·Letter to the Editor·

Clinical manifestations and outcomes of ocular sarcoidosis in Saudi Arabia

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Dear Sir,

We write to report on the clinical manifestations and outcomes of ocular sarcoidosis in patients presenting to uveitis referral centers in the Kingdom of Saudi Arabia. This is the first report focused solely on ocular sarcoidosis from this country.

Sarcoidosis is a chronic multisystem inflammatory disorder of unknown etiology. The disease is characterized by non-caseating granulomas that affect many organs of the body including the eye, lungs, lymph nodes, skin, heart, liver, and muscles [1]. The frequency of ocular involvement in patients with sarcoidosis varies among published clinical reports. This could be a reflection of true differences in the prevalence of eye disease among different populations or it may be due to the lack of thorough screening of patients with sarcoidosis for ocular disease [2]. The incidence of ocular manifestations among patients with sarcoidosis ranges between 1.5% to 12.4% at first presentation and 11% to 83% during the disease course[1].

We studied retrospectively the clinical features and outcomes of ocular sarcoidosis in patients who were evaluated between 2003 and 2013 from two major uveitis referral centers - The Eye Center and The Eye Foundation for Research in Ophthalmology and the King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia. Each patient in the study completed a comprehensive uveitis questionnaire and underwent complete ophthalmic examination, medical evaluation for systemic illness, and laboratory investigations whenever indicated. Laboratory tests including complete blood count, sedimentation rate, chest radiography and tuberculin skin testing were done on all patients. Serologic tests including angiotensin converting enzyme (ACE) level, lysozyme level and liver enzyme tests were performed on six patients. Other causes of granulomatous uveitis were excluded. The diagnosis of ocular sarcoidosis was established clinically by applying the international diagnostic criteria for ocular sarcoidosis from the first International Workshop on Ocular Sarcoidosis (IWOS)[3] and was confirmed by histopathology of biopsy specimens in four cases. The IWOS diagnostic criteria were applied retrospectively. The criteria consist of seven clinical ocular signs and five laboratory investigations. Suggestive intraocular signs included mutton-fat/ granulomatous keratic precipitates and/or iris nodules (Koeppe/Busacca), trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae, snowballs/string of pearls vitreous opacities, multiple chorioretinal peripheral lesions (active and/or atrophic), nodular and/or segmental periphlebitis (candlewax drippings) and/or retinal macroaneurysms in an inflamed eye, optic disk nodule (s)/ granuloma (s) and/or solitary choroidal nodule and bilaterality. Investigational tests included: negative tuberculin test in Bacillus Calmette-Guérin (BCG)-vaccinated patient or in a patient with a previously positive tuberculin skin test, elevated angiotensin-converting enzyme and/or elevated serum lysozyme, positive chest X-ray showing bilateral hilar adenopathy (BHL) and abnormal liver enzyme tests. Based on the combination of ocular signs and results of laboratory tests, four levels of certainty of sarcoidosis were established: 1) definite (biopsy proven); 2) presumed; 3) probable; 4) possible ocular sarcoidosis.

Ten patients (19 eyes) with ocular sarcoidosis were identified. There were 5 male and 5 female patients with a mean age of 39.1±5.6y (range 10-60y). Visual acuity ranged from 20/30 to no light perception with median vision of 20/125 at the last follow-up. Based on the international

Table 4 Clinical characteristics of patients with ocular sarcoidosis

Patient	Age/gender	Systemic findings	Ocular findings	Biopsy specimen
1	43/F	BHL, elevated ACE	Panuveitis	Transbrachial biopsy
2	10/M	BHL	Panuveitis	Skin biopsy
3	43/F	None	Panuveitis	None
4	33/M	BHL, elevated ACE	Panuveitis	None
5	43/M	None	Panuveitis	None
6	41/F	BHL	Panuveitis	Salivary gland+liver
7	41/F	Elevated ACE	Anterior uveitis	None
8	37/F	BHL	Optic neuritis	None
9	40/M	Elevated ACE	Optic neuritis	Optic nerve biopsy
10	60/M	BHL, elevated ACE	Lacrimal gland inflammation	None

BHL: Bilateral hilar lymphadenopathy; ACE: Angiotensin converting enzyme.

diagnostic criteria, four patients (40%) had definite ocular sarcoidosis, three patients (30%) had presumed ocular sarcoidosis and three (30%) had probable ocular sarcoidosis. Out of the four patients with definite ocular sarcoidosis, one patient had accessory salivary gland and percutaneous liver biopsy showing non-caseating granulomas consistent with sarcoidosis, one had transbronchial biopsy of left lower lobe and bronchus revealing well defined non-caseating granulomas, one had a positive skin biopsy and one had a positive optic nerve biopsy that was performed during orbitotomy surgery (patient had no light perception vision before the procedure) (Table 1). Other ocular signs of sarcoidosis included mutton fat keratic precipitates, anterior chamber cells and flare, posterior synechiae, Koeppe nodules of the iris, vitritis and snow balls, retinal exudates (Figures 1, 2), choroiditis and optic nerve granulomas. Two patients had peripapillary choroidal neovascular (CNV) membrane associated with uveitis. One patient had keratoconjuncticitis sicca as the initial presentation of systemic sarcoidosis. Five of six patients (83%) who had their ACE levels checked had elevated serum ACE levels and six patients (60%) had bilateral hilar lymphadenopathy on chest X-ray. Only one patient had respiratory symptoms related to his systemic disease.

All patients were started on topical or periocular steroids to treat their anterior chamber reaction in addition to systemic corticosteroids alone or in combination with mycophenolate mofetil (patients 1 and 6). None of our patients required therapeutic or diagnostic vitrectomy surgery. Seventeen out of the nineteen eyes (89%) had improvement in ocular inflammation over the course of 6mo and 11 eyes (58%) had improved visual acuity after treatment. The CNV membrane regressed in both patients (2 out of 2 eyes) on systemic steroid therapy without the need for intravitreal injections.

The prevalence of ocular sarcoidosis varies among regions. In one study looking at the patterns of uveitis in the Middle

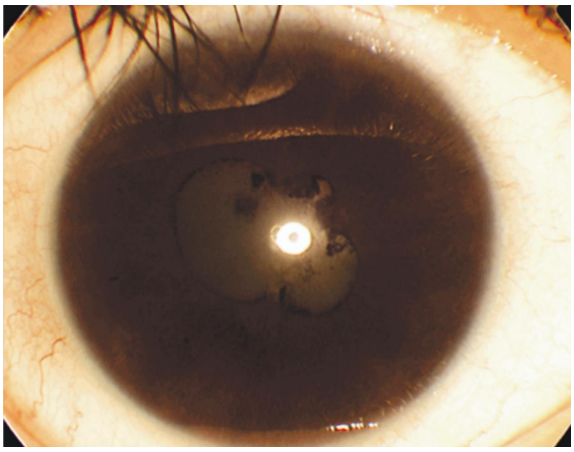

Figure 1 Anterior chamber inflammation with posterior synechiae in a patient with systemic sarcoidosis (patient 1 OD).

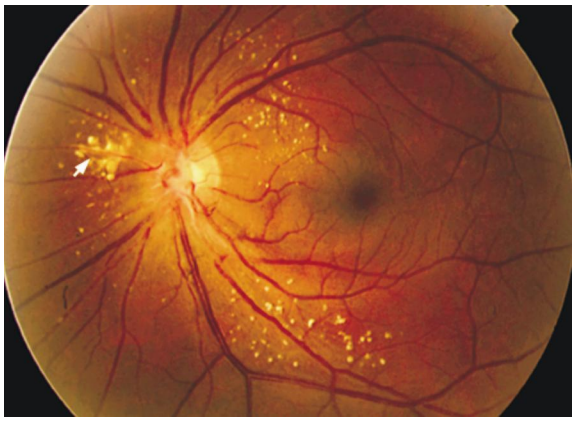

Figure 2 Color fundus image demonstrates "candle wax drippings" sign (white arrow) in a patient with systemic sarcoidosis (patient 4 OS).

East and Europe, sarcoidosis was found to be responsible for 3.4% of panuveitis and 4% of intermediate uveitis cases in the Middle East compared to 8.7% of panuveitis and 3.4% of intermediate uveitis cases in Europe [4]. Our investigation has identified several cases of ocular sarcoidosis which is a very rare cause of uveitis in Saudi Arabia. The most common reported ocular manifestations of sarcoidosis are uveitis (30%-70%) and conjunctival nodules (40%)[5]. In our case

series, 7 out of 10 patients (70%) presented with uveitis (6 with panuveitis and 1 with anterior uveitis), whereas the rest presented with either optic neuritis (n=2) or lacrimal gland inflammation (n=1).

In the absence of systemic pulmonary or skin manifestation of sarcoidosis, the diagnosis of ocular sarcoidosis based on clinical eye examination may be challenging. The definitive diagnosis of ocular sarcoidosis is established by histopathology of biopsy specimens. ACE levels may be increased in serum, cerebrospinal fluid or fluid from bronchoalveolar lavage; however, sensitivity and specificity of serum ACE levels has a limited diagnostic value [6]. In our study, five of six patients (83%) who had their ACE levels checked had elevated serum ACE levels. Six of our patients (60%) had bilateral hilar lymphadenopathy on chest X-ray.

The occurrence of CNV membrane in association with uveitis associated with sarcoidosis is very rare [7]. Two of our patients (20%) developed CNV membrane in the course of their disease. Both responded well to systemic steroids without the need for intravitreal injections. Our patients responded well to topical and systemic steroid treatment; however, two patients required the addition of cytotoxic agents to control their disease without developing signs of systemic toxicity. In conclusion, ocular sarcoidosis in Saudi Arabia is a very rare cause of uveitis. Reported cases in our series presented with characteristic clinical symptoms and signs and responded well to currently established therapy.

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