Case Report

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Diagnosis of systemic sarcoidosis in a patient with bilateral granulomatous pan-uveitis: a case report

Shreeya Thapaliya, MD[a], Prashant Pant, MD[a], Sandip Paudel, MBBS[b,*], Sujha Ghimire, MBBS[c]

Introduction and importance: Sarcoidosis is a systemic disease usually presenting with features of hilar lymphadenopathy like persistent cough, dyspnoea, cough, night sweats. However, its first and only manifestation can be ocular symptoms consistent with uveitis.

Case presentation: The authors present such association in a 53-year-old female who had ocular symptoms on and off, designated as uveitis. Despite medications, her symptoms rather flared up. On diagnostic assesement done years later, chest X-ray showed bilateral hilar lymphadenopathy, serum angiotensin-converting enzyme levels were also raised, and the diagnosis of systemic sarcoidosis was confirmed.

Clinical discussion: Eye involvement can occur way before the systemic presence of the disease is detected and can be present clinically as an isolated entity which makes diagnosis of underlying sarcoidosis a challenge.

Conclusion: Consideringsarcoidosis as one of the differential diagnosis when attending patients with non-resolving uveitis remains the mainstay of this report.

Keywords: case report, granuloma, sarcoidosis, uveitis

Introduction

Sarcoidosis is a chronic multisystemic granulomatous disease occurring as a result of exaggerated immune response in genetically predisposed people exposed to some environmental triggers leading to the formation of granuloma[1]. It commonly affects the young and middle-aged populations. Females are more commonly affected than males[1,2]. The most common manifestation of sarcoidosis is bilateral hilar lymphadenopathy. Lung infiltration occurs in nine out of ten people. Other common lesions occur in the skin and eyes[3].

Ocular sarcoidosis can be seen in 60% of people with systemic sarcoidosis. The most common lesion in the eye is bilateral granulomatous uveitis (iridocyclitis)[4,5]. The diagnosis is based on the visualization of bilateral granulomas and laboratory and radiographic changes. Laboratory investigations include raised angiotensin-converting enzyme (ACE) and lysozyme. Chest X-ray and computed tomography Chest may show bilateral hilar lymphadenopathy[4].

HIGHLIGHTS

- Sarcoidosis is a systemic disease presenting with features of hilar lymphadenopathy.
- The first and only manifestation can be ocular symptoms.
- Sarcoidosis should be considered when attending patients with persistent uveitis.

However common the ocular manifestations may be in sarcoidosis, the diagnosis of systemic sarcoidosis in cases of uveitis is uncommon and has been reported only a few times[6,7]. We report a case of 53-year-old female with uveitis who was diagnosed with sarcoidosis years later on further assessment. This case report has been reported in line with SCARE guidelines[8].

Case report

A 53-year-old female with no known co-morbidities presented with 2 weeks' history of blurring of vision and headache back in 2011 AD. Acute on the onset, the blurring of vision was bilateral (over left eye more than the right). Also, she complained of dull aching headache over the occipital region which had acute onset, with no aggravating and relieving factors. However, there was no history of floaters, eye pain, increased sensitivity to light, increased sensitivity to sound, associated nausea, or vomiting. Likewise, no history of fever, rash, anorexia, weight loss, cough, chest pain, joint pain, or hemoptysis was given. The patient was first in the family to experience such symptoms.

Diagnostic assessment

On examination during the first visit, vital parameters were within their normal range and systemic examination was also

[a]Department of Internal Medicine, Star Hospital, Sanepa, Lalitpur, [b]College of Medicine, Nepalese Army Institute of Health Science and [c]Nepal Medical College, Kathmandu, Nepal

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*Corresponding author. Address: College of Medicine, Nepalese Army Institute of Health Sciences, Kathmandu 44600, Nepal. Tel.: +977 984 292 2639. E-mail: Sandip.paudel.520@gmail.com (S. Paudel).

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normal at the time of first presentation. The Fundus picture showed bilateral multiple evanescent white dots. While, visual acuity and intraocular pressure (IOP) were normal. Traumatic causes of headache with blurred vision were ruled out by appropriate history. Laboratory tests revealed no evidence of infection, and thus infectious causes were ruled out. However, a complete work-up of the patient was not performed due to lack of proper setting and she was clinically diagnosed with uveitis and occipital neuralgia.

After 3 years of initial presentation, her symptoms rather flared up with a vision of 6/6 in both eyes. On slit lamp examination, multiple cells, and flares (mild grade) were seen in the anterior chamber and a dark spot was seen in over the left eye.

Nine years after the initial presentation, routine blood and urine examinations were sent which came out to be normal. But Chest X-ray revealed bilateral hilar lymphadenopathy which was confirmed by computed tomography of the chest (Fig. 1). Infection, inorganic dust disease, sarcoidosis, malignancy were taken as differentials. A complete blood examination showed all blood cells within normal limits. With history of recurrent uveitis and an added evidence of bilateral hilar lymphadenopathy, a strong suspicion on sarcoidosis was made and serum ACE level was sent which was raised to 82 U/l(normal range being 8.00–65.00 U/l). The case was then referred to a rheumatologist and pulmonologist; however, no active intervention was advised.

Treatment

During her first visit, the patient was started on oral prednisolone 60 mg. Three years later when her symptoms flared up, she was started on topical steroids in response to which the IOP raised to 42 mm of Hg on the right and 19 mm of Hg on the left eye. Oral Acetazolamide was added, after which the IOP dropped to 18 mm of Hg on the right and 16 mm of Hg on the left eye.

Nine years later, the patient was prescribed oral prednisolone (60 mg) and oral azathioprine (50 mg). However, after 6–8 weeks on oral medications, her liver function test was deranged and IOP was raised. So, azathioprine was stopped, and steroid was gradually tapered every 5 days. She had no compliance to oral steroids. Thus, the presenting symptoms flared up and her vision started diminishing to 6/24 on the right eye and 2/60 on the left eye. Oblique slit lamp examination of the cornea revealed keratin precipitates and granuloma while, examination of the lens showed the development of cataracts. Optical coherence tomography (OCT) revealed macular oedema. Topical steroids were started again.

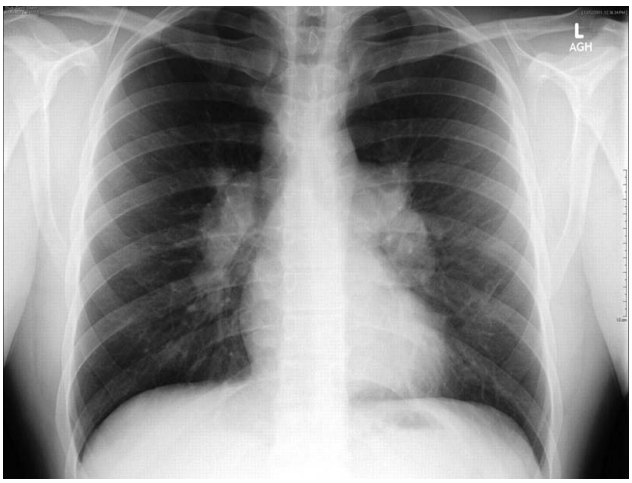

Figure 1. Chest X-ray showing bilateral hilar lymphadenopathy.

Later, the patient was referred to another centre for further management. She was treated for pan-uveitis with oral prednisolone 80 mg tapered 2 weekly, post steroid her vision was 6/18 in the right eye and 6/60 in the left eye. With no improvement in vision, oral methotrexate 15 mg was opted as an alternative treatement. OCT macula showed bilateral peripapillary neovascularization and foveal and sub-foveal inner retinal layers, so she was planned for an intravitreal injection of ranibizumab in both her eyes. (Fig. 2) Whatsoever, there was no improvement in vision. Rather, the disease was complicated by side effects of injection like Subconjunctival haemorrhage and raised IOP. The vision post-injection was 6/12 on the right eye and 6/60 on the left eye.

Since minimal to no improvement was seen with ranibizumab, the intravitreal injection was changed to aflibercept. Currently, the patient received the first dose of intravitreal injection of Aflibercept in both eyes and is on oral methotrexate (15 mg).

Follow-up

The patient is under regular follow-up in a hospital setting at present. Patient is planned for intravitreal Aflibercept injections every four weekly. The patient reported mild redness of the eyes during the first follow-up visit. However, no serious side effects were complained of. All the main events are presented as a timeline below: (Fig. 3)

Discussion

Sarcoidosis has multisystem manifestations, among which eye is affected commonly which manifests as uveitis most of the times[5,9]. According to the standardization of uveitis nomenclature, anterior, intermediate, posterior or pan-uveitis represent the most common forms[10]. Ocular manifestations are common in diagnosed case of systemic sarcoidosis but ocular symptoms that manifests before the systemic presentation and diagnosis of sarcoidosis remains the main theme of this report.

Regarding the frequency of sarcoidosis in the world, studies have reported a relatively higher incidence in Scandinavian countries compared to other parts of the world. Prevalence estimates from Sweden nationwide register show numbers at 11.5 per 100 000 population which is higher compared to the data from the United States. Other parts of the world have a comparatively lower incidence and prevalence of sarcoidosis. The estimates from Asian region shows consistently lower incidences of sarcoidosis. There exists a strong racial difference in the incidence of sarcoidosis. Studies have found a strong predilection for black population compared to the Whites. Even among blacks, black women are affected more so than black males. This is suggested to be due to the result of race-specific genetic associations and environmental socioeconomic factors[11,12].

The most common presenting symptoms in sarcoidosis is bilateral hilar lymphadenopathy. However, ocular symptoms are common extrapulmonarymanifestion in patients with sarcoidosis. Studies have reported a variable frequency of ocular involvement in sarcoidosis, ranging from 12–68%. This

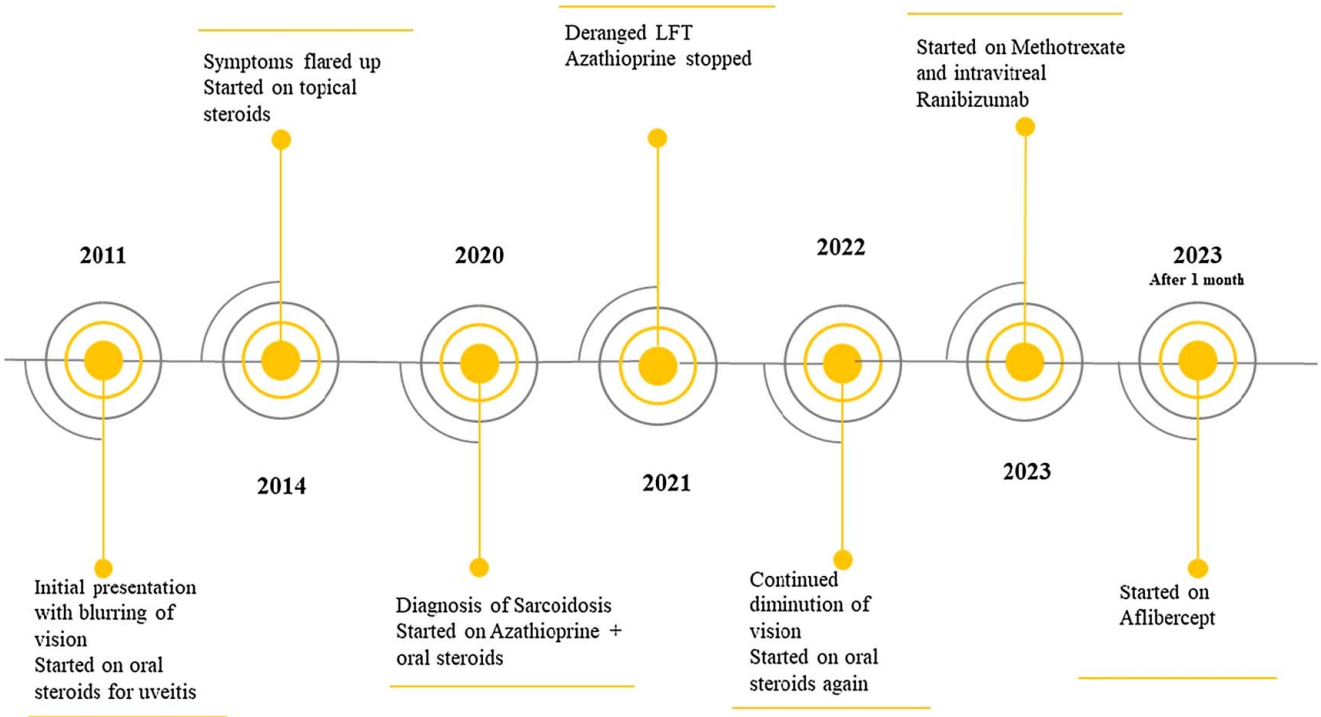

Figure 2. Timeline showing major events. LFT, liver function test.

variability in frequency may be due to certain genetic polymorphisms in HLA and non-HLA gene loci. Almost all the structure in eyes may be affected in ocular sarcoidosis involving uvea, vitreous, retina, orbit, lacrimal glands, and eyelids. Uveitis is the most common manifestation seen in ocular sarcoidosis. It can be present in upto 70% of OS cases. Thus sarcoidosis may be a cause of chronic, noninfectious uveitits[13].

Among the patients with ocular sarcoidosis, two peaks of incidence are reported to be at 20–30 years and 50–60 years[13]. The patient was 53 year old in this case. Eye involvement can occur way before the systemic presence of the disease is detected and can be present clinically as an isolated entity which makes diagnosis of underlying sarcoidosis a challenge. Diagnosis of the disease is missed often when patient first presents with ocular symptoms only[14], which is the case in our patient also. The diagnosis of uveitis in sarcoidosis is based on a picture of clinical features, laboratory investigations, imaging, and histopathological examinations. In patients with suspicion of uveitis associated with sarcoidosis, it is important to evaluate the patient for other systemic manifestations of sarcoidosis. But at the initial years, the patient in this case had no other systemic manifestations. Initially the patient only had complaints of headache and blurring of vision with bilateral 6/6 visual acuity but that deteriorated to 6/24 on the right eye and 2/60 on the left eye. Diagnosis of sarcoidosis in patients with ocular manifestations only, pose a challenge towards timely diagnosis and this can further deteriorate the visual acuity to blindness[15]. In this case, the patients visited multiple healthcare centres to seek medical attention which further delayed the diagnosis. Laboratory tests can help to establish a connection between uveitis and systemic sarcoidosis and one of the frequently used tests is serum ACE levels. Although serum ACE levels was not checked during the initial years, it was found to be raised when checked later. But it is also not reliable as Hien and colleagues reported a similar case of ocular presentation in sarcoidosis and found the serum markers within their normal limits[16]. Imaging modalities like OCT gives detailed cross-sectional images of the retina. This modality revealed macular oedema, bilateral peripapillary neovascularization, and foveal and sub-foveal inner retinal layers in our patient.

Treatment is directed towards reducing the inflammation, preventing further deterioration, and avoid drug toxicity[17]. Asymptomatic cases with minimal changes in the radiograph can have spontaneous remission such that systemic therapy is not routinely indicated but if needed, corticosteroids, immunosuppressive agents, and cytotoxic drugs can be given. In this case, when the patient was put on systemic therapy, patient's liver function test was deranged and IOP was increased, after which the drugs were stopped and patient was put on methotrexate. Intravitreal injection of ranibizumab is useful in macular oedema as it increases the visual acuity and regresses the disease[18,19]. However, the patient showed little to no improvement and later the patient was given intravitreal aflibercept, which also alleviates the signs of macular oedema. A multidisciplinary treatment modality is warranted for better outcome.

The main challenge in the study is regarding the case follow-up. The patient belongs to a rural area and was lost to follow-up several times during the course of treatment. There was absence of compliance due to side effects of drug that is raised intraocular pressure and deranged liver function in the patient. Alternative medications were tried and finally the patient is doing well with intravitreal Aflibercept injections with minimal side effects.

Also, future works to establish the linkage of recurrent uveitis eventually developing sarcoidosis is necessary.

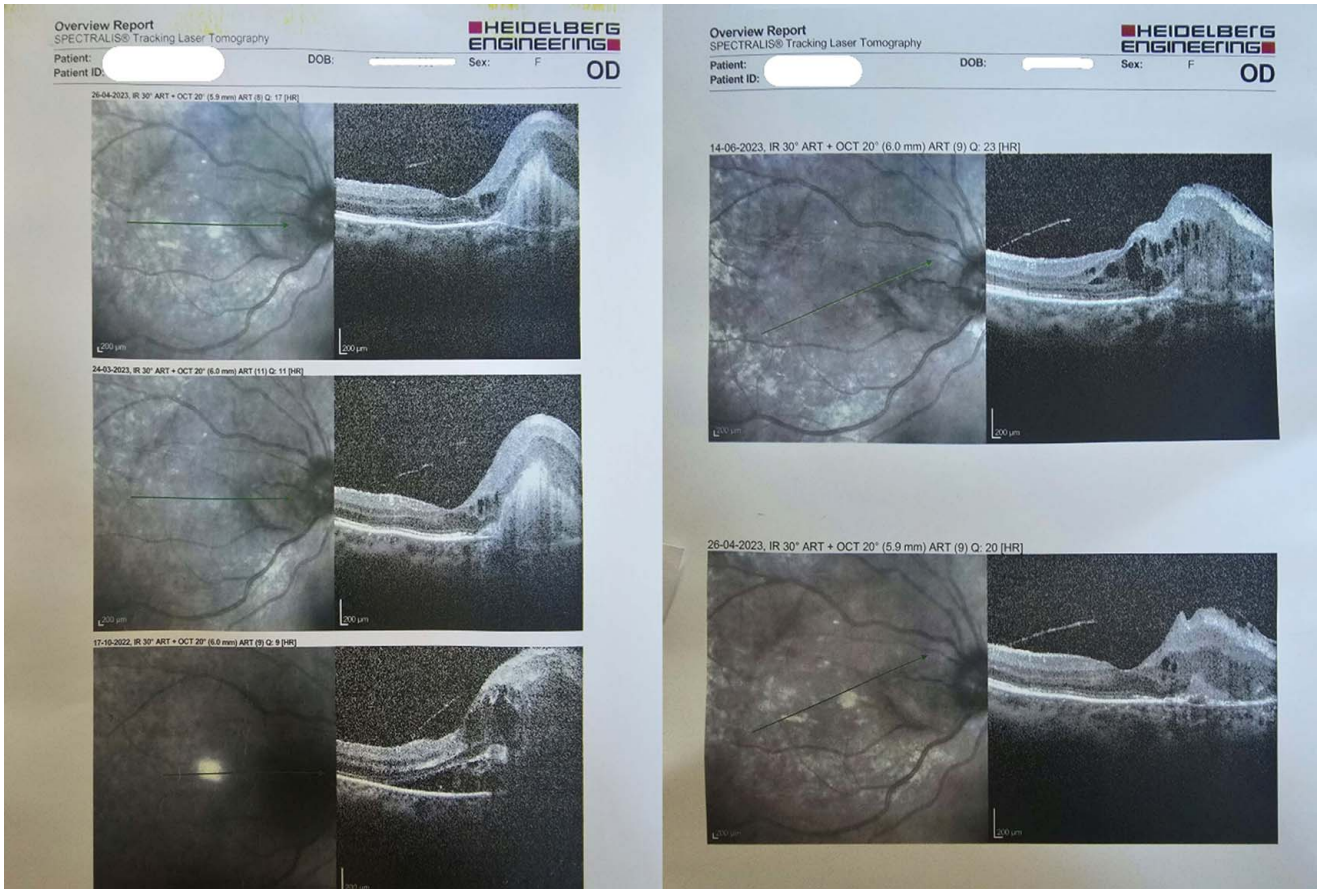

Figure 3. Chronological sequences of optical coherence tomography showing varying degrees of macular oedema.

Conclusion

Although sarcoidosis is a systemic disease, its first and only manifestation can be ocular symptoms consistent with uveitis. Sarcoidosis should be one of the differential diagnosis when attending patients of unresolving uveitis to avoid delay in diagnosis.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in- Chief of this journal on request.

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This article did not receive any grants.

Author contribution

S.T.: conceptualization, data curation, project administration, investigation, resources, supervision, validation, visualization, writing-original draft, writing-review and editing. P.P.: conceptualization, data curation, project administration, validation, writing-original draft, writing-review and editing. S.P.: conceptualization, resources, visualization, writing-original draft, writing-review and editing. S.G.: conceptualization, visualization, writing-review and editing.

Conflicts of interest disclosure

There is no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Prashant Pant.

Data availability statement

Not applicable.

Provenance and peer review

Our paper was not invited.

Patients perspective

Patient was well cooperative and agreed for the consent. She wants her case to be a study purpose for future doctors and health professionals.

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