of autoimmune diseases are thought to be key drivers behind the increased risk (48).

Increased risk of hospitalized infection has been demonstrated in several autoimmune diseases (49-51). However, there had been

no study of hospitalized infection among patients with sarcoidosis. This cohort was utilized to fill this knowledge gap. The cumulative incidence of all hospitalized infection among patients with sarcoidosis at 10 years was 13.2%. The risk was increased by 200% compared to sex- and age-matched subjects. This excess risk is seen in varying degrees for all subtypes of infections examined. Use of oral glucocorticoids was a significant predictor of hospitalized infection in a dose-dependent fashion.

■ CONCLUSIONS

In conclusion, this review summarizes all new data from a recently published cohort of patients with sarcoidosis from Olmsted County, Minnesota. It is a relatively rare disease with manifold clinical manifestations. Comorbidities, especially risk of cardiovascular disease, are frequent.

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