Sarcoidosis is a multi-system granulomatous disorder with an unknown etiology\(^1\). Major organs involved in sarcoidosis are lungs, eyes, skin, and lymph nodes. It is characterized by the presence of non-caseating granulomas.

Common symptoms are vague, such as fatigue unchanged by sleep, lack of energy, weight loss, aches and pains, arthralgia, shortness of breath or skin lesions. The cutaneous symptoms vary which ranges from rashes and noduli (small bumps) to erythema nodosum or lupus pernio. It is often asymptomatic.

It has a worldwide prevalence. It affects adults between 20 and 40 years of age and is slightly more common in women than men.\(^1\) Sarcoidosis is 3 to 4 times more prevalent in US blacks than whites.\(^1\) HIV infection and sarcoidosis rarely coexist, presumably because their immunopathogenesis mechanisms diverge. A definite diagnosis of sarcoidosis can only be made by biopsy of the ocular tissues.\(^2\)

**Pathogenesis**

The processes involved in the pathogenesis of sarcoidosis include accumulation of CD4 + lymphocytes at the affected site. The cytokines and factors secreted by these cells account for the influx of monocytes, alveolotis and non-caseating granuloma formation.\(^3\)

Compartmentalization of the immune response is well recognized in sarcoidosis. At sites of granulomatous inflammation, there is a predominance of T-helper lymphocytes, which proliferate and secret large amounts of lymphokines, including interleukin (IL)-2, monocyte chemotactic factor (MCF) and migration inhibition factor (MIF). The concentration of lymphokines and monokines produced T sites of granulomatous inflammation is highest locally. As a result the traffic

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Figure 1: Erythema nodosum
of T-helper lymphocytes and monocytes is directed towards the granuloma formation. Exposure to an environmental or occupational antigen in a genetically susceptible individual is thought to trigger an immunologic response. The cells and cytokines that lead to granuloma formation have been an area of active study.

**OCULAR SARCOIDOSIS**

It usually presents with bilateral hilar lymphadenopathy, pulmonary infiltrates and eye involvement. 25% patients with sarcoidosis develop ocular symptoms. The 8-15 year age group has almost universal lung involvement, with the eye, skin, liver, and spleen involved in 30-40% of cases. Goto et al conducted an epidemiological survey in Japan and found that most frequent intraocular inflammatory disease identified was ocular sarcoidosis (13.3%). Children of 5 years of age and under are characterized by the triad of uveitis, arthropathy, and skin rash. As sarcoidosis can have protean manifestations, it can present acutely or chronically with both granulomatous and sometimes non-granulomatous uveitis. Investigations to rule out sarcoidosis should be performed in patients presenting with uveitis. The term ocular sarcoidosis should be applied both to isolate ocular disease as well as to ocular involvement in systemic disease.

**Clinical Evaluation in Sarcoidosis**

A detailed history and complete physical examinations should be obtained especially occupational exposure and family history. Complete ophthalmic examination by slit lamp, intraocular pressure measurement and fundus evaluation by indirect ophthalmoscope.

**Clinical Signs of Ocular Sarcoidosis**

Ocular sarcoidosis involves both anterior and posterior segments of the eye. Ocular involvement in sarcoidosis had isolated anterior uveitis, intermediate uveitis, panuveitis with retinal vasculitis, and panuveitis with punched multifocal choroiditis.

**Anterior Segment**

Anterior uveitis is usually bilateral and may be either acute or chronic. Acute iridocyclitis are seen typically in young patients with acute sarcoidosis. Chronic granulomatous iridocyclitis usually affects older patients. Patients may present with aqueous cells and/or aqueous flare. Mutton-fat keratic precipitates (KPs) are usually the signs for granulomatous anterior uveitis. KPs are coalescent precipitates forming small plaques that gradually become more translucent. Iris nodules may be seen at the pupil margin (Koeppe nodules) and/or in iris stroma (Busacca nodules). Seclusio pupillae

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Figure 2: Mutton fat keratic precipitates

Figure 3: Koeppe nodules
and Occlusio pupillae are present in rare cases. Posterior synechiae is the adhesion between the posterior surface of iris and anterior surface of the lens.

Tent-shaped peripheral anterior synechiae (PAS) is formed when protruding trabecular nodules retract the iris towards the trabeculum. Trabecular meshwork (TM) nodules, giant iridociliary sarcoid tumors, granulomatous tumor of the iris and ciliary body, interstitial keratitis, multilobular limbal corneal nodules are the rare signs of ocular sarcoidosis.

**Posterior segment**

Snowballs in the inferior anterior vitreous /string of pearls vitreous opacities are known signs of ocular sarcoidosis. They are very suggestive of a granulomatous process. Snowballs may also be seen in intermediate uveitis. Retinal perivasculitis is frequently found in ocular sarcoidosis. Perivasculitis is seen as segmental periphlebitis and vascular changes often locate at the equatorial or peripheral retina. Retinal haemorrhage appears when periphlebitis occludes the venous circulation. Branch retinal vein occlusion may occur as a rare vascular complication of sarcoidosis. If occlusion is extensive, neovascularisation and vitreous haemorrhage follows.
Bilateral optic neuropathy occurs in cases of long term use of linezolid given for methicillin-resistant Staphylococcus aureus osteomyelitis. Panuveitis may be a sign of ocular sarcoidosis induced by Interferon-alpha which is used for the treatment of different viral, autoimmune and malignant diseases.

Neurosarcoidosis

Neurological involvement occurs in 5-6% of patients with sarcoidosis. Isolated sudden neurosensory hearing loss and uveitis in cases of neurosarcoidosis. Posterior segment involvement may be accompanied by disease of the central nervous system in 25% to 30%. The neurological features includes babinski reflexes, spinal cord...
compression, myasthenia, cranial nerve paresis (V, VI, XI, and XII), hypothalamic-pituitary gland dysfunction, visual field loss and normal pressure hydrocephalus.\textsuperscript{3}

Ocular involvement was characterized by anterior uveitis (in the initial stages), vitreous flare, bilateral disc edema, macular edema, streak hemorrhages, peripheral periphlebitis, nerve fibre bundle defects and candle-wax spots.\textsuperscript{39} Ocular sarcoidosis was accompanied by secondary glaucoma or optic nerve atrophy, the progression of neurosarcoidosis can lead to visual field defects.\textsuperscript{40}

**Laboratory Investigations**

Complete blood count with platelet count and measurement of serum calcium, creatine, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels should be carried out.\textsuperscript{41}

**Mantoux test (Tuberculin sensitivity test)**

It is done to diagnose sarcoidosis and to rule out other causes of uveitis, especially tuberculosis. Tuberculin is a glycerol extract of the tubercle bacillus. A standard dose of 5 Tuberculin units (0.1 ml) is injected intradermally in the forearm and read 48 to 72 hours later. The reaction is read by measuring the diameter of induration in millimeters. The tuberculin skin test in sarcoid patients is negative.\textsuperscript{11} Negative tuberculin test in a BCG-vaccinated patient or in a patient with a previously positive tuberculin (Mantoux) skin test is reported in some.\textsuperscript{42} Cutaneous allergy is an epiphenomenon of active sarcoidosis, a non-specific process which is seen in some granulomatous inflammations and resolves when the underlying granulomatous disease activity wanes.\textsuperscript{3}

**Serum Angiotensin Converting Enzyme (SACE)**

Angiotensin converting enzyme (ACE) is a peptidyldepeptide hydrolase that is located mainly on the luminal surface of vascular endothelial cells but also in cells derived from the monocyte-macrophage system. Increased serum ACE activity has been reported in pathologies involving a stimulation of the monocyte cell line, primarily granulomatous diseases. Sarcoïdosis is the most frequent as macrophage products are produced by sarcoidal granulomas.\textsuperscript{41} ACE is elevated in ocular sarcoidosis and is significantly more elevated in children than in adults.\textsuperscript{11}

**Serum Lysozyme**

Elevated serum lysozyme is seen in ocular sarcoidosis.\textsuperscript{11} Lysozyme is an enzyme that hydrolys glycosidic bonds and is thus able to hydrolyse the cell wall peptidoglycans of some micro-organisms and thereby kill the organism. It is found in monocytes and macrophages. Serum ‘ACE enzyme activity’ falls below detectable levels in patients taking ACE inhibitors and hence serum lysozyme test is recommended. Serum lysozyme is rarely used. In a study on 125 sarcoidosis cases ACE was elevated in 60% of patients\textsuperscript{43} and serum lysozyme in 76%\textsuperscript{43}, because serum lysozyme is less specific for sarcoidosis than serum ACE, its diagnostic value may be limited. However, the sensitivity was high even when serum ACE levels were within normal limits and correlated well with clinical features in sarcoidosis.

**Serum calcium**

Hypercalcemia occurs in about 10% of the patients with sarcoidosis; hypercalciuria is about three times more frequent. These abnormalities of calcium metabolism are due to dysregulated production of 1, 25- (OH) 2-D3 (calcitriol) by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation.\textsuperscript{44}

**Erythrocyte Sedimentation Rate (ESR)**

It is the rate at which red blood cells precipitate in a period of 1 hour. The ESR is increased by any cause
of inflammation. Sarcoidosis shows a raised ESR

**Liver enzyme tests**

Hepatic involvement in sarcoidosis is one of the occult sites where undetected granulomas form. The test is considered to be positive when serum levels of alkaline phosphatase are elevated for liver enzymes aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and alkaline phosphatase.

**QuantiFERON-TB gold test**

It has a higher specificity for detecting M. tuberculosis infection than the conventional tuberculin skin test. Hence it excludes both latent and active tuberculosis if negative. It is to rule out ocular tuberculosis from ocular sarcoidosis.

**Vitamin D**

The active hormone of Vitamin D (1, 25-dihydroxyvitamin-D) (1, 25-D) performs a vital function in immune diseases, including sarcoidosis. It causes hematopoetic stem cells to differentiate into monocytes, white blood cell and then it causes these to differentiate into macrophages and giant cells characteristic of sarcoid granuloma. Without this hormone there would be no formation of granuloma.44

**Chest x-ray**

Bilateral Hilar Lymphadenopathy (BHL) is the most frequent radiological finding in sarcoidosis.11 It is present in 50–89% of cases.42 Other systemic condition that rarely causes BHL is lymphoma only, although symmetrical lymph node involvement is unusual, this is thought to be pathognomonic of sarcoidosis.

Chest X-ray changes are divided into **four stages**45

- Stage 0: Normal Chest X-ray
- Stage 1: Bilateral hilar lymphadenopathy (BHL)
- Stage 2: Bilateral hilar lymphadenopathy (BHL) and pulmonary infiltrates
- Stage 3: Bilateral pulmonary infiltrates without BHL
- Stage 4: Pulmonary fibrosis

**HRCT Scan**

It is used in cases where sarcoidosis was strongly suspected but the chest radiography was negative for BHL. Increasing age, presence of peripheral multifocal chorioretinitis and posterior synechiae were associated with an abnormal HRCT scan.46
Biopsy

It is the removal of tissue from a living subject to examine the presence or extent of a disease. The only confirmatory test is biopsy showing classic non-caseating granulomas. Granulomas are compact, centrally organized collections of macrophages and epithelioid cells encircled by lymphocytes. Macrophages, in the face of chronic cytokine stimulation, differentiate into epithelioid cells, gain secretory and bactericidal capability, lose some phagocytic capacity, and fuse to form multinucleated giant cells.

Fundus fluorescein angiography helps to detect subtle vascular leakage. Optical coherence tomography (OCT) is used to detect the presence of cystoid macular edema, which is a risk factor. A granulomatous lesion of the optic nerve head was more visible in fluorescein angiography which shows hyperfluorescence. Multifocal choroidal lesions located in the posterior pole is only visible with indocyanine green (ICG) were demonstrated.

Herbert P et al Diagnostic Criteria of Ocular Sarcoidosis

DEFINITE OCULAR SARCOIDOSIS: Biopsy-supported diagnosis with a compatible uveitis (both granulomatous and non-granulomatous uveitis)

PRESUMED OCULAR SARCOIDOSIS: Biopsy was not done. A compatible uveitis, where chest x-ray or CT scan revealed the presence of bilateral hilar lymphadenopathy (BHL)

PROBABLE OCULAR SARCOIDOSIS: Biopsy was not done. The chest x-ray did not show BHL. But 3 suggestive intraocular signs and 2 supportive investigations were present. It has been shown that over 60% of such patients were finally diagnosed as having sarcoidosis when biopsy was obtained subsequently.

POSSIBLE OCULAR SARCOIDOSIS: Biopsy was done but found negative. There were at least 4 suggestive intraocular signs with at least 2 positive laboratory results.

TREATMENT

Sarcoidosis treatment suppresses the granulomatous process and its clinical, functional and radiographic consequences but it is not etiological. Systemic or topical corticosteroids are the mainstay for the treatment of systemic and ocular sarcoidosis. As a general rule, systemic...
Corticosteroids are the first-line treatment, given for at least 12 months. Corticosteroids can relieve symptoms, reduce inflammation, and improve the prognosis of ocular and pulmonary sarcoidosis. Most cases of ocular sarcoidosis, such as iridocyclitis, retinal periphlebitis, optic disc inflammation, vitritis and snowballs can be managed with topical or subconjunctival injections of corticosteroids. High doses of systemic steroids are effective in unusual manifestations of retinal vein occlusions, retinal and optic disc neovascularization and vitreous hemorrhage. Systemic corticosteroids starting with moderately high doses (40-60 mg/day) with slow tapering according to the clinical response is necessary. Bilateral choroiditis and papillitis subsides with the treatment of oral prednisolone.

In addition to corticosteroids, topical cycloplegics, such as atropine or homatropine, may be used. Cytotoxic drugs like methotrexate, cyclophosphamide and azathioprine may be used in refractory cases. An alternative option to corticosteroids proposed in case of contraindication or corticoresistant sarcoidosis is methotrexate. Although other drugs are only occasionally needed, the available therapeutical range is wide (azathioprine, infliximab, cyclophosphamide, leflunomide, etc).

The tumor necrosis factor alpha antagonist infliximab has been used successfully in cases of refractory sarcoidosis, whereas the use of etanercept in the treatment of sarcoidosis has been disappointing. Multi-systemic sarcoidosis and refractory retinal vasculitis experienced an excellent response with infliximab.

Leflunomide is well tolerated in patients with chronic sarcoidosis. It appears to be as effective as methotrexate, with less toxicity. It should be considered as an alternative in chronic sarcoidosis patients (ocular and lung involvement) who cannot tolerate methotrexate. A lasting remission was found with the treatment by cyclosporine in granulomatous tumor of the iris and ciliary body.

Pars plana vitrectomy have beneficial effects on restoring vision, stabilizing vitreous inflammation, resolving preoperative cystoid macular edema and reducing systemic corticosteroid treatment in eyes with thick vitreous opacities associated with sarcoidosis that is resistant to corticosteroid treatment preoperatively.

The visual prognosis of sarcoidosis is usually good. Poor visual outcome was seen in posterior segment involvement, significantly more frequent in multifocal choroiditis and panuveitis compared to anterior uveitis. Causes of visual loss were cataract, glaucoma, macular edema, vitreous haemorrhage and retinal detachment.

**Conclusion**

Uveitis precedes systemic sarcoidosis in 30% of cases. In a study by Ganesh et al. in a series of 34 histologically confirmed cases of systemic sarcoidosis, only 3 patients (8.8%) had ocular involvement and all of them had granulomatous anterior uveitis. Uveitis may be the presenting manifestation of sarcoidosis, especially in women. Bilateral panuveitis and chronic bilateral anterior uveitis are the most common clinical presentations.

Sarcoid uveitis is common, mostly in a chronic form, and is prevalent in women past middle age. The onset is insidious. Complications are macular edema, cataract, and glaucoma, resulting in visual loss. The diagnosis is made according to characteristic ocular signs and systemic investigations. The diagnosis of sarcoidosis may be difficult, owing to the lack of definitive diagnostic criteria and a variety of presentations. Histologic confirmation may not always be possible or practical. However, a range of serological and radiological tests, when combined with physical and ophthalmic evaluation, can lead to the presumed diagnosis of sarcoidosis. Effective treatment consists primarily of long-term use of steroids.
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