Ocular Sarcoidosis

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ABSTRACT

Ocular disease occurs in approximately a third of sarcoidosis patients. The rate of disease varies around the world, with Japanese sarcoidosis patients having ocular disease in more than 70% of cases. If untreated, ocular disease can lead to permanent visual impairment, including blindness. The most common manifestation is uveitis, with anterior involvement often being self-limiting, whereas posterior involvement can be chronic. The diagnosis of ocular sarcoidosis in patients with known sarcoidosis usually requires a specific examination by an ophthalmologist. For patients presenting with uveitis of unknown etiology, criteria have been proposed for diagnosing ocular sarcoidosis. The treatment of ocular disease ranges from topical therapy to systemic treatments such as methotrexate. Recent reports have demonstrated that monoclonal antibodies blocking tumor necrosis factor can be quite effective for chronic refractory ocular sarcoidosis.

KEYWORDS: Sarcoidosis, ocular, eye

Ocular disease is an important manifestation of sarcoidosis.1 If the inflammatory changes are treated quickly and effectively, vision loss can be reversed and blindness prevented.2,3 Some patients with newly diagnosed ocular sarcoidosis may have known sarcoidosis due to other organ involvement such as hilar adenopathy with positive bronchoscopy for noncaseating granulomas. However, other patients may present with de novo ocular findings suggestive of sarcoidosis but without obvious extraocular disease. Because ocular disease may be the first manifestation of sarcoidosis, physicians should adopt a multidisciplinary approach to evaluating uveitis. In one large study over half of patients referred for uveitis were found to have an underlying systemic disease, with sarcoidosis being the most common disease identified.4

DEFINITION OF EYE DISEASE

The definition of ocular disease depends on the patient’s presentation. As shown in Table 1, certain criteria have been proposed to support the diagnosis of definite or probable ocular sarcoidosis in a patient with known sarcoidosis.5

On the other hand, the patient may present with ocular findings compatible with sarcoidosis but no symptoms from extraocular disease. In this situation, several groups have tried to identify features that support ocular sarcoidosis, including roentgenographic findings on high-resolution computed tomography (HRCT) or cellular elements in the bronchoalveolar lavage (BAL).6 However, the gold standard for definitive diagnosis remains biopsy confirmation.7 Figure 1 summarizes the findings of a workshop charged with establishing criteria for ocular sarcoidosis.8 As can be seen only those patients with a positive biopsy were classified with definite sarcoidosis. The authors also point out that other causes of granulomatous disease, including tuberculosis, must be excluded.

The figure also defines three other subgroups of patients: presumed, probable, and possible. These criteria
were developed for patients with either ocular disease only or ocular disease plus known systemic disease. Table 2 lists the features defined by this group as supportive of ocular sarcoidosis. These include ocular findings as well as systemic findings. Not all of the ocular findings are specific. For example, shaped peripheral anterior synechiae can be due to multiple causes and are not that specific for sarcoidosis. On the other hand, iris nodules are highly suggestive of sarcoidosis. Major defining features include the presence or absence of bilateral hilar adenopathy and the performance of a biopsy. Patients with a biopsy that is negative for granulomas can still have possible ocular sarcoidosis. Both probable and possible sarcoidosis rely on the presence of multiple ocular and clinical features. This approach has been supported by one retrospective case-controlled study of Japanese patients.9

**EPIDEMIOLOGY AND GENETICS**

The percentage of sarcoidosis patients with eye involvement varies widely, with Fig. 2 revealing the prevalence reported by various international investigators. Obviously some of the variability may correspond to the underlying interest of the investigators as well as the diagnostic criteria utilized for ocular involvement. For example, one U.S. study found over 80% of sarcoidosis patients had evidence of ocular disease10; however, that study included patients with keratoconjunctivitis sicca, a symptom usually excluded in other studies.

Overall a marked difference exists between the reported frequency for Japanese versus European and U.S. patients. When Pietinalho et al applied the same criteria for the diagnosis of ocular involvement in their Finnish and Japanese study populations, ocular disease was six times more frequently identified in Japan than in Finland (Fig. 2).11

Racial differences also influence the mode of presentation for ocular sarcoidosis. Japanese patients are more likely to present with eye symptoms than Scandinavian patients.12 In the United States, African Americans are twice as likely to have ocular disease as Caucasian patients.13 In the American study,13 the criteria listed in Table 1 were used for defining eye disease.5 However, in another study of American sarcoidosis patients, anterior uveitis was more common in African Americans, whereas Caucasians were more likely to develop posterior uveitis with a later disease onset.14

In the United States, females experience a higher frequency of ocular involvement, with the highest prevalence noted in African American females.15 African American females are also more likely to present with adnexal granulomas,10 which includes the adjacent structures of the eye such as the lacrimal apparatus, the extraocular muscles, and the eyelids, eyelashes, eyebrows, and conjunctiva (Fig. 3).15

Although ocular sarcoidosis seems to occur in older patients, a high frequency of ocular disease is reported in childhood sarcoidosis. Although sarcoidosis rarely occurs in patients less than 15 years of age,16 ocular

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**Table 1 Definition of Ocular Involvement in Patient with Biopsy-Confirmed Sarcoidosis**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite ocular sarcoidosis</td>
<td>Uveitis</td>
</tr>
<tr>
<td></td>
<td>Lacrimal gland swelling</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis</td>
</tr>
<tr>
<td></td>
<td>Ocular biopsy demonstrating granulomas</td>
</tr>
<tr>
<td>Probable ocular sarcoidosis</td>
<td>Blindness</td>
</tr>
</tbody>
</table>

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**Figure 1** Proposed criteria for the level of certainty for the diagnosis of ocular sarcoidosis.8 The criteria were proposed for those with known systemic disease and possible ocular disease, as well as for those who present with only ocular disease and possible sarcoidosis. Other known causes of granulomatous disease, such as tuberculosis, must also be ruled out.
disease and arthritis are major features in juvenile sarcoidosis. In fact, the young patient with sarcoidosis will often be confused with a patient with Blau syndrome, a similar familial granulomatous disease in which the Blau gene has been identified. The Blau gene was not identified in a study of sarcoidosis patients.

The genetics of ocular sarcoidosis offers some interesting insights. In one study, the presence of DRB1*0401 was associated with increased risk for ocular disease compared with age-, race-, and sex-matched controls. In a multipoint linkage analysis of African American siblings with sarcoidosis, there was a significant logarithm of the odds (LOD) score for ocular/skin/joint involvement and chromosome 10q26 (LOD = 2.93, p = 0.001). Additionally, in a study of heat shock protein polymorphisms, a strong association was reported between HSP-70/Hom rs2075800 G and uveitis in sarcoidosis patients.

**OCULAR MANIFESTATIONS OF SARCOIDOSIS**

As listed in Table 3, ocular involvement in sarcoidosis encompasses a wide range of clinical manifestations and several organ systems, including the eye itself, the vasculature of the eye, the optic nerve, the extraocular muscles, the bones that comprise the orbit itself, lacrimal glands, and the skin surrounding the eyes. Because involvement of any of these areas can affect the vision and/or operation of the eyes, the general definition of ocular disease encompasses findings related to any of these structures.

**Uveitis**

Uveitis is the most common manifestation of ocular sarcoidosis. The uvea is divided into three areas based on the source of blood flow. The anterior and posterior uvea possess different blood supplies with the...
intermediate area representing a watershed between the two areas. As listed in Table 4, the signs and symptoms vary among the three parts of the uvea.

Anterior uveitis occurs in 20 to 70% of patients, and the typical presentation is an acute iritis or iridocyclitis. Although many patients experience severe pain and photophobia, over a third of patients may have no ocular symptoms. Therefore, it is recommended that all patients with sarcoidosis undergo annual ophthalmologic examination regardless of symptoms.

Intermediate uveitis, a common manifestation of chronic ocular sarcoidosis, involves inflammation occurring in the vitreous, pars plana, or peripheral retina. Diagnosis requires a detailed eye examination of the periphery of the retina. However, the ophthalmologist may be rewarded for the effort with the finding of a string of pearls or snowballs. Because intermediate uveitis can also be found in multiple sclerosis or be idiopathic, this finding is only suggestive of sarcoidosis.

Some series report posterior uveitis in over 20% of ocular sarcoidosis cases. The most common manifestation is periphlebitis associated with segmental cuffing, sheathing, and perivenous infiltrates, referred to as candlewax drippings. Although these findings are highly suggestive of ocular sarcoidosis, these lesions may be subclinical and only identified with fluorescent angiography. Capillary disease can lead to ischemia and subsequent neovascularization and vitreous hemorrhage. Choroidal granulomas can also be observed, and with resolution, they can lead to areas of hypopigmentation or scarring.

Cystoid macular edema can be caused by chronic inflammation of anterior, intermediate, or posterior uveitis. This form of the disease may be particularly refractory to conventional antiinflammatory therapy, and it can play a decisive role in visual outcome of patients with chronic uveitis.

**Optic Neuropathy**

Optic neuropathy is a relatively rare complication of sarcoidosis, it may lead to rapid loss of vision. It involves only one of the many cranial nerves that can be affected by sarcoidosis. Optic nerve involvement can be associated with papillitis, papilledema, and even

### Table 3 Ocular Manifestations of Sarcoidosis

<table>
<thead>
<tr>
<th>Area</th>
<th>Specific Manifestation</th>
</tr>
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<tbody>
<tr>
<td>Uveitis</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>Iritis or iridocyclitis</td>
</tr>
<tr>
<td></td>
<td>Mutton fat precipitates</td>
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<tr>
<td></td>
<td>Busacca nodules</td>
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<tr>
<td></td>
<td>Koeppe nodule</td>
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<tr>
<td>Intermediate</td>
<td>Pars planitis</td>
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<tr>
<td></td>
<td>String of pearls</td>
</tr>
<tr>
<td></td>
<td>Snowballs</td>
</tr>
<tr>
<td></td>
<td>Snowbank</td>
</tr>
<tr>
<td>Posterior</td>
<td>Periphebitis</td>
</tr>
<tr>
<td></td>
<td>(candlewax drippings)</td>
</tr>
<tr>
<td></td>
<td>Neovascularization</td>
</tr>
<tr>
<td></td>
<td>Vitreous hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Choroidal granuloma</td>
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<tr>
<td></td>
<td>Cystoid macular edema</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Adnexal and orbital disease</td>
<td>Lacrimal enlargement</td>
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<tr>
<td></td>
<td>Sicca</td>
</tr>
<tr>
<td></td>
<td>Dacryocystis</td>
</tr>
<tr>
<td>Extraocular muscles</td>
<td>Mass</td>
</tr>
<tr>
<td></td>
<td>Muscle entrapment</td>
</tr>
<tr>
<td></td>
<td>with diplopia</td>
</tr>
<tr>
<td>Skin adjacent to eye</td>
<td>Eyelids, eyelashes,</td>
</tr>
<tr>
<td></td>
<td>and eyebrow nodules</td>
</tr>
<tr>
<td>Orbital</td>
<td>Mass</td>
</tr>
<tr>
<td>Scleral involvement</td>
<td>Scleritis</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Open angle glaucoma</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Cataract</td>
</tr>
</tbody>
</table>

### Table 4 Location and Findings of Sarcoidosis-Associated Uveitis

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
<th>Physical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior chamber</td>
<td>Pain, redness, blurred vision,</td>
<td>Mutton fat precipitates</td>
</tr>
<tr>
<td></td>
<td>blurred vision, asymptomatic</td>
<td>Koeppe or Busacca nodules</td>
</tr>
<tr>
<td>Vitreous; pars plana</td>
<td>Floaters</td>
<td>String of pearls, snowballs</td>
</tr>
<tr>
<td>Retina and choroid</td>
<td>Decreased acuity</td>
<td>Vascular retinitis, macular change</td>
</tr>
</tbody>
</table>
granulomas on the head of the optic head. As depicted in Fig. 4, paleness of the optic disk is the most common finding. Optic atrophy may occur if the patient does not respond to therapy. Optic neuropathy requires systemic therapy, and patients often require steroid-sparing alternatives. The anti–tumor necrosis factor (TNF) agent infliximab has been successfully prescribed for the treatment of some cases of refractory disease. However, infliximab has also been associated with subsequent development of optic neuritis.

Orbital Disease
Ocular sarcoidosis can also affect the adnexa and the orbit. Patients often experience multiple affected areas (Fig. 3) with the disease more commonly reported in older patients. In one study, adnexal disease was more common in African American women.

Orbital disease can lead to eye entrapment and associated diplopia. Although lacrimal disease is common, some patients may develop a mass without lacrimal involvement. Figure 5 demonstrates an orbital mass medial to the optic nerve. In this patient, the mass led to nasolacrimal duct obstruction and associated dacryocystitis. Although a granulomatous mass is one possible cause of dacryocystitis, most cases of dacryocystitis are due to nongranulomatous processes. In two large studies of over 500 patients designed to evaluate the role of biopsy for dacryocystitis, less than 1% of patients were diagnosed with sarcoidosis. In our experience, sarcoidosis patients with dacryocystitis usually have evidence for other organ involvement, including skin, sinus, and chest disease. We usually aggressively treat these patients for sinus sarcoidosis as part of their treatment for dacryocystitis.

The lacrimal gland is the most common adnexal area of involvement. Lacrimal gland disease can appear prior to other manifestations of the disease, and it may lead to subsequent sicca syndrome.

Miscellaneous Conditions
Miscellaneous conditions include scleritis, glaucoma, and cataracts. Glaucoma and cataracts are usually associated with uveitis. As noted, they can also be a complication of the disease treatment with corticosteroids.

Scleritis has been reported in less than 3% of ocular sarcoidosis patients. In contrast, it is a more common manifestation of Wegener granulomatosis. Although scleral involvement is often an asymptomatic nodule, the presence of a scleral nodule can lead to a biopsy, which may confirm the diagnosis of sarcoidosis. Scleral and conjunctival nodules are more readily appreciated by the use of a confocal microscope.

Figure 4 Optic nerve of the left eye (OS) compared with normal appearance of the right eye (OD).

Figure 5 The mass on the medial aspect of the left eye (circled) was biopsied and found to be noncaseating granulomas. The patient had sinus symptoms including recurrent infections and bleeding. She also experienced an associated dacryocystitis.
DIAGNOSIS OF OCULAR SARCOIDOSIS

The diagnosis of ocular sarcoidosis depends on patient presentation. For all patients with known extraocular sarcoidosis, a detailed eye examination is recommended. The criteria for definite or probable ocular disease are given in Table 1.

The diagnostic evaluation of a symptomatic patient depends on the patient’s presentation, with uveitis the most common patient complaint. Because the differential diagnosis as noted in Table 5 includes infectious, noninfectious, and idiopathic causes, a detailed evaluation is necessary. The infections toxoplasmosis and tuberculosis must always be considered. Of the noninfectious causes, idiopathic is the most commonly reported etiology. However, the classification of “idiopathic” remains a diagnosis of exclusion; hence evaluation for other diseases is usually performed. Using a multidisciplinary approach to evaluate ~2000 patients with uveitis, a specific entity was diagnosed in only half of the cases.

Figure 1 and Table 2 provide a proposed strategy to diagnose sarcoidosis in patients with uveitis. The use of several clinical ocular features and laboratory data provides detailed evaluation for the multiple faces of sarcoidosis. In general, there are very few specific features that conclusively diagnose sarcoidosis, but several items support the diagnosis. Specific interest has focused on the efficacy of evaluating lung disease in the patient who presents with uveitis and no pulmonary symptoms. Investigators in Japan who studied patients with ocular findings supporting sarcoidosis confirmed in a significant number of cases the diagnosis of sarcoidosis with transbronchial biopsy (TBB). Although the presence of bilateral hilar adenopathy strongly supports the diagnosis, the value of performing chest tomography scans in uveitis patients remains unclear. In one study of Japanese patients, abnormal high-resolution computed tomography (HRCT) findings were associated with a positive TBB in 19 of 20 patients, whereas a positive TBB was detected in only one of 19 patients with no parenchymal disease on HRCT. In a European study of HRCT evaluation in uveitis patients, only 10 of 50 (20%) exhibited findings on HRCT consistent with sarcoidosis. Increasing age, the presence of peripheral multifocal chorioretinitis, or posterior synechiae were significantly associated with a positive HRCT scan.

The use of BAL to support the diagnosis of sarcoidosis is less clear. In Japan, most patients with uveitis and BAL lymphocytosis without another cause were considered to have sarcoidosis. Increased BAL lymphocytes without another explanation is considered supportive of the diagnosis of sarcoidosis in patients with interstitial lung diseases. Interestingly in the Japanese study, BAL lymphocytosis was identified with equal frequency in patients with or without an abnormal HRCT. Others have also reported increased BAL lymphocytes useful in supporting the diagnosis of ocular sarcoidosis. However, because some uveitis patients with increased lymphocytes did not subsequently develop lung disease, lymphocytosis in the BAL may be a measure of systemic immune response and not necessarily sarcoidosis. Perhaps the passage of time will remain one of the most important features for the diagnosis of sarcoidosis. In our experience, the specific diagnosis of sarcoidosis may become apparent in some cases based on diagnostic confirmation of other organ involvement at a later time.

TREATMENT

The treatment of ocular sarcoidosis, particularly the most common manifestation uveitis, requires a stepwise approach. Figure 6 illustrates one approach to the management of uveitis in the sarcoidosis patient with the first decision the assessment of organ involvement and severity. Eye inflammation severe enough to be sight threatening warrants more aggressive treatment. For mild cases of uveitis or acute anterior uveitis, topical corticosteroids alone are usually adequate. Randomized trials comparing loteprednol etabonate 0.5% ophthalmic suspension (Lotemax, Bausch & Lomb Pharmaceuticals, Inc., Tampa, FL) with prednisolone acetate 1.0% ophthalmic suspension (Pred Forte, Allergan, Inc., Irvine, CA), confirm both drugs are effective in controlling...
inflammation in over 70% of cases. Although loteprednol etabonate was less effective than prednisolone acetate, it was associated with a significantly lower rate of drug-induced increase in intraocular pressure.

For patients with persistent disease despite topical therapy, periocular and intravitreal administration of corticosteroids is frequently used. The intravitreal injection of steroids such as triamcinolone is associated with higher levels of intraocular pressure than the periocular administration in the sub-Tenon capsule. However, both of these techniques are associated with possible increases in pressure, and patients must be monitored after injection.

Unfortunately corticosteroid injections remain effective for relatively short time periods of usually a few months. Chronic uveitis patients may require repeat injections to control inflammation. This is particularly true for patients with intermediate and posterior uveitis. Newer devices have been developed to deliver drug to the posterior eye. Use of these devices has been shown to increase the time between disease flares and reduce the overall rate of uveitis recurrence compared with systemic therapy. However, the delivery device has been associated with a more than 80% chance of implanted eyes requiring cataract extraction and 20% requiring surgery for increased intraocular pressure. Currently a large multicenter trial is under way to determine the overall risk and benefits of a corticosteroid implant versus immunosuppressive therapy for chronic uveitis.

Immunosuppressive therapy may be considered for patients requiring one or more periocular corticosteroid injections. Although systemic corticosteroids may be useful in providing rapid control of ocular inflammation, the long-term side effects, especially cataracts and glaucoma, have led to interest in use of various cytotoxic steroid-sparing drugs. Most of these drugs have been studied in nonspecific uveitis patients with only a few studies performed in sarcoidosis-associated uveitis.

Methotrexate has become a widely used steroid-sparing agent in the treatment of sarcoidosis. Figure 7 summarizes six studies reporting on the efficacy of methotrexate for the treatment of sarcoidosis eye disease. This summary includes one study with three patients with sarcoidosis-associated optic neuritis treated with methotrexate in which the reported response rates ranged from 63 to 100%.

Methotrexate has been used for the treatment of many forms of chronic uveitis. In a retrospective cohort study of 384 chronic uveitis patients, the immunosuppressant drug methotrexate was successful in controlling

![Figure 6](image)

*Figure 6* An approach to the management of uveitis in sarcoidosis patients. Patients with moderately severe disease, which is sight threatening, receive initially more aggressive therapy than those with milder forms of the disease. The four cytotoxic agents appear to be equally effective with individual choices determined based on the patient’s risk factors for toxicity, treating physician preference, drug cost, and other factors.

![Figure 7](image)

*Figure 7* The number of sarcoidosis patient responders and nonresponders to methotrexate for ocular disease. The first author is provided for each report.
the disease in 66% and was steroid sparing in 58%.\textsuperscript{58} Overall drug toxicity led to methotrexate discontinuation in 60 (16%) of cases. Unfortunately patients may require up to 6 months of treatment for responses to occur. This delay in onset of action with methotrexate has been noted in manifestations of sarcoidosis.\textsuperscript{66} An interesting approach to enhance the rate and degree of response has been to give intraocular methotrexate.\textsuperscript{67}

Azathioprine has also been widely employed in the treatment of sarcoidosis.\textsuperscript{68,69} The drug has been reported effective in treating ocular inflammation, particularly intermediate uveitis.\textsuperscript{70} In one retrospective series, 90% of patients with intermediate uveitis from various etiologies sustained remission within 1 year of treatment. However, \~25% of patients withdrew from treatment because of toxicity.\textsuperscript{70} Azathioprine has been reported beneficial in some ocular sarcoidosis patients who fail to respond to methotrexate.\textsuperscript{63}

Mycophenolate has also been reported effective in the management of chronic uveitis. In one retrospective study of 35 patients, control of uveitis was achieved in 86% of cases,\textsuperscript{71} and less than 5% of patients discontinued drug due to toxicity. For sarcoidosis, only one small series of seven patients reported the drug beneficial in controlling chronic uveitis.\textsuperscript{72}

Leflunomide is also an effective treatment for ophthalmic sarcoidosis. In a retrospective study of leflunomide therapy for chronic sarcoidosis, 28 patients displayed ocular disease. Fifteen of these patients experienced complete responses, eight patients reported partial improvement, and only two patients discontinued treatment because of toxicity.\textsuperscript{73}

Table 6 summarizes the findings of a single-institution study of 321 patients with nonspecific ocular inflammation treated with three antimetabolite agents: methotrexate, azathioprine, and mycophenolate.\textsuperscript{59} Approximately 30% of the 257 evaluable patients had systemic diseases, including sarcoidosis. All forms of ocular disease were treated, and two thirds of the patients had uveitis. Mycophenolate was associated with a more rapid rate of response than methotrexate. Although the time to response was similar to mycophenolate, patients treated with azathioprine encountered more toxicity. Patients with either scleritis and/or pan- or posterior uveitis experienced a significantly higher rate of response to mycophenolate compared with either azathioprine or methotrexate. This was a retrospective study over a 22-year period. During the time of the study, one would presume the investigators became more comfortable with dosage and administration. This may partly explain some of the perceived benefits of mycophenolate, a relatively new drug compared with azathioprine and methotrexate. Despite this limitation, this study demonstrates that the clinician has several options when choosing a cytotoxic agent for treatment of chronic ocular disease. The study did not consider the considerable difference in cost for mycophenolate versus methotrexate or azathioprine. This difference in cost may lessen over the next few years as a generic version of mycophenolate becomes available.

Combination immunosuppressive therapy has been discussed as a treatment approach for ocular sarcoidosis with the most common combinations including methotrexate plus azathioprine\textsuperscript{63} and methotrexate plus leflunomide.\textsuperscript{73} Table 6 indicates that other investigators have used combination therapy for ocular inflammation in a clinically significant percentage of cases.\textsuperscript{59} These combinations have provided safe and effective alternative treatments for some patients.

Anti-TNF biologic therapies may be helpful for those patients experiencing persistent disease or an intolerance to cytotoxic immunosuppressive therapy. Etanercept, a soluble TNF receptor antagonist that blocks TNF activity by competitively binding TNF, has been reported in a small series beneficial in treating chronic uveitis.\textsuperscript{74} However, it was not better than placebo in double-blind, randomized trials of etanercept for chronic uveitis.\textsuperscript{75,76} In addition etanercept was found no better than placebo in treating chronic ocular sarcoidosis patients with persistent disease after at least 6 months of methotrexate therapy.\textsuperscript{30} Brief reports, including one case of sarcoidosis-associated uveitis, suggest that uveitis can develop during etanercept therapy.\textsuperscript{77,78}

\begin{table}[h]
\centering
\caption{Single Institution Comparison of Antimetabolite Therapy for Ocular Inflammation\textsuperscript{59}}
\begin{tabular}{lccc}
\hline
 & Methotrexate & Azathioprine & Mycophenolate \\
\hline
Number of patients analyzed & 90 & 38 & 129 \\
Median time to response, months* & 6.5 & 4.8 & 4.0 \\
Response at 6 months & 42\% & 58\% & 70\% \\
Percent requiring dose escalation & 64\% & 32\% & 36\% \\
Second immunosuppressant added & 20\% & 0\% & 15\% \\
Overall complications per patient year & 0.14 & 0.29 & 0.18 \\
Hematologic complications per patient year & 0.006 & 0.08 & 0.005 \\
Rate of discontinuing therapy due to side effects per patient year & 0.09 & 0.24 & 0.09 \\
\hline
\end{tabular}
\end{table}

*Significant difference between groups, p < 0.02.
Infliximab, a chimeric monoclonal antibody that binds TNF, was reported efficacious in 13 of 14 patients with chronic ocular inflammation, including three patients who had previously failed etanercept. In a retrospective study, 22 patients treated with either etanercept or infliximab were analyzed. Patients treated with infliximab experienced significant reduction in uveitis and topical corticosteroid dosages. In an additional study of juvenile rheumatoid arthritis patients with uveitis, eye disease was better controlled in the 21 patients receiving infliximab compared with the 24 patients treated with etanercept.

Adalimumab, a humanized monoclonal antibody directed against TNF, has also been reported effective in treating chronic uveitis, including in patients who have failed other anti-TNF therapies. In other disease states, adalimumab has been shown as a safe alternative for patients intolerant to infliximab. In our own experience adalimumab is effective in treating sarcoid uveitis, and it can be used as an alternative to infliximab, especially in patients who develop significant allergic reactions to infliximab.

Several reports noted the development of uveitis in patients receiving anti-TNF therapy. Although this is more frequently reported with etanercept, it has also been noted with infliximab. To determine whether anti-TNF therapy could be a causative agent for uveitis, Lim et al examined several registries that track ocular events including uveitis. Although they identified cases of uveitis associated with all three anti-TNF agents, the rate of uveitis was significantly higher for etanercept than for the other two agents. Several reports of anti-TNF therapy leading to a sarcoidosis-like reaction have been reported with all three agents. However, the prevalence rate appears highest with etanercept. This granulomatous reaction is only one of several inflammatory diseases associated with anti-TNF therapy. Although the mechanism of granulomatous development during anti-TNF therapy remains unclear, it must be remembered that the intense inflammatory reaction of sarcoidosis is probably not limited to a single cytokine pathway.

CONCLUSION

Ocular disease is an important manifestation of sarcoidosis. As in the other faces of sarcoidosis, patient presentation varies with ophthalmic disease. Eye involvement may sometimes be the first sign of sarcoidosis, or perhaps just one of many organs involved in patients with long-standing chronic disease. Because vision loss can occur in either the symptomatic or the totally asymptomatic patient, a close multidisciplinary management team must include an ophthalmologist as well as a clinician experienced with treating the systemic aspects of sarcoidosis. Because both cytotoxic immunosuppressive therapy and biologic agents targeted against TNF have improved the outcome of refractory sarcoidosis in general, these therapies should be considered in the treatment of chronic ocular sarcoidosis.

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