SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 138-143

Cigarette smoking and male sex are independent and age concomitant risk factors for the development of ocular sarcoidosis in a new orleans sarcoidosis population

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Abstract. *Introduction:* Sarcoidosis is a multi-organ system granulomatous disease of unknown origin with an incidence of 1-40/100,000. Though pulmonary manifestations are predominant, ocular sarcoidosis (OS) affects 25-50% of patients with sarcoidosis and can lead to blindness. *Methods:* A retrospective, single-center chart review of sarcoidosis cases investigated variables associated with the development of OS. Inclusion criteria were biopsy-proven sarcoidosis, disease duration greater than 1 year, documented smoking status on chart review and documentation of sarcoid-related eye disease. Multivariate analysis identified independent risk factors for OS. *Results:* Of 269 charts reviewed, 109 patients met inclusion criteria. The OS group had a significantly higher proportion of smokers (71.4%) than without OS (42.0%, p=0.027) with no difference (p=0.61) in median number of pack years. Male sex was significantly higher in the OS group (57.1% versus 26.1%, p=0.009). Median duration of sarcoidosis was higher in the OS group (10 versus 4 years, p=0.031). Multivariate regression identified tobacco exposure (OR=5.25, p=0.007, 95% CI 1.58-17.41), male sex (OR=7.48, p=0.002, 95% CI 2.15-26.01), and age (OR=1.114, p=0.002, 95% CI 1.04-1.19) as concomitant risk factors for the development of OS. *Conclusion:* To date, there are few dedicated investigations of risk factors for OS, especially smoking. This investigation identified male sex, age, and tobacco exposure as independent risk factors for OS. Though disease duration did not withstand regression analysis in this moderately sized group, age at chart review suggests screening for OS should not remit but rather intensify in aging patients with sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 183-143)*

Key words: sarcoidosis, eye, extra-pulmonary, ocular, uveitis, smoking, tobacco, gender risk, sex

Introduction

Sarcoidosis is a systemic disease with an incidence of 1-40 persons per 100,000 (1, 2) characterized by the presence of non-caseating granulomas that form in almost any organ. It is postulated that they are the result of an exaggerated immune response to yet undetermined antigenic stimuli (3). Genetic background may confer predisposition to the development of sarcoidosis and may depend on an inciting exposure (4-7). Compressive effects and architectural derangement due to granuloma formation lead to a spectrum of organ dysfunction and destruction with wide-ranging manifestations specific

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to involved organs such as skin disfigurement, dyspnea and arrhythmias from cardiopulmonary involvement, or neurologic involvement with seizures, sensory and motor dysfunction (1, 3, 8).

Although pulmonary involvement is the predominant clinical feature, ocular sarcoidosis (OS) is common with a 25-60% prevalence in patients with sarcoidosis (3, 9). OS is the presenting manifestation in 5% of cases of sarcoidosis (3, 8, 9). Sarcoid granulomas form in any part of the eye or its associated tissues. Uveitis (30-70%) and conjuctival granulomas (40%) are the most common manifestations of OS (9-13). However, the lacrimal system, skin of the eyelids, orbital tissues, oculomotor nerves, and optic nerve can also be affected (3). Blindness will develop in at least 10% of patients with sarcoid uveitis making screening essential (14).

A female predominance has previously been identified for OS with the highest predominance in females of African descent (5, 16). Cigarette smokers with sarcoidosis have a higher incidence of extrapulmonary disease, including ocular involvement (17). To date, there are few dedicated investigations of variables associated with development of ocular sarcoidosis. This investigation examines risk factors for OS in our New Orleans population.

MATERIALS AND METHODS

Approval from the Institutional Review Board (IRB #8091) of the Louisiana State University Health Sciences Center-New Orleans (LSUHSC) and the Research Review Committee of the Medical Center of Louisiana-New Orleans (MCLNO) was obtained. A retrospective review was conducted on consecutive charts identified by the sarcoidosis ICD-9 code (135) seen in MCLNO clinics between 2006 and 2012. Data were collected on age, gender, race, biopsy results, smoking status, estimated pack-years of smoking, OS manifestations, and duration of sarcoidosis. Study inclusion criteria were a tissue biopsy consistent with sarcoidosis, diagnosis of sarcoidosis for greater than 1 year, and the presence of documented smoking status on chart review.

Per routine care in our clinics, sarcoidosis patients receive pulmonary function testing (PFT). PFTs performed at our institution carefully document smoking history and served as our primary source for determining tobacco exposure. Where data from PFT reports were not available, smoking status documented on clinic notes was used. Estimated pack-years were calculated as the product of the number of packs smoked per day and number of years smoked. If there was any variation in documented pack-years, the mean value was used.

OS was defined as evidence or history of sarcoid disease in the eye or its adnexa, which was documented on chart review in ophthalmology, pulmonology, or rheumatology clinic notes. Patients were considered to have OS if there was a clearly documented history of sarcoid uveitis or biopsies of ocular tissue consistent with sarcoidosis. Patients with a history of sarcoid involvement of the lacrimal gland, eyelids, extra-ocular muscles, or conjunctiva were also considered to have OS. Finally, charts with any documentation of ocular sarcoidosis without specification of anatomic location were considered to have OS. Duration of disease was calculated by subtracting the age of diagnosis from the age at chart review.

Groupwise comparisons of continuous data were done by t-test if normally distributed or by Mann-Whitney test. Data are expressed as mean ± standard deviation or median [interquartile range]. Frequencies were compared by Chi square or Fisher exact test. Logistic regression was used to analyze the impact of sex, age at chart review, age at onset of sarcoidosis, duration of sarcoidosis, smoking status and pack years on the presence of OS. P-values <0.05 were considered significant.

Results

The review identified 269 charts with an ICD-9 code of 135 with 109 patients meeting the inclusion criteria. Characteristics of the study population are shown in Table 1. For the study population as a whole, 21 (19.3%) patients had OS, 88 did not (80.7%). When specified, anterior uveitis was the most common manifestation of OS (n=10, Table 2). In the OS group, the proportion of smokers (71.4%) was significantly higher than in the group without OS (42.0%, p=0.027). There was no significant difference (p=0.605) in the median number of pack-years between smokers with OS (13 [7;28]) and those without OS (16.5 [7;25]) though pack-years

Table 1. Characteristics of patients with and without OS

		Total	No OS (n=88)	With OS (n=21)	p-value
Sex	female	74 (67.9%)	65 (73.9%)	9 (42.9%)	0.009
	male	35 (32.1%)	23 (26.1%)	12 (57.1%)	
Age at chart review (mean±std)		51.2±10.0	50.4±10.4	54.2±7.7	0.123
Age at onset of sarcoidosis (median; IQR)		42 (35;49)	41 (35;49)	43 (33;49)	0.863
Disease duration (median; IQR)		4 (2;13)	4 (2;12)	10 (4;15)	0.031
Race	Black	97 (89.0%)	78 (88.6%)	19 (90.5%)	1.000
	White	5 (4.6%)	5 (5.7%)	0 (0.0%)	(black vs.
	Hispanic	1 (0.9%)	0 (0.0%)	1 (4.8%)	all other)
	Middle Eastern	1 (0.9%)	1 (1.1%)	0 (0.0%)	
	Unknown	5 (4.6%)	4 (4.5%)	1 (4.8%)	
Smoking Status	Never smoker	57 (52.3%)	51 (58.0%)	6 (28.6%)	0.027
	Ever smoker	52 (47.7%)	37 (42.0%)	15 (71.4%)	
Pack-years of ever smokers (median; IQR)		13 (7;25)	13 (7;28)	16.5 (7;25)	0.605

Table 2. Anatomic locations of OS, when specified

Anatomic Location	N
Anterior uveitis	10
Ocular Sarcoidosis (not otherwise specified)	7
Noncaseating granulomas on conjunctival biopsy	2
Noncaseating granulomas on lacrimal gland biopsy	1
Eyelid lesions	1
Total	21

were not available for 6 patients without and 1 patient with OS. There were more male patients in the OS group compared to those without OS (57.1% versus 26.1%, p=0.009). Median disease duration of sarcoidosis was found to be higher in patients with OS (10 years versus 4 years, p=0.031).

Through multivariate regression analysis, having ever smoked cigarettes (OR=5.24, p=0.007, 95% CI 1.58-17.41), male sex (OR=7.48, p=0.002, 95% CI 2.15-26.01) were found to be independent risk factors, and age at chart review was found to be a concomitant risk factor (OR= 1.11, p=0.002, 95% CI 1.04-1.19) for the development of OS (Table 3). We found considerable interactions of smoking and sex with age at chart review or age at disease onset in our data; triple-interaction terms indicated an highly increased risk for male smokers with higher age or disease onset at younger ages.

Discussion

These analyses point to three concomitant risk factors associated with the development of ocular sarcoidosis in our study population: cigarette exposure, male sex, and age. Krell *et al.* described an as-

Table 3. Results of univariate and multivariate logistic regression for presence of OS

	Univariate				Multivariate			
			95% C.I.for OR				95% C.I.for OR	
	p value	OR	Lower	Upper	p value	OR	Lower	Upper
Male sex	.008	3.768	1.405	10.105	.002	7.480	2.152	26.006
Age at chart review	.126	1.040	.989	1.094	.002	1.114	1.039	1.194
Age at onset of sarcoidosis	.886	.997	.955	1.041				
Duration of sarcoidosis	.099	1.037	.993	1.083				
Smoking status	.019	3.446	1.222	9.721	.007	5.248	1.582	17.410
Estimated pack-years*	.058	1.031	.999	1.063				
Race†	.809	.821	.166	4.062				

* for regression analysis, pack-years were coded as 0 for never smoker
† black versus other races

sociation between cigarette smoking and extrapulmonary manifestations of sarcoidosis, which is consistent with our findings of an increased frequency of OS (17). Beyond OS, cigarette smoking has also been associated with other ocular conditions such as all-cause uveitis, neovascular age-related macular degeneration, and thyroid eye disease (18-22).

Curiously, cigarette smoking may be negatively associated with the occurrence of pulmonary sarcoidosis (23-26). However, all studies have not borne this out and furthermore smoking appears to be associated with worse pulmonary disease severity (17, 27). An associative mechanism of cigarette smoking on pulmonary tissue was elucidated by Gerke *et al.* who found that cigarette smoking appeared to decrease bronchovascular bundle thickening (BVBT) in the lungs of patients with sarcoidosis who smoke. BVBT is a radiological pattern of irregular nodular thickening in peri-vascular and lymphatic distribution suggestive of granuloma formation along the airways and correlates with poor pulmonary function (28).

Either the compounds in cigarette smoke or nicotine itself may hinder the release of TNF-α from alveolar macrophages and T helper cells required for granuloma formation in infectious and non-infectious granulomatous disease (29-34). Decreased concentrations of available TNF-α may dampen the specific inflammatory cascade in the lungs of smokers with sarcoidosis, decreasing granuloma formation and presumably BVBT (28). Other sarcoid-affected organs appear not to benefit from the depressed, smoking-related, TNF-α response observed in the alveoli.

Systemically, cigarette smoking increases vascular H_2O_2 production, a powerful activator of nuclear factor-κB, up-regulating circulating pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and TNF-α associated with granuloma formation (8, 18, 35-40). With the systemic up-regulation of the TNF-α and IL-6 inflammatory cascade by CD4 T-cells, cigarette smoking could hasten granuloma formation in extra-pulmonary tissues thus explaining the greater than five-fold overall OS risk in our study and the increased risk of extra-pulmonary sarcoidosis previously described in ever-smokers (17).

Interestingly, dose of cigarette exposure (pack-years) did not add to the effect ever-smoking on the development of OS in the multivariate model. Whether this lack of dose response is a true association with OS development or an artifact of retrospective data collection remains to be elucidated. Dampening of BVBT in sarcoidosis also correlated dichotomously as an ever-smoker phenomenom without demonstration of dose response (28). Further, bronchoalveolar sampling of soluble Fas, an inhibitor of apoptosis, in sarcoidosis patients revealed low levels in both active and ever-smokers compared to never smokers and a correlative disproportion of granuloma-forming inflammatory cells (41). Interestingly, Krell et al also describe a dichotomous effect of ever-smoking on pulmonary function in sarcoidosis patients (17).

Gender has been postulated to influence the ocular manifestations of sarcoidosis (15-17). In our study, male sex conferred an OR of 7.4 for OS. This is in contrast to the ACCESS study which found OS and neurologic involvement were higher in women with sarcoidosis (15). The ACCESS study was heterogeneous in terms of race. Our study contained a disproportionate number of African Americans, which might explain the difference in findings. However, Krell *et al*, in a study with a similar population, found that females were more likely to have extrapulmonary manifestations of sarcoidosis, although organ involvement was not specified (35). Though the male group did have a higher proportion of cigarette smokers, male gender withstood multivariate analysis and was a strong risk factor for OS.

Age was also found to confer a significant risk for OS concomitant to sex or to smoking. This finding is consistent with the ACCESS study who also found that black males over the age of 40 had a significantly increased odds ratio for eye involvement in sarcoidosis (15). It was initially construed that age at time of chart review was a product of disease duration. Interestingly, disease duration did not withstand multivariate analysis. We have seen considerable interactions between sex, age and smoking with regard to an increasing risk of OS, which should be verified in bigger datasets allowing complex modeling.

While this study adds to previous literature on ocular morbidity associated with sarcoidosis, there remain considerations. Retrospective chart review carries inherent limitations of reliance on accurate documentation by physicians other than the investigators. Further, only documentation from 2006 (post-hurricane Katrina) was accessible for review, with less than 50% of identified charts included due to unavailable biopsy reports, reflecting the fragility

of pre-Katrina paper medical records. Additionally, the proportion of OS-not otherwise specified-cases comprises nearly half of the OS cases with the overall prevalence of OS in our study (19.1%) being lower than previously reported prevalence rates (25-60%) (3, 9). This can, again, be an artifact of retrospective review.

African Americans are disproportionately represented compared to other studies but are reflective of both the local demographics and that of our clinic population. Thus, the results may pertain specifically to populations of African descent. Our prevalence of smoking (47.7%) was also higher than the prevalence of the cigarette smokers in New Orleans (21.6%) (42). This could be due to the lower socioeconomic status of our patients (as patients of lower socioeconomic status have a higher prevalence of smoking) (43) or to another un-identified variable. Income level was not formally determined though the majority of patients attending our clinics are uninsured or are Medicaid recipients. Age at diagnosis of ocular sarcoidosis was also not defined which may be a significant clinical characteristic.

In conclusion, this study is the first dedicated examining risk factors associated with the development of OS and these results support that cigarette smoking, a modifiable habit, is a risk factor for ocular morbidity associated with sarcoidosis. Based on this and prior studies, demonstrating both increased risk and pulmonary functional worsening in ever-smokers, smoking cessation counseling should be a routine component in the management of sarcoidosis. Further examination into the role of compounds present in cigarette smoke in the pathophysiology of sarcoidosis is warranted. Increasing age also conferred a risk of OS, suggesting screening should not remit but rather intensify as patients with sarcoidosis age. Though male gender – in contrast to larger case controlled studies - was found to be a risk factor, this could be a demographic effect of race, suggesting that further studies elucidating racial and genetic differences in OS may provide important insight to pathogenesis of disease mechanisms (15).

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