A Case Series of Ocular Disease as the Primary Manifestation in Sarcoidosis†

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Abstract

Sarcoidosis is an idiopathic, systemic, non-caseating, granulomatous disease with protean clinical manifestations. This disease is highly prevalent in the southern states of United States of America, especially among African-Americans, but uncommon among Asians. Though sarcoidosis concerns physicians of virtually all specialties, it is particularly important to ophthalmologists since a significant number of patients will seek initial medical examination because of ocular disease.

Out of the 262 cases of uveitis examined at the Singapore National Eye Centre over a period of two years, 9 cases were diagnosed as sarcoidosis. We report here 4 patients with active sarcoidosis who presented to us with ocular symptoms as the first and primary manifestation of the disease. All 4 patients developed symptoms and signs of systemic sarcoidosis at a later date. The ocular manifestations included simultaneous bilateral chronic granulomatous iridocyclitis, intermediate uveitis, posterior uveitis characterised by vasculitis with candle wax drippings, and optic nerve head granuloma.

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Key words: Intermediate uveitis, Iridocyclitis, Optic nerve head granuloma, Posterior uveitis, Vasculitis

Introduction

Sarcoidosis is an idiopathic, systemic, non-caseating, granulomatous disease with protean clinical manifestations. Although the first description of sarcoidosis was attributed to Hutchinson,[1] its ocular features received little attention until 1936 when Heerfordt's syndrome of uveitis, salivary gland enlargement and cranial nerve palsies was recognised as a sign of sarcoidosis.[2] Subsequently, sarcoidosis was recognised as one that commonly affects the eyes and ocular adnexae. The frequency of this disease is high in the southern states of USA, with almost three-fourths of the patients being African-Americans.[3] Sarcoidosis is considered relatively rare among the other races in the rest of the world.

Case Reports

We retrospectively examined 262 cases of uveitis seen in our centre between 1 February 1994 to 31 January 1996 obtained from our uveitis clinic database. Nine cases were diagnosed to have uveitis secondary to sarcoidosis. We report here 4 cases of sarcoidosis in whom ocular disease was the primary manifestation of the disease.

Case 1

A 78-year-old Chinese female presented to us in 1994 with symptoms of gradual decrease in visual acuity in both eyes for a duration of 4 months. On examination, she had a visual acuity of 6/24 in the right eye and 6/36 in the left eye. The slit-lamp examination showed 10 to 15 medium sized keratic precipitates with an anterior chamber inflammation characterised by cells 2+ and flare 2+ bilaterally. There were Koeppe and Busacca nodules in the irides bilaterally. There was intense vitritis 3+ with "snow balls". The right fundus also showed several choroidal scars in the posterior pole sparing the macular area. A diagnosis of bilateral chronic granulomatous panuveitis was made and she was investigated. A systemic review comprising of full blood count (FBC), erythrocyte sedimentation rate (ESR), chest X-ray, VDRL, and fluorescent treponemal antibody absorption test (FTA-ABS) were performed. All these test results were reported as normal. The Mantoux test showed no response. Fundus fluorescein angiography showed no active choroiditis or vasculitis. She was treated initially symptomatically with topical steroids and mydriatics.

She defaulted follow-up for 7 months. During her subsequent follow up, the vitritis had increased in intensity and her visual acuity decreased to 6/24 in her right eye and counting fingers at 1 metre in her left eye and was reinvestigated. A subcutaneous nodule was observed over her right cheek. This time, her ESR was 16 mm/hour. Her FBC, liver function tests (LFTs) and total

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serum calcium levels were all normal. She was started on systemic steroids, (tab. prednisolone 60 mg a day and tapered gradually) along with topical steroids and mydriatics for both eyes. The subcutaneous nodule over her right cheek (Fig. 1) decreased in size within a week of initiating systemic steroid therapy. An excision biopsy of the same was done. The histopathology report (Fig. 2) of the biopsied tissue showed coalescing collections of epithelioid histiocytes, abundant lymphocytes, and multinucleated giant cells suggestive of sarcoidosis or tuberculoid leprosy. A diagnosis of sarcoidosis was made based on the histopathology report. The dose of systemic steroid therapy was tapered.

She developed a cataract as a complication of chronic uveitis, systemic and topical steroid therapies. She subsequently underwent an extracapsular cataract extraction with intraocular lens implantation in her left eye with perioperative steroid therapy. She was treated with tab. prednisolone 40 mg once a day for two weeks preoperatively and the dose was tapered postoperatively. Her current visual acuity is 6/18.

Case 2

A 41-year-old Indian male presented to our hospital with a right-sided headache and decreased vision of 3 days' duration. On examination his visual acuity was 6/6 in the right eye and 6/18 in the left eye. He had a left relative afferant pupillary defect (RAPD). The examination of his left fundus showed a swollen optic nerve head. His red/green colour vision, tested with Ishihara's chart was full. He was diagnosed as a case of left optic neuritis and was treated with IV methyl prednisolone 1 gm for 3 days, followed by oral prednisolone 45 mg/day and tapered over two weeks. His FBC, ESR and chest X-ray were within normal limits. The collagen vascular markers antinuclear factor (ANF) and rheumatoid factor (RF) were negative. His anti DsDNA was positive—36.8/ml (normal <18.0). The magnetic resonance imaging (MRI) of the brain and orbits revealed an enlargement and enhancement of the left optic nerve involving the proximal half of the nerve suggestive of an inflammatory origin. There was no space-occupying lesion. Ultrasound scan of the optic nerve showed elevation of the optic disc (Fig. 3).

He was referred to an immunologist for systemic work up. The FBCs, serum antibody IgG, IgA and IgM levels were repeated and were within normal limits. AntiDsDNA was repeated and was found to be negative. A repeat chest X-ray revealed the presence of paratracheal lymph nodes.

Three weeks after the initial presentation, his visual acuity improved to 6/12. The examination of his left eye showed a moderate RAPD, fine keratic precipitates, anterior chamber cells 2+, flare 2+, as well as retrolental cells. The examination of his fundus showed massive irregular swelling of the optic disc (Fig. 4), several segments of focal retinal vasculitis with perivascular sheathing, vitritis with "snow balls". Red/green colour vision, tested with Ishihara's chart was decreased in the left eye (1/17 plates, test plate only). He was diagnosed as a case of sarcoidosis with optic nerve infiltration and was further investigated. Serum calcium levels and LFTs were normal. Mantoux test showed no response at 72 hours. He was given a pulse of oral prednisolone 90 mg a day for 7 days which was gradually tapered over the following weeks. His visual acuity gradually improved to 6/6 over 4 weeks. The disc granuloma decreased gradually in size and all signs of vasculitis and panuveitis subsided. The patient has been followed up for almost 2 years. He has fully recovered and regained his colour vision.

Case 3

A 43-year-old Malay female presented to us with complaints of poor vision on and off for 6 months' duration and a sudden loss of vision for a day in her left eye. On examination, her right eye had a visual acuity of 6/6 and her left eye had a visual acuity of hand movements. The patient's left eye examination showed mild

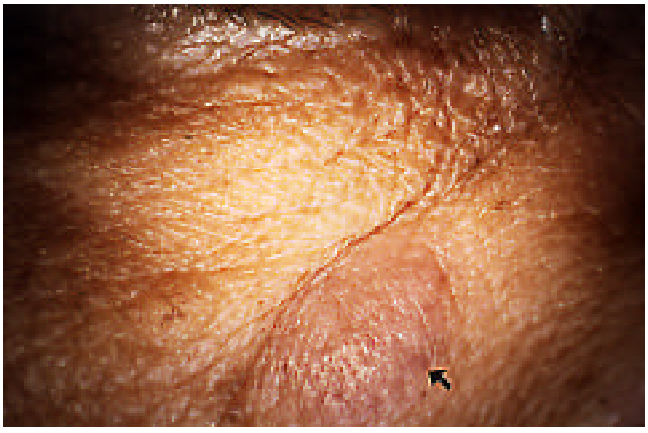

Fig. 1. Right cheek showing a subcutaneous nodule (arrow).

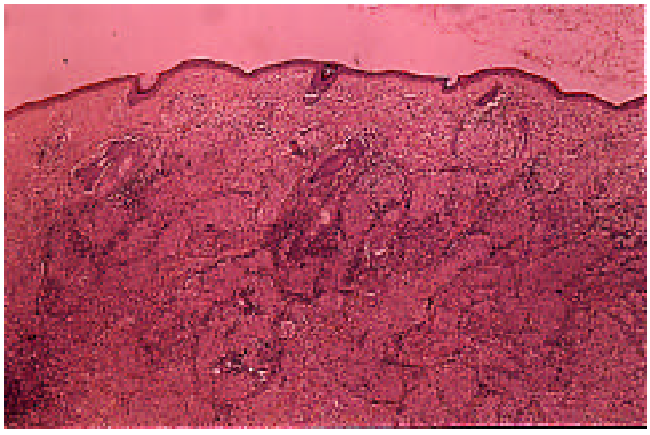

Fig. 2. Non-caseating epitheloid granuloma with giant cells seen on biopsy of the cheek nodule (haematoxylin-eosin staining x40).

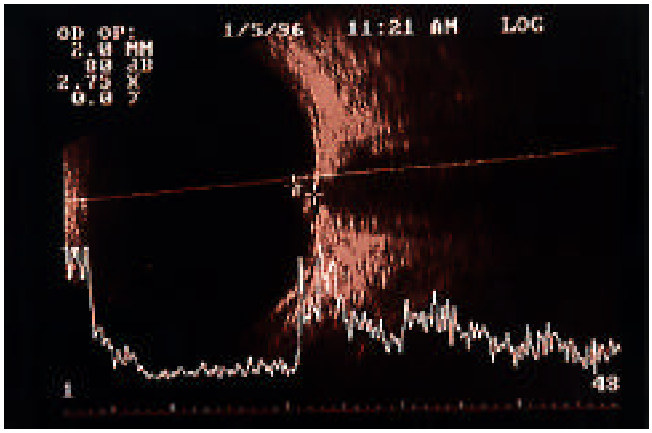

Fig. 3. Swelling of the left optic nerve head as shown by B scan.

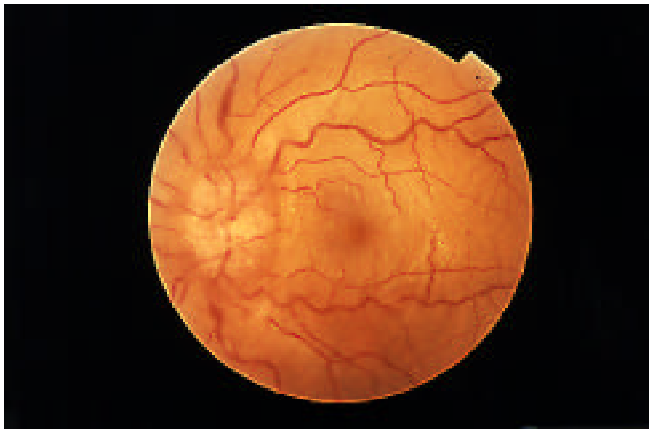

Fig. 4. Left optic disc swelling due to infiltration of the nerve head by sarcoid granuloma.

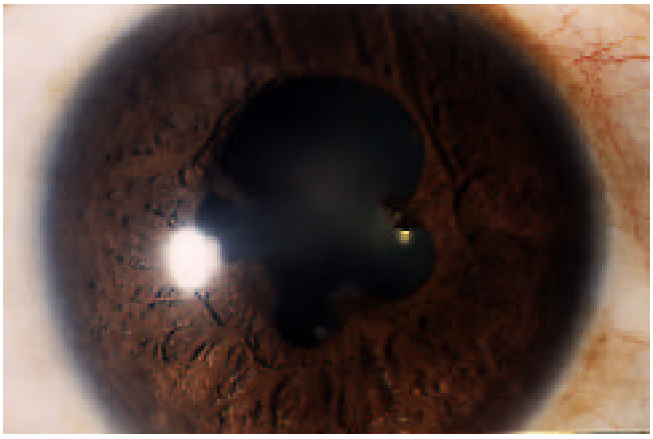

Fig. 5. Left eye with chronic granulomatous anterior uveitis and posterior synechiae.

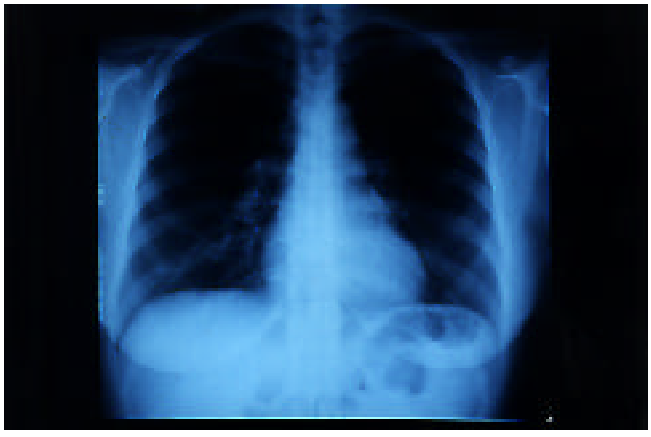

Fig. 6. Chest X-ray revealing bilateral hilar lymphadenopathy.

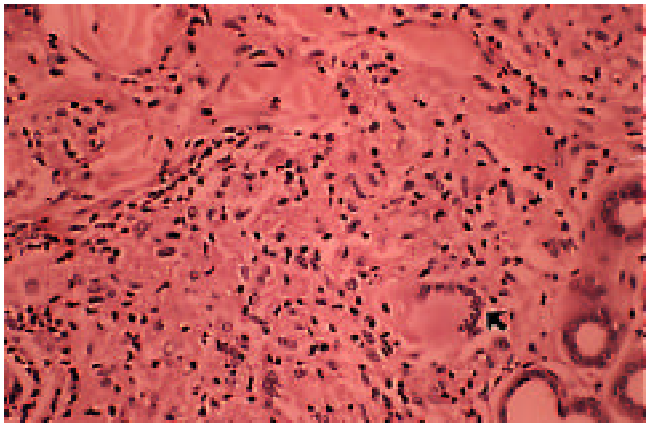

Fig. 7. Cervical lymph node biopsy specimen showing multiple epitheloid granulomas with multinucleated giant cells (arrow) (haematoxylin-eosin staining x400).

flare and occasional cells in the anterior chamber. Iris pigment deposits were noted on the anterior lens surface. There was no view of the fundus due to a vitreous haemorrhage. An ultrasound of the left eye was done which showed blood in the vitreous, posterior hyaloid detachment, and an irregular elevation over the optic nerve head. A presumptive diagnosis of posterior vitreous detachment with vitreous haemorrhage of the left eye was made. No treatment was instituted. Two months later, when the vitreous haemorrhage had cleared, there was evidence of vitreous veils with vitritis and retinal oedema. Initial systemic work-up done included: FBC, VDRL and chest X-ray. All tests were reported as normal. The ESR was 40 mm at the end of one hour. Her visual acuity improved to 6/9 in her left eye, but she continued to have a chronic anterior uveitis (Fig. 5), requiring topical steroid medication. She also developed a chronic anterior uveitis in her right eye requiring topical steroid eye drops.

A year later she presented with bilateral vitritis, snow banking, neovascularisation of the discs, and sheathing of the retinal vessels. This time she was diagnosed as bilateral intermediate uveitis and was reinvestigated. Her FBC and serum calcium levels were within normal limits. The ESR was 16 mm at the end of 1 hour. The Mantoux test showed no response at the end of 72 hours. The X-ray of the chest showed bilateral hilar lymphadenopathy (Fig. 6) and she was referred to a respiratory physician. The bronchoscopic biopsy done showed evidence of non-ceaseating granulomatous inflammation suggestive of sarcoidosis. She was started on oral steroid therapy as well as topical

steroids. Currently her visual acuity is 6/12 in her right eye and 6/15 in her left eye and she has been tapered off systemic steroids and is under a regular follow up.

Case 4

A 71-year-old Malay woman presented to us in 1993, with complaints of decreased vision and occasional redness for a duration of 4 months. She had diabetes mellitus for 10 years. On examination, she had a visual acuity of 6/12 in her right eye and 6/18 in her left eye. The slit lamp examination showed fine keratic precipitates on the cornea, occasional cells in the anterior chamber, and few areas of posterior synechiae bilaterally. The posterior segment was quiet and there was no evidence of diabetic retinopathy. She was started on topical steroids. A year later she developed granulomatous keratic precipitates as well as Koeppe and Busacca nodules on the iris with severe posterior synechiae. She was diagnosed to have bilateral chronic granulomatous anterior uveitis, and was investigated. Her FBC, VDRL, ESR, FTA-ABS and chest X-ray were within normal limits. The Mantoux test was non-reactive at 72 hours.

One year later, she developed diplopia and was admitted to the neurology ward for investigation of a left complete third cranial nerve palsy. The clinical examination showed a left complete oculomotor nerve palsy, multiple bilateral cervical lymphadenopathy that were non-tender and rubbery in consistency, right axillary lymphadenopathy, multiple inguinal lymph nodes, with enlargement of liver and spleen. The computerised axial tomography (CAT) scan of the thorax showed multiple enlarged lymph nodes in the anterior and middle mediastinum. The CAT scan of the abdomen and pelvis revealed hepatosplenomegaly and enlargement of paraaortic lymph nodes. The CAT scan of the head was normal. A biopsy of a cervical lymph node was done. The histopathological examination showed multiple discrete compact epithelioid granules with a few multinucleated giant cells and a hyaline stroma suggestive of non-caeseating granulomatous lymphadenitis (Fig. 7). Her serum calcium level was 2.94 mmol/L, and ESR was 17 mm at the end of one hour. A diagnosis of systemic sarcoidosis was made on the basis of multiple lymphadenopathy, non-caeseating granuloma on biopsy, mononeuritis in the form of oculomotor cranial nerve palsy, raised serum calcium levels and hepatosplenomegaly. She was started on systemic steroids, tab. prednisolone 30 mg a day following which there was resolution of the lymphadenopathy, hepatoslenomegaly and III cranial nerve palsy. Currently she has chronic granulomatous anterior uveitis, with a visual acuity of 6/12 in each eye.

Discussion

Several studies have documented the common occurrence of ocular involvement in sarcoidosis. Estimates of the prevalence of ophthalmic involvement in sarcoidosis have ranged as high as 50%[4] but are generally closer to 25%.[5,6] In a study of manifestations of sarcoidosis worldwide, Siltzbach and associates[5] noted an overall 22% prevalence of ophthalmic involvement. Obenauf and associates[3] noted a 38% prevalence of ophthalmic involvement. James and associates[7] found 27.8% of patients to have ophthalmic manifestations in their large survey of 442 cases. These differences are related to the patient population studied, definitions of ophthalmic involvement and the nature of the evaluations conducted. Indeed, the highest prevalence rate was noted by Crick et al,[4] who classified keratoconjunctivitis sicca as evidence of lacrimal gland involvement in sarcoidosis.

Since Ostenberg's first study on ophthalmic manifestations of sarcoidosis, it has been known that sarcoid may produce lesions in most tissues of the globe and its adnexa. The types of ocular abnormalities encountered are classified into three categories: (1) anterior segment disease, (2) posterior segment disease, and (3) orbital and other disease. In the acute stage, the ocular inflammation is generally unilateral, and as the disease becomes chronic, bilateral involvement usually develops.

Chronic granulomatous uveitis, exemplified clinically by mutton-fat keratic precipitates, iris nodules, and synechiae, is the most common ocular manifestation of sarcoidosis as noted in our cases (1, 3 and 4). Acute iridocyclitis, typified by ciliary injection, aqueous cells and flare, and sometimes fine keratic precipitates, but without evidence of chronic inflammation, does occur in a small percentage of patients as seen in case 2.

Intermediate uveitis can also be a presenting feature in sarcoidosis, with features of snowballs, string of pearls in the vitreous, vitritis with associated snowbanks as documented in our cases (1, 2 and 3).

Posterior segment involvement in sarcoidosis is well documented. These can present as retinal periphlebitis, which can be focal with skip lesions, candlewax drippings, chroidal granulomata as documented in case 2. The disease can manifest with branch retinal vein occlusion, or retinal neovascularisation of the optic disc as seen in case 3, which resulted in vitreous haemorrhage. A variety of lesions of the optic nerve and disc have been reported: papillitis, retrobulbar optic neuritis, optic disc oedema secondary to increased intracranial pressure, optic atrophy and elevated masses extending intraocularly from the optic disc. In our series, case 2, presented with optic disc swelling due to sarcoid infiltration of the optic nerve. Orbital granulomas, lacrimal gland infiltrations, and cranial nerve palsies have also been described.

Sarcoidosis can also present as classical panuveitis involving the anterior and posterior segments of the eye

as in case 1.

The ocular disease can be protean with features of anterior uveitis, intermediate uveitis, panuveitis, or with optic nerve involvement. Table I summarises the ocular lesions noted in our 4 patients. Hence a diagnostic possibility of sarcoidosis should be there in the back of the ophthalmologist's mind while dealing with any patient of chronic uveitis.

Sarcoidosis concerns physicians of virtually all specialties. It is particularly important to the ophthalmologist since a significant number of patients will seek initial medical examination because of ocular disease. Considering clinically detectable lesions, Obenauf and associates[3] in their study of 532 cases reported hilar lymphadenopathy and pulmonary abnormalities to be more common than ophthalmic manifestations. Clearly, all patients with suspected sarcoidosis deserve a thorough ophthalmologic examination. Conversely, patients with ocular findings suggestive of sarcoidosis should be examined for systemic disease. The commonly observed systemic features are hilar lymphadenopathy and pulmonary infiltrations as seen in cases 2 and 3. Multiple lymphadenopathy, oculomotor cranial nerve palsy, and hepatospenomegaly were noted in case 4. Cutaneous manifestations in sarcoidosis can be divided into those that are specific and those that are non-specific.[8] Specific lesions are those that on biopsy reveal non-caeseating granulomas. In case 1 a skin nodule developed which on excision biopsy showed non-caeseating granuloma with epitheloid cells. Non-specific lesions refer to cutaneous changes that on biopsy fail to reveal granuloma formation, but which are associated with sarcoidosis. Erythema nodosum is a principal example of a non-specific cutaneous lesion. The systemic features observed in our patients are summarised in Table II. All 4 patients reported here showed no response to Mantoux test, indicating a depression in cellular immunity that is seen in sarcoidosis (Table III). All our patients responded well to systemic or ocular steroid treatments.

Diagnosis of Sarcoidosis

Traditionally, diagnosis of sarcoidosis requires a positive Kveim's test, an elevated serum angiotensin converting enzyme (ACE) levels[9] and elevated serum lysozyme levels. Unfortunately, since the disease is so rare in this part of the world, these useful tests are not made readily available to us. So we adopt the following steps to aid us in the diagnosis of this enigmatic and perplexing disease.

1) In sarcoid suspect based on ocular features, the intraocular lesions we define as suggestive of sarcoidosis are granulomatous iritis with mutton-fat keratic precipitates or iris nodules, trabecular nodules, tent-like peripheral anterior synechiae, snowball or string-of-pearls vitreous opacities, retinal perivasculitis mainly involving the venules, perivascular cuffing, focal sheathing, candle-wax drippings, spotty retinochoroidal exudates and neovascularisation of the optic discs.
2) The initial systemic investigations recommended are blood cell count, ESR, chest roentgenography, LFTs, tuberculin skin test (Mantoux test) and serum ACE if available. Erythrocyte sedimentation rate is a useful tool as it is elevated in most cases but it is non-specific

TABLE I: SUMMARY OF OCULAR FEATURES IN OUR FOUR CASES

	Panuveitis	Optic nerve infiltration	Intermediate uveitis	Chronic granulomatous anterior uveitis
Case 1	+	–	–	–
Case 2	+	+	–	–
Case 3	–	–	+	–
Case 4	–	–	–	+

+ present
– absent

TABLE III: SUMMARY OF THE POSITIVE INVESTIGATIONS IN OUR FOUR PATIENTS

	ESR	Serum calcium	Chest X-ray	Mantoux test	Non-caseating granuloma observed from:
Case 1	–	–	–	Flat	Skin nodule
Case 2	–	–	+	Flat	–
Case 3	+	–	+	Flat	Bronchial biopsy
Case 4	+	+	+	Flat	Cervical node biopsy

+ positive
– negative

TABLE II: SUMMARY OF THE SYSTEMIC FEATURES DIAGNOSED IN OUR FOUR PATIENTS

	Skin nodule	Hilar lymphadenopathy	Pulmonary infiltration	Multiple lymphadenopathy	Hepatosplenomegaly
Case 1	+	–	–	–	–
Case 2	–	+	–	–	–
Case 3	–	–	+	–	–
Case 4	–	–	–	+	+

+ present
– absent

as a diagnostic criteria. In chest X-rays one should look for bilateral hilar lymphadenopathy or pulmonary infiltrations. Pulmonary parenchymal lesions may be classified as (a) miliary size densities, (b) micronodular lesions, (c) large confluent mass lesions that may progress to cavitation, (d) interstitial fibrosis, or (e) alveolar sarcoid resembling pulmonary oedema.[10] A complete array of tests for liver functions needs to be done. An abnormal LFT indicates subclinical infiltration of the liver and could give additional support for the diagnosis. Mantoux test, if it shows no response at the end of 72 hours, is clinically significant and indicates a suppression of cellular immunity. This is particularly relevant to our local population as every one has received BCG vaccination. Epitheloid cells derived from macrophages are the most likely source of increased serum ACE activity in sarcoidosis.[11] Consequently, the serum ACE level appears to reflect the total body mass of ACE-producing granulomas and hence, disease activity. Serum ACE values are elevated in 60% to 90% of adult patients with sarcoidosis and they correlate well with disease activity.[8] Elevated serum ACE measurements in patients with granulomatous uveitis support a presumptive diagnosis of sarcoidosis.[12-16]

If the initial investigations done are positive, then the patient should be further investigated. A complete systemic work up by a physician is recommended to look for pulmonary involvement, skin lesions, hepatosplenomegaly, lymhadenopathy and possibly any evidence of neurosarcoidosis. Serum calcium levels and total calcium levels are the next recommended tests. A normal value is between 2.1 and 2.6 mmol/L. An elevated value is considered clinically significant and could add support to a diagnosis of sarcoidosis. Gallium citrate scans of the chest can be done, as they are more sensitive than routine chest roentgenograms for showing pulmonary involvement in sarcoid. Views of the head should be included in Gallium citrate scans to ascertain the status of the lacrimal gland whenever the diagnosis of sarcoidosis is being considered.

3) A definitive diagnosis can be achieved by biopsy of suspected tissues. If systemic examination reveals enlarged lymph nodes or suspicious skin lesions, then biopsy of the same is indicated. Histological feature observed in sarcoidosis is a non-caseating granuloma characterised by a central collection of monocytes-macrophages in various states of activation and differentiation. Among these activated monocytes and macrophages, monocytes that have differentiated into epitheloid cells (about 20μ in diameter), and Langhan's giant cells (as large as 300μ in diameter with as many as 30 nuclei) are believed to result from the fusion of two or more cells. This central collection of cells is surrounded by lymphocytes and a few plasma cells.
Blind conjunctival biopsies yield diagnostic results in 10% to 28% of cases of suspected sarcoidosis.[6,9] Most authorities recommend conjunctival biopsies in all cases of suspected sarcoidosis because they are performed easily and virtually without risk.[6,9]

4) More invasive procedures like bronchoalveolar lavage, transbronchial lung biopsy, or liver biopsy can be done, if there is a strong clinical suspicion and biopsy specimens elsewhere are non-diagnostic. The absence of absolute diagnostic criteria should not deter one from pursuing a logical diagnostic course after a detailed ophthalmic or systemic physical examination has suggested the possibility of sarcoidosis. As the mysteries of this enigmatic and perplexing disease are unravelled, more specific diagnostic criteria will undoubtedly be obtained.

Conclusion

The aim of this article is to highlight that sarcoidosis does exist in this region and the eye involvement can be the presenting symptom. So far, in our centre, 9 patients have been diagnosed with sarcoidosis on the basis of ocular features. Seven out of these 9 patients have ocular symptoms as the primary manifestation of the disease. Three of these 9 patients have had a histological confirmation of the diagnosis. Thus the ophthalmologist may be the first physician to see the patient. Therefore it is essential that the ophthalmologist be aware of the available diagnostic options and understands the manifestations of the disease. Sometimes the systemic involvement can occur many years after the ocular presentation and one needs to follow up the patient and take relevant history for the various systemic manifestations from time to time.

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