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Original Article

Exploring Occupational, Recreational, and Environmental Associations in Patients With Clinically Manifest Cardiac Sarcoidosis

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ABSTRACT

Background: Sarcoidosis is a condition of unknown etiology. A number of occupational, recreational, and environmental exposures have been associated with the development of extra-cardiac sarcoidosis. Patients with clinically manifest cardiac sarcoidosis (CS) have a distinct clinical phenotype. We sought to explore the exposures associated with clinically manifest CS.

Methods: Two groups of patients were recruited in a prospective registry: cases (patients with clinically manifest CS) and controls (patients without sarcoidosis and who had similar cardiac presentations to cases). A validated survey, previously used in other sarcoidosis phenotypes, was sent to all patients.

Results: A total of 113 patients met the inclusion criteria and were sent the survey, of whom 79 of 113 (69.9%) completed the survey. We

RÉSUMÉ

Contexte : Les causes de la sarcoïdose demeurent inconnues. Un certain nombre de facteurs de risque professionnels, récréatifs et environnementaux ont toutefois été associés à la survenue de la sarcoïdose extracardiaque. Les patients qui sont atteints d'une sarcoïdose cardiaque cliniquement manifeste ont un phénotype clinique particulier. Nous nous sommes penchés sur les facteurs de risque associés à cette maladie.

Méthodologie : Nous avons recruté deux groupes de patients à partir d'un registre de données prospectives : des cas de sarcoïdose cardiaque (présentant les manifestations cliniques de la sarcoïdose cardiaque) et des cas témoins (patients sans sarcoïdose, mais qui présentaient des signes et des symptômes cardiaques similaires à ceux des patients atteints de sarcoïdose cardiaque). Nous avons

Sarcoidosis is a multisystem inflammatory granulomatous disease characterized by infiltration with non-caseating granulomas.[1] Pulmonary disease is most common, and cardiac, splenic, renal, neurologic, and dermatologic involvement can also occur.[1] Up to 5% of patients with sarcoidosis experience clinically manifest cardiac sarcoidosis (CS).[2,3] These patients usually present with one or more of the following: conduction abnormalities, ventricular arrhythmias, or heart failure. Additionally, up to 25% have clinically silent cardiac involvement found on late gadolinium enhancement–cardiac magnetic resonance imaging (LGE-CMR).[2,3]

Despite intensive research efforts, the etiology of sarcoidosis is still unknown, with the most common hypothesis suggesting a combination of genetic predisposition leading to susceptibility to an unidentified environmental trigger.[1] The **A** **C**ase **C**ontrolled **E**tiologic **S**tudy of **S**arcoidosis (ACCESS) examined exposures associated with primarily pulmonary sarcoidosis.[4] The study found positive associations of sarcoidosis with work in areas with musty odors, and with occupational exposure to insecticides, and a negative association with smoking.[4] It did not identify a single, predominant cause of sarcoidosis.[4] Other studies have shown associations with other factors, including mold exposure,[5] and certain workplace environments (eg, mining, agriculture, metal industry, firefighting, and construction).[4,6]

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Ethics Statement: Institutional ethics approval was obtained at the onset of the registry. Additionally, a second ethics approval was obtained for the questionnaire and data linkage. The institutional review board was the Ottawa Health Science Network Research Ethics Board.

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found 3 environmental associations. First, we found a negative association of CS with smoking, with 8 of 43 (18.6%) CS patients being current or ex-smokers compared to 17 of 36 (47.2%) of the controls. Second, we found a positive association with mold exposure, with 21 of 43 (48.8%) CS patients having a prior history of mold exposure compared to 9 of 36 (25.0%) of the controls. After multivariable analysis, there remained significant associations between CS and smoking (odds ratio 0.14 [95% confidence interval 0.04-0.51], $P = 0.002$) and mold exposure (odds ratio 5.69 [95% confidence interval 1.68-19.25], $P = 0.005$). Finally, patients with CS and self-reported acne had a significantly longer duration of active acne (7.82 $\pm$ 3.97 years) than did control patients 2.67 $\pm$ 1.03 years ($P = 0.006$).

Conclusions: We found a negative association between smoking history and the diagnosis of CS. We also found a significant 5-fold increase in mold exposure and a positive association with duration of acne in patients with CS compared to controls.

Résultats : Au total, 113 patients répondaient aux critères d'inclusion. Nous avons envoyé le questionnaire à ces 113 patients, et 79 d'entre eux (69,9 %) y ont répondu. Nous avons détecté trois facteurs environnementaux. Nous avons d'abord noté une association négative entre la sarcoïdose cardiaque et le tabagisme : 8 patients atteints de sarcoïdose cardiaque sur 43 (18,6 %) fumaient ou avaient déjà fumé, comparativement à 17 témoins sur 36 (47,2 %). Nous avons ensuite observé une association positive avec l'exposition aux moisissures : 21 patients atteints de sarcoïdose cardiaque sur 43 (48,8 %) avaient des antécédents d'une telle exposition, comparativement à 9 des 36 témoins (25,0 %). Les associations entre la sarcoïdose cardiaque et le tabagisme et l'exposition aux moisissures sont demeurées significatives après une analyse multivariée (risque relatif approché [RRA] pour le tabagisme : 0,14 [intervalle de confiance {IC} à 95 % : 0,04-0,51], $p = 0,002$; RRA pour l'exposition aux moisissures : 5,69 [IC à 95 % : 1,68-19,25], $p = 0,005$). Finalement, chez les patients atteints de sarcoïdose cardiaque et d'acné autodéclarée, la durée de l'acné était significativement plus longue (7,82 $\pm$ 3,97) que celle relevée chez les témoins (2,67 $\pm$ 1,03; $p = 0,006$).

Conclusions : Nous avons détecté une association négative entre les antécédents de tabagisme et le diagnostic de sarcoïdose cardiaque. Nous avons également observé que l'exposition aux moisissures était 5 fois plus élevée et que l'acné est présente plus longtemps chez les patients atteints de sarcoïdose cardiaque que chez les témoins.

The current study sought to examine occupational, recreational, and environmental exposures in a population of patients with clinically manifest CS.

Methods

Patients

This study is a single-centre substudy of the ongoing Cardiac Sarcoidosis Multi-Center Prospective Cohort Study (CHASM-CS registry; NCT: NCT01477359) at the University of Ottawa Heart Institute (Ottawa, Ontario, Canada. CHASM-CS is a multi-centre, Canadian and Japanese prospective registry that is recruiting 2 cohorts of patients: those with specific cardiac presentations, to investigate for CS as an underlying diagnosis; and those diagnosed with extra-cardiac sarcoidosis and being screened for CS. The 2 primary aims are as follows: (i) to follow clinical outcomes; and (ii) to assess feasibility of recruitment and examine treatment effect size. These data will be used to assess the need, feasibility, and sample size for a larger study and/or clinical trial.

For this substudy, 2 groups of patients were included from cohort A of the registry.

Inclusion criteria for survey—cases: patients with clinically manifest CS[2]:. (i) positive biopsy for sarcoidosis (either endomyocardial biopsy or extra-cardiac)

AND (ii) one or more of the following clinical features:

- younger than age 60 years, with advanced conduction system disease (sustained Mobitz II atrioventricular (AV) block or third-degree AV block)
- sustained idiopathic ventricular arrhythmia

AND (iii) no alternative explanation for clinical features.

Inclusion criteria for survey—controls: patients without sarcoidosis who had similar cardiac presentations to cases:. (i) investigated for CS as underlying etiology with either of the following presentations:

- younger than age 60 years with advanced conduction system disease (sustained Mobitz II AV block or third-degree AV block)
- sustained idiopathic ventricular arrhythmia;

(ii) negative 18fluorodeoxyglucose positron emission tomography and computed tomography cardiac and whole-body scan.

In both of the above bulleted lists, sustained idiopathic ventricular arrhythmia was defined as being unrelated to coronary artery disease or any cardiomyopathy, and not outflow tract arrhythmia or fascicular ventricular tachycardia.

Questionnaire

A validated survey, previously used in other sarcoidosis phenotypes, was sent to all patients. The survey included questions regarding recreational, occupational, and environmental exposure history (see Supplemental Appendix S1). Recreational exposures were those that occurred outside of work, either at home or elsewhere. Occupational exposures were those that occurred strictly in the work environment. Environmental exposures included those occurring within the

work environment, and/or at home (eg, smoking history, history of acne, history of mold exposure in the work environment). Answers to questions on the survey were mutually exclusive (ie, not duplicated if included in separate categories, although a patient may have responded positively to separate questions from different categories, in which case they were counted separately).

Study procedures

All patients from the CHASM-CS registry at who met the inclusion criteria for the study were sent details of the study, a consent form, and the ACCESS questionnaire.[4] If the patient did not respond to this mailing, then research staff made 2 follow-up calls. Questionnaire results were linked to patient clinical data already stored in CHASM-CS.

Ethics

Institutional ethics approval was obtained at the onset of the registry. Additionally, a second ethics approval was obtained for the questionnaire and data linkage. The institutional review board was the Ottawa Health Science Network Research Ethics Board, and associated approval numbers were: CHASM-CS registry: 20120365-01H; and CS exposure study: 20180431-01H.

Statistics

Categorical variables are presented as percentages; continuous variables are presented as means (± standard deviation). We compared categorical variables using the χ^2 test, and continuous variables using *t* tests. For each question in the questionnaire, odds ratios were calculated using proportions from each group and compared using the χ^2 method. For each group of environmental exposures, a logistic regression analysis was performed.

Statistical analysis was subsequently performed using SPSS software (version 23, SPSS Inc, Chicago, IL), and statistical significance was defined as a *P*-value of < 0.05.

Results

Patients

A total of 113 patients met the inclusion criteria, of whom 79 of 113 (69.9%) completed the survey. Baseline demographics of the patients who responded to the questionnaire are shown in Table 1. The cases (n = 43) and controls (n = 36) were well matched overall. The time between cardiac presentation and survey completion was slightly longer for the cases than for the controls (442.1 ± 496.8 days vs 388.4 ± 492.7 days), $P = 0.03$). This difference is due to the fact that recruitment of the control patients stopped on August 17th, 2017, but recruitment of cases is ongoing.

Sarcoidosis organ involvement

It should be noted that 12 of 43 (27.9%) of the cases had a prior history of extra-cardiac sarcoidosis before cardiac presentation. Supplemental Table S1 shows sarcoidosis involvement in 27 of 43 treatment-naive cases at the time of cardiac presentation.

Occupational and recreational associations

Data regarding occupational and recreational exposures are presented in Table 2. There were no statistically significant associations.

Environmental associations—smoking

There was a statistically significant negative association between CS and smoking (Table 3). Eight of 43 (18.6%) CS patients were ex- or current smokers, compared to 17 of 36 (47.2%) of the controls (OR 0.26 [0.09-0.70], $P = 0.0021$). Additionally, CS patients with a history of smoking had smoked for significantly fewer pack-years (9.95 ± 6.78) compared to controls (20.57 ± 10.82, $P = 0.02$), and they had stopped smoking for more years (23.0 ± 11.5) compared to controls (17.4 ± 11.4, $P = 0.03$; see Table 3).

Environmental associations—mold exposure

There was a statistically significant positive association with potential mold exposure; 21 of 43 (48.8%) CS patients reported a history of mold exposure compared to 9 of 36 (25.0%) of the controls (odds ratio [OR] 2.86 [95% confidence interval {CI} 1.09-7.50], $P = 0.030$). Table 4 shows the details of these data.

Environmental associations—acne history

There was a trend toward a positive association with self-reported acne, with 14 of 43 (32.7%) CS patients reporting a history of acne compared to 6 of 36 (16.7%) controls

Table 1. Baseline characteristics of patients in each group

Characteristic	Patients with CS (n = 43)	Control group (n = 36)	*P*
Age at presentation of CS (y)	55.9± 8.3	53.1 ± 9.8	0.164
Days between presentation and survey	388.4 ± 492.7	442.1 ± 496.8	0.03
Race—Caucasian	39 (90.7)	34 (94.4)	0.53
Female	19 (44.2)	16 (44.4)	0.98
Hypertension	15 (34.9)	13 (36.1)	0.91
Diabetes	6 (14.0)	7 (19.4)	0.51
Congestive heart failure	4 (9.3)	2 (5.6)	0.39
Presenting cardiac feature			
• Sustained Mobitz II and/or third-degree AV block	27 (62.8)	27 (75.0)	0.25
• VT or cardiac arrest	13 (30.2)	9 (25.0)	0.61
• Sustained Mobitz II and/or third-degree AV block and VT	3 (7.0)	1 (2.8)	0.40

Values are n (%) or mean ± standard deviation, unless otherwise indicated.
AV, atrioventricular; CS, cardiac sarcoidosis; VT, ventricular tachycardia

Table 2. Occupational and recreational exposure analysis

Exposure	Patients with cardiac sarcoidosis (n = 43)	Control group (n = 36)	OR (95% CI)	*P*
Occupation				
Military	5 (11.63)	2 (5.56)	2.24 (0.41-12.29)	0.121
Farming/fishing	6 (13.95)	4 (11.11)	1.30 (0.34-5.00)	0.574
Auto industry	4 (9.30)	3 (8.33)	1.13 (0.24-5.41)	0.717
Food preparation/serving	4 (9.30)	3 (8.33)	1.13 (0.24-5.41)	0.717
Painting/printing/photography	5 (11.63)	2 (5.56)	2.24 (0.41-12.29)	0.326
Manufacturing/industry	7 (16.28)	5 (13.89)	1.21 (0.35-4.18)	0.842
Construction/extraction	8 (18.60)	7 (19.44)	0.95 (0.31-2.92)	0.597
Education/library services	4 (9.30)	8 (22.22)	0.36 (0.09-1.31)	0.091
Animal exposure	7 (16.28)	4 (11.11)	1.56 (0.42-5.81)	0.470
Hospital setting/health care	9 (20.93)	4 (11.11)	2.12 (0.59-7.56)	0.257
Marketing/sales/service	20 (46.51)	18 (50.00)	0.87 (0.36-2.11)	0.541
Home care	4 (9.30)	5 (13.89)	0.64 (0.16-2.57)	0.359
Transportation	8 (18.60)	2 (5.56)	3.89 (0.77-19.6)	0.093
Law enforcement	3 (6.98)	1 (2.78)	2.63 (0.26-26.40)	0.352
Information technology	6 (13.95)	6 (16.67)	0.81 (0.24-2.77)	0.497
Nuclear/radiation exposure	5 (11.63)	3 (8.33)	1.45 (0.32-6.52)	0.528
Construction/manufacturing	11 (25.58)	9 (25.00)	1.03 (0.37-2.86)	0.643
Recreation				
Military*	4 (9.30)	0 (0.00)	n/a	n/a
Auto industry	7 (16.28)	3 (8.33)	2.14 (0.51-8.96)	0.297
Exercise industry	20 (46.51)	12 (33.33)	1.74 (0.70-4.35)	0.292
Painting/printing industry	7 (16.28)	5 (13.89)	1.21 (0.35-4.18)	0.606
Agriculture	29 (67.44)	27 (75.00)	0.69 (0.26-1.85)	0.096
Hospital/health care setting	2 (4.65)	0 (0.00)	n/a	n/a
Sales/service industry	1 (2.33)	0 (0.00)	n/a	n/a

Values are n (%), unless otherwise indicated.

CI, confidence interval; n/a, not available; OR, odds ratio.

*Recreational military exposures included armed forces reserves (ie, have not been deployed), whereas occupational military included army, navy, air force, or other branch of military who have been deployed.

($P = 0.11$). Additionally, patients with CS and self-reported acne had a significantly longer duration of active acne (7.82 ± 3.97 years) than control patients 2.67 ± 1.03 years ($P = 0.006$). There was no difference in time elapsed between presentation with CS and last active acne: 416.20 ± 161.92 months compared to 386.97 ± 136.48 months ($P = 0.70$).

Environmental associations—multivariate analysis

There remained significant associations between CS and smoking (OR 0.14 [95% CI 0.040.51], $P = 0.002$) and mold exposure (OR 5.69 [95% CI 1.68-19.25], $P = 0.005$) after multivariate analysis. There was no association with acne (OR 2.06 [95% CI 0.66-6.47], $P = 0.21$) after multivariate analysis.

Discussion

We believe that this is the first study to examine occupational, recreational, and environmental associations with clinically manifest CS. We found a significant negative association between smoking and risk of CS and a positive association with mold exposure. There were no significant occupational or recreational associations. Our study used the questionnaire from the largest case–control study of exposures associated with sarcoidosis.[4,7] In that study, 706 newly diagnosed sarcoidosis patients were recruited to answer a questionnaire (53% were white; 44% were black). They found an independent positive association between work in areas with musty odors and sarcoidosis (OR 1.62 [95% CI 1.24-2.11]) and with occupational exposure to insecticides (OR 1.61 [95% CI 1.13-2.28]), and a

Table 3. Cigarette smoking history among patients with vs without cardiac sarcoidosis

Characteristic	Patients with cardiac sarcoidosis (n = 43)	Control group (n = 36)	*P*
History of having ever smoked cigarettes	8 (18.6)	17 (47.2)	0.006
Smokers	**Patients with cardiac sarcoidosis (n = 8)**	**Control group (n = 17)**	***P***
Daily number of cigarettes smoked	12.8 ± 7.6	13.6 ± 8.5	0.82
Age when started smoking (y)	17.3 ± 1.5	18.2 ± 3.6	0.51
Smoking at the time of diagnosis	2 (25.0)	5 (28.4)	0.88
Duration of smoking (y)	12.1 ± 6.84	21.4 ± 12.1	0.06
Lifetime pack-years	9.95 ± 6.78	20.57 ± 10.82	0.02
Estimated time between stopping smoking and diagnosis (y)	23.0 ± 11.5	17.4 ± 11.4	0.03

Values are n (%) or mean ± standard deviation, unless otherwise indicated.

Table 4. Mold exposures among patients with vs without cardiac sarcoidosis

Characteristic	Patients with cardiac sarcoidosis (n = 43)	Control group (n = 36)	*P*
Number of patients with ≥1 exposures*	21 (48.8)	9 (25.0)	0.030
Specific exposures			
High humidity	12 (27.9)	6 (16.7)	0.236
Water damage to furnishings, ceiling, tiles, or carpets	14 (32.6)	5 (13.9)	0.053
Obvious mold or mildew (not in a bathroom)	10 (23.3)	3 (8.3)	0.075
Musty or moldy odors	13 (30.2)	5 (13.9)	0.085

Values are n (%), unless otherwise indicated.

*Mold exposure was defined as a positive response to any of the conditions in the following question: "In your office or indoor working environment in your employment at the time of your cardiac illness, other than in the workplace bathrooms, have you noticed any of the following conditions: 1) high humidity; 2) water damage to furnishings, ceiling, tiles, or carpet; 3) obvious mold or mildew not in a bathroom; 4) musty or moldy odors."

negative association with smoking (OR 0.65 [95% CI 0.51-0.82]).

Our finding of a negative association with smoking is consistent with other epidemiologic observations from the extra-cardiac sarcoidosis literature in Western countries.[4,8-10] The explanation for this association is unclear, and it is possible that it is due to residual confounding. However, there are some basic science observations suggesting biological plausibility of this finding. For example, smoking has been shown to reduce macrophage activation after dust exposure.[11,12] Additionally, studies have demonstrated that smokers with pulmonary sarcoidosis tend to have lower CD4/CD8 counts in bronchoalveolar lavage specimens compared to those who do not smoke, suggesting that changes in lymphocyte activation may be a potential contributing factor.[9,13] The association with smoking has not been found in studies of Japanese and Northern Indian populations.[14,15]

Our second observation was a positive association between self-reported mold exposure and development of CS (OR 5.69 [95% CI 1.68-19.25], $P = 0.005$). Again, this finding is consistent with data from ACCESS.[4] A number of other studies have shown supportive observations.[5,16,17] The association is postulated to be mediated by exposure to fungal antigens.[16,17] Tercelj et al. performed household air sampling in patients with sarcoidosis and found elevated fungal cell biomass.[16] Further, they showed that if these levels remained significant, sarcoidosis recurrence was more likely to occur.[16] The same researchers also showed that there was reactivity to cell wall antigens in macrophages from sarcoidosis patients; in addition, increased antifungal antibodies have been found in bronchoalveolar lavage specimens in patients with pulmonary sarcoidosis.[17]

Previous work has suggested a link between *Propionibacterium acnes* and sarcoidosis. Indeed, *P acnes* is the only bacterium to have been cultured from lymph node samples of sarcoidosis patients.[18] There have been at least 9 studies examining various molecular or immunohistochemical methods, and a meta-analysis of these studies found that patients with sarcoidosis had a markedly increased association with *P acnes*, compared to controls (OR 19.58 [95% CI 13.06-29.36]).[19] It should be noted that none of the studies specifically examined CS patients.[19] However, a Japanese study examined myocardial tissue from patients with CS (n = 16), myocarditis (n = 15), or other cardiomyopathies (n = 39) using immunohistochemistry with a *P acnes*–specific monoclonal antibody. They found *P acnes* reactivity in 10 of 16 CS samples and none of the other patients. Our results showed a trend toward an association, but this was not statistically significant. However, patients with CS and self-reported acne had a longer duration of active acne (7.82 ± 3.97 years, $P = 0.006$) than control patients (2.67 ± 1.03 years, $P = 0.006$).

There is much interest in trying to understand the different phenotypes of sarcoidosis, and 5 major phenotypes have been described.[20] The Genotype–Phenotype Relationship in Sarcoidosis project is a recent European multicentre registry that studied 2163 Caucasian patients with sarcoidosis who were phenotyped by a standardized protocol. Patients were classified into 5 distinct subgroups according to organ(s) involvement: (i) abdominal organs; (ii) ocular–cardiac–cutaneous–central nervous system disease; (iii) musculoskeletal–cutaneous; (iv) pulmonary and intrathoracic lymph node; and (v) extrapulmonary involvement.[20] Also, our group and others have described another phenotype of primarily Caucasian patients with clinically manifest CS.[21-23] In this phenotype, cardiac manifestations are usually the first presentation of sarcoidosis in any organ, and other organ involvement is usually modest.[21-23] Our current study clearly shows this as well (see Supplemental Table S1). The mean number of affected organs was 1.48 ± 1.2; it should be noted that the lymph nodes were counted as an organ. Only 30% of the patients had lung involvement; one patient had skin disease; and no patients had eye disease. These findings contrast with those of the ACCESS study, in which 95% of patients had lung involvement and only 2.3% had cardiac disease.[7]

Our study has several limitations. The major issue is the small sample, and we suggest that our study should be repeated in larger cohorts. For example, previous work has suggested that certain workplace environments are associated with extra-cardiac sarcoidosis risk. Examples include mining, agriculture, metal industry, firefighting, and construction.[4,6] In this study, we did not find any association between specific occupations and CS, and this may be because of our sample size. We could have greatly increased our sample size by including patients who have clinically silent CS, as this is approximately 5-fold more common.[24] Although the exclusion of these patients is a limitation to the study, we really wanted to focus on the most severely diseased CS patients. Moreover, although our sample size is small, we had a quite distinct and very homogeneous phenotype to study. This is in marked contrast to other epidemiologic studies that have

included a broad range of phenotypes, geographies, and racial groupings.[7,20] However, it also follows that our findings cannot be extrapolated to other races, geographies, and phenotypes of disease.

A second limitation is the method of selection of our controls, which can be criticized, as these are not "normal" subjects. Hence, it follows that we are comparing CS risks/exposures to cardiac risks/exposures, and this may, at least in part, explain the fact that the rate of smoking among control patients (47.2%) is higher than that reported in most Canadian epidemiologic studies. However, there were many advantages to using this population. They were prospectively collected from our institution and were contemporaneously enrolled with the cases. Also, they are very well matched in baseline demographics to the cases. Finally, differential information bias is a potential concern in case-controlled studies of occupational and environmental agents.[4] Additionally, patients with disease might have spent more time considering their past exposures, although in our study, both cases and controls had disease, and hence these biases should be mitigated. The cases and controls were well matched in general. The time between cardiac presentation and survey completion was slightly longer for the cases than the controls. This difference is due to the fact that recruitment of the control patients stopped on August 17, 2017, but recruitment of cases is ongoing. We discontinued control patient recruitment for budgetary reasons. This detail also partially explains the greater number of cases compared with controls. Additional reasons include higher consent rate to registry, and greater response rate to survey requests. Also, referral bias for both cases and control patients may have occurred, amongst other potential types of bias. Finally, it could be argued that we should have included a group of patients with pulmonary sarcoidosis without cardiac involvement, to assess whether the associations are the same.

Conclusions

We found a negative association between smoking history and the diagnosis of CS. We also found a significant 5-fold increase in mold exposure in patients with CS compared to controls, and a positive association with duration of acne. These findings should be further explored in other cohorts.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.07.010.