Sarcoidosis-related Uveitis: Clinical Presentation, Disease Course, and Rates of Systemic Disease Progression After Uveitis Diagnosis

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• OBJECTIVE: To document the clinical presentation, treatment, and visual outcome of sarcoid uveitis and to determine the timing and potential risk factors of sarcoidosis progression to symptomatic systemic disease from the time of sarcoid uveitis diagnosis.

• DESIGN: Retrospective, interventional case series.

• METHODS: Subjects: Patients with dual diagnoses of uveitis and presumed/biopsy-proven sarcoidosis. Procedure: Retrospective review of 143 patient records from the Royal Victorian Eye and Ear Hospital and Eye Surgery Associates in Melbourne, Australia, between October 1990 and April 2014 coded with the dual diagnoses of uveitis and sarcoidosis. Only patients with uveitis and presumed or biopsy-proven sarcoidosis (N = 113) were included. Main Outcome Measures: Ascertainment of rate and time (months) to the development of symptomatic systemic sarcoidosis from uveitis onset; comparison of the patient demographics, characteristics of uveitis, treatment, and visual outcome between those who developed systemic sarcoidosis and those who remained systemically asymptomatic.

• RESULTS: Uveitis was the initial presenting complaint of sarcoidosis in 78.8% (n = 89). Twenty-three patients had concurrent undiagnosed systemic disease at presentation and 29 subsequently developed symptomatic sarcoidosis in an organ uninvolved at uveitis onset. The median time to the development of symptomatic systemic sarcoidosis was 12 months. No statistically significant association was ascertained between any particular uveitis characteristic and extraocular sarcoidosis progression.

• CONCLUSION: Uveitis was the initial presentation of sarcoidosis in the vast majority of our subjects. Concurrent undiagnosed systemic sarcoidosis was common at the time of uveitis onset. A high index of suspicion for subsequent systemic progression should also be maintained, especially within the first 5 years of the uveitis diagnosis. (Am J Ophthalmol 2019;198:30–36. © 2018 Elsevier Inc. All rights reserved.)

SARCOIDOSIS IS A MULTISYSTEM INFLAMMATORY DISease characterized by noncaseating granulomata and a variable clinical profile.[1] About 30%-60% of patients with sarcoidosis develop ophthalmic disease.[2] All ocular structures may be involved, but uveitis is the most frequently encountered manifestation, affecting up to 20%-30% of patients with sarcoidosis,[3] with the highest incidences seen in African-American and Asian populations. In Japan, sarcoidosis has become the leading cause of uveitis, accounting for approximately 15% of cases.[4,5]

Uveitis may be the initial presenting complaint of sarcoidosis in 11%-30% of cases.[6,7] In the absence of clinically apparent systemic sarcoidosis, sarcoid uveitis remains a difficult condition to definitively diagnose. The diagnostic criteria for sarcoid uveitis have recently been revised by the International Workshop on Ocular Sarcoidosis (IWOS) (Supplemental Table; Supplemental Material available at AJO.com).[1] The gold standard for diagnosis is histopathologic confirmation from tissue biopsy. In the large proportion of cases where biopsy confirmation has not been obtained, a presumptive diagnosis of sarcoid uveitis can be made based on the presence of bilateral hilar lymphadenopathy on imaging studies in conjunction with a compatible granulomatous uveitis. Elevated angiotensin-converting enzyme (ACE) levels, bronchoalveolar lavage, and negative tuberculosis testing are useful adjunctive investigation findings.[8] There is also emerging evidence that lymphopenia may serve as an additional indicator of sarcoid uveitis.[9]

Sarcoid uveitis tends to cause either an acute self-limiting anterior uveitis or an insidious chronic intraocular inflammation with frequent relapses and ocular complications.[2] There is limited literature regarding the likelihood and time frame of systemic disease progression once ocular sarcoidosis has been diagnosed. Equally lacking is recommendation regarding the

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Sep 12, 2018.

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.09.013

duration of follow-up for ocular sarcoidosis. Existing studies primarily concern patients affected by pulmonary sarcoidosis and currently recommend that patients be monitored for at least 3 years after termination of corticosteroid therapy, with no further follow-up necessary unless new or worsening symptoms occur.[9]

This study examines the clinical course and disease characteristics of sarcoid uveitis and aims to determine the timing of sarcoidosis progression to symptomatic systemic disease from the time of diagnosis of sarcoid uveitis.

METHODS

A RETROSPECTIVE REVIEW OF PATIENT RECORDS WAS CONducted from 143 patients who presented to the Royal Victorian Eye and Ear Hospital and Eye Surgery Associates in Melbourne, Australia between October 1990 and April 2014 who had been coded with the dual diagnoses of uveitis and sarcoidosis. The study adhered to the tenets of the Declaration of Helsinki and was conducted with the approval of the Royal Victorian Eye and Ear Hospital Human Research and Ethics Committee (reference number 15/1215HS).

A total of 113 patients, 44 with a final diagnosis of biopsy-proven sarcoidosis and 69 with presumed sarcoidosis, were included in the study. The diagnosis of sarcoid uveitis was in accordance with the IWOS criteria for confirmed (biopsy diagnosis with compatible uveitis) and presumed (biopsy not performed; presence of bilateral hilar lymphadenopathy with compatible uveitis) sarcoidosis (Supplemental Table).[1] Other causes of granulomatous uveitis such as tuberculosis and syphilis were excluded based on history, clinical examination, and laboratory evaluation. Those with uveitis and isolated elevated ACE level were also excluded from the study.

Demographic data including patient sex and age at uveitis and systemic sarcoidosis onset were collected. Characteristics of uveitis—in particular, type, onset, duration, and course—were grouped according to the Standardization of Uveitis Nomenclature (SUN) criteria.[10] Clinical signs of ocular sarcoidosis were recorded, as were the best-corrected visual acuity (BCVA) at predetermined time points (0, 1, 3, and 5 years), treatment approach, ocular complications (cataract formation and subsequent surgery, raised intraocular pressure, cystoid macular edema [CME], corneal band keratopathy, retinal neovascularization, papillitis, and surgeries owing to complications other than cataract), and duration of follow-up.

"Systemic sarcoidosis" was defined as symptomatic solid organ disease with measurable functional impairment (for example, abnormal respiratory function test and high-resolution chest computed tomography findings for pulmonary involvement). "Sarcoidosis progression" was defined as the development of symptomatic systemic disease, absent at the time of uveitis onset, requiring further investigation and treatment. Time to the development of symptomatic systemic sarcoidosis was calculated as the time from the date of sarcoid uveitis diagnosis to the date of new organ involvement.

Continuous variables recorded at uveitis onset were summarized as means with 95% confidence intervals (95% CI) or as medians with upper and lower bound of interquartile range (IQR). If they did not appear to be normally distributed, the variables were then compared across progression groups using the 2-sample *t* test and the 2-sample Wilcoxon rank sum (Mann-Whitney) test. Categorical variables were summarized as percentages and compared across treatment groups using Fisher exact test. Kaplan-Meier survival curves were plotted to visualize the median time from uveitis onset until the first recorded occurrence of symptomatic systemic progression in any organ. Visual acuities in the uveitis-affected eye(s) were compared between those patients who did and did not develop symptomatic systemic sarcoidosis. All analyses were undertaken using Stata IC 14.2 for Windows (StataCorp LP, College Station, Texas, USA).

RESULTS

SARCOID UVEITIS SHOWED A FEMALE SEX PREDILECTION (76 female vs 37 male patients, $P < .01$), in whom the disease tended to manifest at a later age (53.6 ± 14.2 years vs 43.5 ± 15.6 years) and follow a more chronic course (67.1% vs 54.8%, $P = .03$).

Ninety-six patients (85.0%) experienced bilateral uveitis. Panuveitis was the most commonly encountered subtype (40.7%, n = 46). This was followed by anterior (31.9%, n = 36), intermediate (18.6%, n = 21), and posterior uveitis (8.8%, n = 10).

Sixty-five percent of patients (n = 73) followed a chronic disease course, lasting > 3 months, with relapses within 3 months of treatment cessation. An isolated, acute episode of uveitis occurred in 16.8% (n = 19) and the remaining 18.6% (n = 21) experienced recurrent episodes of uveitis separated by periods without treatment lasting ≥ 3 months.

All patients received topical corticosteroid for the treatment of intraocular inflammation. Just over half (54.9%, n = 62) received a combination of topical and regional treatment (orbital floor triamcinolone acetonide 40 mg/mL, 0.8-1 mL injected). Systemic immunosuppression with prednisolone was required in 45.1% (n = 51), and 16.8% (n = 19) required additional second-line systemic immunosuppressive therapy (methotrexate, azathioprine, mycophenolate). Mean duration of systemic immunosuppression to achieve adequate control of intraocular inflammation was 26.4 months (95% CI 17.2-40.8 months, range 4-86 months). In all of these patients, the decision to commence systemic immunosuppression was based on ocular indications alone.

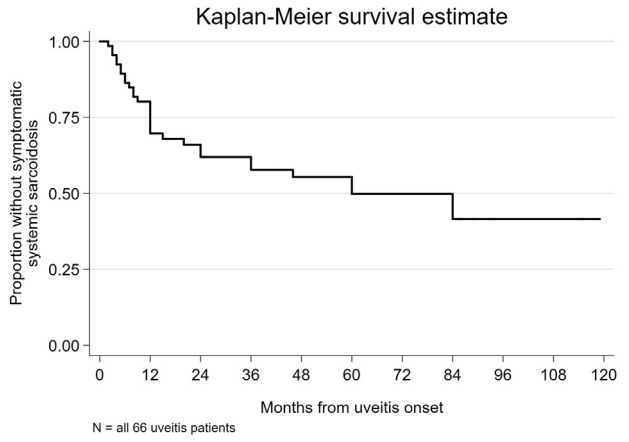

FIGURE 1. Kaplan-Meier survival analysis for the development of systemic sarcoidosis in patients who presented with ocular involvement and did not have concurrent symptomatic sarcoidosis at the time of uveitis onset (n = 66). For those who developed systemic sarcoidosis (n = 29), the median time to first extraocular organ involvement was 12 months.

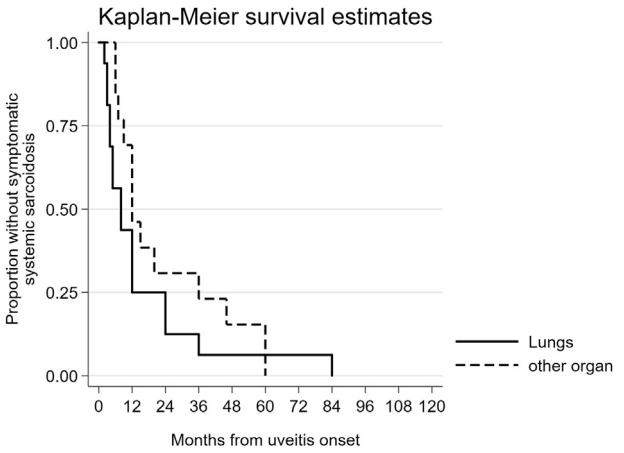

FIGURE 2. The development of symptomatic pulmonary sarcoidosis seemed to show a trend for early involvement compared to other organs. However, the difference did not achieve statistical significance ($P = .247$).

Ocular complications secondary to uveitis and/or steroid treatment occurred in 53.9% of patients (n = 61). Cataract formation, cystoid macular edema, and ocular hypertension were the most commonly observed complications. Varying degrees of cataract formation were noted in 79% (90 of 113) of the cohort. Surgery was carried out to treat visually significant cataract in 54 of the 209 eyes affected by sarcoid uveitis (25.8%). Cystoid macular edema and ocular hypertension requiring medical treatment were observed in 64.6% (n = 73) and 58.3% (n = 66) of the cohort, respectively. Overall, 87 surgical procedures were performed in 71 eyes, including cataract extraction (n = 54), insertion of intraocular steroid implants (n = 9), glaucoma surgery ± subsequent revision (n = 8), retinal detachment repair (n = 7), and epiretinal membrane peel (n = 9).

Uveitis was the initial presenting complaint of sarcoidosis in 89 patients. Within this group, 63 were diagnosed with presumed sarcoidosis based on the presence of bilateral hilar lymphadenopathy and compatible uveitis. Probable sarcoidosis was diagnosed in 26 patients. These patients had granulomatous uveitis but negative imaging at the initial presentation.

Within the "presumed" group, 23 patients had symptoms of undiagnosed systemic sarcoidosis at uveitis onset (for example, exertional dyspnea, dry cough, erythema nodosum, constitutional symptoms), while 40 were systemically asymptomatic. Of these 40 initially asymptomatic patients, 15 then progressed to new symptomatic extraocular sarcoidosis at a later stage and the remaining 25 stayed systemically stable.

All 26 patients in the "probable" group subsequently had their sarcoidosis status revised to "presumed" or "confirmed" (as this was an inclusion criterion for this study). In 12 patients, the revised diagnosis was based on subsequent positive imaging alone; in the other 14 patients, it was the development of positive imaging and systemic symptoms.

Overall, the record review identified 66 patients who presented with sarcoidosis-related uveitis and no symptomatic systemic sarcoidosis at the time of uveitis onset. Median duration of follow-up for this cohort was 62.5 months (IQR 36-83 months; minimum 7 months, maximum 264 months).

Over time, 29 patients (43.9%) developed new symptomatic systemic sarcoidosis. Median time from uveitis onset to first extraocular organ involvement was 12 months (IQR 6-24 months; minimum 2 months, maximum 84months). In 86.2% (n = 25), the development of extraocular sarcoidosis occurred within the first 36 months of uveitis diagnosis; 89.7% progressed within 4 years and 96.6% progressed by 5 years (Figure 1). At the time of systemic sarcoidosis diagnosis, 11 patients (38.0%) had quiescent ocular disease and the remaining 18 patients (62.0%) were receiving treatment for active uveitis.

Pulmonary (37.9%), multiorgan (27.6%), and cutaneous (17.2%) disease were the most frequently observed sites of extraocular sarcoidosis progression. Pulmonary sarcoidosis showed a trend to manifest slightly earlier compared to other organ systems; however, the difference was not statistically significant ($P = .247$; Figure 2).

The characteristics of those who developed extraocular sarcoidosis and those who remained systemically asymptomatic at 3 years are compared in the Table. Patient demographics and uveitis characteristics (type, laterality, temporal course, treatment approach, rate of ocular complication) were similar between the 2 groups. No particular uveitis characteristic nor the use of systemic steroid use achieved statistical significance in predicting the likelihood of subsequent sarcoidosis progression (Table).

Among those who had systemic sarcoidosis at presentation (n = 23) or subsequently developed symptomatic

TABLE. Characteristics of Patients Who Did and Did Not Develop Systemic Symptoms of Sarcoidosis Within the First 3 Years Following Uveitis Onset

	No Systemic Progression Over 3 Years (N = 41 Patients)	Developed Systemic Symptoms of Sarcoidosis Over 3 Years (N = 25 Patients)	*P*
Follow-up time (mo), median (IQR)	62 (19, 80)	71 (48, 91)	.088
Age at uveitis presentation (y), mean (95% CI)	49.6 (44.6, 54.6)	51.6 (45.1, 58.1)	.618[a]
Sex, % male	31.7%	24.0%	.583[b]
Uveitis type, n (%)			
Anterior	9 (22.0)	8 (32.0)	.427
Intermediate	7 (17.1)	7 (28.0)	
Posterior	4 (9.7)	1 (4.0)	
Panuveitis	21 (51.2)	9 (36.0)	
Bilateral, n (%)	33 (80.5%)	20 (80.0%)	1.00[b]
Chronicity, n (%)			
Acute	10 (24.4)	5 (20.0)	.872[b]
Recurrent	5 (12.2)	4 (16.0)	
Chronic	26 (63.4)	16 (64.0)	
Systemic corticosteroid treatment for uveitis, n (%)	18 (43.9)	11 (44.0)	1.00[b]
Second-line systemic treatment for uveitis, n (%)	10 (24.4)	4 (16.0)	.541[b]
Ocular complications, n (%)	28 (68.3)	14 (56.0)	.429[b]

CI = 95% confidence interval; IQR = interquartile range.
All *P* values relate to Wilcoxon rank sum test unless indicated.
[a]*t* test.
[b]Fisher exact test.

systemic disease (n = 29), a multidisciplinary approach was used for the surveillance and treatment of their systemic sarcoidosis. Systemic immunosuppression was required to treat extraocular manifestations of sarcoidosis in 42.3% (n = 22) at some stage during their ophthalmic follow-up period, where the decision to commence and dose adjust systemic immunosuppression was made based on organ-specific inflammatory activity by nonophthalmic specialties. Fifteen of these patients had quiescent eye disease at the time that systemic corticosteroid treatment needed to be added or increased for the treatment of extraocular sarcoidosis related disease. Seven of the 22 patients had concurrent active uveitis, which perceivably benefited from systemic immunosuppression.

The overall visual prognosis was good. A total of 209 eyes were affected by sarcoid uveitis in our cohort. At uveitis onset, 59.8% (n = 125) of affected eyes presented with BCVA worse than 20/20 and 40.2% (n = 84) were 20/20 or better. Over the course of the follow-up period, 67% (n = 140) and 71.3% (n = 149) of uveitic eyes recorded BCVA equal to or better than 20/20 at some point of time up to and including the third and fifth years, respectively. Furthermore, 93.3% (n = 195) of affected eyes were better than 20/50 at some point up to and including the fifth year. BCVA over time between those who developed systemic sarcoidosis and those who did not are plotted in Figure 3. No significant deterioration in visual function was detected in either group over the course of the follow-up period. No patient suffered from bilateral severe visual impairment or blindness.

Thirty-three patients within the whole cohort received a biopsy confirmation of sarcoidosis; the median time to biopsy was 12 months (range 1-150 months). In 14 patients, a systemic sarcoidosis diagnosis preceded the onset of uveitis and the remaining 19 patients presented initially with sarcoid uveitis. There were no significant differences in biopsy sites between the 2 groups. Endobronchial ultrasound-guided biopsy of hilar/mediastinal lymph nodes or lung and cutaneous biopsy each contributed to 33% of histopathologic confirmations. An elevated ACE level was observed in 64% of patients during the investigative process.

Twenty-four patients had a preexisting diagnosis of systemic sarcoidosis at the time of uveitis onset. The average time to ocular involvement was 60.3 months (95% CI 47.6-73.0 months, median 26 months, range 5-132 months).

DISCUSSION

THIS STUDY DESCRIBES THE CHARACTERISTICS, TREATment, and clinical outcome of patients with uveitis secondary to sarcoidosis, as defined by recent international criteria. It also documents the time course to symptomatic systemic

progression of sarcoidosis once uveitis has occurred. We observed that the prevalence of extraocular sarcoidosis progression was markedly higher than previously reported. Just over a third of our patients (n = 29, 32.6%) developed symptomatic systemic sarcoidosis in an organ uninvolved at uveitis onset within an average time frame of 16.6 months (range 2-84 months).

This finding is clinically relevant, as the question that faces ophthalmologists when a patient is diagnosed with presumed sarcoid uveitis is when, if ever, they will develop other systemic manifestations of the disease. The clinical course of sarcoidosis is variable and there is limited data regarding the temporal profile of systemic sarcoidosis progression and the optimal length of follow-up. In 1988, Foster was the first to report a case series of 8 patients in whom uveitis preceded the systemic manifestations of sarcoidosis by as much as 4 years.[11] In a retrospective study, Rizzato and associates reported that 1.5% of 1156 biopsy-proven sarcoidosis patients presented initially with uveitis and experienced systemic disease progression by 1-11 years.[12] A prospective study of 75 patients by Edelsten and associates reported disease spread to other organs in 17% after 10 years of follow-up.[13] In Rochepeau and associates' retrospective study of 83 biopsy-proven sarcoidosis patients, 7.7% developed extraocular disease after a median follow-up duration of 60 months.[14] The inclusion of presumed cases of sarcoidosis in this study has likely contributed to our higher figures.

Notably, a quarter of our patients were diagnosed with both ocular and systemic sarcoidosis at presentation, suggesting that concurrent undiagnosed systemic sarcoidosis is common at the time of uveitis onset. Based on these findings, patients should be screened for symptoms of systemic sarcoidosis as part of the initial uveitis evaluation. Should there be any clinical suspicion of extraocular sarcoidosis, timely referral for multidisciplinary input and targeted investigations are warranted.

Our data also suggest that more than 95% of patients who progressed to systemic sarcoidosis did so within the first 5 years of uveitis onset. Thirty-eight percent of those who developed systemic sarcoidosis had quiescent uveitis at the time of systemic progression. We therefore recommend that sarcoid uveitis patients be monitored for at least 5 years, even those who achieve quiescence of their ocular disease. During this period, one should be alert to the possibility of systemic progression and carry out relevant systems review. Patient education and self-surveillance is also key to timely diagnosis. It is justifiable to retain a high index of suspicion for new symptoms rather than subjecting all those at risk to invasive biopsies or radiation risk associated with repeat imaging.

Our data showed that pulmonary disease was the most commonly observed extraocular manifestation of sarcoidosis. There was also a trend for early pulmonary involvement in patients who developed symptomatic systemic sarcoidosis. Interestingly, Edelsten and associates found that not only was symptomatic pulmonary sarcoidosis the most prevalent extraocular finding at uveitis onset, it had a propensity to manifest earlier than other organ systems (within 2 years of uveitis onset).[13]

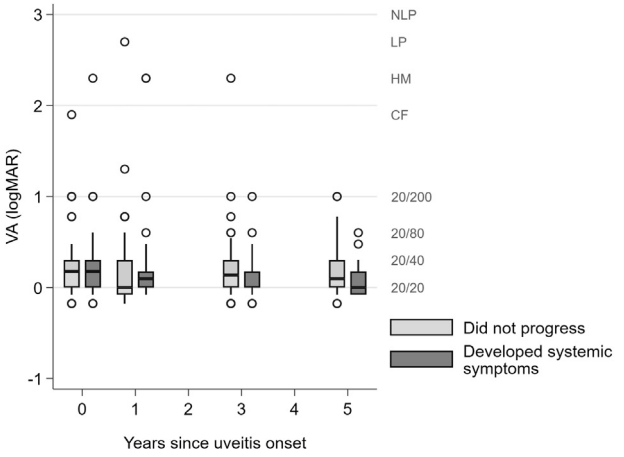

FIGURE 3. Best-corrected visual acuity (VA) over time in those patients who did and did not develop symptomatic systemic sarcoidosis. Graph includes all eyes with uveitis from 66 patients. Boxes represent the median (interquartile range) at select time points; whiskers indicate the 10th and 90th percentiles. CF = count fingers; HM = hand motions; LP = light perception; NLP = no light perception.

Several groups, particularly in the fields of dermatology and respiratory medicine, have attempted to establish links between organ-specific sarcoidosis activity and systemic disease progression. The data are currently inconclusive in this regard.[15–20] In this study, there was no significant correlation between baseline variables such as patient demographics, uveitis type, and ocular course and the extent of extraocular sarcoidosis progression.

In recent studies, sarcoid uveitis is associated with a favorable visual prognosis, with most patients experiencing mild or no visual impairment.[21,22] Rochepeau and associates showed in their retrospective study of 83 patients with biopsy-proven sarcoid uveitis that 89.2% retained BCVA of better than 20/50 with a median follow-up duration of 60 months.[14] Poorer visual prognosis was associated with advanced age, female sex, chronic systemic disease, posterior segment involvement, and the presence of cystoid macular edema and/or glaucoma.[2,13,23] Our data showed good overall visual prognosis, where the majority of eyes affected by sarcoid uveitis retained normal or near-normal vision at all time points.

In our study, the frequency with which systemic corticosteroids were used to treat uveitis compares closely with other reports. Edelsten and associates reported that 51% of 75 patients required oral corticosteroids during a median follow-up period of 4 years.[13] Karma and associates noted that 66% required systemic corticosteroids with a follow-up of 9 years (n = 22),[24] Ohara and associates noted 51%

at 4 years (n = 60),[25] and Dana and associates reported a rate of 60% with a similar mean length of follow-up.[26]

Cataract formation, cystoid macular edema, and ocular hypertension are frequently reported ocular complications in patients with sarcoid uveitis. Our data are in agreement with the literature in this regard. Just over a quarter of the eyes affected by sarcoid uveitis in our cohort developed visually significant cataract requiring surgical intervention. In a cohort of 75 patients with sarcoid uveitis, Edelsten and associates reported that 21% developed cataract requiring surgery.[13] Bodaghi and associates reported incidence rate of 14.3% for cataract formation in a retrospective cohort of 1310 eyes with chronic uveitis from sarcoid and nonsarcoid causes.[27]

The reported incidence rate of cystoid macular edema in the setting of sarcoid uveitis is high in comparison to other causes of uveitis. Miserocchi and associates reported a 56% CME rate in a retrospective review of 44 patients with bilateral uveitis and biopsy-confirmed sarcoidosis.[28] Similarly, Dana and associates reported a CME rate of 58% in 60 patients.[26] Ohno and associates and Rothova noted that 76% of patients with sarcoid uveitis involving the posterior segment eventually developed CME.[29,30] Furthermore, in a retrospective study of 83 biopsy-proven sarcoid uveitis cases, Febvay and associates noted a female predilection for chronic CME (48.3% female vs 14.3% male).[31] Potential risk factors for the development of CME appear to be chronic, active uveitis involving the posterior segment and female sex.

Raised intraocular pressure may result as a direct consequence of active anterior chamber inflammation or in response to corticosteroid treatment; its incidence has been estimated to be 13%-40%.[13,29,32] A Japanese study revealed a high incidence of abnormal gonioscopic findings (61% trabecular nodules and 55% tent-like peripheral anterior synechiae) among 159 patients with systemic sarcoidosis.[33]

Strengths of this study include the characterization of sarcoid phenotype according to international criteria; the long mean duration of follow-up; and the careful delineation of systemic sarcoidosis progression. The study was limited by the retrospective nature of its methodology, particularly the variable duration of follow-up, small sample size, and limitations on the data available for analysis. As patients were recruited into this study from 2 specialized ophthalmic centers, there was a clear selection bias for patients presenting with ocular disease or those with ocular involvement. Similarly, there was a selection bias toward patients with chronic disease requiring more intensive treatment and a corresponding scarcity of those with acute, uncomplicated uveitis. To properly ascertain the rate and time frame of ocular disease progression from the time of systemic sarcoidosis diagnosis, a prospective, longitudinal follow-up study should be conducted at a general hospital, in patients with confirmed systemic disease and no known ocular involvement.

Sarcoid uveitis remains a serious disease and a difficult condition to definitively diagnose. A significant proportion of patients are affected by the chronic form of the disease with a high risk of developing ocular complications. Concurrent undiagnosed systemic sarcoidosis is common at the time of uveitis onset. A systems review for symptomatic extraocular manifestations of sarcoidosis is warranted at the initial ophthalmic evaluation. As the type and severity of uveitis has no bearing on the risk of extraocular sarcoidosis progression, a high index of suspicion for subsequent systemic progression should also be maintained after sarcoid uveitis diagnosis, especially within the first 5 years of uveitis onset.

FUNDING/SUPPORT: CENTRE FOR EYE RESEARCH AUSTRALIA RECEIVES OPERATIONAL INFRASTRUCTURE SUPPORT FROM THE Victorian government. A/Prof Lim (GNT 1109330) is supported by a National Health and Medical Research Council (NHMRC) Early Career Fellowship (Australia). Financial Disclosures: The following authors have no financial disclosures: Shirley Ma, Sophie L. Rogers, Anthony J. Hall, Lauren Hodgson, Jessica Brennan, Richard Stawell, and Lyndell L. Lim. All authors attest that they meet the current ICMJE criteria for authorship.

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