

Epidemiology and Survival of Systemic Sclerosis–Sarcoidosis Overlap Syndrome

Megan Himmel¹, Meyer Balter², Zareen Ahmad¹, Elvira Bangert¹, Shafina Hasmani¹, Rhea Siddha¹,
Mohammad Movahedi³, and Sindhu R. Johnson⁴ 

ABSTRACT. Objective. We evaluated the epidemiology, manifestations, serology, comorbidities, and survival among patients with systemic sclerosis (SSc) with and without sarcoidosis.

Methods. We conducted a retrospective cohort study comparing patients with SSc with and without sarcoidosis. All patients fulfilled the American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for SSc. Sarcoidosis was based on physician diagnosis and/or confirmatory biopsy. The primary outcome was time from diagnosis to all-cause mortality. Survival was evaluated using Kaplan-Meier curves.

Results. We included 1977 patients (1971 with SSc, 6 with SSc–sarcoidosis) with a SSc–sarcoidosis prevalence of 0.30%. Sarcoidosis frequently preceded SSc (66.66%). The most frequent sarcoidosis manifestations were pulmonary (66.66%), lymphadenopathy (66.66%), arthritis (50%), cutaneous (33.33%), and hepatic (16.66%). Patients with SSc and SSc–sarcoidosis had female to male sex ratios of 4.5:1 vs 5:1 and median ages of SSc onset of 48.3 vs 43.8 years, respectively. Interstitial lung disease (35% vs 66.66%) and pulmonary hypertension (24.91% vs 50%) tended to occur more frequently whereas abnormal nailfold capillaries (34.7% vs 16.66%) and digital ulcers (33.33% vs 16.66%) tended to occur less frequently among patients with SSc–sarcoidosis, but the differences were not significant. There was an increased frequency of stroke among the patients with SSc–sarcoidosis (relative risk 8.59, 95% CI 1.02–72.00). The median survival times were 23.4 years for SSc–sarcoidosis and 18.6 years for SSc, with no differences in survival curves (log-rank test, $P = 0.55$).

Conclusion. Sarcoidosis in SSc is rare but appears to occur more frequently than in the general population. It is associated with pulmonary, lymph node, cutaneous, joint, and hepatic involvement. Stroke occurs more frequently in patients with SSc–sarcoidosis but with no differences in survival.

Key Indexing Terms: cohort, epidemiology, sarcoidosis, scleroderma, survival, systemic sclerosis

Systemic sclerosis (SSc; also called scleroderma) is a systemic autoimmune rheumatic disease characterized by immune activation, vasculopathy, and fibrosis. SSc is an uncommon disease with a prevalence of 17.6 per 100,000 person-years and an incidence of 20 per million per year.¹ SSc is thought to reflect a

spectrum of related disorders, which can be subsetted by extent of skin involvement,² age of onset, molecular signatures,^{3,4} and other factors.^{5,6} SSc can overlap with other rheumatic diseases including rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome.⁷ Patients with SSc with an overlap syndrome have been found to have differences in age of onset, disease manifestations, and survival compared to patients with SSc without an overlap syndrome.⁷

Sarcoidosis is an immune-mediated disease characterized by granuloma comprising abnormal collections of inflammatory cells. The disease most commonly affects the lungs (90%) but virtually any organ system can be affected, most commonly skin, eyes, lymph nodes, and liver. A pathologic diagnosis is preferred but certain clinical syndromes highly suggestive of sarcoidosis have been described. Lofgren syndrome, manifesting as hilar adenopathy, arthralgias, and erythema nodosum, is the most common of these syndromes. Sarcoidosis is also an uncommon disease with an incidence of 6.8 per 100,000 per year and a prevalence of 143 per 100,000 in 2015, with a shift in disease burden from females to males.⁸ An overlap between systemic autoimmune rheumatic diseases (formerly connective tissue disease [CTD]) and sarcoidosis was first reported by Enzenauer and West in 1992 where they found that of 569 patients with CTD, 6

This study was in part supported by the Schroeder Arthritis Institute, University Health Network, Toronto, Canada.

¹M. Himmel, MD, PhD, Z. Ahmad, MD, E. Bangert, MD, S. Hasmani, R. Siddha, MBA, Toronto Scleroderma Program, Division of Rheumatology, Department of Medicine, Mount Sinai Hospital; ²M. Balter, MD, Division of Respiriology, Department of Medicine, Mount Sinai Hospital; ³M. Movahedi, MD, PhD, Toronto General Hospital Research Institute, University Health Network, and Institute of Health Policy, Management and Evaluation, University of Toronto; ⁴S.R. Johnson, MD, PhD, Toronto Scleroderma Program, Division of Rheumatology, Department of Medicine, Mount Sinai Hospital, and Schroeder Arthritis Institute, Krembil Research Institute, Toronto Western Hospital, and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada.

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. S.R. Johnson, Division of Rheumatology, Ground Floor, East Wing, Toronto Western Hospital, 399 Bathurst Street, Toronto, ON M5T 2S8, Canada. Email: Sindhu.Johnson@uhn.ca.

Accepted for publication December 31, 2022.

(1%) had concomitant sarcoidosis compared to 0 of 894 control patients with noninflammatory rheumatic disease.⁹ Of these 6 patients with sarcoidosis and CTD, 1 patient was reported to have SSc.⁹ Enzenauer and West went on to describe 4 additional cases of SSc–sarcoidosis overlap in the literature prior to 1992 to further support this association. Since that time, 26 additional cases (30 cases in total as of 2017) have been published describing a SSc–sarcoidosis overlap syndrome.^{10,11}

Little is known about the epidemiology, clinical characteristics, and survival of SSc–sarcoidosis overlap syndrome. The aim of this study was to improve our understanding of SSc–sarcoidosis overlap syndrome compared to SSc. The primary objective was to evaluate survival in patients with SSc–sarcoidosis compared to patients with SSc. Secondary objectives included evaluation of the prevalence of SSc–sarcoidosis overlap syndrome, differences in SSc disease manifestations, serology, and comorbidities.

METHODS

Study design. This was a retrospective cohort study.

Patients. The Toronto Scleroderma Program is the largest single-center longitudinal cohort in Canada. Patients are followed every 6 to 12 months by 3 SSc specialists. Patients who fulfilled the American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for SSc¹² were included in this cohort study. We excluded subjects with localized scleroderma (morphea). Sarcoidosis was based on physician diagnosis and/or confirmatory biopsy.

Outcomes. The primary outcome was the time from SSc diagnosis to death from all causes. Subjects who were alive as of January 1, 2022, were censored. Dates of death were obtained from the clinic chart or online obituary. This approach has been shown to be a valid and reliable method for tracking patients as a source of mortality data,¹³ and has been successfully used in other research work.^{14,15}

Secondary outcomes included the prevalence of SSc–sarcoidosis overlap syndrome, differences in SSc subtype (limited cutaneous, diffuse cutaneous), calcinosis, Raynaud phenomenon, digital ulceration, esophageal dysmotility, telangiectasia, abnormal nailfold capillaries (enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nailfold on visual inspection),¹² interstitial lung disease (ILD; forced vital capacity < 70%, and bibasilar reticular abnormalities with minimal ground glass opacity on high-resolution computed tomography [CT] thorax),¹⁵ pulmonary arterial hypertension (mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg by right heart catheterization), renal crisis (acute renal failure, new onset hypertension, normal or mild proteinuria on urinalysis, microangiopathic hemolytic anemia), and serology (topoisomerase, centromere antibodies).

Data administration. Chart review was conducted by trained research coordinators and/or investigators, all using the same standardized data abstraction form to collect demographic, disease manifestation, treatment, and survival data. Data were double entered by research coordinators into a Filemaker database. Institutional research ethics board approval was obtained from Mount Sinai Hospital for the conduct of this study (MSH REB 21-0186-C).

Statistical analysis. Descriptive statistics were used to summarize the data. Relative risks (RRs) and 95% CI were used to compare categorical data. Survival rates and median survival rates were determined using Kaplan-Meier survival curves.

RESULTS

Patients. We included 1977 patients with SSc (1971 with SSc and 6 with SSc–sarcoidosis). One patient was initially thought

to have SSc–sarcoidosis but was later found to have pneumoconiosis and so was excluded from this analysis. In our SSc cohort, sarcoidosis had a prevalence of 0.3% compared to a population level sarcoidosis prevalence of 0.14%.⁸ Characteristics of the patients with SSc–sarcoidosis are summarized in Table 1. The median age of sarcoidosis onset was 37.5 years (range 33–53 yrs). The majority (66.66%) had a diagnosis of sarcoidosis before the diagnosis of SSc. Among the patients with SSc–sarcoidosis, the most frequent sarcoidosis manifestations were pulmonary (66.66%), lymphadenopathy (66.66%), arthritis (50%), cutaneous (33.33%), and hepatic (16.66%).

Comparison of SSc and SSc–sarcoidosis. The female to male sex ratio was comparable between SSc (4.5:1) and SSc–sarcoidosis (5:1), with similar median ages of SSc onset (48.3 [range 1.46–89.0] yrs vs 43.8 [range 34.3–54.5] yrs, respectively). There were no significant differences in SSc manifestations between the 2 groups (Table 2). However, ILD (35% vs 66.66%) and pulmonary hypertension (24.91% vs 50%) tended to occur more frequently in patients with SSc–sarcoidosis. Anticentromere antibodies were not present in any of the patients with SSc–sarcoidosis. Abnormal nailfold capillaries (34.7% vs 16.66%) and digital ulcers (33.33% vs 16.66%) tended to occur less frequently among patients with SSc–sarcoidosis, but the difference was not statistically significant. There was an increased frequency of stroke among the patients with SSc–sarcoidosis (RR 8.59, 95% CI 1.02–72.0). There were no occurrences of atrial fibrillation, coronary artery disease, peripheral vascular disease, or cancer in the patients with SSc–sarcoidosis. There were no statistically significant differences in hyperlipidemia or diabetes mellitus (DM) between groups (Table 2).

Survival. There were 822 (41.57%) deaths in total, with 820 (41.60%) in the SSc group and 2 (33.33%) in the SSc–sarcoidosis group (RR 1.42, 95% CI 0.26–7.75). Eighty-nine patients with SSc had missing data on either diagnosis date, death date, or last visit date, and were therefore not included in the survival analysis. Probabilities of short-term and long-term survival are reported in Table 3. Although the Kaplan-Meier curves did not cross over 20 years, the differences in survival were not statistically significant (log-rank test, $P = 0.55$; Figure).

DISCUSSION

This study provides interesting insights into the epidemiology, clinical characteristics, and survival of patients with SSc–sarcoidosis. With only 30 cases of SSc–sarcoidosis overlap syndrome described in the literature to date, our study findings add to our understanding of this poorly understood disease. We found that although SSc–sarcoidosis is rare, sarcoidosis among patients with SSc is twice as common as in the general population. Like SSc, SSc–sarcoidosis is more common among women. Sarcoidosis in the general population has a 3:2 female predominance (perhaps higher in African Americans) and is increasingly occurring among men.⁸ We found that sarcoidosis tends to precede diagnosis of SSc and most frequently manifests with pulmonary, lymph node, cutaneous, joint, and hepatic involvement. ILD and pulmonary hypertension tended to occur more frequently, whereas vascular manifestations of SSc tended

Table 1. Summary of patients with SSc–sarcoidosis overlap syndrome.

Case No.	Sex	Age at Sarcoidosis Diagnosis, yrs	Time of Sarcoid Diagnosis in Relation to SSc Diagnosis	Sarcoid Manifestations	Biopsy		Imaging		Sarcoid-Specific Treatment, Medication	Response to Sarcoid-Specific Treatment
					Location	Findings	Modality	Findings		
1	F	33	Before	Lofgren syndrome, erythema nodosum, bilateral ankle swelling, hilar lymphadenopathy	NA	NA	Chest radiograph	Perihilar lymphadenopathy	Naproxen 250 mg 3 times daily for 2 mos	Resolution of erythema nodosum and arthritis
2	M	53	After	Pulmonary, arthritis	NA	NA	Chest radiograph	Bilateral upper lobe interstitial markings	Prednisone 40 mg daily, then tapered to 15 mg daily for 3 yrs Nifedipine 20 mg twice daily Enalapril 10 mg twice daily	Improved shortness of breath, improved interstitial markings on chest radiograph
3	F	53	After	Pulmonary, lymphadenopathy	Mediastinal lymphadenopathy	Nonnecrotizing granuloma	Chest radiograph	Interstitial fibrotic changes, right paratracheal lymphadenopathy, right lower lobe and perihilar peribronchial thickening	Prednisone 60 mg daily then tapered to 5 mg daily for 1 yr Verapamil 240 mg daily Ramipril 5 mg daily	Improved shortness of breath, improved PFT
4	F	34	Before	Pulmonary	Lung	Nonnecrotizing granuloma	Chest CT scan	Bibasilar GGO and features consistent with NSIP	Prednisone 40 mg daily, then tapered to 5 mg daily for 16 yrs MTX 12.5 mg weekly for 1 yr Nifedipine 30 mg daily for 1 yr	Improved shortness of breath, improved GGO on chest CT scan
5	F	44	Before	Pulmonary, lymphadenopathy, hepatic	Left inguinal lymph node	Nonnecrotizing granuloma with no evidence of TB or nontuberculous mycobacterium	Chest and abdomen CT scan	Bilateral subpleural and basilar interstitial reticular opacities; retroperitoneal, pelvic, inguinal, axillary, right paratracheal and right hilar lymphadenopathy	Prednisone 50 mg daily, tapered to 30 mg daily for 6 mos, then tapered to 5 mg daily for 3 yrs	Improved lymphadenopathy on imaging
6	F	42	Before	Cutaneous, arthritis, lymphadenopathy	Skin	Granulomatous dermatitis	Abdomen CT scan		Prednisone 20 mg daily, then tapered to 10 mg daily MTX 25 mg subcutaneously weekly for 9 yrs Tocilizumab 300 mg infusion monthly	Resolution of cutaneous findings

CT: computed tomography; F: female; GGO: ground glass opacity; M: male; MTX: methotrexate; NA: not applicable; NSIP: nonspecific interstitial pneumonia; PFT: pulmonary function testing; SSc: systemic sclerosis; TB: tuberculosis.

to occur less frequently. Stroke occurred more frequently in patients with SSc–sarcoidosis, with no associated increase in other comorbidities or mortality.

In our study, sarcoidosis preceded SSc in two-thirds of cases, whereas in the literature, 16 cases occurred after the diagnosis

of SSc, 8 were diagnosed concurrently, and 6 preceded the diagnosis.¹¹ Among published cases, the location of noncaseating granuloma was predominantly in the lung, lymph nodes (primarily hilar lymphadenopathy), or skin, and less commonly in muscle (1 case of sarcoid myopathy of skeletal muscle, 1

Table 2. Comparison of patients with SSc and patients with SSc-sarcoidosis overlap syndrome.

	Total, N = 1977	SSc, n = 1971	SSc-Sarcoidosis, n = 6	RR (95% CI)
Demographics				
Age, yrs, median (range)	48.3 (1.5-85.0)	48.3 (1.5-89.0)	43.8 (34.3-54.5)	NA
Sex				
Male	359 (18.15)	358 (18.16)	1 (16.66)	
Female	1618 (81.84)	1613 (81.83)	5 (83.33)	1.11 (0.13-9.47)
SSc manifestations				
Diffuse subtype	637 (32.22)	636 (32.26)	1 (16.66)	0.48 (0.05-4.28)
Calcinosis cutis	460 (23.26)	459 (23.28)	1 (16.66)	0.64 (0.07-5.44)
Raynaud manifestation	1872 (94.68)	1866 (94.67)	6 (100)	NA
Esophageal hypomobility	1643 (83.1)	1638 (83.1)	5 (83.33)	0.98 (0.11-8.33)
Sclerodactyly	1674 (84.67)	1669 (84.67)	5 (83.33)	0.87 (0.10-7.41)
Telangiectasia	1304 (65.95)	1300 (65.95)	4 (66.66)	0.95 (0.17-5.17)
ILD	694 (35.1)	690 (35)	4 (66.66)	6.65 (0.74-59.40)
Pulmonary HTN	494 (24.98)	491 (24.91)	3 (50)	7.12 (0.74-68.30)
Scleroderma renal crisis	131 (6.63)	131 (6.65)	0 (0)	NA
Abnormal nailfold capillaries	685 (34.64)	684 (34.7)	1 (16.66)	0.48 (0.04-5.33)
Digital ulcers	658 (33.28)	657 (33.33)	1 (16.66)	0.39 (0.05-3.34)
ACA	438 (22.15)	438 (22.22)	0 (0)	NA
Comorbidities				
CAD	166 (8.40)	166 (8.42)	0 (0)	NA
Systemic HTN	448 (22.66)	447 (22.67)	1 (16.66)	0.68 (0.08-5.82)
DM	129 (6.53)	129 (6.54)	1 (16.66)	2.84 (0.33-24.10)
Hyperlipidemia	179 (9.05)	178 (9.03)	1 (16.66)	2.01 (0.24-17.10)
Peripheral vascular disease	60 (3.03)	60 (3.04)	0 (0)	NA
Cancer	227 (11.48)	227 (11.51)	0 (0)	NA
Stroke	45 (2.28)	44 (2.23)	1 (16.66)	8.59 (1.02-72.00)
Atrial fibrillation	100 (5.06)	100 (5.07)	0 (0)	NA

All values are n (%) unless otherwise indicated. Bold denotes statistical significance. ACA: anticentromere antibody; CAD: coronary artery disease; DM: diabetes mellitus; HTN: hypertension; ILD: interstitial lung disease; NA: not applicable; RR: relative risk; SSc: systemic sclerosis.

Table 3. Comparison of survival probabilities and median survival time between patients with SSc-sarcoidosis overlap syndrome and patients with SSc.

	SSc-Sarcoidosis, n = 6	SSc, n = 1971
Deaths, n (%)	2 (33.33)	820 (41.60)
Probability of survival, % (95% CI)		
1 yr	100	96.09 (95.10-96.89)
2 yrs	100	93.02 (91.74-94.11)
3 yrs	100	90.70 (89.25-91.96)
4 yrs	100	87.64 (85.99-89.11)
5 yrs	100	84.83 (83.02-86.46)
14 yrs	75.00 (12.79-96.05)	60.93 (58.22-63.53)
22 yrs	75.00 (12.79-96.05)	42.71 (39.56-45.82)
Survival time, yrs, median (95% CI)	23.42 (13.91-NA)	18.59 (17.49-19.74)

NA: not applicable; SSc: systemic sclerosis.

case of cardiac sarcoid), salivary glands, liver, and kidneys.^{16,17} Interestingly, ocular sarcoid manifestations were not described. Of the skin lesions, plaques were most common; however, papules and erythema nodosum were also observed.¹⁷ With respect to lung manifestations, hilar lymphadenopathy was most commonly observed, whereas parenchymal changes including

upper-lobe predominant ground glass opacities were noted less often.^{10,16} ILD was common among 72% of cases (18/25).¹⁶ ILD was predominantly nonspecific interstitial pneumonia with ground glass opacities, interstitial pulmonary fibrosis, and honeycomb cystic changes in the lower lung zones.¹⁰

Sarcoidosis has been reported to overlap with other systemic autoimmune rheumatic diseases. The cooccurrence of sarcoidosis with rheumatoid arthritis,^{9,18-20} Sjögren syndrome,²¹ and spondylitis²² are rare. However, the frequency of sarcoidosis overlapping with another rheumatic disease may be underestimated because sarcoidosis signs and symptoms may be mistakenly attributed to the primary rheumatic disease and a secondary diagnosis not considered.^{9,23}

With respect to autoantibody profiles in the literature, 9 cases were positive for anti-Scl70 antibodies, 8 cases were positive for anticentromere antibodies, and 7 cases were negative for both antibodies.¹¹ Interestingly, of the 9 cases of anti-Scl70 autoantibody positivity, 7 of these were male (compared to 1 of 15 patients with either negative antibodies or anticentromere antibodies being male), suggesting that occurrence of this syndrome in males is more likely to be associated with diffuse cutaneous SSc.¹¹ However, the overall predominance tends to be female (70% of cases).^{8,11} With respect to sarcoidosis, angiotensin-converting enzyme (ACE) levels were elevated in 15 of the 25 cases described by Ogane et al.¹⁶ Overall, there is a suggestion that symptoms of SSc and

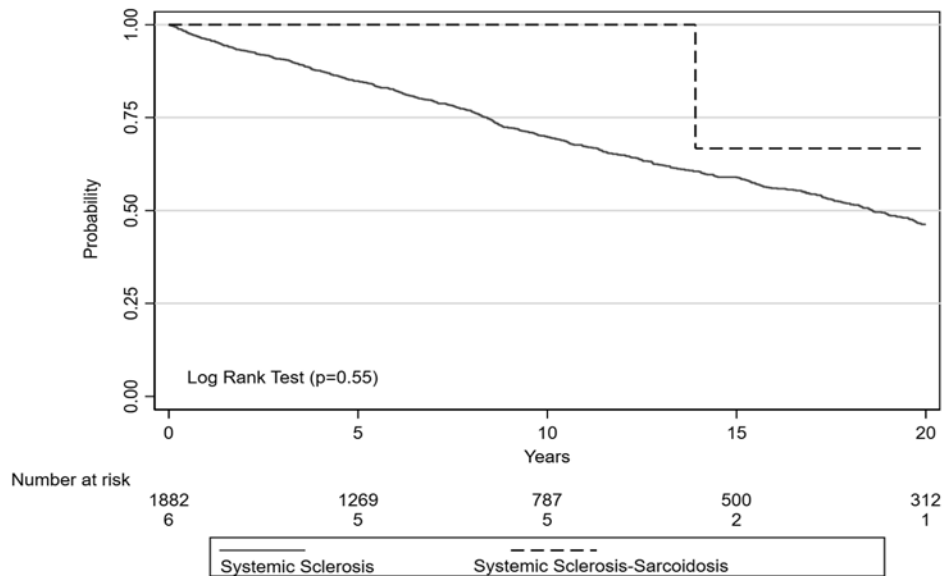


Figure. Kaplan-Meier survival curves for patients with SSc and patients with SSc-sarcoidosis overlap syndrome. SSc: systemic sclerosis.

sarcoidosis are more severe when they coexist, and tend to progress more rapidly.²⁴

The finding of higher risk of stroke in SSc-sarcoidosis overlap syndrome without an increased risk of other comorbidities is an interesting observation. Stroke is a very rare complication of central nervous system sarcoidosis. Ischemic stroke, secondary to neurosarcoidosis, results from noncaseating granuloma in the brain^{25,26} or due to small-vessel vasculitis, large-vessel inflammation, or embolism from cardiac sarcoidosis.²⁷ Hemorrhagic stroke is usually secondary to sinus thrombosis.²⁷ Although neuropathy is not uncommon in SSc,²⁸ stroke is not considered a manifestation of SSc. One metaanalysis of 4 retrospective cohort studies reported an increased risk of ischemic stroke in patients with SSc.²⁹ We found a higher prevalence of DM and hyperlipidemia among patients with SSc-sarcoidosis overlap syndrome compared to patients with SSc that was not statistically significant. It is possible that these comorbidities may explain the increase in stroke. However, our sample size precluded our ability to further explore these observations. Our increased RR of stroke in patients with SSc-sarcoidosis compared to patients with SSc may be real or alternatively may be a chance finding attributable to our small sample size. Nonetheless, this finding is hypothesis generating and warrants further investigation in larger datasets.

The observed trend of increased frequency of pulmonary hypertension in patients with SSc-sarcoidosis is also interesting. Its etiology may be attributable to pulmonary arterial hypertension (World Health Organization [WHO] classification group 1), pulmonary hypertension associated with lung disease (WHO classification group 3), or attributable to sarcoidosis itself (WHO classification group 5).

One of the primary challenges with SSc-sarcoidosis overlap syndrome is determining which disease is responsible for clinical symptoms, and therefore which treatment to pursue. Differentiation between SSc- and sarcoidosis-related symptoms

can, in part, be done through clinical examination, imaging findings (for example, lower lobe predominant ILD is more suggestive of SSc, and hilar lymphadenopathy is more suggestive of sarcoidosis), serum ACE levels (elevated in sarcoidosis only), biopsy (hallmark of sarcoidosis is noncaseating granulomas), and bronchoalveolar lavage (sarcoidosis has a CD4-positive helper T cell predominant alveolitis, whereas alveolitis in SSc will have increased eosinophils and/or neutrophils).²⁴ Treatment of the manifestations of SSc-sarcoidosis overlap syndrome are similar to the treatment of each individual disease. For manifestations of sarcoidosis, corticosteroids (either topical or systemic) are the mainstay of treatment.³⁰ Management of the manifestations of SSc are less likely to involve corticosteroids given the risk of precipitating scleroderma renal crisis. Pulmonary manifestations are managed with mycophenolate mofetil, cyclophosphamide, tyrosine kinase inhibitors, and endothelin receptor antagonists. In 1 case of SSc-sarcoidosis overlap syndrome, myositis was managed with intravenous immunoglobulin.²⁴ Due to the increasing evidence supporting the use of tocilizumab in SSc, and its proven efficacy for treating inflammatory arthritis, tocilizumab was used to treat 1 of our SSc-sarcoidosis patients with success. Infliximab may be another therapeutic and steroid-sparing option for pulmonary sarcoidosis³¹ and inflammatory arthritis; however, its utility for other SSc-associated manifestations is limited.

We found no statistically significant differences in either short-term or long-term survival between patients with SSc and SSc-sarcoidosis. This suggests that sarcoidosis does not confer increased mortality above that conferred by SSc. It could be that both diseases are being better managed. Hospitalization rates in patients with sarcoidosis have decreased over the past 20 years, most substantially in patients of younger age.³² However, a limitation of our study is the small number of patients with SSc-sarcoidosis. The lack of statistical significance in the apparent differences in disease manifestations, comorbidities, and survival may be attributable to the low power to detect meaningful

differences resulting from the small sample size. Patients with SSc–sarcoidosis overlap syndrome appeared to have good survival early in their SSc disease course, with mortality occurring later in their disease course relative to patients with SSc without sarcoidosis. Although this finding is not statistically significant, it warrants further study. It may reflect cardiovascular disease in a group represented with more DM and hyperlipidemia and generally receiving higher doses of prednisone.

A potential limitation of this study is imprecision in our estimated prevalence of SSc–sarcoidosis. All medical charts and CT thorax reports were retrospectively reviewed by a trained research coordinator and/or investigator. However, it is possible that our reporting of SSc–sarcoidosis is an underestimate as all patients were not systematically, prospectively evaluated for sarcoidosis. It is theoretically possible that a patient had sarcoidosis that was missed or not documented. Second, we do not have smoking or family history data, so we are unable to evaluate their effect on our findings.

In summary, we have found that SSc–sarcoidosis overlap syndrome is rare but occurs more frequently in patients with SSc than in the general population. In patients with SSc with ILD and arthritis, concomitant sarcoidosis may be considered part of the differential diagnosis. Patients with SSc–sarcoidosis should be monitored carefully as it is associated with an increased risk of stroke.

REFERENCES

- Bairkdar M, Rossides M, Westerlind H, Hesselstrand R, Arkema EV, Holmqvist M. Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis. *Rheumatology* 2021;60:3121-33.
- LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202-5.
- Hinchcliff M, Huang CC, Wood TA, et al. Molecular signatures in skin associated with clinical improvement during mycophenolate treatment in systemic sclerosis. *J Invest Dermatol* 2013;133:1979-89.
- Johnson SR, Hinchcliff M, Asano Y. Controversies: molecular vs. clinical systemic sclerosis classification. *J Scleroderma Relat Disord* 2016;1:277-85.
- Johnson SR, Feldman BM, Hawker GA. Classification criteria for systemic sclerosis subsets. *J Rheumatol* 2007;34:1855-63.
- Johnson SR, Soowamber ML, Franssen J, et al. There is a need for new systemic sclerosis subset criteria. A content analytic approach. *Scand J Rheumatol* 2018;47:62-70.
- Alharbi S, Ahmad Z, Bookman AA, et al. Epidemiology and survival of systemic sclerosis-systemic lupus erythematosus overlap syndrome. *J Rheumatol* 2018;45:1406-10.
- Fidler LM, Balter M, Fisher JH, To T, Stanbrook MB, Gershon A. Epidemiology and health outcomes of sarcoidosis in a universal healthcare population: a cohort study. *Eur Respir J* 2019;54:1900444.
- Enzenauer RJ, West SG. Sarcoidosis in autoimmune disease. *Semin Arthritis Rheum* 1992;22:1-17.
- Yu M, Sandhu VK, Lezcano SD, Maken K, Kirk S, Torralba KD. Sarcoidosis and systemic sclerosis: strange bedfellows. *Case Rep Rheumatol* 2017;2017:7851652.
- Senda S, Igawa K, Nishioka M, Murota H, Katayama I. Systemic sclerosis with sarcoidosis: case report and review of the published work. *J Dermatol* 2014;41:421-3.
- van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2013;72:1747-55.
- Soowamber ML, Granton JT, Bavaghar-Zaeimi F, Johnson SR. Online obituaries are a reliable and valid source of mortality data. *J Clin Epidemiol* 2016;79:167-8.
- Rosenthal AK, McLaughlin JK, Gridley G, Nyrén O. Incidence of cancer among patients with systemic sclerosis. *Cancer* 1995;76:910-4.
- Johnson SR, Granton JT, Tomlinson GA, et al. Warfarin in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension. A Bayesian approach to evaluating treatment for uncommon disease. *J Rheumatol* 2012;39:276-85.
- Ogane K, Kato T, Mizushima I, Kawano M, Yamagishi M. A case of sarcoidosis developing as sarcoid myopathy concomitant with systemic sclerosis and review of the literature. *Mod Rheumatol* 2012;22:142-6.
- Ueda-Hayakawa I, Nguyen CTH, Kishimoto I, Ly NTM, Okamoto H. Clinical characteristics of sarcoidosis patients with systemic sclerosis-specific autoantibody: possible involvement of thymus and activation-regulated chemokine and a review of the published works. *J Dermatol* 2019;46:577-83.
- Kobak S, Karaarslan AA, Yilmaz H, Sever F. Co-occurrence of rheumatoid arthritis and sarcoidosis. *BMJ Case Rep* 2015;2015:ber2014208803.
- Menard O, Petit N, Gillet P, Gaucher A, Martinet Y. Association of histologically proven rheumatoid arthritis with pulmonary sarcoidosis. *Eur Respir J* 1995;8:472-3.
- Verschuereen K, Van Essche E, Verschuereen P, Taelman V, Westhovens R. Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients. *Clin Rheumatol* 2007;26:1969-71.
- Mansour MJ, Al-Hashimi I, Wright JM. Coexistence of Sjögren syndrome and sarcoidosis: a report of five cases. *J Oral Pathol Med* 2007;36:337-41.
- Kobak S, Sever F, Ince O, Orman M. The prevalence of sacroiliitis and spondyloarthritis in patients with sarcoidosis. *Int J Rheumatol* 2014;2014:289454.
- Kobak S, Sever F, Sivrikoz ON, Orman M. Sarcoidosis: is it only a mimicker of primary rheumatic disease? A single center experience. *Ther Adv Musculoskelet Dis* 2014;6:3-7.
- Carmi O, Berla M, Edelstein E, Levy Y. Coexisting systemic sclerosis-polymyositis and sarcoidosis: case report and review of the literature. *J Clin Rheumatol* 2018;24:238-40.
- Navi BB, DeAngelis LM. Sarcoidosis presenting as brainstem ischemic stroke. *Neurology* 2009;72:1021-2.
- Hodge MH, Williams RL, Fukui MB. Neurosarcoidosis presenting as acute infarction on diffusion-weighted MR imaging: summary of radiologic findings. *AJNR Am J Neuroradiol* 2007;28:84-6.
- Singh SK, Samudralwar R. A rare case of ischemic strokes due to sarcoidosis related cerebral phlebitis (2203). *Neurology* 2020;94:2203.
- AlMehmadi BA, To FZ, Anderson MA, Johnson SR. Epidemiology and treatment of peripheral neuropathy in systemic sclerosis. *J Rheumatol* 2021;48:1839-49.
- Ungprasert P, Sanguankeo A, Upala S. Risk of ischemic stroke in patients with systemic sclerosis: a systematic review and meta-analysis. *Mod Rheumatol* 2016;26:128-31.
- Soto-Gomez N, Peters JI, Nambiar AM. Diagnosis and management of sarcoidosis. *Am Fam Physician* 2016;93:840-8.
- Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med* 2006;174:795-802.
- Fidler LM, Gershon A, Fisher JH, Stanbrook MB, To T, Balter M. Hospitalizations in sarcoidosis: a cohort study of a universal healthcare population. *Ann Am Thorac Soc* 2021;18:1786-94.