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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/16346
DOI URL: http://dx.doi.org/10.21474/IJAR01/16346

RESEARCH ARTICLE

MEDICAL MANAGEMENT OF OCULAR SARCOIDOSIS

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Manuscript Info

Manuscript History
Received: 26 December 2022
Final Accepted: 30 January 2023
Published: February 2023

Key words:-
Sarcoidosis, Eye, Uveitis, Dry Eye, Optic Neuropathy, Orbital Inflammation

Abstract

Sarcoidosis is one of the leading causes of inflammatory eye disease. Ocular sarcoidosis can involve any part of the eye and its adnexal tissues, and may cause uveitis, episcleritis/scleritis, eyelid abnormalities, conjunctival granuloma, optic neuropathy, lacrimal gland enlargement and orbital inflammation. Glaucoma and cataract can be complications from inflammation itself or adverse effects from therapy. Ophthalmic manifestations can be isolated, or associated with other organ involvement. Patients with ocular sarcoidosis can present with a wide range of clinical presentations and severity. Multi-disciplinary approaches are required to achieve the best treatment outcomes for both ocular and systemic manifestations.

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Introduction:-

Sarcoidosis is a chronic idiopathic granulomatous inflammatory disease that was first described by Sir Jonathan Hutchinson in 1878 as a dermatological disorder[1]. It was later in 1909 that Heerfordt, a Danish ophthalmologist, reported for the first time the uveoparotid-fever syndrome (“Heerfordt syndrome”), thus introducing ocular involvement as a clinical manifestation of sarcoidosis[2]. Known to be a systemic disorder, sarcoidosis affects multiple major organ systems such as the lung, skin, lymph nodes, heart, liver, and eye[3,4]primarily the lungs in more than 90% of cases, which tend to be in the spotlight of clinical attention[5].

Extrapulmonary disease frequently involves the lymph nodes, skin, eye, and various systems[6].Because the eye is a very sensitive sensory organ, any symptoms of the eye, even if they are very small, lead patients to visit ophthalmologists soon after they occur. Thus, ophthalmologists will be the first gate where patients visit hospitals, and sarcoidosis is found by ophthalmic and systemic examinations thereafter. Thus, ophthalmologists play an important role in the clinical practice of sarcoidosis[3].

Approximately 30–50% of patients with sarcoidosis develop the intraocular inflammatory disease, that is, uveitis[5,7,8].Sarcoidosis can cause any type of uveitis; anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis. In addition, uveitis can be classified according to the etiology of the disease, that is, infectious uveitis (16% of whole uveitis), noninfectious uveitis (47%), and unclassified uveitis (37%)[9].Infectious uveitis includes intraocular inflammation caused by pathogenic infectious agents, including viruses, bacteria, fungi, and parasites. Noninfectious uveitis includes sarcoidosis, VogtKoyanagi-Harada disease, Behcet’s disease, sympathetic ophthalmia, inflammatory bowel disease-associated uveitis, juvenile idiopathic arthritis-associated uveitis, tubulointerstitial nephritis and uveitis syndrome associated uveitis, and HLA-B27 associated anterior uveitis. The

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precise pathogenic mechanisms of noninfectious uveitis are not fully understood, but immunological and autoimmune mechanisms are considered to play a significant role.This review focuses on distinguishing the clinical manifestations of ocular sarcoidosis (OS), management[3].

Clinical manifestations of ocular sarcoidosis

Ocular disease may be the initial manifestation in patients with sarcoidosis, and may cause severe visual impairment. The involvement may be characterized by granulomatous inflammation which can affect any part of the eye and its adnexa. The most common ocular manifestations are uveitis, dry eye and conjunctival nodules[3].

Location	Description
Lacrimal glands and lacrimal drainage system (10–69%)	Often asymptomatic. Kerato-conjunctivitis sicca (15–31%). Enlargement of the glands is less frequent; the diagnosis can be made by biopsy of the lacrimal gland.
Orbit	Women aged >50 years. Diffuse orbital inflammation, usually unilateral, can result in ptosis, limitations in movement and diplopia.
	Ocular nerve palsy can occur from sarcoid involvement of the third, fourth, and sixth cranial nerves
Lid	Granuloma
Conjunctiva (6–40%)	Paucisymptomatic. granuloma, conjunctivitis
Sclera (<3%)	Scleritis, episcleritis: diffuse inflammation, plaque or nodule; the diagnosis may be made by biopsy of a scleral nodule.
Cornea	Interstitial keratitis (extremely rare)
Optic nerve (1–5%)	Optic neuropathy (++), granuloma, retrobulbar optic neuropathy
	Predominantly Caucasian females. Frequently accompanied by uveitis and other findings of neurosarcoidosis. Patients often have chronic disease and steroid-sparing alternatives are commonly used.
Other neuro-ophthalmic manifestations	Rare: Horner syndrome, tonic pupil and optic-tract involvement

Table 1:- Involvement of ocular structures and adnexa in sarcoidosis[10–13]

Uveitis

The mean age of presentation of uveitis is 42 years. Most sarcoid uveitis is bilateral, and approximately 90% are chronic[14]. Uveitis associated with sarcoidosis can be anterior, intermediate, posterior, or panuveitis.[15]

Anterior uveitis –

The patient presents with eye pain, redness of eyes, blurred vision, and photophobia. Sarcoidosis is characterized by granulomatous uveitis, with mutton fat keratic precipitates, iris, or trabecular meshwork nodules. Busacca nodules are noted in the iris stroma, and the Koeppe nodules involve the pupillary margin. Berlin nodules are present at the angle of the anterior chamber. Hypopyon is usually not seen in sarcoidosis[16].

Without appropriate treatment, there is a development of peripheral anterior synechiae with raised intraocular pressure or posterior synechiae with complicated cataracts. Patients with ocular sarcoid uveitis tend to develop raised intraocular pressure due to outflow obstruction due to trabecular meshwork block by inflammatory cells, trabecular meshwork nodules, or development of peripheral anterior synechiae[17].

Intermediate uveitis –

Patients complain of either floaters or blurred vision. The most common cause of vision loss is the development of cystoid macular edema or vitreous inflammation. Inflammation of pars plana leads to the development of snowballs in the inferior vitreous and snow banking near ora serrata.Neovascularization may develop in the peripheral retina leading to vitreous hemorrhage in a few patients[18]. The vitreous may show the string of pearls appearance[15].

Posterior uveitis –

Choroidal inflammation leads to the development of choroidal granulomas, which may be unifocal or multifocal, and vary in size from small (like Dalen-Fuchs nodules) to significant (like choroidal tumors)[19].Inflammatory new vessels of the optic disc or the retina may cause vitreous hemorrhage[20].

Choroidal neovascularization may develop from choroidal granulomas, which affect vision when present in the posterior pole. Mid peripheral periphlebitis is characteristic of ocular sarcoidosis. Occlusive vasculitis causing capillary nonperfusion and retinal new vessels may also occur. In severe cases, whitish-yellow perivascular exudates are seen along the retinal veins, classically described as "candle-wax drippings" or taches de bougie[21].

Posterior uveitis is complicated with the development of cystoid macular edema, epiretinal membrane formation, intraretinal hemorrhage, and vitreous hemorrhage[22].

Treatment for ocular sarcoidosis

The primary aims for management of ocular sarcoidosis are to restore vision and to prevent complications from related inflammation. Corticosteroid therapy, including topical, regional and systemic routes, is the mainstay of treatment. Other immunomodulators may be required in some patients who are dependent, unresponsive, or intolerant to corticosteroid treatment[10].

Corticosteroids

Corticosteroids are potent anti-inflammatory agents used in the management of uveitis. They can be used topically as eye drops to treat anterior uveitis. However, topical steroids are insufficient in the control of posterior uveitis. The most commonly used topical corticosteroids are prednisolone acetate 1% or difluprednate 0.05%.[23]

Oral corti-costeroids are usually prescribed with an initial doseof 0.5–1mg/kg per day with a gradual tapering toless than 10mg per day[24].

Regional corticosteroids

These agents are used in cases of posterior uveitis or when the patient is poorly compliant to frequent dosages of topical corticosteroids. They can be given as posterior subtenon injection in a dose of 20 to 40 mg of triamcinolone acetonide or intravitreal injection of 1 to 4 mg of triamcinolone acetonide[25,26].

Long-acting sustained slow release steroid implants such as 0.7 mg of dexamethasone, 0.19 mg of fluocinolone acetonide, or 0.59 mg of fluocinolone acetonide provide longer periods of anti-inflammatory effect. The regional corticosteroids may cause glaucoma and cataracts, and thus the patients should be observed closely and promptly treated for the complications[27,28].

Systemic steroids

Systemically dosed steroids are used in cases of bilateral uveitis with systemic involvement or when there is poor disease control with local steroid use. Prednisolone in the dose of 1 to 1.5 mg/kg/day initially followed by slow tapering is the usual treatment protocol[2,10].

Cycloplegic Agents

These agents are used to relieve ciliary spasms and associated ocular pain. They help in breaking or preventing posterior synechiae. Commonly used agents include cyclopentolate 1%, homatropine 2%, and atropine 1%[10].

Systemic Immunosuppressive Agents

These agents are used in cases of corticosteroid-resistant cases or steroid-dependent cases where the side effects of the steroid regimen outweigh the anti-inflammatory effects. Most commonly used agents for the treatment of non-infectious uveitis are methotrexate (7.5 to 25 mg /week; oral, subcutaneous, or intramuscular route), mycophenolate mofetil (500–1500 mg bd; oral route), cyclosporine (2.5 to 10 mg/kg/day bd; oral route), and azathioprine (1 to 4 mg/kg/day; oral route)[10,29,30].

Biologic Agents

These are used in cases of refractory non-infectious uveitis. The most commonly used biologic agents are tumor necrosis factor-alpha inhibitors (TNF α) such as infliximab, adalimumab, etanercept, and golimumab. These agents promise to offer a new option in resistant cases. The patient should be tested for latent tuberculosis and hepatitis B before starting biologic agents to prevent the reactivation of infection[31]. Interestingly, a 'sarcoid-like granulomatosis' has been reported following anti-TNF therapy, including etanercept, infliximab, and adalimumab for various indications, including rheumatoid arthritis and spondyloarthritis[2,32].

Treatment of Orbital Disease

Orbital inflammation is also typically responsive to oral corticosteroids and/or immunosuppressive agents. In patients with accessible orbital lesions or high suspicion for possible malignancy, biopsy or removal of the lesions should be performed. Along with orbital lesions, strabismus and/or abnormal eyelid position can also be observed. The treatment should initially be maximized with anti-inflammatory therapy. If surgical interventions are required, orbital surgery should be carried out first, followed by strabismus and eyelid surgery, respectively[10].

Treatment of Ocular Surface Disease

Conjunctival lesions and KCS usually responds to topical cyclosporine eye drops[33]. For scleritis, initial treatment is with systemic non-steroidal anti-inflammatory drugs (NSAIDs), with steroids and immunosuppressants reserved for resistant cases[10].

Treatment of Ocular Complications

Glaucoma is one of the most common uveitis complications and a serious side effect of chronic corticosteroid use. Glaucoma needs to be monitored at each visit and requires early intervention either medically or surgically. Cataract surgery is usually planned after three months of disease inactivity. Uveitic cystoid macular edema is one of the common causes of ocular morbidity and requires intervention in the form of anti-inflammatory agents[10].

In certain cases, posterior subtenon triamcinolone, intravitreal injection of steroids (triamcinolone, dexamethasone implant, or fluocinolone implant), or anti-VEGF (vascular endothelial growth factor) agents like bevacizumab or ranibizumab are required to control cystoid macular edema. Development of epiretinal membrane at the macula, vitreomacular traction, and vitreous hemorrhage may warrant surgical intervention in the form of vitrectomy[34,35].

Management

Recommendations for the management for ocular sarcoidosis by the International Workshop on Ocular Sarcoidosis (IWOS)[3,22]

A. Inflammatory activity is evaluated and monitored by clinical examinations and specific ocular imaging tools.

B. Anterior uveitis (AU)

1. Ocular manifestations that are indicators for treatment in AU include anterior chamber (AC) cells, new-onset keratic precipitates, iris nodules, angle nodules, new-onset posterior synechia and raised IOP (not corticosteroid-induced).
2. First-line therapy for severe AU (AC cell 3þ, new-onset KPs, iris nodules) is instillation of corticosteroid eye drops (prednisolone acetate 1% or similar) at least 10 times per day.
3. First-line therapy for moderate AU (AC cell <3+) is installation of corticosteroid eye drop atleast 6 times per day.
4. Second-line therapy in severe AU includes subconjunctival dexamethasone injection, periocular triamcinolone acetonide injection and systemic corticosteroid.
5. Second-line therapy for moderate AU includes more frequent corticosteroid eye drops, subconjunctival dexamethasone injection, periocular triamcinolone acetonide injection and systemic corticosteroid. 6. Inactive AU does not require treatment. 7. Mydriatic eye drops are used when AU is active.

C. Intermediate uveitis (IU)

1. Ocular manifestations that are indicators for treatment in IU include diffuse vitreous opacities, snowball-like vitreous opacities, snowbanks and macular edema.
2. First-line therapy for active bilateral IU includes local corticosteroid (periocular, intravitreal, implant) and systemic corticosteroid.
3. First-line therapy for active unilateral IU is exactly the same as above.
4. Second-line therapy for active bilateral IU includes local corticosteroid (periocular, intravitreal, implant), systemic corticosteroid, and non-biologic corticosteroid-sparing systemic immunosuppressive drugs.
5. Second-line therapy for active unilateral IU is exactly same as above.

D. Posterior uveitis (PU)

1. Ocular manifestations that are indicators for treatment in PU include macular edema, optic disc nodules/granulomas, nodular and/or segmental periphlebitis, active chorioretinal peripheral lesions and choroidal nodules.
2. First-line therapy for active bilateral PU includes systemic corticosteroid alone or with corticosteroid-sparing non-biologic systemic immunosuppressive drugs and local corticosteroid (periocular, intravitreal, implant).
3. First-line therapy for active unilateral PU is exactly the same as above.
4. Second-line therapy for active bilateral PU is same as first-line, with exception that biologic drugs are included.

5. Second-line therapy for active unilateral PU is exactly same as above.
E. Drugs
1. Mean initial dose of systemic prednisone/prednisolone is 0.5-1.0 mg/kg/day, to a maximum dose of 80 mg/day.
2. Mean duration of the initial dose of systemic prednisone/prednisolone is 2-4 weeks.
3. The mean duration of total treatment with systemic prednisone/prednisolone is 3-6 months.
4. The initial corticosteroid-sparing immunosuppressive drugs include methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine.
5. In selected settings of severe disease, some specialists may consider intravenous pulse corticosteroid.
6. Biologic drugs (adalimumab) are used if necessary.

Conclusion:-

Ocular sarcoidosis is a sight-threatening eye disease for which detailed immunopathogenesis remains unclear. A positive diagnosis of ocular sarcoidosis is sometimes difficult if the supporting pathological findings cannot be obtained. Diagnostic tools and treatments have been modified and improved in recent years. Exploring the detailed mechanisms of inflammation, finding highly sensitive diagnostic biomarkers and developing new prolonged and effective treatments should be the three most important topics in the future.

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