Orbital and Adnexal Sarcoidosis

Venkatesh C. Prabhakaran, MS, MRCOphth; Perooz Saeed, MD; Bita Esmaeli, MD; Timothy J. Sullivan, FRANZCO; Alan McNab, MD, FRANZCO; Garry Davis, FRANZCO; Alejandra Valenzuela, MD; Igal Leibovitch, MD; Anat Kesler, MD; Jennifer Sivak-Callcott, MD; Erika Hoyama, MD; Dinesh Selva, FRANZCO

Objective: To present the clinical features and management in a series of patients with orbital and adnexal sarcoidosis.

Methods: This multicenter retrospective study included patients with biopsy-proven noncaseating granuloma involving the orbit or adnexa and evidence of systemic sarcoidosis. Clinical records were reviewed for initial examination findings, radiological findings, treatment modalities, and outcome.

Results: The study included 26 patients (19 female, 7 male; mean age, 52 years). The most common feature at the first examination was a palpable periorcular mass followed by discomfort, proptosis, ptosis, dry eye, diplopia, and decreased vision. The disease affected the lacrimal gland (42.3%), orbit (38.5%), eyelid (11.5%), and lacrimal sac (7.7%). Among orbital lesions, the anteroinferior quadrant was preferentially involved. Treatment modalities included steroids, surgical debulking, and methotrexate. During a mean follow-up of 18.75 months, 84.6% of patients showed a complete response to the treatment, but 19.2% of patients developed further signs of sarcoidosis.

Conclusions: Orbital soft tissue involvement is more common in patients older than 50 years and in women. The anterior inferior quadrants of the orbits appear to be preferentially affected. Although a good response to treatment with oral steroids is seen, long-term follow-up is recommended because active systemic disease can develop months to years later.

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Sarcoidosis is a multisystem disease of unknown cause that is characterized histologically by the presence of granulomas in the affected organs. The diagnosis of sarcoidosis is based on a positive biopsy (demonstrating noncaseating granulomas), a constellation of typical clinical features (such as restrictive lung disease, erythema nodosum/lupus pernio, and uveitis), and positive chest radiography (hilar lymphadenopathy and/or parenchymal infiltrates) in the absence of any condition that can cause similar clinico-radiological and pathological changes.

Ocular involvement varies with race and sex and is seen in approximately 25% of patients with sarcoidosis. Uveitis is the most common ocular manifestation, but sarcoidosis may involve any part of the eye, orbit, or lacrimal system. Orbital and adnexal manifestations of sarcoid (to distinguish from asymptomatic involvement) are uncommon with few series in the literature, and there is a tendency in the ophthalmic literature to confuse isolated orbital granulomatous disease with sarcoidosis. We report on a large series of patients with orbital and adnexal sarcoidosis, all of whom had evidence of systemic involvement. We also review the literature on this subject to better define the clinical features and management of orbital-adnexal sarcoidosis.

METHODS

This is a multicenter retrospective study of all patients with orbital and adnexal sarcoidosis who were seen in 7 orbital units: Royal Adelaide Hospital, Adelaide, Australia, January 2000 to June 2007 (5 cases); Royal Brisbane Hospital, Brisbane, Australia, January 1996 to October 2006 (5 cases); Royal Victoria Eye and Ear Hospital, Melbourne, Australia, January 1990 to June 2007 (3 cases); Academic Medical Center at the University of Amsterdam, Amsterdam, the Netherlands, January 1998 to October 2006 (8 cases); M. D. Anderson Cancer Center, Houston, Texas, September 2004 to October 2006 (3 cases); West Virginia University, Morgantown, January 2006 to June 2007 (1 case); and Tel Aviv Medical Center, Tel Aviv, Israel, January 2006 to October 2006 (1 case).

The inclusion criteria for the study were biopsy-proven noncaseating epithelioid granuloma in the lacrimal gland, orbit, eyelids, or lacrimal sac together with 1 or more of the
Table 1. Signs and Symptoms at Initial Examination of Patients With Orbital and Adnexal Sarcoidosis

<table>
<thead>
<tr>
<th>Signs and Symptoms at Initial Examination</th>
<th>Cases, No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Mass/swelling</td>
<td>23 (88.5)</td>
</tr>
<tr>
<td>Proptosis/globe displacement</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>Discomfort</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>Ptosis</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Restricted ocular motility</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Decreased vision</td>
<td>3 (11.5)</td>
</tr>
</tbody>
</table>

Our study included 26 patients (19 female, 7 male) with a mean age of 52 years (median, 50 years; range, 28-83 years). Nineteen cases were unilateral and 7 bilateral. There were 16 white patients, 7 African American patients, 2 Indian patients, and 1 Japanese patient. The mean duration from initial clinical signs and symptoms to diagnosis was 8.2 months (median, 4 months; range, 1 month to 5 years).

Seven patients had previously diagnosed sarcoidosis (4 pulmonary, 2 pulmonary and cutaneous, and 1 cutaneous). Additional medical history included diabetes mellitus (3 patients), hypertension (5), large cell lymphoma of the inguinal area (1), psoriatic arthritis (1), and breast cancer (1). None of the patients had a prior history of tuberculosis or occupational lung diseases. The ophthalmic history included dry eye (5 patients), significant pain (1 patient). The signs and symptoms of all patients at their first examinations are summarized in Table 1.

The most common complaint was that of a slowly progressing mass (88.5%). Although discomfort was present in 30.8% of patients, significant pain was not a feature. Although dry eye symptoms were elicited in 5 patients (19.2%) (4 with lacrimal gland involvement and 1 with orbital involvement), only 1 had objective evidence of dry eye on Schirmer test. Decreased vision was an initial sign in 3 patients and was secondary to anterior uveitis in 2 cases and cataract in the other.

Computed tomographic data were available for 22 patients and MRI data for 9 patients. Those with lacrimal gland involvement showed well-defined homogenous enlargement of the gland, but the cases with orbital involvement tended to manifest as a more diffuse process. The lacrimal gland was involved in 11 cases (42.3%) (7 unilateral and 4 bilateral and 1 case with associated lateral rectus involvement) (Figure 1). Orbital involvement was present in 10 patients (38.5%) and could be categorized as discrete (Figure 2) or diffuse (affecting more than 2 quadrants) (Figure 3). Three patients had diffuse orbital disease, and, interestingly, all 3 suffered from active systemic sarcoidosis. In all patients with discrete lesions, the anterior orbit was involved, and of the 7 cases, 6 involved the inferior orbital quadrants and 1 the superior orbit. Extension into the eyelid from the anterior orbital process was noted in 5 of the 7 cases. Extraocular muscles were involved in 6 cases (in conjunction with orbital soft tissue in 5 cases and lacrimal gland in 1 case). One patient with discrete orbital involvement also demonstrated irregular thickening of the left optic nerve sheath on computed tomography (Figure 2).

Three patients (13.5%) (all female) had solitary eyelid involvement. In 2, the lower lid was affected and this...
was the initial manifestation of the disease. The third patient, who had a history of sarcoidosis, developed sarcoidal granulomas over the medial canthi, both sides being affected at different times. The lacrimal sac and nasolacrimal duct was involved in 2 patients (7.7%) (both female).

A biopsy of the orbital or adnexal lesion was performed in all cases and in each case showed granulomatous inflammation with epithelioid histiocytes, giant cells, and lymphocytes (Figure 4). None demonstrated caseating necrosis, and special stains for fungal and tuberculous infection showed negative results. Polarization was performed to rule out the presence of foreign material.

Chest x-ray was performed in all 26 cases and findings suggestive of sarcoidosis (hilar lymphadenopathy with or without parenchymal involvement) were present in 17 (65.4%). Positive chest x-rays were seen in 6 of the 11 cases with lacrimal gland involvement and 11...
of the 15 cases with extralacrimal gland involvement (Table 2). In 1 patient with a negative chest x-ray, a PET scan demonstrated hilar uptake.

Serum ACE estimation was performed in 24 cases and was found to be elevated (in comparison with the referral laboratory range) in 15 (62.5%). The serum ACE was elevated in 8 of the 11 cases with lacrimal gland involvement and 6 of the 13 extralacrimal cases in which it was estimated (Table 2). In 1 patient with bilateral lacrimal gland enlargement and seventh nerve palsy, serum ACE was normal but the cerebrospinal fluid ACE was elevated.

Additional systemic investigations performed included gallium scintigraphy (5 patients, all with lacrimal gland involvement; positive in 4), serum lysozyme (8 patients; elevated levels in 2), serum calcium (13 patients; elevated levels in 1), liver function tests (19 patients; abnormal results in 3), pulmonary function tests (16 patients; abnormal results in 7), tuberculosis test (9 patients; anergy in 1 case), mediastinal lymph node biopsy (2 patients, both positive), liver biopsy (2 patients; positive in 1), and a nasal mucosa biopsy that showed granulomatous inflammation in 1 patient with lacrimal sac involvement.

Three patients (11.5%) had pulmonary symptoms and signs at the initial examination (previously undiagnosed sarcoid), and 1 of them also had sinus, parotid, and epididymal involvement at the initial examination. Four patients had active anterior uveitis at diagnosis or in the follow-up period, and residual signs of old uveitis were present in 2 patients. Cutaneous involvement (lupus pernio) was present in 3 patients. Other extrapulmonary manifestations of sarcoidosis (uveitis, optic disc swelling, seventh nerve palsy, epididymal mass, miliary liver lesions) occurred in 5 patients (19.2%) during the follow-up period (within 1 year of initial ophthalmic symptoms in all except in 1 patient who developed miliary liver and lung lesions 5 years following orbital involvement). The patient who developed a right-sided facial palsy (4 weeks into the follow-up period) also had bilateral granulomatous anterior uveitis, vitritis, and left optic disc edema (suggestive of Heerfordt syndrome). None of the patients with neurological symptoms had evidence of central nervous system involvement on neuroimaging.

Management modalities included steroids (oral prednisolone: 19 patients, 73.1%; intraorbital steroid injection: 1 patient, 3.8%), surgical debulking (10 patients, 38.5%), and methotrexate (4 patients, 15.4%). Five patients (2 each with orbital and eyelid disease and 1 with lacrimal sac involvement) had only surgical debulking. One patient with lacrimal gland involvement did not elect to have any further treatment. The steroid dose ranged from 25 mg to 80 mg and was tapered on an individual basis. The duration of treatment ranged from 2 to 36 months (mean, 6.9 months; median, 3 months). Intraorbital steroid injections (3 injections of triamcinolone acetonide, total 100 mg, over 2 months) were used in 1 patient who was not tolerant to oral steroids. Four patients required additional treatment with methotrexate (in 2 patients as a steroid-sparing agent, in 1 patient for active systemic disease, and in 1 patient in whom steroids were ineffective in controlling ophthalmic disease).

The mean follow-up period was 18.75 months (median, 9 months; range, 3-60 months). In 22 patients (84.6%), the response to treatment was graded as good with significant decrease in the size of the lesion and symptom resolution. Two patients who were treated with oral steroids had a partial decrease in the size of the lesion but were symptomatically better. Progression was noted in 2 patients: 1 patient with orbital disease who developed new orbital lesions while on prednisolone and methotrexate and 1 patient with eyelid involvement,

### Table 2. Summary of Demographic and Clinical Data According to Anatomical Location of Orbital-Adnexal Sarcoidosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lacrimal Gland (n = 11)</th>
<th>Extralacrimal Orbit (n = 10)</th>
<th>Eyelid (n = 3)</th>
<th>Lacrimal Sac (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>46.1 (28-66)</td>
<td>59.3 (38-83)</td>
<td>54.3 (33-79)</td>
<td>44.5 (40-49)</td>
</tr>
<tr>
<td>F/M ratio</td>
<td>6.5</td>
<td>8.2</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>6W, 2AA, 2I, 1J</td>
<td>6W, 4AA</td>
<td>3W</td>
<td>1W, 1AA</td>
</tr>
<tr>
<td>Prior history of sarcoidosis, No.</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Positive chest x-ray, No. (%)</td>
<td>6 (54.5)</td>
<td>9 (90)a</td>
<td>0</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Elevated serum ACE, No. (%)</td>
<td>9 (81.8)b</td>
<td>3 (30)</td>
<td>3 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment</td>
<td>Observation</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Surgical debulking</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Oral steroid</td>
<td>10</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Intrallesional steroid injection</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Response</td>
<td>Complete</td>
<td>10</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Progression</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AA, African American/African; ACE, angiotensin converting enzyme; CSF, cerebrospinal fluid; I, Asian Indian; J, Japanese; PET, positron emission tomography; W, white.

a Including 1 patient in whom hilar uptake was demonstrated by PET.
b Including 1 patient in whom CSF ACE was elevated.
treated only with surgical debulking, who developed bilateral lacrimal gland enlargement and swollen optic discs 3 months into the follow-up period. During the follow-up period, no patient developed recurrence.

**COMMENT**

We present a series of biopsy-proven orbital and adnexal sarcoidosis, including treatment details and outcomes. Our study highlights the clinical features of extralacrimal orbital sarcoidosis, an uncommon condition that may be the initial feature of systemic sarcoidosis. We found that orbital involvement is more commonly seen in the fifth to seventh decades and is more frequent in women. It appears to occur in 2 forms, diffuse and discrete: diffuse involvement that may occur more commonly in patients with active systemic sarcoidosis and discrete lesions that appear to have a predilection for the anterior inferior quadrants of the orbit.

Ophthalmic involvement in systemic sarcoidosis is common (25%-60% of patients) with anterior uveitis being the most common manifestation. However, involvement of the orbit and adnexal structures is much less common with conflicting data on incidence due to the differing diagnostic criteria for sarcoidosis employed in the various studies. Most cases reported as solitary orbital sarcoid may represent idiopathic granulomatous orbital inflammation. This entity was reviewed by Mombaerts and coworkers, who found that it affected men more commonly, that it was usually seen in the fourth decade, and that 50% of cases affected the lacrimal glands. We agree with Mombaerts and colleagues that the term *orbital sarcoid* should not be used in the absence of any evidence of systemic disease because this may hamper a more rigorous investigation into the causes of a solitary orbital granulomatous lesion. Also, the distinction between solitary orbital sarcoid and granulomatous pseudotumor (idiopathic inflammation) is probably academic because both are diagnoses of exclusion and are moreover etymological cousins (sarcoid deriving from *sarcoma*-like; in other words, a pseudotumor). It should be emphasized that all the patients in our series had evidence of systemic involvement with sarcoidosis.

Within the orbit, sarcoidosis can involve the lacrimal gland, soft tissues of the orbit, and the optic nerve. The lacrimal gland is said to be commonly affected in sarcoidosis, and 2 large studies found incidence rates of 15.8% and 7%. It should be noted, however, that biopsy confirmation was obtained only in a minority of cases in both studies and that the diagnosis of lacrimal gland involvement was based on clinically evident enlargement of the gland or on the presence of dry eye symptoms. It is interesting to note that in our series, with biopsy confirmation of lacrimal gland involvement, only 5 patients had dry eye symptoms and only 1 patient had objective evidence of aqueous deficiency. In our series, there were almost equal numbers of patients with lacrimal and extralacrimal orbital disease: this may reflect a referral bias in that most patients with systemic sarcoidosis and lacrimal gland enlargement may not be referred to an orbital center.

Orbital soft tissue involvement is a distinctly uncommon manifestation of sarcoidosis. The first case was reported by King in 1939, and since then scattered case reports and 1 case series have appeared in the literature. In 3 large series on ophthalmic manifestations of sarcoidosis, orbital involvement was seen in 2 of 202 patients (1%) in 1 series and in none of the patients in the other 2 series. As previously discussed, analysis of the literature on orbital sarcoidosis is complicated by the tendency of some authors to report solitary orbital granulomas with no evidence of systemic disease under the rubric of sarcoidosis. Analysis of only reported cases with systemic involvement demonstrates that orbital sarcoidosis predominantly occurs in older persons (mean age, 55.9 years, range, 27-85 years) and is more common in women (ratio, 4:3). A racial predilection was not evident from the cases reviewed. A prior history of sarcoidosis is rare, but the chest X-ray usually reveals hilar lymphadenopathy. In cases with a normal chest X-ray but a high suspicion of sarcoidosis, high-resolution computed tomography of the chest may be more sensitive. In cases where information regarding the location was available, the inferior orbit was involved in 60%. Further systemic involvement was diagnosed in 2 patients 1 year following the diagnosis of orbital disease (lung parenchymal involvement in 1 patient and positive liver biopsy in another). In cases where details of treatment were reported, the orbital lesion was uniformly responsive to oral steroids. These data are similar to the findings in our study. It may be noted here that extracocular muscle involvement may be seen in association with orbital lesions (especially in cases of diffuse involvement), as was the case in our patients, but solitary muscle enlargement secondary to sarcoidosis is a rare event with only a few cases reported, and these have been reviewed in a report by Cornblath and colleagues.

Involvement of the skin of the eyelids with cutaneous sarcoidosis may be seen (in the form of millet-seed nodules or rarely destructive skin lesions), but sarcoidal granulomas within the eyelid appear to be an uncommon finding. In our series, all 3 patients with eyelid involvement were female, the lower lid was involved in 2 cases, and in both this feature was the initial feature of systemic disease. All 3 cases were treated successfully with surgical excision. Eyelid sarcoidosis appears to be much more common in women, may have a predilection for the lower lid, and may often be the first feature of sarcoidosis.

Sarcoidosis of the lacrimal sac and nasolacrimal duct is also an uncommon event. Harris and coworkers reviewed the literature on sarcoidosis of the lacrimal sac and found that it usually occurs in association with nasal mucosa involvement. Patients with sarcoidosis of the nasolacrimal system are also at increased risk of failure following dacryocystorhinostomy. Both our patients with lacrimal sac sarcoidosis had recurrence of epiphora following dacryocystorhinostomy.

Management of orbital and adnexal sarcoidosis depends on the extent and site of disease, degree of functional impairment, and presence or absence of active systemic disease. Although up to two-thirds of cases of systemic sarcoidosis show spontaneous remission, there are insufficient data on the natural history of orbital and adnexal disease to recommend observation as a plan of
management. Oral steroids have been the mainstay of treatment in these patients, and most reported cases (including those in this study) show a good response. In cases without active systemic disease, a short course of oral prednisolone (starting at 1 mg per kilogram of body weight and tapering over 3 months) may be considered as initial therapy. In those who fail to respond or are steroid-intolerant, cytotoxic agents such as methotrexate may be used. In localized orbital disease, periocular steroids (1-mL injection of triamcinolone acetonide 40 mg/mL) may be considered, and this was effective in 1 of our patients who was unable to tolerate steroids. Surgical debulking or excision appears to be an effective treatment and may be considered for localized orbital disease and especially for eyelid disease.

A long-term follow-up of these patients by a pulmonary specialist is recommended because they can develop systemic disease months to years later and also because steroid-responsive cases of systemic sarcoidosis are at increased risk for relapses. Patients should also be counseled regarding the multisystem nature of sarcoidosis and the possibility of developing active systemic disease in the future. One of the limitations of our study is the short period of follow-up in most cases; thus we are unable to comment on the long-term risk of recurrence or of developing active systemic disease in this subset of patients with extrapulmonary sarcoidosis.

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Correspondence: Venkatesh Prabhakaran, MS, MRCOphth, Oculoplastic and Orbital Division, Department of Ophthalmology and Visual Sciences, Royal Adelaide Hospital, North Terrace, Adelaide 5000, South Australia, Australia (eye@health.sa.gov.au).

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