



Sarcoidosis and uveitis

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Sarcoidosis is an extraordinarily variable disease of unknown etiology that causes noncaseating granulomatous inflammation in one or more organs. This article presents recent evidence on pathogenesis, reviews the main ocular and systemic manifestations, and discusses current approaches to diagnosis and management.

Pathogenesis and immunology

The microscopic structure of the noncaseating granuloma of sarcoidosis is well-understood, but the aberrant behavior of the cell constituents is gradually becoming apparent. An excellent review has been written by Agostini et al [1]. An unknown trigger provokes the accumulation of monocyte-macrophages, which transform to epithelioid cells and sometimes multinucleate giant cells. This core becomes surrounded by lymphocytes, predominantly CD4+ T cells, but with some CD8+, and some B cells, to form the characteristic granuloma, which in contrast to the tuberculous granuloma does not caseate.

The initial accumulation of lymphocytes is provoked by interleukin-12, secreted by monocyte-macrophage cells, and their migration from the circulation toward the site of inflammation is facilitated by interleukin-16 and other lymphotactic cytokines. The CD4+ T cells are induced by interleukin-12 into a T_H1 secretor profile (including interferon- γ and interleukin-2), which is predominantly inflammatory and which enhances the granuloma structure while suppressing the secretion of extracellular protein. At

this stage the granuloma is capable of regression without scarring.

In those sarcoid granulomas that become chronic, and typically in progressive pulmonary sarcoidosis, there is a change to a T_H2 secretor profile, including interleukin-4, which stimulates the deposition of an extracellular protein matrix. Fibroblasts are attracted and become hyperplastic, and there is an expansion in mesenchymal cell numbers. The result is progressive scarring and fibrosis, which in the lung becomes radiologically visible as interstitial pulmonary fibrosis and which compromises lung function.

The initiator of this characteristic sequence of events remains unknown, but the availability of DNA polymerization techniques has provided tantalizing glimpses of a possible microbial trigger. Nucleic acid fragments have been identified from *Mycobacterium tuberculosis*; atypical mycobacterium, such as *M avium* and *M paratuberculosis* [2]; Propionibacterium, including *P acnes* and *P granulosum* [3]; and human herpesvirus 8 [4]. Nevertheless, convincing evidence of a microbial cause remains elusive, and bacterial DNA was not found in the Kveim-Siltzbach reagent [5]. At present sarcoidosis is thought to be an aberrant immune response to perhaps more than one antigen in the predisposed.

Ocular manifestations

Demography and prevalence

The reported prevalence of sarcoidosis varies markedly between countries, from 1.2:100,000 populations in Spain to 64:100,000 in Sweden, with the United States having 39:100,000 [2]. There is a clear racial predilection in blacks, with a prevalence of 200:100,000 in the United Kingdom and reportedly

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a 10-fold higher risk compared with whites in the United States. The disease may present at any age but typically in young to middle-aged adults; there is no convincing evidence of a gender bias. The age at disease onset for the 85 patients with presumed or confirmed sarcoidosis in the Manchester Uveitis Clinic is shown in Fig. 1. There may be an element of genetic predisposition to the disease, as suggested by the reports of familial cases, which in some cohorts approach one fifth of all cases [6].

Sarcoidosis causes about 7% of uveitis in specialist clinics (6.7% in this clinic). Symptomatic uveitis affects 20% to 30% of those with sarcoidosis at some time, 80% of these being within 1 year of onset of the disease and 30% having uveitis as the presenting complaint [7]. One quarter of patients with sarcoidosis for longer than 5 years have uveitis [8]. Asymptomatic uveitis and retinal vasculitis have been shown to be more frequent, suggesting that at least one ophthalmologic examination should be performed for all patients with sarcoidosis.

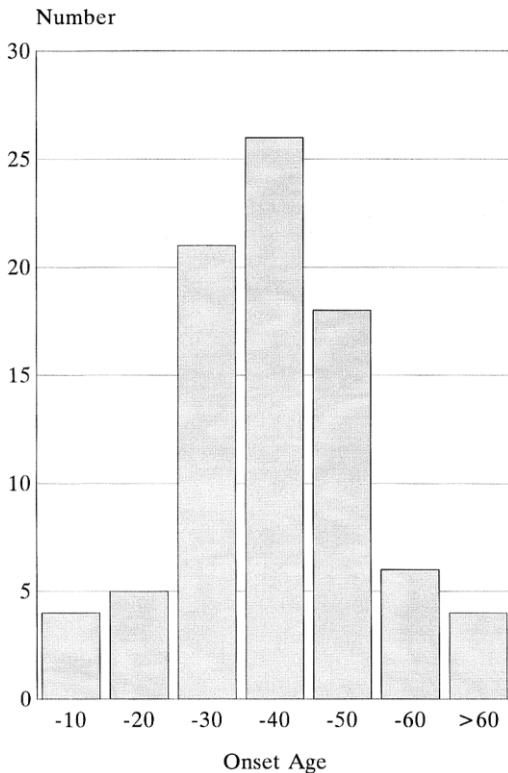


Fig. 1. The age at onset of disease for the 85 patients with sarcoidosis attending the Manchester Uveitis Clinic.

Anterior and intermediate uveitis

The classic picture of mutton-fat keratic precipitates, substantial anterior chamber cells and flare, posterior synechiae, and often a raised intraocular pressure is commonly assumed to be a granulomatous uveitis (Fig. 2). In uveitis clinics, sarcoidosis is the most frequent cause of such a presentation, as in this clinic, where it causes one quarter of such cases. Nevertheless many other forms of uveitis can present similarly, including bacterial causes, such as tuberculosis, syphilis, leprosy, and Lyme disease; other infections, such as toxoplasmosis and acute retinal necrosis; multiple sclerosis; sympathetic uveitis; Vogt-Koyanagi-Harada syndrome; and phakoanaphylactic uveitis.

This picture may be the paradigm for sarcoid uveitis but statistically a nongranulomatous uveitis is a more likely presentation (being twice as common in this clinic). Indeed, it is more likely for the patient with acute systemic sarcoidosis of the Löfgren's syndrome type (with any combination of cough, dyspnea, night sweats, weight loss, fatigue, polyarthropathy, erythema nodosum, sore red eyes) to present with a bilateral nonfibrinous, nongranulomatous anterior uveitis. In these cases the inflammation is often self-limiting, as is the systemic disease. An association has also been claimed between sarcoidosis and Fuchs' heterochromic uveitis in some patients [9].

The author's experience is that the nongranulomatous forms of sarcoid anterior uveitis are rapidly responsive to topical steroid and often self-limiting after a few months, as may be the disease itself. In contrast, the often late presentation of granulomatous uveitis may mean that some weeks of treatment are necessary before full control is achieved. A raised intraocular pressure is common at presentation, which usually subsides as the anterior chamber angle is relieved of its choking exudate but which may persist because of peripheral anterior synechiae.

A predominantly intermediate pattern of uveitis is seen in only a minority of patients with sarcoidosis (10% in this clinic). Conversely, sarcoidosis is responsible for about 7% of cases of intermediate uveitis, being the second most important systemic association after demyelination.

Posterior uveitis and retinal vasculitis

Sarcoidosis can cause multifocal choroiditis and characteristically these lesions are smallish (less than one half disk diameter), creamy or white, with little substance, not commonly affecting the macula but predominantly postequatorial, and more commonly in

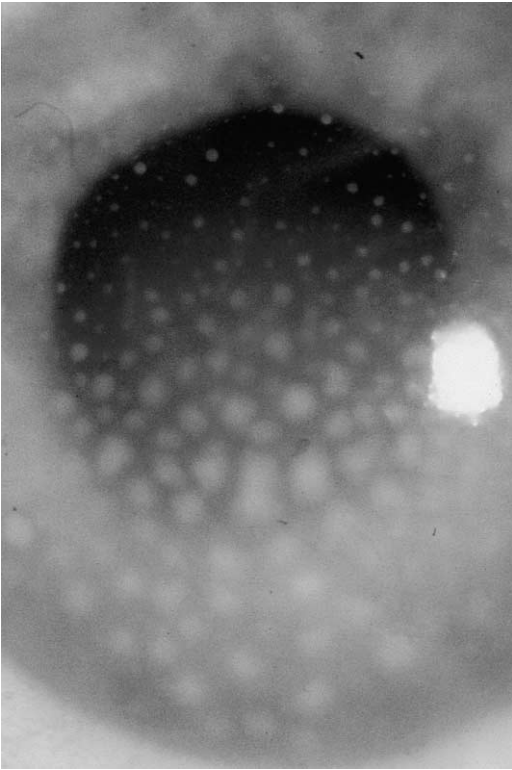


Fig. 2. Granulomatous uveitis with mutton-fat keratic precipitates in a patient with sarcoidosis.

the inferior half of the fundus. Much less commonly a single subretinal mass is seen [10,11], in which case the differential diagnosis must include metastatic tumor. Coalescent choroidal infiltration has also been reported, both peripheral [12] and peripapillary [13]. Sarcoidosis has also been described in association with acute posterior multifocal placoid pigment epitheliopathy [14] and mimicking birdshot retinochoroidopathy [15].

Retinal vasculitis is a common manifestation of sarcoid uveitis and sarcoidosis is among the commonest causes of retinal vasculitis. In typical form it has features that distinguish it clearly from other causes of retinal vasculitis: it is phlebitis, not an arteriolitis [16,17]; it is usually nonocclusive and hardly ever abruptly occlusive [18]; it is patchy rather than confluent; and it may exhibit a dramatic perivenous creamy white exudation. The eye may show both choroiditis and vasculitis simultaneously (Fig. 3). A significant minority of those with retinal vasculitis do eventually go on to shut down peripherally, however, and may show neovascularization and hemorrhage [19].

Recently, a different form of sarcoid-associated retinal vasculopathy has been recognized in patients over 60, some with associated systemic hypertension: a possible arteriolitis with aneurysm formation and caliber abnormalities [20,21]. This distinct entity may occur in association with peripheral multifocal choroiditis.

Fluorescein angiography in sarcoidosis reveals venule wall staining and leakage; macular, peripapillary and diffuse edema; and ischemia and neovascularization. Indocyanine green, however, is capable of revealing additional choroidal features, including early lobular hypofluorescence, choroidal vasculitis, and both focal and diffuse late hyperfluorescence [22,23].

Macular edema is the most frequent and most important sight-threatening consequence of sarcoid uveitis and is probably the most common indication for systemic corticosteroid treatment. Where medical treatment is unsatisfactory, vitrectomy has been found beneficial in one series [24].

Optic nerve-head granuloma is a rare but important complication of sarcoidosis [25], which may lead to a

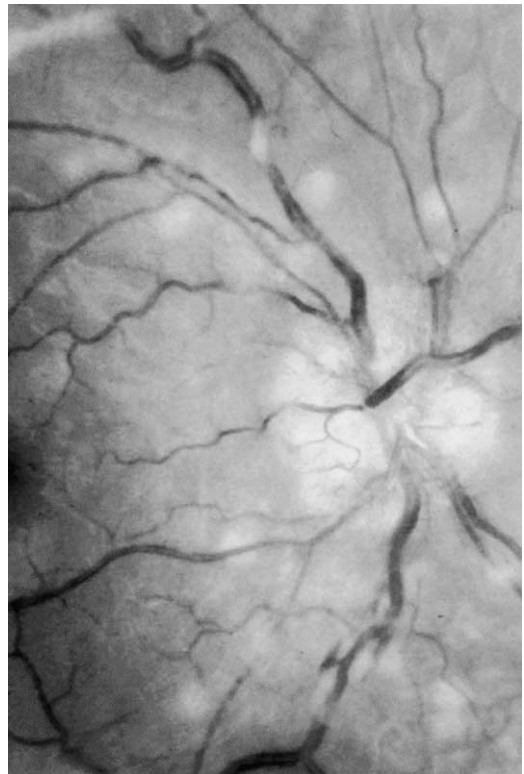


Fig. 3. The fundus in a patient with acute sarcoidosis and panuveitis. There is mild papillitis, multifocal choroiditis, and nonocclusive patchy periphlebitis.

substantial nerve-fiber bundle field defect or possibly vascular occlusion [26]. Retrobulbar optic nerve involvement is discussed under neurosarcoidosis.

Sarcoidosis may affect children including those less than 5 years. The ocular manifestations are similar to those seen in adulthood with the exception that retinal periphlebitis does not occur [27]. Older children tend to present with lung involvement, but those developing the disease below 5 years of age are more likely to have arthritis, uveitis, and skin involvement without pulmonary disease.

Systemic manifestations

Pulmonary sarcoidosis

Asymptomatic bilateral hilar and mediastinal lymphadenopathy affect more than 80% of patients with sarcoidosis [2] and the diagnosis is made from this incidental finding in as many as one third of patients. In a patient with uveitis the main differential diagnoses are tuberculosis and lymphoma. About one quarter present with mild pulmonary symptoms including dyspnea on exertion, nonproductive cough and wheeze, together with associated constitutional symptoms including tiredness, weight loss, and fever. If pulmonary infiltration becomes severe with fibrosis, dyspnea and cough worsen, sometimes with chest pain. A small minority are disabled by pulmonary fibrosis and progressive lung disease is responsible for most of the 3% mortality from the disease [2].

Sarcoidosis of the skin

The skin is frequently involved in sarcoidosis; lupus pernio is a violaceous, raised plaque often on the cheeks or nose; cutaneous sarcoidosis (Boeck's sarcoids) may be a multifocal maculopapular rash (Fig. 4), a single nodular lesion, or a tender apparently vasculitic rash. Erythema nodosum is also seen occasionally but here the differential diagnosis is wide.

Neurosarcoidosis

Neurologic involvement in some form affects more than 10% of patients with sarcoidosis. The risk is higher when posterior uveitis is present [28] and persists for up to 15 years following diagnosis [29]. Possible manifestations include cranial nerve palsies (especially facial nerve palsy, which may occur as a component of Heerfordt's syndrome, comprising uveitis, parotid, and other salivary gland enlargement and sometimes lacrimal gland enlargement). Optic neurop-



Fig. 4. Sarcoidosis of the skin causing multiple maculopapular lesions. Biopsy showed noncaseating granulomas.

athy is unusual and may manifest in several ways [30]; funduscopy may show an optic nerve-head granuloma, profound papillitis with congestion, or progressive optic atrophy. Involvement may be intraneural or secondary to compression by cerebral involvement.

Cerebral sarcoidosis is notoriously difficult to diagnose and to treat. In addition to cranial nerve palsies it may cause an encephalopathy or compressive signs and may affect either the hypothalamus or pituitary, causing hypopituitarism in some patients. Chiasmal compression is sometimes seen. On imaging the usual lesions of sarcoidosis are nodular or diffuse leptomeningeal thickening together with parenchymal lesions. These signs are nonspecific, however, and intracranial sarcoidosis has mimicked meningioma, glioma, carcinomatous infiltration, and various forms of meningitis [31]. In the context of an undiagnosed granulomatous or posterior uveitis, lymphoma and multiple sclerosis can offer a particularly difficult diagnostic dilemma; in these circumstances meningeal or brain biopsy should be considered if other investigations including MRI scanning, cerebrospinal fluid analysis, and alternative biopsy have been unproductive.

Other extrapulmonary manifestations

Liver involvement is very common but significant liver damage is rare; cardiac sarcoidosis is subclinical in a large minority but may cause pericarditis, cardiomyopathy, or congestive failure. Arrhythmias sometimes occur and may cause sudden death. Polyarthropathy may occur and is usually nondestructive, sometimes with associated myositis. Bone cysts and destruction may occur, particularly in the phalanges. Nephrocalcinosis may occur in those with increased calcium excretion. The literature contains myriad case reports of unusual manifestations including large-vessel vasculitis, muscle masses mimicking tumors, and endocrine gland involvement. The disease is truly protean in its manifestations.

Diagnosis

There is a plethora of tests for sarcoidosis available to the ophthalmologist or colleagues, and these are described next with estimates of their value in diagnosis.

Chest radiography and pulmonary function testing

Any patient with ocular signs suggesting the possibility of sarcoidosis should undergo chest radiography; asymptomatic hilar lymphadenopathy is common and may aid diagnosis, and it is essential to identify signs of interstitial fibrosis as early as possible. The classification of pulmonary sarcoidosis is based on the chest radiograph: stage 1 sarcoidosis shows hilar lymphadenopathy with clear lung fields, stage 2 shows bilateral hilar lymphadenopathy with evidence of parenchymal involvement, and stage 3 shows pulmonary infiltrates without lymphadenopathy. High-resolution CT of the chest has a high diagnostic yield comparable with transbronchial lung biopsy [32] and is increasingly used. The parenchymal lesions, however, are not pathognomonic for sarcoidosis. Any radiologic suspicion of sarcoidosis should lead to pulmonary function testing, which even if normal serves as a baseline measurement. It is the author's practice to request consultation with a chest physician for any patient in whom sarcoidosis is suspected.

Serum angiotensin converting enzyme

Angiotensin converting enzyme (ACE) is an enzyme active in the renin-angiotensin pathway and is normally present in serum up to a level of approximately 55 IU/L. The enzyme is actively secreted by

macrophages within sarcoid granulomas and the level of serum ACE reflects the total body mass of active granulomas. A raised level of ACE has become a mainstay in the diagnosis of sarcoidosis. It is not pathognomonic and levels may also be raised in Gaucher's disease, miliary tuberculosis, Hodgkin's disease, diabetes mellitus, systemic lupus erythematosus, and some other inflammatory disorders including some chronic fibrosing lung diseases. In the context of physical signs suggesting sarcoidosis it has a sensitivity over 80% [33], however, and sarcoidosis is by far the most common cause of a raised ACE level. In localized sarcoidosis (which is often suspected by the ophthalmologist) ACE secretion is not dramatic; a normal ACE level does not exclude the disease. In adolescents and especially in pubertal children, ACE levels are higher than in the adult [34]. In this age group the author accepts an ACE level of up to 75 IU/L as normal, although he always asks for a pediatric opinion.

Serum lysozyme

Serum lysozyme is often raised in sarcoidosis above its normal limit of 8 mg/L. In itself it is not a sensitive test, the predictive value for sarcoidosis of a lysozyme greater than 10 mg/L being only 12%. If both ACE and lysozyme are raised, however, the predictive value for sarcoidosis rises to 83% [35].

Calcium metabolism

Calcium metabolism may be abnormal in sarcoidosis but its clinical importance in both diagnosis and management is sometimes exaggerated. Sarcoid granulomas secrete vitamin D and hypercalcemia is detected in about 10% of patients. Symptomatic hypercalcemia is much less common, affecting fewer than 1 in 50. If an attempt is made to identify an abnormal calcium metabolism, serum calcium alone is an inadequate test; the spectrum of abnormalities, if present, resembles hypervitaminosis D, with raised serum calcium, normal serum phosphate, normal or slightly raised serum phosphatase, and increased 24-hour urinary calcium excretion.

Systemic corticosteroid treatment is commonly used in sarcoidosis. Corticosteroid-induced bone loss is frequent in patients with uveitis (Jones NP, et al. Steroid-induced osteoporosis in patients with uveitis, submitted for publication) and it should be remembered that because a proportion of patients with sarcoidosis have, in addition, an abnormal calcium metabolism, they are at increased risk of osteoporosis. This may modify decisions on treatment.

Anergy

The patient with sarcoidosis who has previously been exposed to bacille Calmette-Guérin vaccination may fail to show a response to intradermal tuberculo-protein. This is the most well-known manifestation of anergy, which may also be seen after stimulation with other agents. It is the author's practice to use tuberculin skin testing only in patients where both tuberculosis and sarcoidosis are high on the differential diagnosis.

Gallium scintigraphy

Gallium 67 is concentrated at sites of inflammation in sarcoidosis, and in some other diseases. The isotope is injected intravenously and after a 72-hour delay imaging with a gamma camera shows sites of uptake. In the head and neck these may include the salivary glands, the lacrimal glands, and the eyes; in the thorax, both lung field and mediastinum; and in the abdomen typically both liver and spleen are affected.

Because other diseases, including Sjögren's syndrome and tuberculosis, can lead to uptake of Gallium 67, the test has a low specificity for sarcoidosis, but is highly sensitive. Using scintigraphy and ACE testing together, specificity approaching 100% has been claimed [33].

Cytology and biopsy

Confirmation of the diagnosis of sarcoidosis can only be made by solid-tissue biopsy showing classic noncaseating granulomas, and preferably at more than one site. In practice such certainty is often an unattainable luxury and a high proportion of patients are treated on the presumption of sarcoidosis. Nevertheless, any opportunity for surface biopsy should be taken. The ophthalmologist has the opportunity to obtain a biopsy of the conjunctiva [36]; the usefulness of "blind" conjunctival biopsy (ie, biopsy where no lesions are seen on examination) is a contentious subject but has been advocated in the presence of peripheral multifocal choroiditis, where 70% were biopsy-positive [37]. The author's practice is to obtain a biopsy whenever the diagnosis is unconfirmed, but where conjunctival lesions are seen, characteristically in the lower fornix.

Sarcoidosis frequently involves the lacrimal gland with or without enlargement [38] and it may be tempting to obtain a biopsy of an enlarged gland. Because of the risk of damage to lacrimal ducts, and because sarcoidosis may occasionally cause fibrosis within the gland, however, it is the author's prac-

tice not to do so because of the risk of subsequent dry eye.

The ophthalmologist also has the opportunity to obtain a biopsy of an easily accessible skin lesion suggestive of sarcoidosis. Although erythema nodosum is sometimes seen in sarcoidosis, it has many possible causes in the context of uveitis, and is also seen in Behçet's disease and acute posterior multifocal placoid pigment epitheliopathy. Its histology is unhelpful in the differential diagnosis and biopsy is unjustified. It should be noted that the Kveim antigen is no longer available for reasons of safety and the test should now be considered historical.

If referred to a chest physician with radiologic signs or pulmonary symptoms, it is now usual to undertake bronchoscopy with either bronchoalveolar lavage or biopsy. In bronchoalveolar lavage, about 50 mL of isotonic saline is injected down a bronchus and then aspirated; the cytologic mix including the CD4:CD8 ratio may give strong supportive evidence for sarcoidosis [39] but is not pathognomonic. In those with typical ocular sarcoidosis but inadequate evidence of systemic disease, however, lymphocytosis has been found on bronchoalveolar lavage [40]. Transbronchial or endobronchial biopsy has a substantial diagnostic yield, but some risks, including pneumothorax and hemoptysis. It is nevertheless considered justified, having a somewhat higher diagnostic yield than CT of the chest [32] and has a high diagnostic yield in patients with ocular signs typical of sarcoidosis, but no hilar lymphadenopathy [41].

A diagnostic protocol

The ophthalmologist confronted with a patient with signs suggestive of sarcoidosis will wish to pursue the diagnosis to a reasonable level of certainty, but do so in a way that minimizes invasive investigations, delay, and expense. Clinics tend to devise their own local diagnostic approach. The author's approach is to perform serum ACE and lysozyme and chest radiograph as a routine; to obtain a biopsy of any visible and accessible skin or conjunctival lesion; to refer any patient with chest symptoms or signs to chest physicians for further investigation; and to pursue the diagnosis further (as described previously) only in those where the ocular manifestations are atypical or where the differential diagnosis is difficult (especially when tuberculosis is under consideration). The author considers a biopsy showing noncaseating granuloma from any site as confirmed sarcoidosis; consistent ocular signs in association with hilar lymphadenopathy and a raised ACE level or both raised ACE and lysozyme as "presumed" sarcoidosis; and in

a patient with ocular signs typical of sarcoidosis but without any evidence of systemic disease, the author tentatively uses the term *ocular sarcoidosis*, implying limited organ-involvement sarcoidosis as is so frequently described in other organs.

Management of sarcoid uveitis

The anterior uveitis of sarcoidosis is characteristically steroid-sensitive. In those with mutton-fat keratic precipitates and anterior chamber exudate there is a high risk of posterior synechiae and mydriasis is frequently needed. Glaucoma is frequent. As with any chronic uveitis requiring topical or systemic corticosteroid treatment, cataract surgery may be needed. Only one paper has been specifically devoted to this subject in sarcoidosis [42] but others have included it in larger series [43]. In general, the risks are those of the manifestations rather than the diagnosis; sarcoid uveitis is not in general prone to hyperacute flare-ups or fibrinous uveitis. In the author's experience surgery for cataract in this disease (including that combined with glaucoma drainage surgery) is relatively straightforward as long as inflammation is suppressed preoperatively.

Systemic corticosteroid treatment is frequently used to treat sarcoid uveitis. In some patients there are dual indications, systemic disease requiring treatment in any case and the uveitis benefiting from this. Where systemic disease does not require treatment, however, the ophthalmologist must identify criteria for treatment. In the author's clinic patients with significant macular edema not responding to depot steroid injection, patients with occlusive vasculitis (including those with neovascularization, which may regress), and those with optic nerve involvement are treated with prednisolone. Using these criteria 40% of patients have required treatment, over 50% being treated in some series [29].

Systemic corticosteroids are usually rapidly effective in sarcoid uveitis but a small proportion of patients are corticosteroid-resistant or require an unacceptable dose of steroid to maintain remission. In these cases (5% [this clinic] to 15% [29]) additional immunosuppression is used. For systemic disease, methotrexate has been found beneficial [44] and has showed promise in some patients with uveitis [45]. The usefulness of azathioprine and cyclosporin has been inadequately investigated in sarcoid uveitis. Anti-tumor necrosis factor- α treatment is investigational for a variety of severe inflammatory disorders and has been used with success in systemic sarcoidosis [46] and with mixed results in nonsarcoid uveitis

[47] but there are no data specifically for sarcoidosis-associated uveitis.

Visual prognosis

Several studies have examined the outlook for patients with sarcoidosis and uveitis. Although a substantial minority are self-limiting [8,48], the remainder follow a relapsing course. The main causes of visual loss are macular edema and glaucoma. About 5% of patients have a visual acuity worse than 20/120 in both eyes [29] and about 1 patient in 10 is blind in at least one eye [49]. Visual loss seems more common in those over 40 years at presentation [29] and in blacks [50]. Any patients with sarcoidosis and sight-threatening uveitis should be treated by a uveitis specialist.

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