

Clinical Features and Diagnostic Evaluation of Biopsy-Proven Ocular Sarcoidosis

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Objectives: To compare the clinical characteristics of uveitic sarcoidosis in African American and non-African American patients with biopsy-proven sarcoidosis and to determine which diagnostic test results were most often suggestive of sarcoidosis in patients who were ultimately diagnosed as having the disease.

Method: Retrospective review of consecutive patients with biopsy-proven sarcoidosis evaluated by the uveitis service between 1989 and 2009.

Results: A total of 63 patients with uveitic sarcoidosis were identified: 39 (62%) were African American ($P < .001$) and 43 (68%) were female. African American patients presented at an earlier age ($P < .001$) and were more likely to have granulomatous anterior segment inflammation ($P < .001$). The levels of serum markers angiotensin-converting enzyme and lysozyme were elevated in 40% and 42% of patients tested, respectively.

The levels of at least 1 marker were elevated in 18 patients (58%). Imaging study results were reported as consistent with sarcoidosis in 25 patients (69%) who underwent chest radiography and in 19 patients (100%) who underwent computed tomography.

Conclusions: In this series, African American patients were more likely to be diagnosed as having uveitic sarcoidosis and to present with uveitis if they were younger than 50 years. White patients were more likely to present when they were older than 50 years. A clinical picture that included granulomatous anterior segment inflammation was more common in African American patients. The use of serum markers (angiotensin-converting enzyme and lysozyme) positively identified more patients with biopsy-proven sarcoidosis when used in combination with appropriate chest imaging.

Arch Ophthalmol. 2011;129(4):409-413

SARCOIDOSIS IS AN INFLAMMATORY disease of unknown etiology. The hallmark of the disease is the noncaseating granuloma, and definitive diagnosis requires tissue biopsy.¹ Although the lungs are the most common site of inflammation, sarcoidosis can also involve other organs such as the eyes and orbit, skin, lymph nodes, salivary glands, heart, spleen, liver, and nervous system. In the United States, African Americans have a higher incidence of sarcoidosis than whites; in both groups, the disease is more commonly diagnosed in female patients.² African Americans with sarcoidosis are more likely than whites to have a positive family history.³ Ocular involvement has been described in 25% to 50% of reported cases of sarcoidosis and can be a source of considerable morbidity if not properly diagnosed and treated.⁴⁻⁸

Patients who present with only ocular findings pose a unique challenge, as establishing a definitive diagnosis with in-

traocular biopsy can be associated with significant morbidity.⁹ In such patients, clinical diagnoses have been previously made based on findings of granulomatous inflammation, elevated levels of serologic markers such as angiotensin-converting enzyme (ACE)¹⁰ and lysozyme,¹¹ and chest imaging with characteristic findings of hilar lymphadenopathy and pulmonary nodules.¹⁰ Variable sensitivities and specificities have been described for ACE, lysozyme, and chest radiography for the diagnosis of ocular sarcoidosis.¹²⁻¹⁴

This purpose of this study was to determine the proportion of patients with uveitis secondary to biopsy-proven sarcoidosis with elevated levels of serum markers and chest imaging findings consistent with sarcoidosis as part of their diagnostic evaluation. We also compare the clinical presentation of ocular sarcoidosis in African American patients with that in non-African American patients.

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Table 1. Demographics of Adult Patients With Sarcoidosis Compared With All Adult Patients Evaluated by the Uveitis Service Between 1989 and 2009^a

Variable	Adult Patients With Biopsy-Proven Sarcoidosis (n=63)	All Adult Patients With Uveitis (n=3912 ^b)	P Value
Age, average (range), y	45 (20-84)	47 (18-90)	
Female	43 (68)	2431 (62)	
African American ^b	39 (62)	1038 (27)	<.001
Non-African-American	24 (38)	2874 (73)	<.001
White	19 (30)	2243 (58)	
Asian	3 (4)	198 (5)	
Hispanic	2 (3)	390 (10)	

^aValues other than age are expressed as number (percentage).

^bThe proportion of African American patients with sarcoid uveitis was significantly higher than the proportion of African American patients in the cohort of all adult patients with uveitis evaluated during the same period ($P<.001$). Patient race was recorded in 3869 individuals (99%), and this was the denominator used for calculations involving race in the total uveitis category.

METHODS

Approval was obtained from the institutional review board at the University of Illinois at Chicago to retrospectively review the charts of patients evaluated by the uveitis service between January 1989 and December 2009. The charts of patients older than 18 years with a diagnosis of uveitis and biopsy-proven sarcoidosis were identified. Exclusion criteria included a positive specific treponemal antibody test result or a positive test for tuberculosis (purified protein derivative or QuantiFERON Gold; Cellestis Limited, Carnegie, Victoria, Australia). Data were collected on demographics and medical history. Clinical data, which included assessment of best-corrected visual acuity, pupillary response, ocular motility, external ocular examination results, and findings of examination of the eyelids and conjunctiva, cornea, anterior chamber, iris, lens, vitreous, and retina, were also collected at presentation. The results of diagnostic testing (evaluation of ACE and lysozyme levels, chest radiography, and computed tomography [CT] of the chest) were gathered for each patient. Tests were ordered by many different physicians, including members of the uveitis service, pulmonologists, and internists. For this reason, many patients did not uniformly undergo all of the diagnostic tests. Uveitis was classified according to the Standardization of Uveitis Nomenclature criteria.¹⁵

Serum ACE and lysozyme levels were considered positive if they were elevated above the normal range provided by the testing laboratory. The results of chest imaging (radiography and CT) were considered positive if they revealed signs of hilar lymphadenopathy, pulmonary granulomas, or a ground glass parenchymal appearance. All imaging findings were interpreted by radiologists at the institutions that performed the study, and outside films were not routinely rereviewed at our institution.

Patients were analyzed by race, sex, and clinical diagnosis. Patients with only extraocular manifestations of sarcoidosis, such as orbital inflammatory syndrome, were excluded from the study. Excel (Microsoft, Redmond, Washington) was used to perform statistical analysis, and an unpaired *t* test was used for analysis of the continuous variable age at presentation. All other analyses involved categorical variables and were performed with the Fisher exact test.

A total of 63 adult patients with uveitis related to biopsy-proven sarcoidosis were evaluated between 1989 and 2009. Forty-one patients (65%) were referred with a diagnosis of sarcoidosis. The average age at presentation was 45 years (age range, 20-84 years), and no significant difference in age at presentation was measured between men and women. Thirty-nine patients (62%) were African American, and the remaining 24 patients (38%) were white (n=19 [30%]), Asian (n=3 [4%]), and Hispanic (n=2 [3%]) (**Table 1**). Forty-three patients (68%) were female. During this same period, a total of 3912 new adult patients with uveitis were evaluated, and 62% were female. Patient race was recorded in 3869 patients (99%), and the distribution was 27% African American, 58% white, 5% Asian, and 10% Hispanic. A significant difference was calculated in the proportion of African American patients with uveitic sarcoidosis compared with the proportion of African American patients in the total uveitis patient population during the same period ($P<.001$). Specifically, the proportion of African American patients was higher in the group of patients with ocular sarcoidosis. Most patients had confirmation of sarcoidosis through the findings of lung biopsy (n=34 [54%]), followed by the findings of lymph node (n=10 [16%]) and skin (n=7 [11%]) biopsies. The confirmatory biopsy sites are shown below.

Biopsy Site	No. (%)
Lung	34 (54)
Lymph nodes	10 (16)
Skin	7 (11)
Conjunctiva	4 (6)
Vitreous	2 (3)
Gastric mucosa	1 (2)
Nasal mucosa	1 (2)
Testicle	1 (2)
Liver	1 (2)
Bone marrow	1 (2)
Ankle	1 (2)

A family history of sarcoidosis was reported in 5 patients: 4 African American and 1 white.

African American patients presented with eye disease at an earlier age than non-African American patients (40 years vs 54 years [$P<.001$]). Three African American patients (8%) presented after they were older than 50 years compared with 17 non-African American patients (67%) ($P<.001$). Ocular involvement was bilateral in 56 patients (89%), and no significant difference between the percentage of patients with bilateral disease was measured between African American and non-African American patients ($P=.41$). When classified by Standardization of Uveitis Nomenclature criteria, no difference was noted between the 2 cohorts of patients. However, African American patients were more likely to present with granulomatous anterior involvement (including patients with purely anterior uveitis, anterior and intermediate uveitis, and pan-uveitis) than non-African American patients ($P<.001$) (**Table 2**).

Serum markers were measured in 31 patients. The levels of ACE were elevated in only 12 patients (40%) and those of lysozyme in 9 patients (42%). The levels of at least 1 marker were elevated in 18 patients (58%), al-

though only 20 patients underwent testing for both ACE and lysozyme. Of the 10 patients who had only ACE measured, 6 (60%) had results that were within the normal range; 1 of these patients was taking oral prednisone at the time of testing. One patient was taking an ACE inhibitor at initial presentation and had only lysozyme measured. The level was elevated.

Chest imaging was performed in 41 patients, with 14 patients undergoing both chest radiography and CT. The findings of radiography were considered consistent with sarcoidosis in 69% (25 of 36) of tested patients and those of CT in 100% of 19 patients (**Table 3**). Five of the patients with negative findings on chest radiography subsequently underwent chest CT, the findings of which were read as suggestive for sarcoidosis; 4 of these patients were white women who were older than 50 years. Of the patients who underwent both measurement of serum ACE levels and chest radiography, 75% had at least 1 result that was suggestive of sarcoidosis. With the inclusion of chest CT (ie, evaluation of ACE levels plus any chest imaging), the percentage of patients who were positively identified increased to 89% (25 of 28 patients). The evaluation of lysozyme levels combined with the findings of chest radiography identified 11 patients (69%) with biopsy-proven sarcoidosis, and the evaluation of lysozyme levels plus the findings of any imaging (chest radiography and/or chest CT) identified 17 patients (85%). Of the patients who had 1 or both serum tests performed in combination with chest radiography, 20 of 24 patients (83%) had at least 1 test result consistent with a diagnosis of sarcoidosis. The results of any serum test (ACE and/or lysozyme) plus the findings of any imaging (chest radiography and/or chest CT) identified 27 patients (93%) with biopsy-proven sarcoidosis (**Table 4**).

COMMENT

In this series of sarcoid uveitis, we describe the clinical presentation and the results of diagnostic testing performed on patients with a final diagnosis of biopsy-proven sarcoidosis. African Americans represented the majority of the patient population, which is consistent with studies of patients in the United States that focused on all manifestations of sarcoidosis² as well as specifically on ocular sarcoidosis,¹⁶ although these studies included patients with clinically diagnosed as well as biopsy-proven disease. Our findings are in contrast to those of 1 large series involving patients with biopsy-proven sarcoidosis and any ocular or orbital involvement, in which no racial predilection was measured.¹⁷ However, when patients in that series with uveitis were analyzed separately (n=27), 59% were African American and 41% were white.

In our series, African American patients presented with ocular sarcoidosis at a younger age than non-African American patients. Similar findings have been reported in a study of systemic sarcoidosis² and in a series on sarcoidosis associated with keratoconjunctivitis sicca, uveitis, and adnexal granulomas.¹⁶ In our series, two-thirds of whites with sarcoid-related uveitis presented when they were older than 50 years. This finding has significant clinical

Table 2. Comparison of African American and Non-African American Patients Evaluated for Sarcoid Uveitis^a

Variable	African-American Patients (n=39)	Non-African American Patients (n=24)	P Value
Age, average (range), y	40 (22-63)	54 (20-84)	<.001
Age older than 50 y at presentation	3 (8)	17 (71)	<.001
Classification of uveitis			
Anterior	12 (31)	7 (29)	>.99
Anterior and intermediate	3 (8)	1 (4)	>.99
Intermediate	1 (3)	2 (9)	.55
Posterior	2 (5)	4 (17)	.19
Pan-	21 (54)	10 (42)	.440
Any anterior granulomatous inflammation	28 (72)	6 (25)	<.001

^aValues other than age are expressed as number (percentage).

implications. More than 10% of uveitis cases present for the first time in patients older than 60 years,¹⁸ and sarcoidosis should be on the list of differential diagnoses, particularly in white patients. Careful clinical examination and diagnostic evaluation combined with an appropriate index of suspicion for sarcoidosis may spare patients invasive testing and surgery to rule out masquerade syndromes.¹⁹

In this study, the results of individual serum tests (ACE and lysozyme) identified fewer than half of the patients with biopsy-proven sarcoidosis. Variable sensitivities and specificities have been described in the literature for ocular disease. Testing for ACE reportedly has a sensitivity of 58% to 84% and a specificity of 83% to 95%; testing for lysozyme has a sensitivity of 60% to 78% and a specificity of 76% to 95%,¹²⁻¹⁴ although none of these studies included more than 22 patients with biopsy-proven sarcoidosis. In our study, of the 31 patients who underwent testing for ACE and/or lysozyme, only 18 had elevated levels of at least 1 of the markers. This percentage may have been higher if all 31 patients had undergone testing for both ACE and lysozyme. Since ACE and lysozyme levels were normal in many patients with biopsy-proven sarcoid uveitis, a negative result should not exclude a clinical diagnosis of sarcoidosis. This consideration is particularly true in patients who are taking ACE inhibitors or in those who are receiving systemic immunosuppression.²⁰

The findings of imaging studies alone positively identified more patients than the results of testing for ACE and lysozyme, individually or in combination. The findings of chest radiography were considered positive in 69% (25 of 36) of patients, and those of CT were positive in 100% of 19 patients. Four of the 5 patients who had negative results on chest radiographs followed by positive results on chest CTs were white women who were older than 50 years. Although the findings of CT studies identified patients with sarcoidosis more often than those of radiography, other factors should be considered when selecting the appropriate imaging study for diagnostic evaluation. The amount of radiation produced by a chest CT

Table 3. Patients With Biopsy-Proven Sarcoidosis Who Tested Positive for Serum Markers and Chest Imaging Findings

Variable	No. Tested	No. Suggestive of Sarcoidosis	% Identified
Serum markers			
ACE	30	12	40
Lysozyme	21	9	42
ACE and lysozyme	20	3	15
ACE or lysozyme	31	18	58
Chest imaging			
Radiography	36	25	69
CT	19	19	100

Abbreviations: ACE, angiotensin-converting enzyme; CT, computed tomography.

Table 4. Patients With Sarcoidosis Who Tested Positive for Combinations of Serum Markers and Chest Imaging Findings

Variable	No. Tested	No. With at Least 1 Result Suggestive of Sarcoidosis	% Identified
ACE or CR	24	18	75
ACE or any imaging (CR or CT)	28	25	89
Lysozyme or CR	16	11	69
Lysozyme or any imaging (CR or CT)	20	17	85
Any serum test or CR, 1+ serum test and CR	24	20	83
Any serum test or imaging, 1+ serum level, and 1+ imaging	29	27	93

Abbreviations: ACE, angiotensin-converting enzyme; CR, chest radiography; CT, computed tomography; 1+, 1 or more of the tests (ACE and/or lysozyme; CR and/or CT) were suggestive of sarcoidosis.

is substantial, and the overall risk of radiation-related cancer is higher in younger patients.^{21,22} Appropriate use of chest CT should be considered in the workup of uveitis, particularly in older white patients with negative findings on chest radiography and a high suspicion for sarcoidosis.^{23,24} We recognize that many clinicians now skip the step of chest radiography. However, because of the concerns regarding radiation exposure and increased cancer risk, we do not perform chest CT as our first screen for sarcoidosis.^{21,22} We reserve it for patients with negative findings on chest radiography but in whom there is a high clinical suspicion for sarcoidosis.

In this series, the results of imaging studies combined with those of serum marker analysis identified 69% to 93% of patients with sarcoidosis, depending on the combination of tests performed. The findings of chest radiography combined with ACE and lysozyme levels identified 83% of patients with sarcoidosis. When the 5 patients with negative findings on chest radiography and positive findings on chest CT were included, the identification rate increased to 93%. This study lacked a control group of patients with nonsarcoid uveitis; therefore, we cannot comment on the false-positive rate of these diagnostic tests.

International criteria were recently published to aid in the diagnosis of ocular sarcoidosis.²⁵ An international prospective study of patients with uveitis is currently un-

der way to determine which diagnostic tests and clinical features will best be able to clinically diagnose sarcoidosis in the absence of biopsy confirmation.

The data from this series suggest that ocular sarcoidosis is diagnosed more commonly and at an earlier age in African American patients than non-African American patients. Anterior segment involvement is more often granulomatous in African American patients. In patients with ocular disease that is suggestive of sarcoidosis, obtaining serum ACE or lysozyme levels will miss many patients with sarcoidosis. The combination of testing for ACE and lysozyme levels and chest imaging may identify the vast majority of patients with ocular inflammation secondary to sarcoidosis, as evidenced by the identification of 93% of biopsy-proven cases in this series.

Submitted for Publication: May 12, 2010; final revision received July 15, 2010; accepted July 16, 2010.

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Financial Disclosure: None reported.

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Correction

Error in Author's Name: In the Letter to the Editor titled "Association of Proliferative Diabetic Retinopathy With Insulin Use and Microalbuminuria" by Chun et al, published in the January 2010 issue of the *Archives* (2010; 128[1]:146), the corresponding author's name is incorrect in both the signature block and the Correspondence address. Shu-Hsun Chun should be Shu-Hsun Chu, and Dr Chun should read Dr Chu. This article was corrected online.